EVIDENCE TABLES

4 Referral, diagnosis and investigations (REFER 1, INVEST, PROG)

REFER 1

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
van der Horst, Speyer I, Visser H et al. Diagnosis and course of early-onset arthritis: Results of a special early arthritis clinic compared to routine patient care. *British Journal of Rheumatology.* 1998; 37(10):1084-1088 ID 1084	Cohort 2+ Single centre trial: The Netherlands	N=474 (N=335 referred to the EAC and N=233 fulfilled the entry criteria) **Drop-outs/exclusions:** At one year: N=88 with OA or post-traumatic arthritis (total of N=340 available for follow-up) N=52 (13%) lost to follow up	**Inclusion criteria:** Patients were referred if at least two of the following features were present: joint pain, joint swelling or reduction of joint mobility. Any of these features had to have a history of < two yrs The patients were included in the study if 1) the arthritis was confirmed by a rheumatologist 2) the history of symptoms indeed last < 2 yrs and 3) the patients had not been visiting a rheumatologist elsewhere for the same problem **Exclusion criteria:** See inclusion criteria **Baseline characteristics:** EAC: 59% women, median age 53 yrs, mean duration of	Early Arthritis Clinic (EAC) N=233 N=50 patients with 'definite' or 'probable' RA GP campaign was started by the rheumatology group. All patients referred were seen within one week Diagnosis: After two weeks diagnosis was made according to the international classification criteria and revised after three months and one year	Routine clinic 1993-1996 N=241 N=91 patients with 'definite' or 'probable' RA	One year	Time to presentation; disease presentation	None reported

			symptoms 122 days*, acute symptoms 73% and diagnosis made after two weeks 68% Routine: 48% women, median age 47 yrs, mean duration of symptoms 31 days*, acute symptoms 54% and diagnosis made after two weeks 75% * p<0.00001	The diagnosis 'probable' RA was made using both clinical judgement and the 1958 ACR criteria but without the 6 weeks duration RA observed by a physician After three months 'definite RA' was defined according to the 1987 ACR criteria Treatment of most RA patients included NSAIDs, plus sulphasalazine or hydroxychloroquine When there was persistent disease activity patients were switched to methotrexate, but prednisone				

1.1 Effect size

EAC (N=233) vs ROUTINE CLINIC (N=241) (All patients referred):

- The duration of symptoms was significantly shorter in patients referred to the EAC compared with the routine clinic (p<0.00001)
- Patients who were referred to the routine clinic were more likely to have 'definite or probable' RA than those referred to the EAC (OR 0.56 (95%CI 0.32 to 0.97)
- Overall, diagnosis of 'definite' RA (ACR 1987) criteria made at two weeks after the first visit rarely required revision in the following year. In the case of the diagnosis of 'probable' RA, 51% switched to 'definite' RA within one year.

EAC and the routine clinic (N=91) - patients with definite or probable RA only):

- An acute onset of symptoms was seen more often (54% and 39%)
- An atypical presentation, namely asymmetrical arthritis (28% and 22%) monoarthritis or oligoarthritis (30% and 25%)
- Erosions present (25% and 28%)
- There were no significant differences in:
- The median duration of symptoms (NS)
- The median age (NS)
- Arthritis location (NS)

- At least 25% of the RA patients in both groups already had erosions at their first visit, where as 84% of the RA patients had a symptom duration of less than one year

AUTHORS CONCLUSION
The diagnosis of 'definite' RA can be made within two weeks after the first visit by a rheumatologist in 70% of the cases, even when the presentation of the arthritis is atypical. An early diagnosis of RA rarely changes in the following year. Furthermore, RA is often erosive at presentation, which justifies considerable effort to motivate both patients and GPs to regard early RA as a medical emergency and thereby to reduce the time lag even more

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
Kaarela, K. Prognostic factors and diagnostic criteria in early rheumatoid	STUDY DESIGN: Case-series Single centre, Finland (but	Level II (1 major area of bias)	Total N=442 entered, N=200 available and included at the 8-year	N/a	**Inclusion criteria:** Patients > 16 years with swelling of at least 1 joint and duration of	The N=200 patients at 8 year follow-up with RA or arthritis were divided into several subgroups: A. Seropositive and erosive	Assessments made by Rheumatologists At the time of the first	See below	None reported	

arthritis. Scand J Rheumatol Suppl. 1985;57:1-54. ID 413	patients recruited from many centres in Finland). AIM: To establish new diagnostic criteria for RA and to compare the usefulness of the ARA criteria, NY criteria and new criteria in the early stages of RA. To study the sensitivity and specificity of different combinations of the new and ARA diagnostic criteria for RA in the early stages of the disease.	• Not blinded Investigators • True population (patients with inflammatory arthritis symptoms but in whom specific diagnosis has not been diagnosed)	follow-up Patients referred to the Rheumatism Foundation Hospital from GPs, health centres and out-patient clinics of hospitals in one area of Finland.		disease ≤6 months. **Baseline characteristics of the N=200 at 8 year follow-up**: Mean age 41, 69% female.	arthritis (N=93) B. Seropositive and non-erosive arthritis (N=15) C. Seronegative and erosive arthritis (N=17) D. Seronegative and nonerosive arthritis (N=75) RA diagnosis was made on 3 bases: 1. RA with 5 erosive joints (N=78) 2. Seropositive and erosive RA (N=93) 3. Seropositive or erosive RA (N=125) **New clinical criteria for RA** (joint involvement at initial examination – joints included were finger PIP, MCP, MTP, wrist, elbow, shoulder, sternoclavicular, jaw, subtatlar, talocrural, knee & hip: 1. Symmetrical swelling in PIP or MCP or MTP joints 2. Symmetrical swelling or	hospitalisation (1-6 months from the onset of disease) all patients were studied in accordance with the diagnostic criteria of RA (ARA and New York criteria were used as well as some new criteria). After 3 years the patients were re-examined and divide up into different groups according to the diagnosis of their inflammatory joint disease. Diagnostic criterion was definite RA according to the ARA criteria.			

						tenderness in PIP or MCP or MTP joints 3. Swelling in 3 joints 4. Swelling in 4 joints 5. Swelling in 5 joints 6. Swelling in 6 joints 7. Swelling in 1 joint + swelling or tenderness in another 2 joints 8. Swelling in 1 joint + swelling or tenderness in another 3 joints 9. Swelling in 1 joint + swelling or tenderness in another 4 joints 10. Swelling in 1 joint + swelling or tenderness in another 5 joints 11. Symmetrical swelling in PIP or MCP or MTP joints + Swelling in 5 joints 12. Symmetrical swelling or tenderness in PIP or MCP or MTP joints + Swelling in 1 joint and swelling or tenderness in				

						another 4 joints ARA criteria 1-8 NY criteria Sensitivity, specificity and Yuden Index (se + sp – 100) were all calculated to determine the value of the diagnostic criteria.				

Additional results:

- **Power of each criterion to predict the diagnosis of RA in the early stages of the disease (multiple regression analysis):** The first ARA criterion did not add significantly to the explanation power. The 8th criterion explained the greater part of the variance. In patients with RA and 5 erosive joints the 3rd NY criterion had its only peak here. The 12th new criterion was the best clinical criterion and the 1st ARA criterion was the best anamnestic criterion.
- **Sensitivity and specificity (Yuden index):** The 8th ARA criteria had the best Yuden index for RA patients (in each of the 3 main diagnostic groups - RA with 5 erosive joints, Seropositive and erosive RA, Seropositive or erosive RA). The 12 new criterion had the second best sum of sensitiviy and specificity. The 11th new criterion and the 2nd NY criterion were more specific but low sensitivity limited their value. The 3rd NY criterion was too demanding at the early stage and the 7th ARA criterion was therfr reckoned more valuable. Of the anamnestic criteria, the 1st ARA criterion was estimated to be more useful than the 1st NY criterion because of its superior specificity and better Yuden Index (except in the 3rd RA group - Seropositive or erosive RA). The rest of the ARA criteria had better low specificity or sensitivity. The NY criteria didn't seem very useful at the very early stage of RA.
- The sen and spec of the 1st 10 new criteria in the 3 diagnostic RA groups was as follows: Swelling in 3 joints had 20% better specificity than that of 2 joints. As the number of swollen joints increased, specificity increased, but sensitivity (and in the 2nd diagnostic group also Yuden Index) decreased. To attain better specificity and Yuden index than that given by 3 swollen joints, the number of inflamed (swollen or tender) joints should be 5. Symmetrical swelling in PIP or MCP or MTP joints was 20% more specific than the 5th ARA criterion, but the 2nd new criterion had a better Yuden Index than the 1st new criterion.
- **Sensitivity and specificity of combinations of criteria:** The spec of the 8th ARA criterion was 86% - with the addition of 2 symmetrically swollen PIP or MCP or MTP joints it was 97%. This combination and those with 4, 5 or 6 swollen joints were unnecessarily exacting. Better sensitivity and 93% specificity could be obtained if the number of inflamed (swollen or tender) joints wee counted. Where seopositive cases wee excluded from the control group, the specificity is 100%.
- The sens of the 1st ARA criterion was 81% and when this is added to combinations, the sens decreases. The specif from 95% to 100% reveals how seldom this combination led to a nonerosive result. When the 2nd new criterion was replaced by the 1st, specificity was 97-100% but sensitivity 34%-53%.
- When X-ray changes is added to the combination of polyarthritis, morning stiffness and RF, the positive result does not indicate another disease but RA. However, X-ray changes are not the 1st sign of RA and so the sens of this combination was at best 38%. As nodules are also rare at the ego=inning of the disease, in practice, fulfilment of the definition of classic RA requires X-ray changes. Thus this concept also only identified a third of patients wit RA at the early stage of the disease. The former combination was slightly more sensitive, probably because symmetrical swelling in joints is not demanded by the 12th new criterion.

Best predictors:
combinations of 8th ARA criteria (swelling in 1 joint and swelling or tenderness in another 4 joints) + (symmetrical swelling or tenderness in PIP or MCP or MTP joints) or (3 swollen and tender joints): Increase in specificities for predicting: RA with 5 erosive joints, 83% or 82%; RF+ and RF- RA both 93%; RF+ or erosive RA both 100%)

Not good predictors: NY and ARA criteria (except 8th ARA criterion which had highest Yuden Indexes* for predicting RA with 5 erosive joints; RF+ and RF- RA; RF+ or erosive RA – Yuden Indexes of 53, 69 and 72 respectively; specificities 75%, 86% and 98%)

*Yuden Index (Sensitivity + specificity –100; maximum = 100)

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
Machold KP, Stamm TA, Eberl GJ, Nell VK, Dunky A, Uffmann M, Smolen JS. Very recent onset arthritis--clinical, laboratory, and radiological findings during the first year of disease. J Rheumatol. 2002 Nov;29(11): 2278-87.	STUDY DESIGN: Case-series 3 Multicentre, Austria (several Rheumatology centres). AIM: To describe clinical and radiological findings in patients with very early arthritis (<3 months of symptoms) during 1 year of observation.	Level Ib (No major area of bias) • blinded Investigators • True population (patients with early arthritis symptoms)	Total N=219 completed questionnaires, N=108 followed for at least 1 year	N/a	**Inclusion criteria:** Patients with 'early arthritis' defined as: any inflammatory joint disease of ≤3 months duration from onset of symptoms. Inflammatory joint disease defined as: swelling or pain not related to trauma in at least 1 joint in addition to lab signs of inflammations such as elevated ESR or CRP or leukocytosis or positive RF.	RA diagnosis given if patients fulfilled ACR criteria for RA or clinical examination revealed polyarthritis of ≥6 weeks duration without evidence of other inflammatory rheumatic diseases upon investigation. Clinical examination: joint counts and HAQ. Radiographs also taken of hands and forefeet to assess erosions and joint damage. Lab investigations: ESR, CRP, RF and blood chemistry.	Baseline assessment (near disease onset) and 1 year follow-up Assessments made by Rheumatologists The EAA (Early Arthritis Action) several centres in Austria to which rheumatology clinics	See below	Grant from Osterreichische Gesellschaft fur Rheumatologie.	

ID 914							sent their data. Questionnaires (modified version of a published protocol) with questions on history, clinical findings and lab investigations as wel as therapy and its efficacy were given to Rheumatology centres willing to participate. After initial visit, patients were planned to be seen at least every 3 months. Questionnaires were filled in at			

							each visit and clinical and lab examinations were performed.			

Additional results:

- The most frequent diagnosis was RA (61.1% of individuals) at some time in the observation period.
- In 68% of the patients diagnosed with RA followed for 1 year, the tentative diagnosis proved correct during follow-up, thus correct diagnoses were made by rheumatologists at the 1st visit in over 70% of all patients with early arthritis.
- EAA aim = to shorten lag-time from onset of symptoms to diagnosis of inflammatory rheumatic disease. Patients classified as 'non-RA' after 1 year had significantly shorter median symptom duration at entry compared to those classified as RA after 1 year (median 4 weeks and 8 weeks respectively, p<0.01). One item of the questionnaire at the 1st visit concerned the patients' rating of acuteness of the onset of their arthritis. A significantly higher proportion of patients in the non-RA group rated onset of their arthritis as acute compared to the RA patients (57% and 40% respectively, p<0.01).
- The ACR criteria were found not to be very sensitive for their usefulness of distinguishing RA from other disorders. At first visit 52% of the RA patients fulfilled 4 or more criteria, but 48% presented with <4 criteria for RA. In the non-RA group 81% fulfilled <4 criteria at first visit and and 19% would have fulfilled the ACR criteria at forst visit). The ACR negative RA patients all had polyarthritis of the hands and only 2 individuals had <3 criteria over time.
- 47% of the RA patients were RF+ at the first visit (vs 33% non-RA)
- ESR and CRP values did not differ significantly between RA and non-RA patients.
- Number of tender (mean 9.8 vs 6.0) and swollen joints (mean 7.9 vs 4.4) was higher in the RA group at initial visit than non-RA group, and involvement of hands (pain or swelling of wrists or finger joints was significantly more frequent (89.4% vs 60%, p=0.0006). However there was NS difference for Pain (VAS) and Pain or swelling of MTP joints.
- Among the 47 patients with very early RA and 1 year follow-up, 13% had erosions at the first visit, and in additional 21% there were signs ofnonerosive joint involvement (mainly soft tissue swelling). Mean Larsen socre was 3.5 at initial visit.

Risk of development of new erosions during the 1st year of disease in early RA was related to the presence of RF (p<0.05; OR 9.7, 95% CI 1.1 to 89.9)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
U. Arndt, F. Behrens, H. R. Ziswiler, J. P. Kaltwasser, and B. Moller. Observational	STUDY DESIGN: Case-series 3 1 EAC: Germany	Total N=345 admissions, (N=220 referred after introduction of questionnaire;	**Inclusion criteria:** patients referred to the EAC.	Assessments made by Rheumatologists	Assessments made by rheumatologists	EAC diagnosis was done at the first 2 consultations (time not mentioned).	Questionnaire primarily designed to cover the ACR classification criteria for RA, the criterion of inflammatory back	None reported

study of a patient and doctor directed pre-referral questionnaire for an early arthritis clinic. *Rheumatology International* 28 (1):21-26, 2007. ID 603	• Subjects were from admissions to the EAC. AIM: To develop a physician and patient questionnaire designed for identifying early RA and SpA in patients admitted to an early arthritis clinic (EAC).	N=125 referred before introduction = control cases); Patients taken from GP referrals to an Early Arthritis Clinic (EAC) in Germany.					pain in its original version and the ESSG criteria for the diagnosis of SpA. Other info gathered was signs of serious general symptoms, important functional limitations, lab data (ESR, CRP and Abs) and previous therapeutic attempts. Diagnosis: RA by ACR 1987 criteria and ICD-10 (International classification of diseases); Suspected RA not yet fulfilling ACR criteria and SpA according to ESSG criteria and other arthritis conditions.	

Effect size

- Accordance of referral and EAC diagnosis was statistically significant (p<0.001) however, RA appeared overestimated and SpA underestimated in their prevalence among the referral diagnoses and non-inflammatory conditions were frequently misdiagnosed as inflammatory entities.
- A substantial number of patients with RA referral diagnosis could be also classified as inflammatory connective tissue disorders due to present but undetected or misinterpreted symptoms. 12 / 22 RA patients had symptom duration >1 year.

1 PREDICTION OF RA

- Reporting of any joint swelling was significantly associated with the referral diagnosis of RA or suspected RA (Likelihood ratio, LR 8.2, p=0.004)
- Swollen joints were predominantly localised in the hands (N=45, 66%) or knee (N=12, 18%), however, restriction of the swollen joint status to localisations at hands or fingers was not predictive for RA diagnosis at EAC, nor did this information significantly coincide with a definitive or tentative RA referral diagnosis. (this was due to the fact that diagnoses had to be revised to OA in N=7, other arthritis than RA in N=5 and inflammatory CTD in N=2 patients). Synovitis could not be objectified in N=21 other of the referred patients, thereby forestalling confirmation of suspected RA.
- Patient information on morning stiffness was neither predictive for referral nor EAC RA diagnosis.
- Information about limitations when clenching the hands completely to a fist was significantly associated with RA referral diagnosis (LR 6.1,p=0.013) and even more closely with RA EAC diagnosis (LR 10.3, p=0.001)
- Patient reported limitations of finger flexion and referral diagnosis at EAC wedre equivalent indicators for definitive RA diagnosis at EAC (in multivariate regression analysis)
- Pathologic lab findings for 1 or more of the lab parameters (ESR, CRP or RF) and information about previous DMRD treatment, both exceeded these items in predicting RA
- More general questions on every day function gave no predictive information.

- After introduction of the questionnaire, the rates of monthly referrals and proportion of referring medical specialists remained stable. However, prescription of NSAIDs and use of corticosteroids increased.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. Devlin, A. Gough, A. Huissoon, P. Perkins, R. Jubb, and P.	STUDY DESIGN: Case-series 450 referral	Total N=1633 referred, N=903 fulfilled	**Inclusion criteria:** GPs were to refer any patient with the signs and symptoms suggestive of a recent onset of inflammatory arthritis. 'Early'	Assessments made by Rheumatologists	Assessments made by rheumatologists	Review appointments at 3, 6, 12 months and thereafter	History and clinical examination: pattern of joint involvement at	None reported

Emery. The outcome of knee synovitis in early arthritis provides guidelines for management. *Clinical Rheumatology* 19 (2):82-85, 2000. ID 300	GP practices: UK • Subjects were all referrals to the EAC. AIM: To examine the clinical outcome of patients presenting to an early arthritis clinic (EAC) with synovitis of the knee and followed-up to determine clinical outcome.	inclusion crietria Patients taken from GP referrals to an Early Arthritis Clinic (EAC) in UK.	was defined as <12 months **Exclusion criteria:** patients who had received prior CS or DMARDs. Lag time from referral to appointment was maximum of 2 weeks.	Patients were followed up if they had early inflammatory arthritis regardless of diagnosis; if they fulfilled diagnostic criteria any time during the follow-up period, the diagnosis of RA was applied (patients with chronic inflammatory disease and non-inflammatory disease were excluded). After initial assessment, patients were treated with pharmacological and physical modalities as appropriate.		annually	onset and progression; clinical synovitis (defined as presence of either warmth or swelling with a reduced range of movement); remission (defined as absence of any clinical synovitis); radiographs taken; ESR; CRP levels; RF. RA diagnosis: by ACR 1987 criteria	

Effect size

THE RELATIONSHIP BETWEEN CLINICAL FEATURES AND THE DIAGNOSIS OF RA:

- 45% of patients at presentation to the clinic had either no clinical evidence of inflammatory disease or had symptoms >12 months.
- Of the remaining N=903 included patients presenting with inflammatory arthritis:
    - 47% presented with RA or fulfilled ACR criteria during follow-up; 20% fulfilled criteria for other arthropathies and 33% had undifferentiated inflammatory arthritis.
    - Clinical synovitis was present in 14% of patients presenting with inflammatory arthritis (N=130 / 903), 56% of these (N=73/103 ie. **8% of total** with inflammatory arthritis = 73/903) fulfilled criteria for RA diagnosis during the study period. That is, 8% of IA patients with clinical synovitis developed RA. Thus 17% of all the RA patients defined in the study presented with knee involvement.
    - All of these (N=73 patients who developed RA) had clinical evidence of symmetrical synovitis of the small joints of the hands and feet at the first visit
    - Of the N=57 patients who did not develop RA, N=13 presented with a monoarthritis, N=23 with oligoarthritis (<3 further joints involved) and N=21 with a polyarthritis and went on to develop other diagnoses over time.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
B. J. Harrison, D. P. M. Symmons, E. M. Barrett, and A. J. Silman. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. *Journal of Rheumatology* 25 (12):2324-2330, 1998. ID 823	STUDY DESIGN: Case-series Multicentre, UK. Patients were from multiple GP practices and hospital clinics – all patients were notified to NOAR.	Level II (1 main area of bias) • No mention of blinding of Investigators • True population (patients with early Inflammatory polyarthritis)	Total N=486 Patients were the all new cases of inflammatory polyarthritis in the Norwich Health Authority area, notified by GPs to the NOAR. **Drop-outs at 3 year follow-up:** 16%	N/a	**Inclusion criteria:** adults aged >16 years with the following criteria: swelling of 2 or more joints, disease duration more than 4 weeks but <1 year. **Baseline characteristics: Median disease duration since onset of symptoms: 5 months,** 68% female, median age 55 years.	Assessments made by specially trained research nurses At baseline patients were classified as having RA or not by applying 1987 ARA criteria (List format and classification tree format). At 1, 2 and 3 years patients were classified as having RA (1987 ARA criteria) if they satisfied the complete set of criteria at any of the assessment visits, or the individual components of the criteria set applied cumulatively, up to and including the current visit. Ability of patients to determine which patients presenting with early synovitis have 'true' RA is not known and whether the 1987 ARA criteria for RA in patients newly	RA (ARA criteria) Diagnosed 1, 2 and 3 years later at follow-up	See below	Arthritis Research Campaign	

						presenting with inflammatory polyarthritis predict persistent, disabling or erosive arthritis.				

Additional results:

- At baseline, 38% satisfied criteria in the list format and 67% in the tree format (this is higher than list format because substitution of MCP swelling for missing radiographic information).
- If early morning stiffness was modified to include patients who had ever had morning stiffness >60 mins, then 48% satisfied the list format criteria.
- Most of the patients (97%) who satisfied the tree format also satisfied the list format.
- There was a substantial decrease in the proportion of patients that could be classified as having RA from baseline to 1 year. This was due to a decrease in the number of swollen joints with time.

USING THE CRITERIA TO IDENTIFY PATIENTS WITH A PHYSICIAN DIAGNOSIS OF RA

- Validity of criteria was assessed by applying the criteria at baseline in both list and tree formats. Gold standard was the diagnosis made by the hospital physician when the patients were first seen. Info was available for N=279 patients of whom 50% were given a physician diagnosis of RA.
- When the criteria were used to identify patients with a physician diagnosis of RA, the likelihood ratios were only slightly higher than unity. This implies that there is only a marginal improvement in prediction capacity over that which would be expected by chance.
- Ability of criteria at baseline to identify patients with a physician diagnosis of RA
    - List: sensitivity 62%, specificity 50%
    - Tree: sensitivity 78%, specificity 35%

Authors' conclusion: The specificities of the criteria were poor and thus the overall discriminatory ability showed little improvement over random probability.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. Kaarela, R. Hameenkorpi, and H. Isomaki. The value of the diagnostic criteria in	STUDY DESIGN: Case-series 3 Single centre, Finland.	Level II (1 main area of bias) • No mention of blinding of Investigators	Total N=442 Patients at the Rheumatism foundation	N/a	**Inclusion criteria:** Patients with recent inflammatory joint disease.	Assessments made by Rheumatologists At the time of the first hospitalisation (1-6 months from the onset of disease) all patients were studied in	RA (ARA criteria) Diagnosed 3 years later at follow-up	See below	None reported	

rheumatoid arthritis. *Scandinavian Journal of Rheumatology* 12 (1):43-45, 1983. ID 421	AIM: To analyse the diagnostic criteria for RA in patients with an inflammatory joint disease and correlate their presence or absence in the early stage of the disease with the situation after 3 years.	• True population (patients with Inflammatory joint disease)	hospital, Finland.			accordance with the diagnostic criteria of RA (ARA and New York criteria were used). After 3 years the patients were re-examined. At this time, N=100 of these showed symptoms of active arthritis, fulfilling the ARA criteria for definite RA. The sensitivity, specificity, detection rate and mis-classification rate of ARA and New York criteria were thus determined. The sensitivity, specificity, detection rate and mis-classification rate for the ARA criteria 1-7 and New York criteria 1-4. ARA criteria 9-11 were excluded. Yuden Index (se + sp – 100) The absolute diagnostic value (ADV) was also calculated: ADV1 = [(detection rate)^2 x sensitivity] / 100^2				

						ADV2 = [(specificity)^2 x sensitivity] / 100^2 RF was evaluated only as a New York criterion. **NY criteria (Present or not):** 1. History of polyarthritis 2. Clinical polyarthritis 3. X-ray changes 4. RF **ARA criteria (present or not):** 1. Morning stiffness 2. Pain or tenderness 3. 1 swollen joint 4. 2 swollen joints 5. Symmetrical swelling 6. Nodules 7. X-ray changes				

Additional results:

	RA patients (N=100) **Presence Y/N**	Other joint disease patients (N=311) **Presence Y/N**	Sensitivity (%)	Specificity (%)	Detection rate (%)	Mis-classification rate (%)	Yuden Index (se + sp – 100)	ADV 1	AD
NY criteria									
1. History of polyarthritis	Y 93 / N 7	Y 180 / N 131	**93**	**42**	34	5	35	11	17
2. Clinical polyarthritis	Y 68 / N32	Y 61 / N 250	**68**	**80**	53	11	48	19	44

3. X-ray changes	Y 39 / N 61	Y 30 / N 281	**39**	**90**	57	18	29	12	32	
4. RF	Y 87 / N 13	Y 45 / N 266	**87**	**86**	66	5	73	38	64	
2 ARA criteria										
1. Morning stiffness	Y 78 / N 22	Y 109 / N 202	**78**	**65**	42	10	43	14	33	
2. Pain or tenderness	Y 94 / N 6	Y 274 / N 37	**94**	**12**	26	14	6	6	1	
3. 1 swollen joint	Y 96 / N 4	Y 256 / N 55	**96**	**18**	27	7	14	7	3	
4. 2 swollen joints	Y 86 / N 14	Y 168 / N 143	**86**	**46**	34	9	32	10	18	
5. Symmetrical swelling	Y 73 / N 27	Y 99 / N 212	**73**	**68**	42	11	41	13	34	
6. Nodules	Y 6 / N 94	Y 4 / N 307	**6**	**99**	60	23	5	2	6	
7. X-ray changes	Y 63 / N 37	Y 77 / N 234	**63**	**75**	45	14	38	13	36	

- **ARA criteria:** Criteria 2, 3 and 4 showed the best sensitivity, while the best specificity was criterion 6.
- **NY criteria:** Criterion 1 showed the best sensitivity, while the best specificity was criterion 3.
- When the values were measured wit the Yuden Index or the ADV, the best criteria were the RF, symmetrical polyarthritis (especially the NY clinical criterion), morning stiffness and X-ray changes.
- The others had either a low sensitivity or specificity, which decreased their power in discriminating RA from the other diseases.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and** **1.2 Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**

El Miedany Y., D. Palmer, and Gaafary M. El. Diagnosis of early arthritis: outcomes of a nurse-led clinic. *British Journal of Nursing* 15 (7):394-399, 2006. ID 3096	STUDY DESIGN: Case-series 3 Multicentre, Egypt Patients were from GPs in the Trust who referred patients presenting with joint pains and a clinical picture suggestive of early arthritis.	Total N=108	**Inclusion criteria:** Patients with early arthritis defined as those with clinical picture suggestive of inflammatory disorder (joint pain or swelling, limited range of motion and morning stiffness) but in whom a specific rheumatic disease has not been diagnosed. **Exclusion criteria:** Patients satisfying the ACR criteria for RA; and those with a specific rheumatic diagnosis. Mean disease duration of patients was 6.1 months	GPs guidelines for referrals included: Synovitis, Symmetrical symptoms, MCP and MTP joint involvement, positive squeee test on the MCP and/or MTP joints, significant early morning stiffness (>30 mins), relatively good response to NSAIDs, family history of RA. Patients were assessed in a dedicated specialised nurse-led EAC.The rheumatologist assessed the patient clinically after reviewing the patient's proforma and clinical findings reported by the nurse. A proforma specific for the EAC was developed by the senior rheumatologist designed to document the history of present illness and assess the possibility of having other rheumatologic causes of joint pain as well as review of other body systems. Physical examination was also carried out for signs and symptoms	Not mentioned	Proportion of patients who had each of the signs and symptoms of RA..	Not mentioned

Effect size

- N=108 patients were seen. N=99 had a rheumatologic diagnosis: N=69 early RA (< 1 year duration), 6 RA and others.
- Clinical characteristics of the patients diagnosed to have early RA (see table below):
    - Pain in the hand joint, symmetrical arthritis, positive squeeze test of the MCP joints and long duration of morning stiffness were the most common clinical parameters among patients presenting with persistent inflammatory arthritis.
    - Inflammatory markers were negative predictors of persistent inflammatory arthritis

Clinical characteristics of the patients suffering from early arthritis	**% of patients**
1. Hand joint pain	97
2. Joint pain >3 joints	93
3. Symmetric arthritis	49
4. Positive compression test: MCP joints	68
5. Positive compression test: MTP joints	45
6. Morning stiffness duration (mean)	44 mins
7. Subcutaneous nodules	0
8. Baseline HAQ	0.83
9. Erosions by X-ray	0
10. RF positive	36
11. ESR (mean)	23 mm/hr
12. CRP (mean)	8.6 mg/L

- It took 3 weeks for the patients to be fully assessed in the rheumatology clinic instead of 16 weeks. DMARD therapy was initiated within a few weeks (2-5 weeks) once diagnosis was confirmed (instead of 8-10 months previously).

Authors' conclusions: this early arthritis clinical model helped to shorted=n the referral lag time (duration between symptoms onset and first rheumatologist assessment) as well as lag time to DMARD therapy (duration between symptom onset and the institution to DMARD therapy). The authors developed a protocol to be applied through a specialised EAC that is able to discriminate between different categories of early arthritis, to shortening the time taken to reach the correct diagnosis and provide the appropriate management.

Reference	Study type	Evidence level	Number of	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Source of	Additional comm

			patients					PPV and NPV	funding	ents
G. S. Alarcon, R. F. Willkens, J. R. Ward, D. O. Clegg, J. G. Morgan, K. N. Ma, J. Z. Singer, V. D. Steen, H. E. Paulus, M. E. Luggen, R. P. Polisson, C. M. Ziminski, C. Yarboro, and H. J. Williams. Early undifferentiated connective tissue disease. IV.Musculoskeletal manifestations in a large cohort of patients with undifferentiated connective tissue diseases compared	Case series 3 Multicentre USA	Level II (1 main area of bias) • No mention of blinding of Investigators • True population (patients with early undifferentiated connective tissue disease)	**Total: N=99** N=67 (patients with early undifferentiated connective tissue disease CTD) N=32 (patients with RA) **Drop-outs:** N=10 (year one) N=12 (year three) N=11 (year five)	N/a	**Inclusion criteria:** Patients with early undifferentiated CTD with symptom duration < one tear Baseline characteristics: Year one: mean age 50.4 yrs, mean disease duration 5.7 yrs, joint counts (mean): large (pain/tenderness) 1.4, large (swelling) 0.6, medium (pain/tenderness) 1.5, medium (swelling) 1.6, small (pain/tenderness) 10.2, small (swelling) 10.9 Mean ESR 40.0 Year three: mean age 49.3 yrs, mean joint count 9.3	Baseline characteristics measured	RA diagnosis Diagnosed 5 years later at follow-up	See below	None reported	

with cohorts of patients with well-established connective tissue diseases: followup analyses in patients with unexplained polyarthritis and patients with rheumatoid arthritis at baseline. *Arthritis & Rheumatism* 39 (3):403-414, 1996. ID 3095										

Additional results:

- Clinical factors associated with RA diagnosis
  - At baseline N=67 patients entered the cohort with UPA.
  - In 20% of patients with UPA, the condition evolved into RA; thus, among those initially classified as having UPA, RA was diagnosed in N=10 patients at year one, N=12 at year three and N=11 at year five
- Baseline predictors of outcome among patients with UPA (univariate analysis)
  - Of the patients diagnosed as having RA at years one to five were older than those in the other categories, but these differences achieved statistical

significance at year one only (p<0.05) o Patients whose conditions evolved into RA had higher baseline joint counts (swelling, small joints) than patients who at years one to five when diagnosed as nor having RA (p<0.05 at years one and three, NS at year five) o Other demographic and clinical features, such as duration of symptoms, type of onset, and serologic status for anti RNP and RF, failed to predict year one to five outcomes with the possible exception of antinuclear antibody positivity (NS) • Odds of diagnosis being changed from UPA (polychotomous logistic regression) o Only two outcomes were used for this analysis, either the evolution of RA or no evolution to RA o At year one, pain/tenderness in small joints was a significant predictor of diagnosis changing from UPA to RA (OR 0.63, 95% CI 0.27 to 1.46, p=0.0289) o At year one, swelling count in small joints was a significant predictor of diagnosis would changing from UPA to RA (OR 2.93, 95%CI 1.06 to 8.10, p=0.0041) o At year three and five the presence of antinuclear antibodies was a significant predictor of diagnosis would changing from UPA to RA (year 3: OR 1.35, 95% CI 0.26 to 7.17, p=0.0059 and year 5: OR 2.1, 95% CI 0.35 to 12.34, p=0.0101); o At year three, swelling count in small joints was not a significant predictor of diagnosis would changing from UPA to RA (NS) o At year three, ESR was not a significant predictor of diagnosis would changing from UPA to RA (NS) o At year five, ESR was a significant predictor of diagnosis would changing from UPA to RA (year 5: OR 3.55, 95% CI 1.2 to 10.5, p=0.04)										
Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
G. J. Gormley, W. K. Steele, A. Gilliland, P. Leggett, G. D. Wright, A. L. Bell, C. Matthews, G. Meenagh, E. Wylie, R. Mulligan, M. Stevenson, D. O'Reilly, and A. J. Taggart.	STUDY DESIGN Case-series 3 Three referral GP practices: Belfast • Subjects chosen at random: no details given	Level Ib (No major areas of bias) • Blinded Investigators • True population (patients with features suggestive of early IA)	Total N=96	N/a	**Inclusion criteria:** Any patients with features suggestive of early IA who symptoms were less than two years duration and who had not been seen by a hospital rheumatologist before All patients referred by their GP to one of the	Diagnostic accuracy Clinically significant predictors of IA Assessments made by GP or RNs Three of the GPs had no prior hospital training in rheumatology and one had worked for 6 months as a senior house officer in a rheumatology unit, 12 months prior to the study	RA diagnosis by rheumatologist Diagnosed 6 months later at follow-up	See below	None reported	

Can diagnostic triage by general practitioners or rheumatology nurses improve the positive predictive value of referrals to early arthritis clinics? *Rheumatology* 42 (6):763-768, 2003. ID 194	AIM: To determine whether diagnostic triage by GPs or rheumatology nurses (RNs) can improve the positive predictive value of referrals to early arthritis clinics (EACs)				three EACs were considered eligible for the study. Subjects were chosen at random from the EAC Patients were referred to an Early Arthritis Clinic (EAC) according to the following referral guidelines developed by local GPs and rheumatologists, and incorporated in to established criteria for referrals to EACs (details not specified). The guidelines indicated referral for the following clinical features: 1) History Pain and/or swelling in several joints Significant stiffness in the morning or after rest Deteriorating function of the	commencing. Each GP/RN was provided with a copy of the referral guidelines for the EAC and with relevant abstracts from a standard rheumatology text. Each was trained by several rheumatologists in the application of these guidelines at four half-day clinic sessions. Participants observed the rheumatologist assessing patients, and, after discussion with the specialist then observed the trainee as they assessed other patients chosen at random from the EAC.				

					affected joints Symmetry of the affected joints A good response to NSAIDs 2) Examination Tenderness, swelling and warmth of the affected joints Restricted range of movement **Inappropriate referrals included:** Patients with primary fibromyalgia, non-inflammatory OA, soft tissue rheumatism or mechanical low back pain.					

Additional results:

ASSESSMENTS MADE BY GPs vs RHEUMATOLOGISTs

- 50/96 (52.1%) referrals were deemed to have IA by the assessing rheumatologist.
- A total of 49/96 (51.0%) referrals were deemed appropriate by the rheumatologist
- The kappa coefficient was 0.77 (95%CI 0.64 to 0.90)
- The agreement between the RNs and the rheumatologists was 0.79 (0.67 to 0.91)
- There was no significant difference in the performance of the GPs and the RNs (NS) or in the assessment of individual GPs or those of the two RNs (NS)
- Of those patients assessed by the rheumatologist as:
    - Having IA and as being appropriately referred, GPs correctly identified 90% (true positives)
    - Having non-IA and being inappropriately referred, GPs correctly identified 87% (true negatives)
    - Having IA and being appropriately referred, GPs considered 10% to be inappropriate referrals (false negatives)

- Having non-IA and being inappropriately referred, the GPs considered 13% to be appropriate referrals (false positives)
- The PPV for GPs was 88%

THE RELATIONSHIP BETWEEN CLINICAL FEATURES AND THE DIAGNOSIS OF IA:

- For both GPs and RNs, a history of significant stiffness in the morning or after rest (GPs: OR 12.7, 95% CI 3.6 to 45.8, p<0.0001 and RNs: OR 5.0, 95% CI 1.7 to 14.7, p<0.003 respectively) and a findings of observed joint swelling (GPs: OR 39.4, 95% CI 7.4 to 208, p=0.0001 and RNs: OR 16.4, 95% CI 5.1 to 53.3, p=0.0001) were the most important features for distinguishing IA from the non-IA conditions
  - If the symptom of significant stiffness in the morning or after rest was detected, RNs were five times more likely and GPs thirteen time more likely to diagnose IA
  - If the sign of joint swelling was detected, RNs were 16 times more likely and GPs 39 times more likely to diagnose IA
  - Other symptoms such as joint pain, joint swelling, loss of function, good response to NSAIDs and signs of metacarphophalangeal/metatarsophalangeal joint involvement, joint tenderness, redness, heat and reduced range of movement did not have statistically significant discriminatory value (NS)

SIX-MONTH FOLLOW-UP

- All patients were reassessed by the rheumatologist six months after their initial visit
- N=90 (94%) of the diagnosis remained unchanged
- N=6 the diagnosis changed from IA to one of non-IA, but there was no case of a diagnosis changing from non-IA to IA
- N=23 (24%) a diagnosis of RA was given at six months

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
A. Duer, M. Ostergaard, Petersen K. Horslev, and J. Vallo. Magnetic resonance imaging and bone scintigraphy in the differential diagnosis of unclassified arthritis.	Case-series 3 Denmark no details given of how patients were chosen	Level II (2 main areas of bias) • No mention of blinding of Investigators • Narrow population (patients unable to be classified conventionally)	Total N=41	N/a	**Inclusion criteria:** Patients with arthritis (≥2 swollen joints, >6 months' symptom duration) and subjective symptoms in the hand (pain and/or swelling) who remained unclassified despite conventional clinical, biochemical and radiographic examinations. **Exclusion criteria:**	MRI of the wrist and MCP joints of the most symptomatic hand; Radiographs (Larsen score); MRI synovitis, MRI erosion pattern, Scintographic	Physician diagnosis (ACR criteria) Diagnosis made 2 years later at follow-up	See below	Danish Rheumatism Association and a memorial reward.	

Annals of the Rheumatic Diseases 67 (1):48-51, 2008. ID 3510					Patients who fulfilled the ACR criteria for RA or had radiographic bone erosions **Baseline characteristics:** All patients: mean age 55 years; female 85%; symptom duration 1.5 years	patterns all compatible with RA				

Additional results:

- At 2 years, 11/13 patients with an original tentative diagnosis of RA developed RA (ACR criteria) and the other 2 were reclassified.

THE RELATIONSHIP BETWEEN BASELINE CLINICAL FEATURES with MRI and SCINTOGRAPHY AND THE DIAGNOSIS OF IA:

- RF+ was similar in both groups (patients who developed RA and those who did not – 36% and 33% respectively)
- More patients who went on to develop RA vs those who did not develop RA had:
  - Radiographic Larsen score grade 1 (36% and 3% respectively)
  - MRI synovitis compatible with RA (100% and 40% respectively)
  - MRI erosions compatible with RA (64% and 23% respectively)
  - Scintigraphy compatible with RA (64% and 26% respectively)
  - MRI synovtis OR MRI erosion: both compatible with RA (100% and 50% respectively)
  - MRI synovtis AND MRI erosion: both compatible with RA (64% and 13% respectively)
  - MRI synovtis AND MRI erosion AND scintigraphy: all compatible with RA (45% and 0% respectively)

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
A. H. Van der Helm-van Mil, S. Le Cessie, H. Van Dongen, F. C. Breedveld,	Case-series 3 The Netherlands Patients from an	Level II (1 main area of bias) • No mention of blinding of Investigators	Total N=570	N/a	**Inclusion criteria:** Patients referred directly when arthritis was suspected – patients were included if a physical examination revealed arthritis	HAQ; morning stiffness; tender and swollen joints; compression pain of	RA diagnosis (ACR criteria) Measured 1 year later at	See below	None mentioned	

R. E. Toes, and T. W. Huizinga. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis & Rheumatism* 56 (2):433-440, 2007. REF ID: 3108	Early Arthritis Clinic	• Population reflects that to which the test would apply (patients with UA)			**Exclusion criteria:** None mentioned **Baseline characteristics:** All patients: mean age 52 years; female 61%	MCP and MTP joints; ESR; CRP; RF; anti-CCP; Radiographs (SHS)	follow-up			

Additional results:

- At 1year, 117/570 patients with UA developed RA, 94 developed other rheumatologic disease and 150 achieved clinical remission.

THE RELATIONSHIP BETWEEN BASELINE CLINICAL FEATURES OF UA PATIENTS and THE DIAGNOSIS OF RA:

- Significant predictors of RA development (multivariate analysis):
  - Older age
  - Joint symptoms in the small joints of hand/feet (OR 1.8, 95% CI 1.1 to 3.1, p=0.024),
  - asymmetric localisation of the affected joints (data not given)

	o localisation of affected joints in both upper and lower extremities (OR 3.5, 95% CI 1.7 to 7.5, p=0.001)
	o morning stiffness (significant for each of the 3 categories of VAS scale: at VAS >90 OR 9.4, 95% CI3.0 to 28.7, p<0.001)
	o tender joints (>10: OR 3.3, 95% CI 1.5 to 7.0, p=0.003);
	o swollen joint counts (>10 OR 2.8, 95% CI 1.1 to 7.6, p=0.038)
	o CRP level (>50 mg/l OR 5.0, 95% CI 2.0 to 12.1, p=0.00)
	o RF+ (OR 2.3, 95% CI 1.2 to 4.2, p=0.009);
	o anti-CCP+ (OR 8.1, 95% CI 4.2 to 15.8, p<0.001)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Houssien DA, Scott DL. Early referral and outcome in rheumatoid arthritis. *Scandinavian Journal of Rheumatology.* 1998; 27(4):300-302. Ref ID: 3100	Retrospective Case series 3 Single centre trial: UK.	Total N=200	**Inclusion criteria:** Adults with RA (ACR criteria). **Exclusion criteria:** None stated **Baseline characteristics:** Mean age 59 yrs, 74% female and mean disease duration 11 yrs Concomitant medication: 70% were receiving slow-acting anti-rheumatic drugs: N=36 gold N=32 methotrexate N=29 sulphasalazine N=12 penicillamine N=5 anti-malarials N=2 azathioprine N=21 steroids	Early referral N=123 Within one year of developing symptoms The time patients were referred was assessed by direct questioning and review of medical records Referral was defined as referral to any specialist rheumatology unit and the onset of the first symptoms related to RA was taken as the start as the disease, not the time of the first diagnosis	Late referral N=77 After one year of developing symptoms	NA	Health Assessment Questionnaire (HAQ); Nottingham Health Profile (NHP)	Arthritis and Rheumatism Council

Effect size

EARLY vs LATE REFERRAL:

- There was a significant difference in the mean NHP physical function scores; patients referred late had worse scores than those referred early (mean difference 11.0, 95% CI 3.2 to 18.8, p<0.006)
- There was a significant difference in the mean HAQ scores; patients referred late had worse scores than those referred early (mean difference 0.34, 95% CI 0.09 to 0.58, p<0.007)
- In the multiple regression model, late referral was the most powerful predictor of functional disability measured using the MAP* physical function score (p=0.025)
- Late referral (adjusted and unadjusted) was no a statistically significant predictor of HAQ score (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Irvine S, Munro R, Porter D. Early referral, diagnosis, and treatment of rheumatoid arthritis: evidence for changing medical practice. *Annals of the Rheumatic Diseases.* 1999; 58(8):510-513 ID 3002	Case series (retrospective) 3 Single centre trial: UK.	Total N=198	**Inclusion criteria:** Adults with RA (ACR criteria). **Exclusion criteria:** None stated **Baseline characteristics:** Pre 1986: mean age 44 yrs*, 78% female 1986-1989: mean age 53*, female 65% 1990-1993: mean age 64 yrs*, 71% female 1994-1997: mean age 64 yrs*, female 71% * (p<0.001)	Groups arbitrarily split according to date of their first clinic assessment • Before 1986 • 1987-9 • 1900-3 • 1994-7	See intervention	NA	Delay to rheumatological assessment; delay to DMARD therapy, radiographic changes at presentation	None reported

Effect size

Delay to rheumatological assessment:

- There was a significant reduction in the delay between the onset of symptoms and GP referral to a specialist rheumatology clinic; the delay decreased from before 1986 to 1994-7 ($p<0.03$)
- There was a significant variation in the median time from GP referral to clinic appointment ($p<0.001$). The authors note' this is of doubtful clinical significance, as the variation is only from one to three months. The rate of seropositivity for rheumatoid factor was similar in patients referred early (that is, < 3 months from symptom onset) compared with those referred later (75 vs 80% respectively)'.

Delay to DMARD therapy:

- The proportion of patients exposed to DMARD treatment was similar across time (no statistics reported)
- There was a significant reduction across time in the delay from symptom onset to the first use of DMARD ($p<0.00q$)
- There was a significant reduction across time in the delay from the first clinic attendance to first use of DMARD ($p<0.001$)
- The median delay to starting a DMARD from the first clinic appointment is one month in the 1994-1997 group, and in this group 44% of patients were prescribed a DMARD within six months of symptom onset, compared with 5% of patients from the other three groups
- 'The most significant factor in the delay to starting DMARD remains the time from initial symptoms to presentation a rheumatologist'

Radiographic changes at presentation (N=183)

- There was little difference in the percentage of patients with erosive changes at presentation until the delay to a clinic appointment was greater than one year (no statistics reported)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and 1.3 Comparison	Length of follow-up	Outcome measures	Source of funding

K. Kumar, E. Daley, D. M. Carruthers, D. Situnayake, C. Gordon, K. Grindulis, C. D. Buckley, F. Khattak, and K. Raza. Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. *Rheumatology* 46 (9):1438-1440, 2007. ID 3263	STUDY DESIGN: Case-series 3 2 centres, UK EAC in rheumatology department from 2 clinics in UK. Patients who are referred with symptoms of <12 weeks are seen within 2 weeks of referral.	Total N=169 (N=168 fulfilled ARA criteria for RA)	**Inclusion criteria:** Patients with pragmatic clinical diagnosis of RA made; not required to fulfil ARA classification criteria for RA. **Exclusion criteria:** Patients in whom the GP had made a diagnosis of RA and had commenced DMARD treatment. **Baseline characteristics:** Age mean 58 years; female 62%; RF+ 73%; RA (ARA criteria) 99% of patients.	N/a	n/a	Reasons for delay in assessment by Rheumatologists.	Grant from the Arthritis Research Campaign, UK.

Effect size

- Median delay from onset of symptoms to assessment in secondary care was 23 weeks (IQR 12-54 weeks).
- Only 30% of patients were seen in secondary care within 12 weeks of the onset of inflammatory joint symptoms.
- Median delay before the patient was assessed in primary care was 12 weeks (IQR 4-28 weeks).
- Delays in referral to secondary care after the patient had been seen in primary care (median 2 weeks) and in the patient being seen in secondary care after referral from primary care (median 3 weeks) accounted for a much smaller proportion of the delay.
- For 57% of patients, more than half of the overall delay in assessment in secondary care was accounted for by delay in assessment in primary care.
- There was no correlation between patient age and no difference between men and women and the time to assessment in primary care .
- RF+ patients had a greater delay from symptom onset to assessment in primary care (median delay 13 weeks) compared with RF- patients (median delay 4 weeks).

Authors' conclusions: Patient dependent factors, leading to delay in consulting primary care physicians are the principal reasons for the delay in patients with RA being seen by Rheumatologists in our population.

INVEST

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. Aho, T. Palosuo, M. Heliovaara, P. Knekt, P. Alha, and Essen R. von. Antifilaggrin antibodies within "normal" range	Case-control (nested) Multicentre: 12 municipalities in 4 regions in Finland. Participants were from a	Level III (as 2 major areas of bias) • No mention of blinded Investigators • Case-control design • Population was true population to whom	N=19,072 **Drop-outs:** Not mentioned		**Inclusion criteria:** those at risk of developing RA; **Baseline characteristics of RF+ RA patients:** Age mean 45 years, female 65% (pre-RA).	RF; AFA.	RA diagnosis (ACR criteria)	See below	Not mentioned	

predict rheumatoid arthritis in a linear fashion.[see comment]. *Journal of Rheumatology* 27 (12):2743-2746, 2000. REF ID: 545	population register or a questionnaire – all those who were at risk (had history of arthritis or other rheumatic diseases) – all those who later developed arthritis were identified.	test would apply (patients who developed RA)			Case-control design was applied to study AFA for its prediction of clinical RA. 3 controls per case were selected by individual matching using gender, age and municipality as matching factors.					

Additional results:

Prediction of RA development (distinguishing from other diseases) from diagnostic tests, in pre-RA patients:

- N=26 patients developed RA by end of follow-up
- Pre-illness serum AFA was directly proportional to the risk of RF+ RA; The RR in the highest quintile compared to the lowest one was 5-fold. (RR 5.4 and 0 respectively). No effect was seen for RF- RA.
- Subgroups of RF+ RA cases and their matched controls were then analysed by quintiles of AFA concentration. No clear difference emerged between men and women.
- A linear increase in the relative odds up to 24 was noted in subjects RF+ at baseline; there was hardly any effect for RF- subjects at baseline. The interaction of baseline RF and AFA was NS.
- The linear relation between AFA and the risk of RF+ RA remained significant after adjustment for baseline RF status, but not after further adjustment for Waaler-Rose titre (RF).
- Significant increases in the risks of RF+ RA were observed in subjects with elevated AFA during the periods <5 years and 5-10 years from drawing the specimen to the onset of clinical disease, whereas only a weak association was suggested during the follow-up period >10 years.
- The relationship between RF and AFA was also studied using a cross-sectional design of the baseline examination. A significant association of the same order of magnitude emerged between RF and AFA both in pre-illness sera (RF+ and RF- cases combined) and in control sera.
- No correlation existed between IgG concentration and AFA level.

Authors' conclusions: AFA still within the 'normal' range predicts RA in a linear fashion. AFA andRA are associated markers of the rheumatoid immunological process.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. Aho, T. Palosuo, M. Lukka, P. Kurki, H. Isomaki, H. Kautiainen, and Essen R. von. Antifilaggrin antibodies in recent-onset arthritis. *Scandinavian Journal of Rheumatology* 28 (2):113-116, 1999. REF ID: 618	Case-series Single centre: a hospital in Finland.	Level II (as 1 major areas of bias) • No mention of blinded Investigators • Case-series design • Population was true population to whom test would apply (patients with various inflammatory joint disorders)	N=306 pre-RA **Drop-outs:** Not mentioned		**Inclusion criteria:** patients inflammatory joint disease of <1 year's duration. **Baseline characteristics of RA patients:** Not mentioned.	AFA; RF.	ARA criteria (3 year follow-up) / Erosiveness of joints	See below	Not mentioned	

Additional results:

Prediction of RA development (distinguishing from other diseases) from diagnostic tests, in pre-RA patients:

- The latex test was the most sensitive – 0.70 (but least specific 0.90 test for RA. The least sensitive 0.31 and most specific 0.99 test was that for AKA. Between these extremes, the tests for APF (0.47 and 0.96) and AFA (0.49 and 0.95) behaved very much in the same fashion.
- Six positive test results with reactive arthritis; 2 of the patients were APF+ and 2 were RF+. 4 positive test results for APF and 1 for AKA were noted in the non-rheumatoid forms of arthritis; these cases were AFA-.
- The distribution of the test results for APF in patients with peripheral oligo/polyarthritis according to the AFA level. The agreement between APF and AFA was very good

the agreement between AKA and AFA was moderate. 3 AKA+ cases were AFA-.

Authors' conclusions: AFA still within the 'normal' range predicts RA in a linear fashion. AFA andRA are associated markers of the rheumatoid immunological process.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. Aho, T. Palosuo, P. Knekt, P. Alha, A. Aromaa, and M. Heliovaara. Serum C-reactive protein does not predict rheumatoid arthritis. *Journal of Rheumatology* 27 (5):1136-1138, 2000. REF ID: 958	Case – control (nested): 2 Multicentre: 12 centres in Finland In each of the 4 regions, all inhabitants or a random sample of inhabitants of 1 rural municipality and 1 urban or semi-urban municipality as well as the employees of 1 factory were invited to attend the examination.	Level III (3 main areas of bias) • No mention of blinding of Investigators • Case-control study • Narrow population (cases and controls chosen – those who developed RA vs those who did not)	N=19,072 (population at risk) N=124 cases; N=365 controls **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** Population at risk (no previous history of arthritis or other rheumatic disease); age ≥20 years. **Baseline characteristics:** Cases (developed RA): Age mean 46 years, female 69%, pre-RA Controls: Age mean 46 years, female 69%, pre-RA There were NS differences between the groups for baseline characteristics Controls for each case that developed RA: individual matching – gender, age and municipality.	Morbidity; mortality; RF; CRP	Participants who later developed arthritis (survey data and Social Insurance Institution's population register – physician's diagnosis) 12-16 year follow-up	See below	National Public Health Institute and Social Insurance Institution, Finland.	

Additional results:

Prediction of RA development from baseline characteristics:

- There was no difference between the cases who developed RA and their controls for RR of RA development when the data was stratified by baseline quintiles of CRP distribution.
- There was no difference when the data was stratified according to baseline characteristics: age, gender, RF status

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
J. Avouac, L. Gossec, and M. Dougados. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. *Annals of the Rheumatic Diseases* 65 (7):845-851, 2006.	MA SR included: N=107 trials MA included: N=68 trials with data (N=14 on predicting development of RA – of these N=11 used UA and N=3 RA patients given blood before development of RA) Trials were similar in terms of: • Test method used (ELISA) **RA predictive trials only:**	MA III • The MA was not very well conducted. No test for heterogeneity or quality assessment performed • However the included trials were case-series and	Total N=8206 with ACR criteria for RA **Baseline characteristics:** All RA patients: mean age 56 years; female 55% to 95%.		**Inclusion criteria:** Adults aged >16 years; For diagnostic properties: patients with confirmed RA (ACR criteria), control population of healthy subjects and patients with other rheumatic diseases. For predictive value of a-CCP: patients with early undifferentiated arthritis and patients who had donated blood samples before the development of RA. Trials included were both from published and unpublished data. Search was from 1999 (when first a-CCP tests were used	a-CCP tests (first or second generation) using cut-off value for a positive test used in each paper. For prediction of RA development: Range 5-36 months	% of people who developed RA (ACR Criteria) and the ability of a-CCP to predict the future development of RA in healthy subjects or in patients with early UA.	See below	Not mentioned	

ID 128	Trials differed with respect to: • Type of diagnostic test used: N=5 trials used a-CCP1, N=10 trials used a-CCP2. • Cut-off for a-CCP+: a-CCP1 range 21.4 IU to 1000 IU, a-CCP2 3.8IU to 50 IU. • Study size (UA patients a-CCP1 N=1327; UA patients a-CCP2 N=2017; RA patients given blood before RA development a-CCP1 N=79, a-CCP2 N=142) • Study duration – length of follow-up (UA patients: range 5-36 months; RA patients given blood before RA development: range <1.5 years to 9 years) Tests for heterogeneity and quality assessment were not performed.	some were case-control studies. There is no mention of whether the trials were blinded but the population was suitable. Therefore this is a level III study (as 2 areas of bias)			for RA diagnosis) – 2006. **Exclusion criteria:** Juvenile RA.					
Additional results: **<u>Results: predictive performance of a-CCP (Early UA patients)</u>**										

- 11 studies (N=2877 patients), mean symptom duration <9.5 months, mean follow-up 17 months. Of theses, 51% were classified as having RA at end of follow-up
- 23% and 23% were a-CCP1+ and a-CCP2+ at baseline and 45% and 46% were a-CCP1 and a-CCP2+ at time of diagnosis.
- Mean OR for developing RA from UA was: **a-CCP1** OR 20 (95% CI 14 to 31) and **a-CCP2** OR 25 (95% CI 18 to 35).

Results: predictive performance of a-CCP (Blood donor patients)

- 3 studies looked at patients with RA who had donated blood samples before development of RA
- 1 study (N=83 patients) a-CCP2 predicted development of RA with 4% sensitivity (9 years before symptoms) and 25% (>1.5 years before symptoms) and 98% specificity. Sensitivity increased to 52% in samples examined wthin 1,5 years of disease onset and specificity was 98% sensitivity of RF was 30%. OR 28 (95% CI 8 to 95).
- 1 study did further analysis of the same patients and found that logistic multivariate regression, a-CCP2 had highest predictive value with OR 15.9 for a-CCP2 and 6.8 for RF.
- 1 study (N=79 patients) looked at patients with blood samples 5 years before symptom onset. The sensitiveity and specificity of a-CCP1 for RA were 29% and 99.5% respectively. OR 64.5 (95% CI 8.5 to 489).

Author's conclusions:
A-CCP Abs appear to be highly predictive of the future development of RA in both healthy subjects and patients with UA.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
C. E. Bayliss, R. L. Dawkins, G. Cullity, R. E. Davis, and J. B. Houliston. Laboratory diagnosis of rheumatoid arthritis.	Case series Single centre: Australia (patients referred to Rheumatology clinic)	II • Compares index test with reference standard (Rheumatologist diagnosis ACR criteria	N=93 **Drop-outs at follow-up:** N=8 – 9% (insufficient data)		**Inclusion criteria:** patients with effusion in 1 knee with a history of pain or swelling in 1 or more joints. **Baseline characteristics of all patients:** Range age 13 to 81 years; female 54%; disease duration (pre-RA).	Lab tests: histopathology on needle biopsy specimens; RF	ARA criteria up to 3 years later to confirm diagnosis	See below	Not mentioned	

Prospective study of 85 patients. *Annals of the Rheumatic Diseases* 34 (5):395-402, 1975. REF ID: 925	Pre-RA patients	up to 3 years later) • Blinded Investigators • However not all patients included in analysis			None had nodules, vasculitis or other extraarticular manifestations of rheumatoid disease.					

Additional results:

Prediction of RA development from baseline characteristics:

- On initial assessment, N=24 of the N=85 could be classified as definite RA, N=21 as probable and 37 as possible. At the time of final review, N=32 of te N=85 satisfied the ACR criteria for RA - 29 of these 32 had definite RA and the remaining N=3 had juvenile RA.
- Of the N=30 cases wit histological changes considered to be RA+, N=23 were ultimately classified as RA (77%). N=9 ultimately classified as RA had non-specific histological changes which were recorded as RA-
- Immunofluorescence: of the N=17 cases with distinctive IgM staining (RA+), N=15 had RA (88%). All but 1 of the N=17 cases were considered to be RA+ by histopathology.
- Relatively high white cell counts were found in N=22/26 patients with RA (77%), whereas N=35/51 non-RA cases had low counts. Low counts were distinctly unusual in RA.
- RF: RF+ was found in N-12/32 cases wit RA but was also in N=6/53 cases without RA.
- Rose and Ball test for RF in the synovial fluid: RF+ was only found in N=4/32 cases if RA and 1/42 non-RA.

Authors' conclusion: Laboratory investigation can improve diagnostic sensitivity and specificity in relatively early RA. Histopathology on needle biopsy specimens narrowed the differential diagnosis to RA and closely related conditions even at an early stage of disease and also allowed recognition of other conditions which would not otherwise have been detected. Immunofluorcesence on similar specimens further narrowed differential diagnosis since the presence of IgM was found to be very suggestive of RA. Other tests were of less value.

Reference	Study type	Evidence level	Number of	Prevale	Patient characteristics	Type of	Reference	Sensitivity &	Source of	Additi onal

			patients	nce		test	standard	specificity PPV and NPV	funding	comments
V. Devauchelle-Pensec, J. M. Berthelot, S. Jousse, I. Samjee, T. Josseaume, D. Colin, G. Chales, HenaffC Le, J. B. Thorel, S. Hoang, A. Martin, P. Youinou, GoffP Le, and A. Saraux. Performance of hand radiographs in predicting the diagnosis in patients with early arthritis. *Journal of Rheumatology* 33 (8):1511-1515, 2006.	Case series Multicentre: Patients from 7 hospitals in Brittany, France.	Level Ib (as no major areas of bias) • Blinded Investigators • Case-series design • Population was true population to whom test would apply (patients with very early arthritis)	N=258 **Drop-outs:** Not mentioned		**Inclusion criteria:** age ≥16 years, swelling of 1 or more joints, absence of previous diagnosis of a specific inflammatory joint disease and symptom duration ≤1 year. **Baseline characteristics of RA patients:** Age mean 50 years, female 68%, mean disease duration <2 years (early RA).	extraarticular manifestations; CRP; a-CCP; RF (IgG, IgA and IgM); ANA (antinuclear antibodies); radiographs (chest, hands, feet and pelvis).	ACR criteria (joint examination) at Mean follow-up 30 months (assessments every 6 months)	See below	Brest Hospital Centre and the 1995 Clinical Research Hospital Program, France.	

REF ID: 1855										

Additional results:
Prediction of RA development from diagnostic tests, in UA (pre-RA) patients:

- At the end of the follow-up, N=93 (36%) of patients were given a diagnosis of RA, 13% unknown diagnosis and the rest had other arthritis.
- Erosions typical of RA were significantly associated with a final diagnosis of RA. Radiogrpahic evidence of hydroxyapatite or CPPD deposition was strongly associated with a final diagnosis of the corresponding disease ($p<0.0001$)
- Only 3 diagnoses were predicted by baseline hand radiographs (RA, CPPD deposition disease and hydroxyapatite deposition disease).
- Hand radiographs were able to predict RA with a sensitivity of 23%, specificity 88%, NPV 66% and PPV 50%.
- Overall, baseline hand radiographs predicted the diagnosis made 2 years later in N=31 of the N=258 patients, with a sensitivity of 30%, specificity 85%, NPV 60% and PPV 58%.

Authors' conclusions: In a group of patients with recent arthritis, the overall performance of hand radiographs in predicting a diagnosis 2 years later was modest. However, they had an exceptional diagnostic value for calcium deposition diseases.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
I. E. Hoffman, I. Peene, H. Pottel, A. Union, F. Hulstaert, L. Meheus, K. Lebeer, Clercq L. De, L. Schatteman, S. Poriau, H. Mielants, E. M. Veys, and Keyser	Case series Multi centre: Belgium (patients from 3 hospitals) Pre-RA patients	Level Ib (as no major areas of bias) • Investigators blinded to diagnostic test results • Case-series design • Population was true population to whom test would apply (diagnostic	N=829 (N=144 diagnosed at follow-up with RA) **Drop-outs at follow-up:** N=74 (9%)		**Inclusion criteria:** Patients referred to rheumatologists with a new diagnostic problem for which RA was included in the differential diagnosis. Patients did not necessarily have early arthritis. **Baseline characteristics:** Patients who developed	RF; anti-pepA and B Abs; ACPA.	Development of RA (ACR criteria) 1 year later	See below	Innogenetics, Belgium.	

F. De. Diagnostic performance and predictive value of rheumatoid factor, anti-citrullinated peptide antibodies, and the HLA shared epitope for diagnosis of rheumatoid arthritis.[see comment]. *Clinical Chemistry* 51 (1):261-263, 2005. REF ID: 219		problem: patients with differential diagnosis)			RA: Age mean 58 years, female 65%, disease duration mean 19.3 months (pre-RA). Non-RA patients: Age mean 51 years, female 66%, disease duration mean 15.9 months (pre-RA).					

Additional results:

Prediction of RA development/diagnosis at 1 year from baseline characteristics:

N=144 patients developed RA.

- At least 1 swollen joint at baseline was found in most (96%) of all patients who developed RA and only in some (38%) who did not have RA.
- At high specificities, the a-pepA Abs had the best sensitivity. Combining the RF test with an ACPA test increased the PPV. Combining one serologic marker with the finding of swollen joints also provides a high PPV.

Most patients: at least 1 swollen joint (96%); a-pepA Abs (best sensitivity, h specificity); RF test + ACPA test (increased PPV); one serologic marker + swollen joints (increased PPV) – data values not given

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
M. K. Koivula, M. Heliovaara, J. Ramberg, P. Knekt, H. Rissanen, T. Palosuo, and J. Risteli. Autoantibodies binding to citrullinated telopeptide of type II collagen and to cyclic citrullinated peptides predict synergistically the development of seropositive rheumatoid arthritis. *Annals of the Rheumatic Diseases* 66 (11):1450-	Case – control (nested) Multicentre: 12 centres in Finland In each of the 4 regions, all inhabitants or a random sample of inhabitants of 1 rural municipality and 1 urban or semi-urban municipality as well as the employees of 1 factory were invited to attend the examination.	Level III (as 3 main areas of bias) • No mention of blinding Investigators • Case-control design • Narrow population (as cases of known diagnosis were compared to controls)	N=19,072 (population at risk) **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** Population at risk (no previous history of arthritis or other rheumatic disease); age ≥20 years. **Baseline characteristics:** Cases (developed RA): Age mean 46 years, female 69%, pre-RA; a-CCP (units) 172.7. Controls: Age mean 46 years, female 69%, pre-RA; a-CCP (units) 16.1. There were NS differences between the groups for baseline characteristics except a-CCP was significantly higher in the RA cases. Controls for each case that developed RA: individual matching – gender, age and municipality.	RF; Abs: a-CCP2; arginine (A) and citrullinine (C) containing telopeptides (C/A ratios of type I and II collagens).	Participants who later developed arthritis (survey data and Social Insurance Institution's population register – physician's diagnosis)	See below	Partial grants from MRC of the Academy of Finland and the Graduate School of In Vitro diagnostics.	

1455, 2007. REF ID: 3146										

Additional results:

Prediction of RA development from baseline characteristics:

- The mean baseline levels of Abs to CCPs wre higher in the cases than controls for patients who developed RF+ RA cases and for RA cases in total. However, there was NS difference between RF- RA cases and controls.
- Among total cases of RA, men had significantly higher levels of a-CCPs than women. Among the controls, the correlations between gender, age and the Abs were much weaker.
- In the highest tertile of a-CCPs, the RR of RF+ RA cases was significantly increased. The AB predictors however, tended to confound the effects of each other, and after entering all 3 into the multifactorial model, only a-CCPs retained statistical significance.
- Possible effect-modification by gender and age on the association between each Ab and the risk of RF+ RA: a-CCP levels were statistically significant (p=0.02)
- Subjects in the highest tertiles of both the C/A (II) ratio and a-CCPs had RR 20.1 (95% CI 4.4 to 92.1) for developing RF+ RA compared with those in the lowest tertiles of theses Abs.
- There was a synergistic effect modification for the C/A (I) ratio and a-CCPs, but their interaction was NS. No effect modification was suggested between the C/A (I) and (II) ratios.
- The RR for RA development restricted to 5 year follow-up did not differ significantly from the entire follow-up period.
- Smoking showed no association with the levels of a-CCP or any confounding effect on the results.
- Abs to CCPs were higher in cases than controls (higher mean levels: 173 vs 16.1, p=0.00008)

Authors' conclusion: Abs to citruliinated telopeptides of Type I and II collagen and to CCPs exert a synergistic effect on the risk of RF+ RA.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. Nishimura, D. Sugiyama, Y. Kogata,	MA MA: + Studies within MA: -	III MA well	Total N=30235 (N=14949 for anti-CCP;		**Inclusion criteria:** All studies that evaluated the utility of assaying anti-CCP Ab or RF for diagnosis of known or suspected RA,	Anti-CCP RF tests	ACR criteria	See below	Partially funded by	

G. Tsuji, T. Nakazawa, S. Kawano, K. Saigo, A. Morinobu, M. Koshiba, K. M. Kuntz, I. Kamae, and S. Kumagai. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Annals of Internal Medicine* 146 (11):797-808, 2007. ID 36	to ++ SR and MA included: N=86 studies (N=37 studies on anti-CCP; N=50 studies on RF) Studieswere similar in terms of: • Intervention (anti-CCP or RF) Studies differed with respect to: • Study size (range not mentioned) • Study design (Prospective in N=18/37 anti-CCP; N=25/50 RF) • Study quality – max score of 5 (N=1 very good quality; N=22, 30% reasonable quality; N=9, 10% poorer quality) • Study duration – length of follow-	conducted (assessed quality and heterogeneity and discussed limitations and quality of included studies). But the studies it pooled were of range of quality (most did not mention blinding of investigators and most used a narrow population, therefore give MA level III rating)	N=15286 for RF)		enrolled at least N=10 participants, published agfter 1987, provided enough information to calculate the sensitivity and specificity for diagnosis of RA. RA diagnosis (ACR criteria); symptom duration <1 year. Most studies (90%) enrolled patients with known or suspected RA Control patients varied in studies. anti-CCP studies: patients with UA (N=5); patients with other rheumatic diseases (N=13); healthy persons (N=1);;= hep-C carriers (N=1); mix of healthy persons and patients with other diseases (N=17). RF studies: patients with UA (N=5); other rheumatic diseases (N=16); healthy persons (N=2); hep-C carriers (N=1); polymyalgia rheumatica (N=1); mix of healthy persons and patients with other diseases (N=22).				Grant-In-Aid for Young Scientists (Ministry of Education, Japan); and from Ministry of Health, Japan.	

	up (range not mentioned) • Comparison group (mainly patients with UA; healthy patients; other diseases; other rheumatic diseases) • Intervention - type of anti-CCP test (anti-CCP1 N=8; anti-CCP2, N=29) • Intervention – type of RF test (IgM, IgA, IgG) Tests for heterogeneity and quality assessment performed.									

Additional results:

Results: diagnostic accuracy of anti-CCP and IgM RF, IgA RF and IgG RF

Test	LR+	LR-	Sensitivity	Specificity
Anti-CCP	12.5 (95% CI 9.7 to 16.0)	0.36 (95% CI 0.3 to 0.4)	67% (95% CI 65 to 68)	95% (95% CI 95 to 96)
IgM RF	4.9 (95% CI 4.0 to 6.0)	0.38 (95% CI 0.3 to 0.4)	69% (95% CI 68 to 70)	85% (95% CI 84 to 86)
Anti-CCP1	13.0 (95% CI 5.7 to 29.0)	0.53 (95% CI 0.5 to 0.6)	-	-
Anti-CCP2	12.8 (95% CI 9.6 to 17.0)	0.32 (95% CI 0.3 to 0.4)	-	-
Anti-CCP+RF+	15.7 (95% CI 8.3 to 29.8)	0.46 (95% CI 0.4 to 0.6)	-	-

Anti-CCP+ or RF+	4.3 (95% CI 2.7 to 6.9)	0.3 (95% CI 0.3 to 0.4)	-	-

Studies that directly compared anti-CCP with IgM RF were similar to summary data from all studies. For anti-CCP and IgM RF: LR+ 12.3 and 3.9 respectively; LR- 0.4 and 0.41 respectively. LR+ and LR- for IgA and IgG RF were similar to those for IgM RF.

Author's conclusions:
Anti-CCP antibodies are more specific than RF for diagnosing RA and may better predict erosive disease.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
M. A. Quinn, M. J. Green, Ortega H. Marzo, S. Proudman, Z. Karim, R. J. Wakefield, P. G. Conaghan, and P. Emery. Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application	Case series Single centre: France (patients from a rheumatology clinic) Pre-RA patients	Level II (as 1 main area of bias) • No mention of blinding of investigators • Case-series design • Population was true population to whom test would apply (UA patients)	N=60 **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** patients experiencing polyarthritis for <1 year (mean 6 months) referred by GPs for active but unclassified polyarthritis. **Exclusion criteria:** Patients suffering from monoarthritis or tenosynovitis alone and those with RA diagnosis already made. **Baseline characteristics of all patients:** disease duration mean 6 months (pre-RA).	RF; anti-perinuclear factor (APF).	Development of RA (ACR criteria) 3 years later at follow-up		Not mentioned	

of a structured management protocol. *Arthritis & Rheumatism* 48 (11):3039-3045, 2003. REF ID: 321										

Additional results:

Prediction of RA development from baseline characteristics:

- RA developed in N=40 (67%) of patients; of these N=36 (90%) were APF+ at the end of the study (the other 10% had other diagnoses). The rest of the patients had other rheumatic diseases.
- The sensitivity and specificity of APF for predicting RA development was 77% and 75% respectively.
- APF+ was noted for the first time at an average of 7.5 months after onset of the first arthritis
- In 45% of RA cases, APF were positive when ACR criteria were not yet fulfilled. Among the remaining RA cases, 28% were APF+ when 4 ACR criteria were present for the first time and at this time RF was only positive in 50% of cases (mean time 7 months)

Authors' conclusion: APF are useful in the diagnosis of early RA.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
A. Saraux, I. Valls, V. Voisin, A. Koreichi, D. Baron, P.	Case series Single centre: 1 rheumatolog	Level II (as 1 major areas of bias)	N=138 (N=39 RA) **Drop-**		**Inclusion criteria:** patients admitted for the first time to a rheumatology clinic for evaluation of peripheral	RF; Antiperinuclear factors; antikeratin	ACR criteria at 3-6 year follow-up	See belwo	Brest Hospital Centre and the	

Youinou, and Goff P. Le. How useful are tests for rheumatoid factors, antiperinuclear factors, antikeratin antibody, and the HLA DR4 antigen for the diagnosis of rheumatoid arthritis? *Revue du Rhumatisme (English Edition)* 62 (1):16-20, 1995. REF ID: 770	y department in France.	• No mention of blinded Investigators • Case-series design • Population was true population to whom test would apply (patients with various inflammatory joint manifestations)	**outs:** N=9 (6.5)		inflammatory joint disease. **Baseline characteristics of RA patients:** Age mean 57 years, female 62%, mean disease duration <2 years (early RA).	Ab; antinuclear factors; roentgenograms (hands, feet, pelvis, lumbar spine and painful joints).			1995 Clinical Research Hospital Program, France.	

Additional results:

Prediction of RA development (distinguishing from other diseases) from diagnostic tests, in UA (pre-RA) patients:

- Discrimination was best for positivity of 2 of the 3 following tests: RF; antiperinuclear factors and the HLA DR4 antigen (Sensitivity 51%, specificity 88%)

Authors' conclusions: The likelihood of RA was greatest in those patients with positivity of 2 of the 3 following markers: RF, antiperinuclear factors and the HLA DR4 antigen.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
E. Solau-Gervais, J. L. Legrand, B. Cortet, B. Duquesnoy, and R. M. Flipo. Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in the absence of anti-cyclic citrullinated peptide antibodies: A prospective study. *Journal of Rheumatology* 33 (9):1760-1765, 2006. REF ID: 1724	Case series Single centre: France (patients from 1 hospital Rheumatology department) Pre-RA patients	Level Ib study • Blinded Investigators • Population was true population to whom test would apply (Patients suggestive of early inflammatory rheumatism; polyarthralgia or polyarthritis patients)	N=30 **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** patients with polyarthritis or polyarthralgia suggestive of early inflammatory rheumatism (involving wrists and MCP joints symmetrically and with morning stiffness ≥45 mins)). **Exclusion criteria:** oral crticotherapy >1 month; established diagnosis with DMARD therapy; a-CCP+; erosions as established by radiolographs of wrists, feet and hands. **Baseline characteristics of all patients:** Mean age 47 years; symptom duration mean 8 months (pre-RA); no patients had erosions at baseline (as seen by radiographs) and all were a-CCP-.	morning stiffness; joint scores (tender and swollen); squeeze test; ESR; RF; CRP; ANA (anti-nuclear Abs); radiographs of hands wrists and feet (erosions); DAS28; MRI (OMERACT score – synovitis and tenosynovitis).	Development of RA (ACR criteria) 1 year later	See below	Not mentioned	

Additional results:

Prediction of RA development from baseline characteristics:

- At follow-up, RA developed in N=16 (53%) of patients; the remaining 47% developed other forms of inflammatory joint disease or had undifferentiated arthritis (non-RA group). At 1 year, all patients (except 1) had DMARD treatment.
- The group that developed RA was significantly different to the group that did not develop RA only for baseline swollen joint count (which was higher) and OMERACT score for erosions in the MCP joints and the second and third MCP joints (specificity 70%, sensitivity 64%).

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
J. Van Aken, H. Van Dongen, S. Le Cessie, C. F. Allaart, F. C. Breedveld, and T. W. Huizinga. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or	Case – control Single centre: RA cases from an EAC, The Netherlands	Level II (as 1 major areas of bias) • Blinded Investigator • Case-control design • Population reflects those to whom it would apply (patients with UA)	N=330 **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** Patients with suspected arthritis (undifferentiated arthritis diagnosed at the 2nd visit – probable RA by ACR criteria and arthritis of unknown cause) **Baseline characteristics:** UA→RA: Age mean 53 years, female 69%, disease duration 130 days (pre-RA). RA→RA: Age mean 55 years, female 64%, disease duration 131 days (early RA).	Functional disability (HAQ); morning stiffness; DAS; Radiographs (Sharp van der Heijde score); RF; ESR; CRP.	RA diagnosis (ACR criteria) 1 year later	See below	Dutch League against Rheumatism	

with rheumatoid arthritis: an observational cohort study. *Annals of the Rheumatic Diseases* 65 (1):20-25, 2006. REF ID: 3168										

Additional results:

Prediction of RA development (distinguishing from other diseases) from diagnostic tests, in pre-RA patients:

- N=26 patients developed RA by end of follow-up
- Pre-illness serum AFA was directly proportional to the risk of RF+ RA; The RR in the highest quintile compared to the lowest one was 5-fold. (RR 5.4 and 0 respectively). No effect was seen for RF- RA.
- Subgroups of RF+ RA cases and their matched controls were then analysed by quintiles of AFA concentration. No clear difference emerged between men and women.
- A linear increase in the relative odds up to 24 was noted in subjects RF+ at baseline; there was hardly any effect for RF- subjects at baseline. The interaction of baseline RF and AFA was NS.
- The linear relation between AFA and the risk of RF+ RA remained significant after adjustment for baseline RF status, but not after further adjustment for Waaler-Rose titre (RF).
- Significant increases in the risks of RF+ RA were observed in subjects with elevated AFA during the periods <5 years and 5-10 years from drawing the specimen to the onset of clinical disease, whereas only a weak association was suggested during the follow-up period >10 years.
- The relationship between RF and AFA was also studied using a cross-sectional design of the baseline examination. A significant association of the same order of magnitude emerged between RF and AFA both in pre-illness sera (RF+ and RF- cases combined) and in control sera.
- No correlation existed between IgG concentration and AFA level.
- Significantly more cases (those that went on to develop RA) were RF+ at baseline than controls (42% vs 12%, $p<0.001$)

Authors' conclusions: AFA still within the 'normal' range predicts RA in a linear fashion. AFA andRA are associated markers of the rheumatoid immunological process.										
Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
A. H. Van der Helm-van Mil, S. Le Cessie, H. Van Dongen, F. C. Breedveld, R. E. Toes, and T. W. Huizinga. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis & Rheumatism* 56 (2):433-440,	Case series Single centre: The Netherlands (patients from 1 EACs – referred from a number of GPs) Pre-RA patients	Level II (as 1 major areas of bias) • No mention of blinded Investigators • Case-series design • Population was true population to whom test would apply (patients with UA)	N=570 with UA **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** patients with early arthritis (UA and other) **Baseline characteristics:** UA→RA: Mean age 56 years; female 68%; HAQ mean 1.0. UA→UA: Mean age 49 years; female 53%; HAQ mean 0.7.	severity of morning stiffness, HAQ; ESR; RF; CRP; a-CCP.	Development of RA (ACR criteria) at 1 year follow-up	See below	Not mentioned	

2007. REF ID: 3108										

Additional results:

Prediction of RA development from baseline characteristics:

- RA developed in N=177 (31%) of patients; the remaining did not progress to RA.
- Univariate analysis: All baseline characteristics were predictors of RA except for smoking
    - HAQ
    - a-CCP(51% vs 11%, p<0.001)
    - RF+ (44% vs 14% p<0.001)
    - CRP (median level 14 vs 8, p<0.001)
    - ESR
    - symptoms – morning stiffness, swollen and tender joints

- Multivariate analysis:
    - Age
    - Gender
    - localisation of joint symptoms (small/large joints, symmetric/asymmetric, upper/lower extremities)
    - morning stiffness
    - tender and swollen joint counts
    - CRP level (5-50 mg/titer OR 1.6, 95% CI 0.9 to 3.0, p=0.13; >50 mg/titer OR 5.0, 95% CI 2.0 to 12.1, p=0.00)
    - Presence of RF (OR 2.3, 95% CI 1.2 to 4.2 p=0.009)
    - a-CCP Abs anti-CCP+ (OR 8.1, 95% CI 4.2 to 15.8, p<0.001)

Authors' conclusion: In patients who present with UA, the risk of developing RA can be predicted, thereby allowing individualised decisions regarding the initiation of treatment with DMARDs in such patients.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
K. N. Verpoort,	Case series	Level II	N=262 (N=110		**Inclusion criteria:** arthritis of a recent	a-CCP tests	ACR criteria	See below	Dutch Arthritis	

DerZijdeC Jol-Van, DerVoortE Papendrecht-Van, A. Ioan-Facsinay, J. W. Drijfhout, TolM Van, F. C. Breedveld, T. W. J. Huizinga, and R. E. M. Toes. Isotype distribution of anti-cyclic citrullinated peptide antibodies in undifferentiated arthritis and rheumatoid arthritis reflects an ongoing immune response. *Arthritis and Rheumatism* 54 (12):3799-3808, 2006.	Single centre: The Netherlands. Patients from an early arthritis clinic.	(as 1 main area of bias) • No mention of blinding of investigators • Case-series design • Population was true population to whom test would apply (UA patients)	undifferentiated arthritis, N=152 RA) **Drop-outs:** Not mentioned		onset (symptoms <2 years); if RA patients (ACR diagnosis). **Baseline characteristics of RA patients:** Age mean 51 years, female 72%, RF+ 76%, mean disease duration 2 years (early RA).	(IgG1, IgG2, IgG3, IgG4, IgA and IgM).	(measured 1 year later in all UA patients)		Association and other non-Pharma sources.	

REF ID: 1859										

Additional results:

Prediction of RA development from diagnostic tests, in UA (pre-RA) patients:

- Of the N=110 a-CCP+ patients with UA at baseline, N=74 fulfilled RA (ACR criteria) at 1 year follow-up. N=7 developed other diseases and the remainder still had UA.

Whether a-CCP response in UA→RA patients differed from that in UA→UA patients

- IgA, IgM, IgG2 and IgG3 a-CCP were present in significantly higher frequencies in the UA →RA patients than the UA→UA patients ($p<0.05$)
- Among UA→UA patients a median of 3 isotypes were used in the a-CCP response, compared with a median of 5 among UA →RA patients ($p=0.004$). Thus it seems there is more extensive a-CCP usage in UA→RA patients.
- A higher risk for the development of RA within 1 year of follow-up was observed in patients with UA who were IgA a-CCP+ (RR 1.3, 95% CI 1.0-1.7), IgM a-CCP (RR 1.4, 95% CI 1.1 to 1.8) or IgG a-CCP (RR 1.4, 95% CI 1.1 to 1.8).
- A trend towards higher levels of all isotypes of a-CCP except IgG1 was observed in UA→RA patients compared wit h UA→UA patients, when all samples were taken into consideration. Data not given but all were NS. When only those patients who were positive for a respective isotype were considered, only the levels of IgG4 a-CCP were higher in UA→RA patients ($p=0.007$).

Summary

- These results, taken together show that at the population level, the a-CCP response in a-CCP+ patients with UA in whom RA was not diagnosed within 1 year was less diverse with respect to isotype usage compared with the response in patients in whom RA did develop, and that levels of most isotypes of a-CCP were similar in both patient groups.

Authors' conclusions: These data indicate development of the a-CCP isotype repertoire into full usage early in the course of arthritis. The sustained presence of IgM a-CCP indicates ongoing recruitment of new B cells into te a-CCP response, reflecting a continuous (re)activation of the RA-specific a-CCP response during the course of a-CCP+ arthritis.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments

F. Wolfe, K. Ross, D. J. Hawley, F. K. Roberts, and M. A. Cathey. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol* 20 (12):2005-2009, 1993. REF ID: 3181	Case series Single centre: RA cases from an arthritis centre in USA	Level II (as 1 main area of bias) • No mention of blinding of investigators • Case-series design • Population was true population to whom test would apply (UA patients)	N=1141; N=503 with RA **Drop-outs at follow-up:** None for RA patients		**Inclusion criteria:** RA (ACR criteria) or undifferentiated polyarthritis; early disease (< 2 years) **Baseline characteristics:** Age mean 51 years, female 62%, disease duration < 1 year inclusion criteria (early RA).	Functional disability (HAQ); ADL; joint count; ESR; RF. Remission	RA (ACR criteria) At Mean follow-up 6.9 years. All RA patients had ≥13 months follow-up	See below	Grants from the Kansas Chapter, Arthritis Foundation and the NI of Arthritis and other non-Pharma sources, USA..	

Additional results:

Prediction of RA development from baseline characteristics:

- At 6 months or less only 14% of cases progressed to RA.
- The ACR criteria (1958 and 1987) performed equally well in predicting those who would later be classified as RA (both: 31% at 0-6 months duration, 42% and 39% at 0-24 months duration respectively). However, both sets of criteria had little specificity.
- Of those with UA that developed into RA vs patients that developed other disorders baseline characteristics were: 13% vs 12% had arthralgia, 3% vs 16% had questionable swelling, 13% vs 10% had oligo swelling, 30% vs 13% had atypical swelling, 30% vs 4% had typical swelling, 12% vs 6% had other.

Reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity PPV and NPV	Source of funding	Additional comments
A. Young, N. Sumar, K. Bodman, S. Goyal, H. Sinclair, I. Roitt, and D. Isenberg. Agalactosyl IgG: an aid to differential diagnosis in early synovitis. *Arthritis & Rheumatism* 34 (11):1425-1429, 1991. REF ID: 820	Case series Multicentre: UK (patients from 2 EACs) Pre-RA patients	Level II • Case-series design (however once diagnosis was made the statistics compare those who developed RA vs those who did not develop RA) • No mention of blinding of investigators • Population was true population to whom test would apply (Synovitis patients) •	N=60 **Drop-outs at follow-up:** Not mentioned		**Inclusion criteria:** patients with synovitis for <1 year. **Baseline characteristics of all patients:** Mean age 51 years; female 67%; disease duration mean 8 months (pre-RA).	morning stiffness, pain (VAS); joint scores; grip strength; HAQ; ESR; RF; ANA (anti-nuclear Abs); % of IgG that lack Galactose above the age-corrected mean (GAL0)	Development of RA (ACR criteria) over 2-3 year follow-up	See below	Not mentioned	

Additional results:

Prediction of RA development from baseline characteristics:

- RA developed in N=39 (65%) of patients; the remaining 35% developed other forms of inflammatory joint disease.
- GAL0 levels were significantly higher in the patients that developed arthritis vs those that developed other disease (77% vs 14%, p<0.001)
- ARA clinical criteria at study entry predicted the eventual outcome (development of RA) in 68% of the patients, whereas the RF+ distinguished 83% and GAL0 levels

78%.

- Combining RF+ and GAL0 improved this to 91% (90% sensitivity, 95% specificity and 94% PPV)

Authors' conclusion: A combination of RF+ and GAL0 levels above the age-corrected mean gave a PPV for RA in 94% of patients.

Bibliographic reference	Study type	Evidence level	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity	Positive and Negative predictive value	Source of funding	Additional comments
B. Van der Cruyssen, I. E. A. Hoffman, I. Peene, A. et al. Prediction models for rheumatoid arthritis during diagnostic investigation: Evaluation of combinations of rheumatoid factor, anti-citrullinated protein/peptide antibodies and the human leucocyte antigen-shared epitope. *Annals of the Rheumatic Diseases* 66	Case series Multi centre: Belgium (patients from 3 hospitals) Pre-RA patients	1b • Compares index test with reference standard (Rheumatologist diagnosis ACR criteria 1 year later) • Blinded Investigators	N=1003 (N=153 diagnosed at follow-up with definite RA)		**Inclusion criteria:** Patients referred to rheumatologists with a new diagnostic problem for which RA was included in the differential diagnosis. Patients did not necessarily have early arthritis. **Baseline characteristics:** Patients who developed RA: Age mean 58 years, female 66%, disease	RF a-CCP HLA	Rheumatologist diagnosis ACR criteria Diagnoses were established after 1 year of follow-up	Not given	Plots of PPVs given at different cut-off values of RF titre	Grant from Ghent University	

(3):364-369, 2007. ID 3522					duration mean 19.3 months (pre-RA). Non-RA patients: Age mean 51 years, female 66%, disease duration mean 15.9 months (pre-RA).						

Additional results:

Prediction of RA development/diagnosis at 1 year from baseline characteristics:

N=153 patients developed RA.

- ACPA testing in combination with shared HLA shared epitope had no additional value in predicting patients with UA who would develop RA 1 year later
- RF testing had additional value to ACPA testing alone, particularly in a subpopulation with at lease 1 swollen joint (lower RF titres become more relevant)

Authors' conclusion: The potential additional value of shared epitope testing disappears when ACPA testing is available. Combined RF and ACPA testing is useful, especially when RF is considered as a continuous parameter reflecting an increasing probability for RA at higher RF titres. The value of continuous RF testing increases when the a priori chance is higher (if patients present with at least 1 swollen joint at baseline)

PROG

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. A. Quinn, P. G. Conaghan, P. J. O'Connor, Z.	RCT 1++ Single centre,	N=20 (N=10 IFX + MTX; N=10	**Inclusion criteria:** Age >18 years; RA < 1 year duration (ACR criteria); poor prognosis	IFX (3 mg/kg/day) + MTX (7.5 mg once/week)	MTX + placebo	1 year (with follow-up at 2 years – 1	MRI (synovitis, bone oedema, erosion score;	ARC, UK.

Karim, A. Greenstein, A. Brown, C. Brown, A. Fraser, S. Jarret, and P. Emery. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis & Rheumatism* 52 (1):27-35, 2005. REF ID: 2943	UK • Randomised (adaptive stratified technique using RF+ as the stratum) • Double blind • Tue ITT analysis • Sample size calculation	placebo + MTX) **Drop-outs at follow-up:** N=1 (IFX + MTX) N=0 (MTX)	disease (PISA scoring system – score ≥3 indicates poor prognosis); no previous DMARD or oral CS tretment; MCP joint involvement;stable dose of NSAIDs for 2 weeks prior to screening. **Exclusion criteria:** current inflammatory condition with signs and symptoms that might confound the diagnosis; previous use of a-TNF agents, cyclophosphamide, nitrogen mustard, chlorambucil or other alkylating agents; known allergy to murine proteins; contraindication for IFX; serious disease. **Baseline characteristics:** IFX + MTX: Mean age 51 years; disease duration mean 7 months (early RA); HAQ 1.3. MTX: Mean age 53 years; disease duration mean 6 months (early RA); HAQ 1.3. There were NS differences between the groups for any of the baseline characteristics.	MTX dose was escalated in both groups according to stabdardised step-up protocol; all patients wre receiving 15 mg/week by week 14. Further increments up to 25 mg were titrated against evidence of active clinical disease, aiming for remission. In both groups no other DMARDs were allowed until after the 1 year assessment. No CS were permitted during te first 14 weeks; thereafter, IA or IM CS were allowed as clinically required, to a dose of 120 mg methylprednisolone in each 3-month study period.	MTX dose as for the combination group. **IN BOTH GROUPS, TREATMENT WAS WITHDRAWN AT 1 year**	year after treatment withdrawn)	ACR 20, 50 and 70; Remission (ACR); QoL (RAQoL); HAQ; DAS28; radiographs (Sharp-van der Heijde score – total, erosions and JSN); CRPAEs.	
Effect size* • In patients with poor prognosis, IFX + MTX was significantly better than MTX for: o Reduction in synovitis (MRI) at 14 weeks and 54 weeks ($p<0.05$) o Reduction in bone oedema (MRI) at 54 weeks ($p<0.05$)								

- New erosions (MRI) at 24 weeks and 54 weeks (p<0.05)
- ACR20, ACR50 and ACR70 at 14 weeks (p<0.05) and ACR50 and ACR70 at 54 weeks
- Remission time (median 26 weeks vs 0 weeks respectively, p<0.05)
- DAS8 score at 14 weeks (p<0.05)
- CRP levels (AUC) over 54 weeks (p<0.05)
- HAQ score at 14, 54 weeks and 2 year follow-up (p<0.05)
- RAQoL score at 14, 54 weeks and 2 year follow-up (p<0.05)

- In patients with poor prognosis, IFX + MTX was better than MTX for:
  - Remisison rates over 2 years (N=7 vs N=2 respectively)
  - Use of MTX and CS therapy

- In patients with poor prognosis, there was NS difference between IFX + MTX and MTX for:
  - Radiographic progression (Sharp Van-der Heijde score) at 24 weeks
  - ACR20 at 54 weeks; ACR20, 50 and 70 at 2 years follow-up
  - DAS8 score at 54 weeks and at 2 years follow-up
  - CRP levels (AUC) between 54 weeks and 2 year follow-up

- In patients with poor prognosis, IFX + MTX was similar to MTX for:
  - Withdrawals (N=1 and N=0 respectively)
  - AEs (N=2 and N=0 respectively)

Authors' conclusion: Remission induction with infliximab + MTX provided a significant reduction in MRI evidence of synovitis and erosions at 1 year. At 2 years, functional status and QoL benefits were sustained, despite withdrawal of infliximab therapy. These data have significant implications for the optimal use of expensive biologic therapies.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. M. Proudman, P. G. Conaghan, C. Richardson, B. Griffiths, M. J. Green, D. McGonagle, R. J. Wakefield, R. J. Reece, S. Miles, A. Adebajo, A. Gough, P. Helliwell, M.	RCT 1+ Multicentre: UK (network of clinics for patients with early arthritis) • Randomised (method not	N=82 (N=42 SSZ; N=40 combination) **Drop-outs at follow-up:** N=23 (SSZ	**Inclusion criteria:** Age >18 years; RA < 1 year duration (ACR criteria); poor prognosis disease **Exclusion criteria:** Duration >1 year; current or previous treatment with immunosuppressive, cytotoxic, DMARD therapy or CS; concomitant therapy with drugs	SSZ 500 mg/day SSZ dose was increased to a max of 2000 mg/day (500 mg/week intervals). If there was no improvement	Combination: **CSA** (1.5 mg/kg/day) **+ MTX** (7.5 mg/week) **+ CS (methylprednisolone**, 10 mg for each small joint, 20 mg for each wrist and ankle and 40 mg for each knee)	48 weeks	ACR 20 and 50; Remission (ACR); patient's and physician's global assessment of disease activity; pain (VAS); HAQ;	Novartis and ARC, UK.

Martin, G. Huston, C. Pease, D. J. Veale, J. Isaacs, D. M. van der Heijde, and P. Emery. Treatment of poor-prognosis early rheumatoid arthritis. A randomized study of treatment with methotrexate, cyclosporin A, and intraarticular corticosteroids compared with sulfasalazine alone. *Arthritis & Rheumatism* 43 (8):1809-1819, 2000. REF ID: 3159	mentioned) • Allocation concealment • No mention of blinding • Power study • Not true ITT analysis	N=15, Combination N=8)	that may interfere with the pharmacokinetics of CSA (excluding NSAIDs); treatment with any experimental drugs within 3 months prior to the start of the trial; severe concomitant disease; history of malignancy; sensitivity to salicylates or sulphur-containing compounds. **Baseline characteristics:** SSZ: Mean age 50 years; female 55%; disease duration median 9 months (early RA); Pain (VAS) 53. Combination: Mean age 51 years; female 65%; disease duration median 8 months (early RA); Pain (VAS) 52. There were NS dfiiferences between the groups for any of the baseline characteristics.	after 8 weeks, dose was further increased to 3000 mg/day if tolerated. Clinically significant, painful joint effusions were aspirated and injected with IA CS. In both groups simple analgesics and NSAIDs (except Diclofenac) were permitted if dosage had been stable for 1 month prior to study entry. Oral CS were not permitted.	CSA dose was increased at 2-wekly intervals to a max dose of 4.2 mg/kg/day if tolerated. MTX dose was increased to a max of 20 mg/week (in 2.5 mg increments every visit) provided that the dose of CSA had been maximised and that 8 weeks had elapsed since the study start. CS was injected into all joints with active RA (ie. up to 15 joints injected)		DAS28; CRP; radiographs (Sharp-van der Heijde score – total, erosions and JSN); AEs.	
Effect size* • In patients with poor prognosis, CSA + MTX + methylprednisolone was significantly better than SSZ for: o CS treatment (over 48 weeks) o Swollen joint count at 24 and 48 weeks o Tender joint count at 24 weeks o Withdrawals due to lack of efficacy over 48 weeks • In patients with poor prognosis, there was NS difference between SSZ and CSA + MTX + methylprednisolone for: o Concomitatnt NSAID therapy o ACR20 and ACR50 at 48 weeks o Remissions (% patients, ACR) at 48 weeks								

- o Tender joint count at 48 weeks
- o CRP at 24 and 48 weeks
- o ESR at 24 and 48 weeks
- o HAQ score at 24 and 48 weeks
- o Pain (VAS) at 24 and 48 weeks
- o DAS28 score at 24 and 48 weeks
- o Patient's global assessment at 24 and 48 weeks
- o Radiographic progression - Sharp van-der Heijde score (total score, erosions and JSN) at 48 weeks
- o Withdrawals due to AEs over 48 weeks

Prognostic indicators: exclude from prognosis part A of question due to sample size N<200

- Multivariate analysis showed that clinical response at 48 weeks was significantly associated with baseline function, DAS28 and radiographic damage. Low HAQ score, high DAS score and low erosion score were associated wit a >20% improvement.
- Worse radiographic damage at 48 weeks was associated with high baseline CRP.

Authors' conclusion: In poor prognosis RA patients, 'aggressive' combination therapy led to more rapid disease suppression but did not result in significantly better ACR response or remission rates. This suggests that in poor prognosis disease, an approach based on identifying patients with poor treatment responses before extra therapy is added (step-up approach) may be more appropriate than the use of combination therapy in all patients from the onset.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van Dongen et al. Efficacy of Methotrexate Treatment in Patients with Probable Rheumatoid Arthritis. *Arthritis & Rheumatism* 56 (5):1424-1432, 2007. REF ID: 3559	RCT 1+ Multicentre: The Netherlands (4 hospitals) • Randomised (method not mentioned) • Single blind • Power study • No mention of ITT analysis	N=110 (N=55 MTX, N=55 placebo) **Drop-outs at follow-up:** N=5 (9%) in each group	**Inclusion criteria:** Age >18 years; outpatients of the Rheumatology clinics; symptoms < 2 years duration; diagnosis of UA (ACR criteria for probable RA) **Exclusion criteria:** RA (ACR criteria); impaired kidney or liver unction; bone marrow insufficiency; DMARD use in the past. **Baseline characteristics:** MTX: Mean age 51 years; female 64%; disease duration	MTX (2.5 mg, six/day) Every 3 months the medication was increased by 2 tablets if DAS >2.4 to a maximum of 12 tablets or 30 mg MTX.	Placebo	30 months	DAS; ESR; radiographs (Sharp-van der Heijde score); anti-CCP; RA diagnosis (ACR criteria)	Dutch Arthritis Fondation and The Ntherlands Organisation for Scientific Research, The Netherlands.

			mean 312 days (early UA); HAQ 0.75. Placebo: Mean age 51 years; female 69%; disease duration mean 263 days (early RA); HAQ 0.75. The two groups were similar for all baseline characteristics.					

Effect size*

After 30 months, 40% of the MTX group and 53% of the placebo group developed RA.

ANTI-CCP

- In patients with poor prognosis (anti-CCP+), MTX was significantly better than Placebo for:
  - Number of patients developing RA at 30 months (67% vs 93%, p<0.001)
  - Slowing radiographic progression, SHS score (p=0.03)
  - DAS score (p<0.001)

- In patients with good prognosis (anti-CCP-), there was NS difference between MTX and placebo for:
  - Number of patients developing RA at 30 months
  - Slowing radiographic progression, SHS score
  - DAS score

RF:

- In patients with poor prognosis (RF+), MTX was significantly better than Placebo for:
  - Number of patients developing RA at 30 months (55% vs 68%, p=0.036)
  - Slowing radiographic progression, SHS score (p=0.03)

- In patients with good prognosis (RF-), there was NS difference between MTX and placebo for:
  - Number of patients developing RA at 30 months
  - Slowing radiographic progression, SHS score

Prognostic indicators: excluded from prognosis part A of question due to sample size N<200								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
L. R. Lard, H. Visser, I. Speyer, Bruinsma IE vander Horst, A. H. Zwinderman, F. C. Breedveld, and J. M. Hazes. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies.[see comment]. *American Journal of Medicine* 111 (6):446-451, 2001.	Cohort study (prospective): 2+ Single centre, The Netherlands • All patients included in analysis (even drop-outs)	Total N=206 (N=97 early treatment), N=109 delayed treatment) **Lost to follow-up/ withdrawals:** N=16, 15% (delayed treatment), N=4, 4% (early treatment)	**Inclusion criteria:** RA 'definite RA' diagnosis (ACR criteria), early RA; active disease (at least 3 of the following: morning stiffness >30 mins, >5 swollen joints, Ritchie score >15 or ESR >28 mm/hr. The delayed treatment group were patients who visited the clinic 1993-1995 at which time patients with RA were treated consistently according to delayed therapy strategy. Early treatment group visited the clinic 1996-1998 in which time standard treatment was to give all patients with RA DMARDs as soon as possible. Only patients with diagnosis of probable or definite RA were included. **Baseline characteristics:** Early treatment group: mean age 54 years; Female 72%; disease duration mean 128 days (early RA); Sharp score mean 1. Delayed treatment group: mean age 58 years; Female 79%; disease duration mean 162 days (early RA); Sharp score mean 0.	Early treatment: prompt treatment with DMARDs + NSAIDs. Time to start DMARD treatment from 1st visit: mean 15 days	Delayed treatment: NSAIDs then DMARDs if still had active disease after several months. DMRADS were: chloroquine (300mg, 200 mg then 100mg per day at months 1, 2 and 3 and thereafter respectively) or salazopyrine (2000 mg/day). Chloroquine was used preferentially. Time to start DMARD treatment from 1st visit: mean 123 days (approx 4 months).	2 years	Progression of radiographic joint damage (modified Sharp score); functional capacity (HAQ); modified DAS; Ritchie articular index score; CRP; AEs.	Not mentioned.

ID 3005			There were NS differences between the groups for any of the baseline characteristics except for time to start DMARD treatment.					

1.4 Effect size

EARLY TREATMENT vs DELAYED TREATMENT

Subgroup analysis

- In patients with definite RA, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with probable RA, the median change in joint damage was NS different in the early treatment group compared to the delayed treatment group.
- In patients with RF+, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with RF-, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with Sharp score >0 at baseline, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.

Authors' conclusion: early introduction of DMARDs was associated with better disease outcome after 2 years.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
van Aken J., L. R. Lard, Cessie S. Le, J. M. Hazes, F. C. Breedveld, and T. W. Huizinga. Radiological outcome after four years of early	Cohort study (prospective): 2+ Single centre, The Netherlands • Completers only included in the analysis	Total N=206 (N=97 early treatment), N=109 delayed treatment) **Lost to follow-up/ withdrawals:** 25%	**Inclusion criteria:** RA 'definite RA' diagnosis (ACR criteria), early RA; active disease (at least 3 of the following: morning stiffness >30 mins, >5 swollen joints, Ritchie score >15 or ESR >28 mm/hr. The delayed treatment group were patients who visited the clinic 1993-1995 at which time patients with RA were treated consistently according to delayed therapy	Early treatment: prompt treatment with DMARDs + NSAIDs. Time to start DMARD treatment from 1st visit: mean 15 days	Delayed treatment: NSAIDs then DMARDs if still had active disease after several months. DMRADS were: chloroquine (300mg, 200 mg then 100mg per day at months 1,	4 years	Progression of radiographic joint damage (modified Sharp score); functional capacity (HAQ); modified DAS; Ritchie articular index	Dutch Arthritis Foundation

versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Annals of the Rheumatic Diseases* 63 (3):274-279, 2004. ID 127			strategy. Early treatment group visited the clinic 1996-1998 in which time standard treatment was to give all patients with RA DMARDs as soon as possible. Only patients with diagnosis of probable or definite RA were included. **Baseline characteristics:** Early treatment group: mean age 54 years; Female 72%; disease duration mean 128 days (early RA); Sharp score mean 1. Delayed treatment group: mean age 58 years; Female 79%; disease duration mean 162 days (early RA); Sharp score mean 0. There were NS differences between the groups for any of the baseline characteristics except for time to start DMARD treatment.		2 and 3 and thereafter respectively) or salazopyrine (2000 mg/day). Chloroquine was used preferentially. Time to start DMARD treatment from 1st visit: mean 123 days (approx 4 months).		score; CRP; AEs.	

1.5 Effect size

EARLY TREATMENT vs DELAYED TREATMENT

Subgroup analysis:

- In patients with definite RA, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years and from 0-4 years but there was NS difference from 1-4 years.
- In patients with probable RA, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years but there was NS difference from 0-4 years and from 1-4 years.
- In patients with Sharp score >0 at baseline, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years and from 0-4 years but there was NS difference from 1-4 years.
- In patients with Sharp score 0 at baseline, the median change in joint damage (modified Sharp progression rate) was NS different in the early treatment group compared to the delayed treatment group from 0-2 years, from 0-4 years and from 1-4 years.

Authors' conclusion: early introduction of DMARDs was associated with better disease outcome after 2 years.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. Bukhari, M. Lunt, B. J. Harrison, D. G. Scott, D. P. Symmons, and A. J. Silman. Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort. *Arthritis &*	Case series 3 Multicentre, NOAR register	N=439 **Drop-outs:** Not mentioned	**Inclusion criteria:** patients newly presenting with inflammatory polyarthritis; adults with RA (ACR criteria). **Baseline characteristics of RA patients:** Age mean 55 years, female 71%, RF+ 32%, mean disease duration 5 months (early RA).	None	5 years after presentation	Swollen and tende joints; RF; CRP; Radiographic progression (Larsen method).	Arthritis Research Campaign, UK.

Rheumatism 46 (4):906-912, 2002. REF ID: 476							

Effect size*

Prediction of disease severity from baseline characteristics:

2 year results

- High CRP level (patient in the top third) was the most powerful predictor of radiographic severity (Larsen score – 4 fold increase) at 2 years.
- High-titer RF, presence of nodules and being in the upper third of number of swollen joints were predictors of radiographic severity (Larsen score – 2 fold increase) at 2 years.
- Multivariate analysis: top third CRP level and high RF- titre remained predictors. However in the subgroup of patients already with erosions, these variables had a lesser effect on severity – only the highest third of CRP had a markedly greater increase in score. This increase persisted in multivariate analysis. Most of the variables therefore had a greater effect on predicting erosions rather than the SEVERITY of the erosions.

5 year results

- Baseline CRP was less strongly predictive at 5 years and was similar to high RF titre and presence of nodules. The most predictive was Larsen score at 2 years. In multivariate analysis, CRP and RF remained predictors of radiographic severity (Larsen score). However in the subgroup of patients already with erosions, CRP, RF and presence of nodules had a lesser effect on severity – only the presence of nodules persisted in multivariate analysis.
- Predictors of progression only in patients who already had erosions (ie. after adjustment for baseline severity) – only RF at high titre was an important predictor, with a 50% increase in progressin score in those who had erosions at first film. The influence of RF at high titre persisted in multivariate analysis. None of the other variables at baseline were useful predictors of progression after adjustment for baseline severity.

Authors' conclusions: High titre RF is an important variable in predicting continuing severity of radiographic damage during the first 5 years after presentation with inflammatory polyarthritis.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
J. Dixey, C. Solymossy, and A. Young. Is It Possible to Predict Radiological Damage in Early Rheumatoid Arthritis (RA)? A Report on the Occurrence, Progression, and	Case series 3 Multicentre: UK (Patients from 9 rheumatology departments in UK hospitals). ERAS study	N=866 **Drop-outs at follow-up:** Not mentioned	**Inclusion criteria:** RA (ARA criteria); duration <2 years; not treated with second-line medication **Baseline characteristics:** Age mean (not mentioned), female 66%, disease duration <2 years (early RA).	None	3 years	Swollen and tender joints; nodules; HAQ; Pain (VAS); Grip strength; ESR; RF; DAS; Radiographs (Larsen score).	Grant from ARC and BUPA Research Foundation

Prognostic Factors of Radiological Erosions over the First 3 Years in 866 Patients from the Early RA Study (ERAS). *Journal of Rheumatology* 31 (SUPPL. 69):48-54, 2004. REF ID: 1141							

Effect size*

Prediction of disease severity from baseline characteristics:

Univariate analysis

- Odds ratios >2 for predicting presence of erosions or not (Larsen score at 3 years): baseline RF, erosion score and nodules and 1 year ESR.

Multivariate analysis

- Combination factors predictive of 3 year Larsen erosion score: baseline RF and ESR (PPV 68%), 1st year erosion score and ESR (PPV 84%)
- Severity of erosions was not correctly classified in 82% by baseline erosion score, swollen joint count and nodules PPV 77%)

Authors' conclusions: Prognosis for radiological outcome was possible using routinely obtained clinical and lab measures.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
K. Forslind, I. Hafstrom, M. Ahlmen, B. Svensson, and the BARFOT Study Group. Sex: a major predictor of remission in	Case series 3 Multicentre: 6 rheumatology units in Sweden. BARFOT study	N=698 **Drop-outs at 5 year follow-up:** N=90 (13%)	**Inclusion criteria:** RA (ACR criteria); duration <1 year **Baseline characteristics:** Age mean 58	None	5 years	Remission (DAS28 <2.6 with or without ongoing treatment); HAQ; Pain (VAS); Morning stiffness; physician's assessment of current disease activity; functional impairment (SOFI index); ESR; CRP; RF; a-CCP.	Grant from The Swedish Rheumatism Foundation and other non-Pharma sources, Sweden.

early rheumatoid arthritis? *Annals of the Rheumatic Diseases* 66 (1):46-52, 2007. REF ID: 3144			years, female 64%, disease duration mean 6 months (early RA).				

Effect size*

Prediction of remission from baseline characteristics:

Univariate analysis

- Remission at 3 months, 6 months, 1 year, 18 months, 2 years and 5 years follow-up was significantly predicted by baseline: gender, duration of disease, a-CCP, RF, DAS28, HAQ. However SOFI was not a predictor.

Multivariate analysis

- Remission at 3 months, 6 months, 1 year, 18 months, 2 years and 5 years follow-up was significantly predicted by baseline: Male gender, short disease duration, low DAS28, low HAQ, RF-. Male gender was a major independent predictor of remission.

Authors' conclusions: Early remission of RA by DAS28 score <2.6 was higher in men than women. Women had more severe disease despite DAS before treatment being similar.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
K. Forslind, M. Ahlmen, K. Eberhardt, I. Hafstrom, and B. Svensson. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice:	Case series 3 Multicentre, Sweden Patients recruited from the BARFOT study, who had sera samples available.	N=379 entered **Drop-outs / lost-to follow-up:** Not mentioned	**Inclusion criteria:** adults with early RA (<12 months duration); ACR criteria **Baseline characteristics:** Age mean 55 years, female 65%, RF+ 61%, mean	None	2 years	DAS28; global health and pain (VAS); functional disability (HAQ); CRP and ESR; Anti-CCP; RF; Radiographs (Larsen	Funds from the Swedish Research Council, Swedish Rheumatism Association, King Gustav's 80-year Foundation, and insurance company AFA.

Role of antibodies to citrullinated peptides (anti-CCP). *Annals of the Rheumatic Diseases* 63 (9):1090-1095, 2004. REF ID: 1194			disease duration 6 months (early RA), HAQ 0.9			score)	

Effect size*

Prediction of severity of RA from baseline characteristics:

- Radiological progression (change in Larsen score) at 2 years was significantly greater for anti-CCP+ patients than anti-CCP- patients

Univariate analysis

- Severe radiological damage and progression was predicted by: baseline Larsen score (OR 12.9 and 9.9 respectively), anti-CCP+ (OR 3.6 and 2.9), RF+ (OR 2.7 and 2.6), high ESR (OR 2.7 and 2.5) and high CRP (OR 2.2 and 1.9). All p-values <0.001. Other predictors were greater age, smoking and male gender. Pain (VAS) and functional disability (HAQ) were not predictors.
- Larsen score had the highest sensitivities and predictive values for radiographic outcomes. The predictive values for radiographic damage and progression in patients who were both anti-CCP+ and RF+ were similar to those in patients who were only positive for 1 of the 2 tests.

Multivariate analysis

- Radiolographic joint damage and radiographic progression at 2 years was predicted mainly by Larsen score, anti-CCP and ESR.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
F. Guillemin, N. Gerard, Leeuwen M. van, L. M. Smedstad, T. K. Kvien, Heuvel W. van den, and EURIDISS Group. Prognostic	Case series 3 Multicentre: 3 countries in Europe (EURODISS) study.	N=516 **Drop-outs at follow-up:** N=198 (38%)	**Inclusion criteria:** adults aged 20-70 years with RA (ACR criteria); duration 0-4 years; Steinbroker functional stage 1-3. **Baseline characteristics:** Age mean 52 years, female 70%, mean disease duration 2	None	3 years (mean 30 months)	HAQ disability score; Ritchie Index; nodules; other extraarticular manifestations; ESR; RF; radiographs (Sharp-van der Heijde); Erosions; JSN.	French Ministry of Health

factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. *Journal of Rheumatology* 30 (12):2585-2589, 2003. REF ID: 3132			years (early RA), HAQ score 0.93.				

Effect size*

Prediction of disease severity from baseline characteristics:

Univariate analysis

- Joint damage (Sharp van-der Heijde score), high ESR, high HAQ score and poor physician global assessment at baseline were significant predictors of radiological damage (Sharp van-der Heijde score) at 3 years.
- RF+ was not a predictor of radiological damage (Sharp van-der Heijde score) at 3 years.

Multivariate analysis

- Joint damage (Sharp van-der Heijde score), RF+, high ESR, shorter time from diagnosis, worse overall patient estimation of health at baseline were all significant predictors of radiological damage (Sharp van-der Heijde score) at 3 years.

Authors' conclusions: Final joint damage was predicted by baseline modified Sharp score, RF+, time from disease diagnosis, patient global health assessment, ESR and follow-up duration. These disease characteristics should be focused on in the early years of RA to identify patients at higher risk of developing severe disease and who are candidates for aggressive therapy.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
C. H. Van Jaarsveld, E. J. ter Borg, J. W. Jacobs, G. A.	Case series 3 Multicentre: RA cases from 6	N=577 entered N=249 had available data	**Inclusion criteria:** RA (ACR criteria); early RA (< 1 year)	None	3 years (assessments every 6 months)	Functional disability (HAQ); Joint score (Thompson – tenderness and	Dutch League against Rheumatism

Schellekens, Meyling FH Gmelig, Frankfort C. van Booma, B. A. de Jong, W. J. van Venrooij, and J. W. Bijlsma. The prognostic value of the antiperinuclear factor, anti-citrullinated peptide antibodies and rheumatoid factor in early rheumatoid arthritis. *Clinical & Experimental Rheumatology* 17 (6):689-697, 1999. REF ID: 634	rheumatological centres in The Netherlands, participating in an RCT		**Baseline characteristics at diagnosis:** Age mean 56 years, female 71%, disease duration < 1 year inclusion criteria (early RA).			swelling); Radiographs (modified Sharp score – erosions, JSN and total damage score); RF; ESR; a-CCP; APF (anti-perinuclear factor).	
Effect size* **Prediction of outcome from baseline characteristics:** • There was NS difference in mean functional disability between the RF and APF groups at baseline,1 year, 2 years and 3 years. • There were NS differences in median joint score between RF+ and RF- patients; however, APF- patients had significantly lower joint score and more rapid decrease in joint score compared to APF+ patients • APF was better at predicting joint involvement than RF: at 2-3 years the median joint score was significantly lower for RF+APF- patients compared to RF+APF+ patients. • APF+ patients suffered significantly more involvement of the large joints and small joints compared to APF- patients (p=0.01 and p<0.01 respectively). The results were comparable for Indirect immunofluoresence (IIF) and a-CCP. • RF status was not significantly associated with the number of affected large joints, however RF+ patients had more (but NS) small joints affected than RF- patients • APF- patients had a more rapid decrease in large joint involvement compared to APF+ patients; the decrease in large joint involvement was NS different between							

RF+ and RF- patients.

- Patients who were either RF+, a-CCP+ or APF-IIF+ had significantly worse radiological damage scores at follow-up compared with those who were negative for these tests.
- RF+APF+ patients had higher radiological damage scores, RF+APF- had intermediate damage scores and RF-APF- patients had low damage scores. For RF+ and RF- patients, APF+ was significantly associated with more radiological damage. There were NS differences between the RF+APF- patients and the RF-APF+ patients nor between the RF-APF+ patients and the RF+APF+ patients.
- Patients who were RF+APF+ had more radiological damage than those who were RF-APF-. Paients with 1 positive test had intermediate scores.
- There was NS difference between RF+ and RF- patients for obvious radiological damage in the wrist, however, APF+ patients had significantly more frequent involvement of the wrist compared to APF- patients (p=0.02).
- RF+ and APF+ patients significantly more often ahd radiological dame in the small hand and foot joints compared with RF- and APF- patients (p<0.01).

Authors' conclusions: APF has prognostic value in addition to RF for joint involvement and radiological damage in early RA. The CCP test for APF involvement may facilitate its use in clinical practice. However, the prognostic value of the 2 tests loes in their ability to predict mild disease. Reliable identification at baseline of individual patients with progressive disease is still not possible.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
E. J. Kroot, B. De Jong, M. A. Van Leeuwen, H. Swinkels, F. Van den Hoogen, ' T. H. Van, L. Van de Putte, M. Van Rijswijk, W. Van Venrooij, and P. L. van Riel. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. *Arthritis and Rheumatism* 43 (8):1831-	Case series 3 Multicentre: RA cases from 2 hospitals in The Netherlands	N=273 **Drop-outs at follow-up:** Not mentioned	**Inclusion criteria:** RA (ACR criteria); early RA (< 1 year); not received treatment with DMARDs **Baseline characteristics at diagnosis:** A-CCP+: Age mean 51 years, female 62%, disease duration < 1 year inclusion criteria (early RA). A-CCP-: Age mean 52 years, female 73%, disease duration < 1 year inclusion criteria (early RA).	None	3 years and 6 years	Functional disability (HAQ); Ritchie Articular Index (RAI); number of tender and swollen joints; DAS; Radiographs (modified Sharp score – erosions, JSN and total damage score); RF; ESR; a-CCP	Dutch League against Rheumatism, Netherlands Foundation for Research and The Netherlands Technology Foundation.

1835, 2000. REF ID: 1384							

Effect size*

Prediction of radiologic damage from baseline characteristics:

- Baseline a-CCP+ patients had significantly more radiologic damage at 6 years than baseliene a-CCP- patients

Multivariate analysis

- Radiologic damage at both 3 and 6 years was significantly predicted by IgM-RF status and by radiologic score at study entry.
- Radiologic damage at 3 years was predicted at 3 years by DAS
- A-CCP+ was significantly associated with radiologic damage at 6 year follow-up but not at 2 years
- IgM RF+ and DAS significantly influenced change in radiologic score (progression from baseline) at 3 years follow-up
- IgM RF+ and a-CCP were significant predictors of change in radiologic score (progression from baseline) at 6 years follow-up
- Gender, disease activity, IgM RF+, and age at enrolment were significant predictors of HAQ functional disability at both 3 and 6 years
- Age at study entry and disease activity were significant predictors of change in radiologic score (progression from baseline) at both 3 and 6 years follow-up

Authors' conclusions: a-CCP+ patients develop significantly more severe radiology damage than patients who are a-CCP; however the predictive value in multiple regression analysis was rather moderate

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. P. Linn-Rasker, A. H. Van der Helm-van Mil, F. C. Breedveld, and T. W. J. Huizinga. Arthritis of the large joints - in particular, the knee - at first presentation is predictive for a	Case series 3 1 centre, The Netherlands	N=285 entered with definite early RA (N=28 had sustained remission at 1 year, N=28 had most severe RA at 1 year) **Drop-outs:**	**Inclusion criteria:** adults with newly diagnosed early arthritis. After 1 year of follow-up N=285 patients fulfilled ACR criteria for RA. From these 2 categories of patients with extreme disease courses were selected – those with severe RA and those who had entered	None	3 years (assessments made at 1, 2 and 3 years)	Morning stiffness; Swollen joint count (joint groups: shoulders, elbows, wrists, MCP joints, interphalangeal joints, knees, ankles and MTP joints); CRP and ESR;	Not mentioned

high level of radiological destruction of the small joints in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 66 (5):646-650, 2007. REF ID: 1421			sustained remission (remitting RA). **Baseline characteristics:** Remitting RA (N=28) - Age mean 59 years, female 64%, RF+ 21%, mean disease duration 127 days (early RA), Sharp score 0. Most severe RA (N=28) - Age mean 59 years, female 61%, RF+ 82%, mean disease duration 152 days (early RA), Sharp score 10.			Anti-CCP; RF; Radiographs (Sharp-van der Heijde score)	

Effect size*

Prediction of severity of RA from baseline characteristics:

Univariate analysis

- At baseline: Patients with most severe disease harboured a-RF and a-CCP Abs more often, had significantly more swollen joints and significantly more often arthritis of the shoulders, elbows, proximal interphalangeal joints, knees and ankles. There was no difference in prevalence of swollen MCP and MTP joints between the groups.

Regression analysis

- Groups of joints associated with disease outcome (remitting RA or severe RA): Only the presence of a swollen knee was associated with disease outcome.
- Total number of swollen joints and swelling of the knee were independently associated with the level of radiological joint destruction of the small joints of hands and feet at 1 year follow-up.
- Only swelling of the knee was associated with the level of radiological joint destruction of the small joints of hands and feet at 2 and 3 year follow-up.
- Joint destruction at 1 year follow-up was significantly predicted by: total number of swollen joints, presence of a-CCP Abs, CRP level and symptom duration. Presence of arthritis of the knee was not a predictor for disease severity.
- Presence of a-CCp Abs, symptom duration, age, gender, RF and morning stiffness were not significantly different between the patients with RA with or without arthritis

of the knee. There was a significant difference in the level of CRP: patients with arthritis of the knee at first presentation had higher CRP levels compared with patients with RA without involvement of the knee.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. Odegard, R. Landewe, derHeijdeD van, T. K. Kvien, P. Mowinckel, and T. Uhlig. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: A ten-year, longitudinal observational study in 238 patients. *Arthritis and Rheumatism* 54 (1):68-75, 2006. REF ID: 1539	Case series 3 Multicentre, EURODISS project	N=238 **Drop-outs:** N=89 (37%)	**Inclusion criteria:** adults aged 20-70 years with RA (ACR criteria); duration 0-4 years; Steinbroker functional stage 1-3. **Baseline characteristics:** Age mean 52 years, female 74%, RF+ 68%, mean disease duration 2.3 years (early RA), HAQ score 0.93.	None	10 years (assessments made at 1,2, 5 and 10 years)	Grip strength; HAQ score; Radiographic progression (Sharp van der Heijde); RF and ESR.	Not mentioned

Effect size*

Prediction of mortality from baseline characteristics:

- HAQ score was associated with radiographic progression (modified Sharp score) after adjustment for ESR.
- Radiographic damage (Modified Sharp score) and progression of radiographic damage (modified Sharp score) was associated with grip strength.

Authors' conclusions: Both radiographic damage and disease activity are contributors to impaired physical function in RA, both early and late in the disease process.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. J. Plant, A. L. Williams, M. M. O'Sullivan, P. A. Lewis, E. C. Coles, and J. D. Jessop. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis and Rheumatism* 43 (7):1473-1477, 2000. REF ID: 1605	Case series 3 UK	N=359 **Drop-outs:** Not mentioned	**Inclusion criteria:** active RA patients who entered a 5-year RCT of DMARD therapy.. **Baseline characteristics of RA patients:** Age mean 51 years, female 72%, RF+ 76%, mean disease duration 2 years (early RA).	None	5 years	Time-integrated CRP (AUC); Radiographic progression (Larsen score – damged joint = Larsen score ≥2). **Average time-integrated CRP over 5 year period:** Normal >6 mg/L Minor 6 to <12 mg/L Medium 12 to <25 mg/L High ≥25 mg/L	Arthritis Research Campaign, UK and several Pharma companies.

Effect size*

Prediction of disease severity from baseline characteristics:

5 year results

- There was a significant correlation between time-averaged CRP levels and change in Larsen score
- Subgroup analysis based on disease duration: Significant correlation between time-averaged CRP and change in Larsen score among patients with disease duration ≤2 years and amongst those with disease duration >2 years.
- Mean baseline damaged joint count was greater in the higher CRP groups.
- Medium and high CRP groups had greater new joint involvement rather than damaged joint progression, this was less evident in the normal CRP group.

- Damaged joint progression and new joint involvement was related to the number of damaged joints at baseline and was worse at 5 years in the higher CRP groups.

Authors' conclusions: High CRP levels over time are associated with greater radiologic progression. Although progression still occurred in both previously normal and damaged joints despite the presence of normal CRP levels, this consisted of proportionately less new joint involvement compared with damaged joint progression.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Priolo, L. Bacarini, M. Cammisa, A. Cerase, R. Ferrara, and Alberighi O. la Casa. Radiographic changes in the feet of patients with early rheumatoid arthritis. GRISAR (Gruppo Reumatologi Italiani Studio Artrite Reumatoide)[see comment]. *Journal of Rheumatology* 24 (11):2113-2118, 1997. REF ID: 684	Case series 3 Multicentre: Italy (Patients from an RCT comparing cyclosporin A vs other DMARDs).	N=284 **Drop-outs at follow-up:** Not mentioned	**Inclusion criteria:** RA (ARA criteria); previously untreated or treated with a maximum of 1 DMARD (an anti-malarial or auranofin) whose administration had been discontinued due to AEs or lack of efficacy; duration between 6 months and < years; active disease **Baseline characteristics:** Age mean (not mentioned), female 78%, disease duration mean 1.4 years (early RA).	None	1 year	ARA criteria; Radiographs (hands, wrists and feet – Larsen-Dale method).	Partially funded by Sandoz P.F., Italy

Effect size*

Prediction of disease severity from baseline characteristics:

- More patients with baseline foot involvement showed radiographic progression at 1 year follow-up than those with foot erosions (63% and 42% respectively)

Multiple correspondence analysis

- Patients with a better prognosis (RF-) and outcome (progression in eroded joint count = 0) are closely associated with the no erosion subgroup
- Patients with only hand and wrist erosions had a lower association with better prognosis and outcome
- Patients with a worse prognosis (RF+) and outcome (progression in eroded joint count >0) are closely associated with the subgroups of only foot erosions or with hand, wrist and foot erosions.

Summary:

- Patients with foot erosions tend to be associated with a worse outcome.
- RF+ also correlates well with the presence of foot erosions.

Authors' conclusions: Foot involvement is indicative of more aggressive disease.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
J. Ronnelid, M. C. Wick, J. Lampa, S. Lindblad, B. Nordmark, L. Klareskog, and R. F. van Vollenhoven. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater	Case series 3 1 centre, Sweden	N=279 entered **Drop-outs / lost-to follow-up:** Year 1 = 12% Year 2 = 14% Year 3 = 17% Year 5 = 46%	**Inclusion criteria:** adults with early RA (<12 months duration); ACR criteria. **Baseline characteristics (N=182 completers at 5 years):** Age mean 56 years, female 70%, RF+ 63%, mean disease duration 5 months (early RA), HAQ 0.9	None	5 years (assessments made at 3 months, 1, 2 and 3 years)	Patient's global assessment; Pain (VAS); functional disability (HAQ); DAS28 CRP and ESR; Anti-CP; RF; Radiographs (Larsen score)	Funds from the Swedish Research Council, Swedish Rheumatism Association, King Gustav's 80-year Foundation, and insurance company AFA.

radiological progression. *Annals of the Rheumatic Diseases* 64 (12):1744-1749, 2005. REF ID: 3164							

Effect size*

Prediction of severity of RA from baseline characteristics:

- Anti-CP+ and RF+ at baseline predicted greater radiological progression (greater change in Larsen score at 2 years)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
C. Turesson, W. M. O'Fallon, C. S. Crowson, S. E. Gabriel, and E. L. Matteson. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. *Journal of Rheumatology* 29 (1):62-67, 2002.	Case series 3 Multicentre: RA cases from several hospitals on a register in 1 town in USA.	N=424 **Deaths by 43 year follow-up:** N=90 (13%)	**Inclusion criteria:** RA (ACR criteria); early RA (patients assessed from diagnosis) **Baseline characteristics at diagnosis:** Age mean 60 years, female 74%, disease duration (early RA).	None	43 years (or until death or loss-to follow up if before this time) Mean follow-up 15 years	Development of Extra-articular manifestations of RA (ExRA – including rheumatoid nodules); Mortality; RF.	Grant from The Swedish Association against Rheumatism, NIH (USA) and other non-Pharma sources, Sweden.

REF ID: 487							

Effect size*

Prediction of mortality from baseline characteristics:

Multivariate analysis

- ExRA (Malmo criteria) was the strongest significant predictor of mortality (RR 4.3, CI 2.9 to 6.3)
- Presence of subcutaneous rheumatoid nodules and presence of RF were moderate significant predictors of increased mortality (RR 1.5 and 1.9 respectively)
- Patients who had both ExRA Malmo and RF+ had an even worse prognosis (increased risk of mortality) than those who did not

Authors' conclusions: Virtually all the excess mortality occurred in a subgroup of patients with severe extraarticular disease, suggesting that extraarticular disease is the major predictor of mortality in patients with RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
T. Uhlig, L. M. Smedstad, and P. Vaglum. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. *Rheumatology* 39 (7):732-741, 2000. REF ID: 2996	Case series 3 2 centres, Norway Patients recruited from 2 departments of Rheumatology (this study was part of the EURIDISS project)	N= 238 entered **Drop-outs / lost-to follow-up:** Year 1 = 4% Year 2 = 9% Year 5 = 23%	**Inclusion criteria:** adults aged 20-70; RA (ACR criteria); ≤ 4 years duration. **Exclusion criteria:** other incapacitating diseases; stage IV Steinbroker functional class. **Baseline characteristics (N=182 completers at 5 years):** Age mean 51 years, female 74%, RF+ 69%,	None All patients received routine combined care from a rheumatologist of a GP independently of the scheduled observational visits.	5 years (additional assessments at 1 and 2 years)	Grip strength; Ritchie articular index; HAQ; AIMS (physical disability, psychological status, pain); ESR, CRP; Radiographs (Modified Sharp-van der Heije method of joint damage)	The Research Council, Norway and various other non-pharma organisations.

			mean disease duration 2 years (early RA), HAQ 0.9				

Effect size*

Prediction of severity of RA from baseline characteristics:

- Radiographic progression had differed between patients with and without RF, and between those with and without radiographic abnormalities at baseline (p<0.001)

Bivariate analysis

- Predictors of radiographic damage at 5 years (modified sharp score ≤30 or >30) were: RF+, ESR and radiolographic damage (modified sharp score). Functional disability (HAQ score) and CRP levels were not predictors.
- Predictors of functional disability at 5 years (HAQ ≤2.0 and >1.0) were: HAQ score, ESR and radiolographic damage (modified Shap score). RF+ and CRP were not predictors.

Linear regression

- The best predictor of radiographic damage at 5 years was radiographic damage at baseline, ESR and CRP. Physical function and RF+ were not predictors.
- The best predictor of functional disability (HAQ) at 5 years was functional disability (HAQ) at baseline and age. Radiographic damage was not a predictor.

*for bivariate analysis, p<0.15 set as level of significance. All other analyses used p<0.05

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. Wallberg-Jonsson, H. Johansson, M. L. Ohman, and S. Rantapaa-Dahlqvist. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset.	Case series 3 Single centre: Sweden. Patients presenting to a Rheumatology clinic.	N=211 **Drop-outs at follow-up:** Not mentioned	**Inclusion criteria:** patients RF+; disease duration <1 year. **Baseline characteristics:** Age mean 52 years, female 60%, mean disease duration (early RA <1 year inclusion).	None	Mean duration od disease at follow-up: 17-21 years	CV events; ESR,; rheumatoid nodules; erosions (duration)	Grant from University of Umea, Sweden; Swedish Rheumatism Foundation and other non-pharma sources.

Journal of Rheumatology 26 (12):2562-2571, 1999. REF ID: 1881							

Effect size*

Prediction of mortality and CV events from baseline characteristics:

Univariate analysis

- The risk of CV event and mortality was significantly increased by baseline: male gender, higher age at disease onset, earlier progression of erosions, higher ESR, CS treatment given early in disease
- Prolonged / extensive CS treatment had NS effect on CV or mortality outcomes
- DMARD treatment (>2 drugs) was associated with decreased risk of CVD and mortality.

Multivariate analysis

- The risk of mortality was increased by male gender, higher age at disease onset and last value ESR.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Wolfe and J. T. Sharp. Radiographic outcome of recent-onset rheumatoid arthritis. A 19-year study of radiographic progression. *Arthritis and Rheumatism* 41 (9):1571-1582, 1998. REF ID: 1918	Case series 3 1 centre, USA	N=256 **Drop-outs:** Not mentioned	**Inclusion criteria:** adults with RA (ACR criteria); duration <2 years at first clinic visit ;seen at a single Arthritis centre. **Baseline characteristics:** Age mean 52 years, female 73%, RF+ 74%, mean disease duration 0.77 years (early RA), HAQ score 0.9.	None	19 years (assessments made at 2 year intervals)	Ritchie score; grip strength; HSAQ; AIMS; Pain (VAS); Global severity (VAS); tender joints; RF and ESR.	Not mentioned

Effect size*

Prediction of mortality from baseline characteristics:

- ESR, joint count and grip strength were predictors of radiographic progression (Sharp scores)
- Age and gender were not associated with rate of radiographic progression
- Right hands were significantly more abnormal than left hands

Multivariate regression analysis

- ESR, RF+, joint count, disease duration and grip strength were all associated with the rate of radiographic progression (Sharp score or Sharp count)
- Prednisone use was also significant

Univariate analysis

- Use of MTX, penicilamine and prednisone were associated with more rapid rates of progression in Sharp scores
- There was no assocoiation between use of IM gold or HCQ with rate of progression in Sharp scores

Authors' conclusions: Acute phase reactants are by far the strongest determinants of radiographic progression.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Wolfe, K. Michaud, O. Gefeller, and H. K. Choi. Predicting mortality in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 48 (6):1530-1542, 2003. REF ID: 3173	Case series 3 1 centre, USA	N=1,387 entered **Drop-outs:** N=212 deaths	**Inclusion criteria:** adults with arthritis seen at a single Arthritis centre. **Baseline characteristics:** Age mean 55 years, female 73%, RF+ 85%, mean disease duration 7 years (established RA), HAQ score 1.2.	None	20 years (assessments made at 2 year intervals)	Morning stiffness; Tender joint count; HAQ score; PAIn (VAS); AIMS score; CRP and ESR; RF; Radiographs (Larsen score); Mortality (all causes).	Not mentioned

Effect size*

Prediction of mortality from baseline characteristics:

Univariate analysis (adjusted for age and gender)

- HAQ disability was the most important predictor of mortality (OR 2.93, 95% CI 2.43 to 3.54, p<0.001) followed by Global disease severity, pain, depression, anxiety and grip strength. Lab variables were less important.
- RF+ and nodules were weak predictors of mortality
- Radiographic progression rates were weak predictors of mortality.
- Age was the strongest predictor of mortality

Recent onset RA (<1 year duration) vs established RA (>1 year duration)

- There was NS difference between recent onset RA and established RA for predictors of mortality.
- In women, the OR for HAQ as a predictor of mortality was higher than that of men (3.4 and 2.5 respectively)

Multivariate analysis

- Of all the Univariate factors, only radiographic progression was a significant predictor of mortality
- HAQ score over the first 2 years had a greater predictive ability for mortality than the baseline HAQ score

Authors' conclusions: HAQ score was the most powerful predictor of mortality followed by other patient self-report variables. Lab, radiographic and physical examination data were substantially weaker in predicting mortality.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Wolfe, K. Ross, D. J. Hawley, F. K. Roberts, and M. A. Cathey. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol* 20 (12):2005-2009, 1993. REF ID: 3181	Case series 3 Single centre: RA cases from an arthritis centre in USA	N=1141; N=503 with RA **Drop-outs at follow-up:** None for RA patients	**Inclusion criteria:** RA (ACR criteria) or undifferentiated polyarthritis; early disease (< 2 years) **Baseline characteristics:** Age mean 51 years, female 62%, disease duration < 1 year inclusion criteria (early RA).	None	Mean follow-up 6.9 years. All RA patients had ≥13 months follow-up	Functional disability (HAQ); ADL; joint count; ESR; RF. Remission	Dutch League against Rheumatism, Netherlands Foundation for Research and The Netherlands Technology Foundation.

Effect size*

Prediction of remission from baseline characteristics:

- 7.6% of RA patients had remission at follow-up
- Positive latex test (RF) was a good predictor of RA remission
- Logistic regression analysis showed that ACR criteria, latex test RF-) and lower duration of disease at baseline were significant predictors of RA remission.

Authors' conclusions: resolution of RA criteria occurs predominantly in those who are seronegative.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
A. Young, C. Bielawska, M. Corbett, and I. Roitt. A prospective study of early onset rheumatoid arthritis over fifteen years: prognostic features and outcome. *Clinical Rheumatology* 6 Suppl 2:12-9, 1987 Sep.:12-19, 1987. REF ID: 864.	Case series 3 Single centre, UK Patients recruited from outpatient clinic (a referral centre for GPs)	N= 218 entered (N=210 analysed) **Drop-outs / lost-to follow-up:** At year 3 31%	**Inclusion criteria:** adult RA (ARA criteria); < 1 year duration; prior to initiation of DMARD therapy. **Baseline characteristics:** Age mean 51 years, female 61%, RF+ 74%, erosions of hands and feet 71%, nodules 28%.	None	Up to 15 years Mean follow-up was 5.8 years	Grip strength, morning stiffness, functional grade, pattern of joint involvement, joint score, weight, measured walk and climb, ESR, RF and anti-nuclear antibody titre. Radiographs (Lawrence score: non-erosive, mild, moderate or sever erosion)	Not mentioned

Effect size

Prediction of severity of RA from baseline characteristics:

- Discriminant analysis showed that a combination of RF, haemoglobin (Hb) and platelet level as the most powerful combination for predicting the severity of RA according to 4 different methods of assessment.
- RF was of no value on its own in predicting functional status but in combination with Hb and platelet count achieved success in 62% of patients.
- The most powerful single prognostic indicator for the severity of RA using the other assessment methods was RF titre at onset, but greater accuracy was achieved in combination with other variables.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
L. Innala, H. Kokkonen, C. Eriksson, E. Jidell, E. Berglin, and S. R. Dahlqvst. Antibodies against mutated citrullinated vimentin are a better predictor of disease activity at 24 months in early rheumatoid arthritis than antibodies against cyclic citrullinated peptides. *Journal of Rheumatology* 35 (6):1002-1008, 2008. REF ID: 3551	Prospective case series 3 Patients recruited from 1 hospital in Sweden	N=210 RA patients **Drop-outs:** None mentioned	**Inclusion criteria:** RA (ACR criteria); early RA. **Exclusion criteria:** None given. **Baseline characteristics** Age at disease onset mean 56 years, female 69%, mean disease duration 6 months (Early RA)	None	2 years (assessments at 6, 12 and 18 months)	Anti-CCP and anti MCV (modified citrullinated Vimentin); Radiographic changes (Larsen score); DAS28; EULAR 28 response and DAS28 response	Grant from the Swedish Research Council; King Gustav V's fund and the Swedish Rheumatism Association

Effect size*

Baseline predictors of radiographic progression at follow-up (2 years):

- Baseline anti-CCP+, anti-MCV+, RF+ and ESR were significant predictors of radiological progression at 2 years

- Therapeutic response at 6, 12 or 24 months significantly predicted less radiological progression
- Anti-CCP, anti-MCV and RF remained significant predictors for radiological progression calculated with therapeutic response at 6 months and at 12 and 24 months

Authors' conclusions: Anti-MCV antibodies are associated with more severe RA disease as measured by DAS28, ESR and swollen joint count over time compared with anti-CCP2, 3 and 3.1 antibodies. Radiological progression was predicated equally by all antibodies.

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CCP2, 3 and 3.1 antibodies. Radiological progression was predicated equally by all antibodies.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. W. Syversen, P. I. Gaarder, G. L. Goll, S. Odegard, E. A. Haavardsholm, P. Mowinckel, derHeijdeD van, R. Landewe, and T. K. Kvien. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: Results from a 10-year longitudinal study. *Annals of the Rheumatic Diseases* 67 (2):212-217, 2008. REF ID: 3518	Case series 3 Multicentre: Norway (Patients from EURODISS project).	N=238 **Drop-outs at follow-up 10 years:** N=113 (47%)	**Inclusion criteria:** RA; duration maximum 4 years **Baseline characteristics:** Age mean 52 years, female 74%, disease duration mean 2 years (early RA).	None	10 years	anti-CCP; ESR; Radiographica progression (Sharp Van der Heijde score – SHS).	Grant from Eastern Norway Regional Health Authority and several Foundations

Effect size*

Prediction of disease severity from baseline characteristics:

- Univariate analysis found that significant baseline predictors of radiographic progression (SHS) after 10 years were:
  - Anti-CCP level ($p<0.01$)
  - IgA and IgM RF ($p<0.01$)
  - ESR ($p<0.01$)

- High CRP (p<0.01)
- Female gender
- Radiographic progression rate at baseline

- Age and baseline HAQ were not predictors of radiographic progression (SHS) after 10 years in univariate analysis

- Multivariate analysis found that significant baseline predictors of radiographic progression (SHS) after 10 years were:
  - Anti-CCP+ (strongest predictor)
  - Female gender
  - High ESR (p<0.01)
  - IgM RF+
- IgA RF and high CRP wre not maintained as predictors of radiographic progression (SHS) after 10 years in the multivariate analysis
- The probability of radiographic progression in women who are anti-CCP+, IgM RF+ and have a high ESR was 92% compared with 9.3% in men who were anti-CCP-, IgM RF- and had low ESR.
- The logistic regression model showed that an increase of 1 U/ml anti-CCP will increase the odds of radiographic progression by 0.8% and an increase of 50 U/ml gives a 49% increase.
- Mean progression differed significantly (p<0.05) between the anti-CCP- group (<25 U/ml), the low to moderate group (25 to 200 U/ml) and the high level group (>200 U/ml). Compared with anti-CCP- patients those with low to moderate levels (OR 3.5; 95% CI 1.5 to 8.4) and high levels (OR 13.3, 95% CI 4.0 to 43.8) were more likely to develop radiographic progression (even after adjusting for other baseline predictors).
- Patients with high levels of anti-CCp were also more likely to progress compared to those with low to moderate levels (OR 4.8, 95% CI 1.2 to 19.2).

Authors' conclusions: Anti-CCP, RF, ESR and female gender were independent predictors of radiographic progression and could be combined into an algorithm for better prediction. Patients with high levels of anti-CCP were especially prone to radiographic progression, indicating that the anti-CCP level may add prognostic information.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Bouwstra JK de Vries, Ruiterman YP Goekoop, K. N. Verpoort, G. M. Schreuder, J. A. Ewals, et al. Progression of joint damage in early rheumatoid arthritis: association with	Prospective case series 3 Patients recruited from 1 hospital in Sweden	N=508 **Drop-outs:** Not mentioned	**Inclusion criteria:** As for BEST study (ID3494 and 2186). **Exclusion criteria:** As for BEST study (ID3494 and 2186). **Baseline characteristics** Age mean 57 years,	Group 1: sequential monotherapy Group 2: step-up combination therapy Group 3: initial combination therapy with CS Group 4: initial combination therapy with infliximab	2 years	HAQ; RF; ACPA; Radiographic progression; morning stiffness; CRP; DAS	Dutch College for Health Insurance; Centocor and Schering-Plough

HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. *Arthritis & Rheumatism* 58 (5):1293-1298, 2008. REF ID: 3553			female 71%, mean disease duration 5 months (Early RA); HAQ mean 0.9; Pain (VAS) mean 45..				

Effect size

Group 1: sequential monotherapy
Group 2: step-up combination therapy
Group 3: initial combination therapy with CS
Group 4: initial combination therapy with infliximab

Baseline predictors of radiographic progression at follow-up:

- Among patients with sequential monotherapy, step-up combination therapy and initial combination therapy including infliximab (Groups 1,2 and 4), radiographic progression scores were significantly higher in RF+ patients compared with RF- patients and in ACPA+ patients compared with ACPA- patients (P<0.05 for all comparisons).
- Among patients treated with initial combination theapy (Inclusing prednisone (Group 3), radiographic progression scores were comparable (there was NS difference) between RF- and RF+ patients, between ACPA- and ACPA+ patients, RF- and RF+ patients an ACPA- and ACPA+ patients (p>0.05)

LOGISTIC REGRESSION ANALYSES

- RF and ACPA were predictive of progressive disease in patients treated with sequential monotherapy, but not in the other treatment groups

Authors' conclusions: In patients with early RA treated with the goal of tight control of DAS RF and ACPA were predictive of progressive disease only in patients treated with sequential monotherapy. This suggests that effective treatment can prevent radiographic progression, even patients with risk factors for severe damage.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. Bas, T. V. Perneger, E. Mikhnevitch, M. Seitz, J. M. Tiercy, Lombard P. Roux, and P. A. Guerne. Association of rheumatoid factors and anti-filaggrin antibodies with severity of erosions in	Case-series 3 Multicentre, Switzerland	N=264 **Drop-outs / lost-to follow-up:** Year 1 = 12% Year 2 = 14% Year 3 = 17% Year 5 = 46%	**Inclusion criteria:** adults with RA according to ACR criteria RF+, AFA+ (N=84): mean disease duration 13 yrs, mean age 63 yrs, 67% female RF+, AFA- (N=61): mean disease duration 15 yrs, mean age 60 yrs, 80% female RF-, AFA+ (N=9); mean disease	Patients with RA (N=199) Unselected non-RA patients (N=65) AFA and RF status	Disease duration up to 50 yrs (approximated)	Patient's global assessment; Pain (VAS); functional disability (HAQ); DAS28 CRP and ESR; Anti-CP; RF; Radiographs (Larsen score)	Subvention federale pour la lutte contre le rhumatisme de l'office Federal de la Sante Publique and Novartis

rheumatoid arthritis. *Rheumatology* 39 (10):1082-1088, 2000. REF ID: 418			duration 18 yrs, mean age 56 yrs, 89% female RF-, AFA-: (N=45): mean disease duration 13 yrs, mean age 60 yrs, 80% female **Baseline characteristics (N=182 completers at 5 years):** Age mean 56 years, female 70%, RF+ 63%, mean disease duration 5 months (early RA), HAQ 0.9				
Effect size* **Association between RF and AFA status by regression of Larsen score as a function of disease duration:** • A regression model showed that AFA status at baseline was not a statistically significant predictor of radiological progression (greater change in Larsen score) (NS) • A regression model showed that RF status at baseline was a statistically significant predictor of radiological progression (greater change in Larsen score), but for patients with a disease duration greater than 12 years only (p=0.001)							
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. P. Leigh and J. F. Fries. Mortality predictors among 263 patients with rheumatoid arthritis. *Journal of Rheumatology* 18 (9):1307-1312, 1991. REF ID: 3121	Case series 3 USA	N=263 **Drop-outs:** N=54 died (21%)	**Inclusion criteria:** patients taken from the community; definite or classic RA (ARA criteria). **Baseline characteristics of RA patients:** Age mean 52 years, female 86%, HAQ score 1.1; mean disease duration 12 years (established RA).	None	8 years	HAQ disability score; baseline characteristics; Mortality (days survived over the 8 year follow-up)	Grant from NIH, USA.
Effect size* **Prediction of mortality from baseline characteristics:**							

8 year results: Univariate analysis

- Age, followed by prednisone use and HAQ score were the best predictors of mortality at 8 year follow-up
- Global ill health status, no occupation and work hours were the other vearibles with the highest predictive value.

8 year results: Multivariate analysis

- The 8 most important predictors were: age, prednisone use, HAQ disbility score, male gender, never married, penicillamine use, divorced and no occupation.

8 Year results: Survival model

- Male gender, never married, years of schooling and age were the only factors predictive of mortality.

Authors' conclusions: Results confirm studies suggesting that HAQ disability index is a useful prognosticator of length of survival.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
J. P. Leigh and J. F. Fries. Predictors of disability in a longitudinal sample of patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 51 (5):581-587, 1992. REF ID: 807	Prospective case series 3 1 county, USA	N=330 Completed/included sample N=209 Drop-outs: 9% died 9% lost to follow-up	**Inclusion criteria:** adults with definite or classical RA with five or more criteria (classification not specified) **Baseline characteristics** Age mean 52 years, female 86%, mean disease duration 12 yrs (at baseline 1981) and 19 yrs (1989) ESTABLISHED RA	None	1981 to 1989	Health Assessment Questionnaire (HAQ) score)	National Institute of Health and Stanford Arthritis Center

Effect size*

Regression analysis of HAQ at follow-up:

- A regression model showed that the most powerful predictor of HAQ score in 1989 was HAQ score in 1981, followed by the number of work hours in 1981, employment as a farmer, and 1981 global health status (deceased subjects included)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding

M. J. Plant, M. M. O'Sullivan, P. A. Lewis, J. P. Camilleri, E. C. Coles, and J. D. Jessop. What factors influence functional ability in patients with rheumatoid arthritis. Do they alter over time? *Rheumatology* 44 (9):1181-1185, 2005. REF ID: 1606	Case series 3 1 centre, UK	N=541 (from secondary analysis of 5-yr RCT of DMARD therapy) N=421 patients with HAQ scores at baseline and after 5 yrs	**Inclusion criteria:** adults with active RA defined by the presence of at least three of the following criteria: six painful joints, three swollen joints, ESR > 28 mm/h, morning stiffness > 45 min, radiological progression. All of the patients were in an RCT trial of DMARD therapy **Baseline characteristics** Age mean 51 years, female 72%, RF+ 80%, mean disease duration 4 yrs, ESTABLISHED RA, HAQ 1.64	None	5 years	Health Assessment Questionnaire (HAQ) score)	None reported

Effect size*

Regression analysis of HAQ (adjusted) (N=366):

- A multiple regression model showed that at baseline, the Ritchie Articular Index (RAI) and CRP levels were significant predictors of HAQ scores ($p<0.001$ for both)
- A multiple regression model showed that at 5 years, the RAI, VAS pain score, early morning stiffness and radiographic progression (modified Larsen score) were significant predictors of HAQ score ($p<0.001$ for all)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Y. S. Sherrer, D. A. Bloch, D. M. Mitchell, S. H. Roth, F. Wolfe, and J. F. Fries. Disability in rheumatoid arthritis: comparison of prognostic factors across three	Case series 3 Multicentre: 3 centres (ARAMIS) in USA.	N=2,448 **Drop-outs at follow-up:** Not mentioned	**Inclusion criteria:** consecutive patients with diagnosis of RA. **Baseline characteristics of 3 study centres:** Age range 48 to 54 years, female range 64 to 72%, mean disease duration range 7 to 12 years (established RA).	None	Mean follow-up mean range at each of the 3 centres: 1.7 years to 12 years	HAQ disability score; demograhic factors; historical factors (pain, morning stiffness, fatigue); grip strength; walking time; number of joints involved; weighted joint count; symmetry; nodules; ESR; RF; radiographs (erosions and radiologic grade).	Grant from the NIH, USA.

populations. *Journal of Rheumatology* 14 (4):705-709, 1987. REF ID: 3165							

Effect size*

Prediction of disease severity from baseline characteristics:

- Women had significantly greater disability scores than men at end of follow-up ($p<0.05$)
- The probability of developing significant disability was higher with older age at onset.
- Patients with higher initial ESR and latex titre had greater disability at follow-up than those with normal ESR.
- Overall in the 3 populations of RA patients the top baseline predictors of worse disability were: Age, female gender, duration of illness, radiologic variable, initial disability, elevated ESR and latex titres.

Authors' conclusions: Future functional disability was predicted by initial level of disability, radiographic variables, elevated ESR and latex titres.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
S. Sihvonen, M. Korpela, A. Mustila, and J. Mustonen. The predictive value of rheumatoid factor isotypes, anti-cyclic citrullinated peptide antibodies, and antineutrophil cytoplasmic antibodies for mortality in patients with rheumatoid arthritis. *Journal of Rheumatology* 32 (11):2089-2094,	Case series 3 Single centre: Finland; Patients from an RCT.	N=604 **Deaths at follow-up:** N=160 (26%)	**Inclusion criteria:** definite or classic RA (ARA criteria). **Baseline characteristics:** Age mean 59 years, female 78%, mean disease duration range 15 years (established RA).	None	12 years	HAQ; ESR; a-CCP; pANCA and ANCA (anti-neutrophil cytoplasmic Abs); Mortality.	Grant from the Medical Research Fund of Tampere University Hospital and the Finnish Cultural Foundation, Finland.

2005. REF ID: 157							

Effect size*

Prediction of mortality from baseline characteristics:

Univariate analysis

- Increased mortality at 2 years was predicted by the following baseline characteristics: RF+, High levels of a-CCP (but not a-CCP+ >25U). Positivity for RF and/or a-CCP did not predict mortality. Positivity for pANCA and high ANCA titres did not predict mortality.

Multivariate analysis

- Increased mortality at 2 years was predicted by the following baseline characteristics: age, gender, disease duration, RF+. However, If HAQ or subcutaneous nodules were added to the model, RF+ did not predict increased mortality, nor did RF+ predict mortality if the model included only patients with a-CCP Ab determination.
- High IgA and IgM RF levels predicted increased mortality in the model including age, disease duration and RF+. High level of IgG RF was not a predictor. If HQ or subcutaneous nodules wee added to the model, the IgA RF level still predicted increased mortality.
- High levels of a-CCP predicted increased mortality in the age, gender, disease duration adjusted multivariate model. If HAQ or subcutaneous nodules were added into the model, high a-CCP level did not predict mortality. Positivity for RF and/or a-CCP did not predict mortality.
- Positivity for pANCA and high ANCA titres did not predict mortality.

Authors' conclusions: Patients with RA with RF+ (especially IgA and IG=gM isotypes), carry a risk of dying earlier than patients without these serological findings.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
M. M. Strating, W. H. Van Schuur, and T. P. Suurmeijer. Predictors of functional disability in rheumatoid arthritis: results from a 13-year prospective study. *Disability & Rehabilitation* 29	Case series 3 Multicentre: RA cases from 5 hospitals in The Netherlands. EURODISS	N=292 **Drop-outs at follow-up (21 years):** 36%	**Inclusion criteria:** RA (ACR criteria); **Baseline characteristics:** Age mean 63 years, female 71%, disease duration 14 years (established RA).	None	13 years (last wave of data collection – T4) and 8 years after this (21 years) patients given a final questionnaire – T5	Disability (Groningen Activity Restriction Scale, GARS); Joint tenderness (Ritchie Articular Index – RAI); Pain (NHP); distress (GHQ-28); ESR.	Dutch Arthritis Association and Ministry of Public Health, Welfare and Sports, The Netherlands.

(10):805-815, 2007. REF ID: 3166							

Effect size*

Prediction of functional disability from baseline characteristics:

Univariate analysis

- At 13 years follow-up, more functional disability was significantly correlated with: higher age, longer disease duration, higher ESR scores over time, higher RAI scores over preceding years, more pain and distress over preceding years and more disability over the preceding years
- At 21 years follow-up, more functional disability was significantly correlated with: female gender, longer disease duration, higher RAI scores over preceding years, more pain and distress over preceding years, less social companionship over the preceding years, and more disability over the preceding years

Multivariate analysis

- At 13 years follow-up, more functional disability was significantly predicted by: disease duration, disability over the preceding years, ESR over the preceding years, pain and distress over the preceding years. However, RAI over the preceding years was not a significant predictor
- At 21 years follow-up, more functional disability was significantly predicted by: gender, disease duration, RAI and disability over the preceding years, pain over the preceding years. However, social companionship, distress and ESR over the preceding years were not significant predictors

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
C. Turesson, R. L. McClelland, T. J. H. Christianson, and E. L. Matteson. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. *Annals of*	Case series 3 1 centre, USA	N=265 **Drop-outs / lost-to follow-up:** Year 1 = 12% Year 2 = 14% Year 3 = 17% Year 5 = 46%	**Inclusion criteria:** adults with severe extra-articular RA (ExRA) (N=81) **Baseline characteristics** **ExRA:** Mean disease duration 9.5 yrs, mean age 51 yrs, 56% male, RF positive at any time 93%, Erosive disease 72% **Baseline characteristics** **Controls:** Mean age 51 yrs, 49% male, RF positive at any time 59%*, Erosive disease 48%*	Controls (N=184) with no evidence of ExRA (including rheumatoid nodules)	ExRA mean 15.6 yrs Controls 7.8 yrs significant difference ($p<0.001$)	Cardiovascular disease, new onset coronary artery disease	Funds from the Swedish Research Council, Swedish Rheumatism Association, the Swedish Association for Medicine, Lund University, Mayo Clinic

the Rheumatic Diseases 66 (1):70-75, 2007. REF ID: 1798			* significant differences at baseline				

Effect size*

Incidence of cardiovascular disease ExRA vs controls:

- First ever CVD events occurred after diagnosis of RA in N=34 patients with ExRA and N=15 controls
- New onset coronary artery disease was identified after onset of RA in N=28 patients with ExRA and N=22 controls
- The presence of ExRA was a significant predictor (adjusted for age, sex and smoking) of first ever CVD and of new onset coronary artery disease

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Wolfe and S. H. Zwillich. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis & Rheumatism* 41 (6):1072-1082, 1998. REF ID: 667	Case series 3 1 centre, USA AIM: Predictors of TJA	N=1810 N=1600 (patients with at least one year clinic follow-up) N=34 040 clinic visit N=1430 (patients seen prior to their first TJA)	**Inclusion criteria:** adults with RA diagnosed according to ARA criteria at some point during their disease course **Baseline characteristics** Total sample N=657 seen within two years of disease onset N=943 after two years disease duration Mean age 54 yrs, 28% male, mean disease duration 6 yrs	None	Up to 23 yrs	Total Joint Arthroscopy (TJA)	National Institute of Health

Effect size*

Predictors of total joint arthroscopy (N=1430):

- Multivariate analysis (adjusted for age and disease duration using time-varying covariates) showed that ESR, WBC count, haemoglobin level, HAQ Disability score,

global severity score, erosions and smoking (past or current) were significant predictors of TJA (no values reported)

- Multivariate analysis (adjusted for age and disease duration using first-visit values) showed that ESR, WBC count, haemoglobin level, HAQ Disability score, global severity score, BMI, disease duration and smoking (past or current) were significant predictors of TJA (no values reported)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
L. Mathsson, M. Mullazehi, M. C. Wick, O. Sjoberg, VollenhovenR Van, L. Klareskog, and J. Ronnelid. Antibodies against citrullinated vimentin in rheumatoid arthritis: Higher sensitivity and extended prognostic value concerning future radiographic progression as compared with antibodies against cyclic citrullinated peptides. *Arthritis and Rheumatism* 58 (1):36-45, 2008. REF ID: 3517	Prospective case series 3 Patients recruited from 1 hospital in Sweden	N=273 **Drop-outs:** 12.8% at 1 year, 13.9% at 2 years, 17.6% at 3 years and 46.9% at 5 years	**Inclusion criteria:** with RA (ACR criteria); early RA (< 12 months disease duration). **Exclusion criteria:** None given. **Baseline characteristics** Age mean 57 years, female 71%, mean disease duration 5 months (Early RA); HAQ mean 0.9; Pain (VAS) mean 45..	None	5 years (assessments at 1, 2 and 3 years)	Anti-CCP and anti MCV (modified citrullinated Vimentin);RF; Radiographic changes; CRP, ESR, Physicans' assessment of disease activity, Number of tender and swollen joints, DAS28 score, Global VAS score, Pain (VAS) score	Swedish Fund for Research without Animal Experiments; Swedish Rheumatism Association and several other Foundations.

Effect size*

Baseline predictors of radiographic progression at follow-up:

- Anti-MCV+ was strongly associated with boith anti-CCP+ and RF+ at baseline. Patients with anti-MCV+at baseline were significantly younger than anti-MCV- patients (median age 55 years and 61 years respectively, p=0.012)
- The only clinical difference between anti-MCV+ patients and anti-MCV- patients were significantly higher ESR (P=0.016)
- During follow-up, anti-MCV+ patients showed higher disease activity (Physican's assessment and DAS28 score) and had more swollen and tender joints than anti-

MCV- patients

- Anti-MCV+/anti-CCP- had slightly better prognosis (Physicians' assessment of disease activity) than anti-CCP+ patients. Both these groups showed the same general treatment at baseline, and there were NS differences.
- Anti-MCV+/anti-CCP- never differed from anti-MCV-/anti-CCP- patients for any measure (CRP, ESR, Physicans' assessment of disease activity, Number of tender and swollen joints, DAS28 score, Global VAS score, Pain (VAS) score) except Anti-MCV+/anti-CCP- had significantly more functional disability (HAQ) at 3 years than Anti-MCV-/anti-CCP- patients.

Authors' conclusions: The presence of anti-MCV was predictive of subsequent high disease activity and continued radiographic progression. Changes in anti-MCV level showed strongest correlation with changes in clinical parameters than did changes in anti-CCP level. Patients subgroup who were anti-MCV+/anti-CCP- showed a higher rate of radiographic destruction than anti-MCV-/anti-CCP- patients.

5.1 Patient perceptions and beliefs (PATIENT)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. Wong, D. Mulherin, and K. H. Sousa. The influence of medication beliefs and other psychosocial factors on early discontinuation of disease-modifying anti-rheumatic drugs. *Musculoskeletal Care* 5 (3):148-159, 2007. ID 34	Observational-correlation study: 3 UK: from a Rheumatology department	Total N=68 patients	**Inclusion criteria:** Adults with RA who had been prescribed their first DMARD. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 56 years; female 60%; Disease duration mean 2 months (early RA). There were NS differences between patients who continued to take their DMARDs at 1 year and those who did not, for any of the baseline characteristics.	Semi-structured interview	1 year	Sociaodemographic and health data; reasons for discontinuation of DMARDs; questionnaires: HAQ, RHD (relationship with hospital doctors, BMQ (Beliefs about medication questionnaire), SOS (Significant others scale), STAI-SF (Spielberger State-Trait Anxiety Inventory – Short Form).	South Staffordshire Healthcare Trust

Effect size

- Older, less anxious patients (STAI-SF) were significantly more likely to discontinue to take their initial DMARDs within the first year
- None of the other variables were significantly associated with continuing to take DMARDs

Author's conclusions:
Contrary to expectation, older and less anxious patients were more likely to discontinue to take their initial DMARDs within the first year. The study may have implications for counselling older and less anxious patients prior to DMARD therapy. However, there are limitations in generalising the results because of the small population sample. It also did not take into account drug intolerance as a pertinent factor for early discontinuation.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Goekoop-Ruiterman YP, de Vries-Bouwstra JK Allaart CF Kerstens PJ Grillet BA de Jager MH Han KH Speyer. Patient preferences for treatment: report from a randomised comparison of treatment strategies	Observational study (retrospective): 3 Multicentre trial 20 centres in The Netherlands (BEST study).	Total N=508 asked; N=440 responded. **Drop-outs at 2 years:** N=440 (87% completed the questionnaire)	**Inclusion criteria:** Adults ≥ 18 years with early RA (ACR criteria); disease duration ≤2 years; active disease. **Exclusion criteria:** Previous treatment with DMARDs other than anti-malarials; concomitant treatment with an experimental drug; malignancy within the last 5 years; serious disease; serious or opportunistic infections within last 3 and 6 months; known allergy to murine proteins.. **Baseline characteristics:** Group 1: mean age 54 years; Female 68%;	Group 1: sequential monotherapy Group 2: step-up combination therapy Group 3: initial combination therapy with CS Group 4: initial combination therapy with infliximab For all groups the protocol described a number of subsequent treatment steps for patients whose medication failed. The decision whether to adjust medication was made every 3 months based on the DAS44 score. Gp1: started 15 mg/week MTX, increased to 25-30 mg/week if DAS44 >2.4. Subsequent steps for insufficient response: SSZ monotherapy, leflunomide monotherapy, MTX + infliximab, gold + methylprednisolone and finally MTX + CyA and prednisone. Gp2: started 15 mg/week MTX, increased to 25-30 mg/week if DAS44 >2.4. Subsequent steps for insufficient response: add SSZ, followed by	Patients had been in trial for mean 2.2 years at the time of the questionnaire	Questionnaire: patients' preference for a specific treatment	Dutch college of Health Insurances; Schering-Plough abd Centocor Inc.

in early rheumatoid arthritis (BeSt trial). *Annals of the Rheumatic Diseases* 66 (9):1227-1232, 2007. REF ID: 3494			Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. Group 2: mean age 54 years; Female 71%; Duration of RA = Early RA (mean 26 weeks); D-HAQ score mean 1.4. Group 3: mean age 55 years; Female 65%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. Group 4: mean age 54 years; Female 66%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. There was NS difference between the groups for any of the baseline characteristics. Concomitant treatment with NSAIDs and IA corticosteroid injections were allowed.	add HCQ then prednisone. If failed to respond to combination of these 4 they were switched to MTX + infliximab, MTX + CyA + prednisone and finally to leflunomide. Gp3: started 7.5 mg/week MTX + 2000 mg/day SSZ and 60 mg/day prednisone (pred was tapered in 7 weeks to 7.5 mg/day). If DAS44 >2.4 MTX was augmented to 25-30 mg/week .Subsequent steps for insufficient response: combination was replaced by combination of MTX + CyA + prednisone, followed by MTX + infliximab, leflunomide monotherapy, gold + methylprednisolone and finally by AZA + prednisone. If persistent good response (DAS44 ≤2.4), first prednisone was tapered to 0 after 38 weeks, then mTX tapered to after 40 weeks. Gp4: started 25-30 mg/week MTX + infliximab 3mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter. If DAS44 >2.4, dose of infliximab increased after 3 months to 6 mg/kg/every 8 weeks. Every 8 weeks dose was reassessed and adjusted if DAS44 >2.4, to 7.5 mg/kg/every 8 weeks and finally every 10 mg/kg/every 8 weeks. If still had DAS44 >2.4 while on MTX + 10 mg/kg infliximab, medication was switched to SSZ, then to leflunomide, then to combination of MTX, CyA and prednisone then to gold + prednisone and finally to AZA + prednisone. If persistent good response (DAS44 ≤2.4 for at least 6 months), infliximab dose was reduced (from 10 to 7.5, 6 then 3 mg/kg) every next infusion until stopped.			

Effect size

Group 1: sequential monotherapy GI: 12%, CV: 4%
Group 2: step-up combination therapy GI: 9%, CV: 4%
Group 3: initial combination therapy with CS GI: 9%, CV: 7%
Group 4: initial combination therapy with infliximab GI: 12%, CV: 6%

- **There were no differences in adherence to the treatment protocol between patients who expressed their dislike for their allocated treatment group and patients who did not.**
- **Outcomes were comparable between patients with or without strong dislikes for a certain group.**

1. **Improvement of general health since start of treatment:** Much to very much: 50%, 56%, 47%, 74% (Gp 1 – 4; all groups significantly less than group 4 but NS difference from each other)
2. **Rapid relief of symptoms:** 52%, 54%, 78%, 85% (Gp 1 – 4; groups 1 and 2 significantly less than groups 3 and 4 but NS difference from each other).
3. **Current state of health with medication they had to take was acceptable for the next year:** 85%, 88%, 72%, 85% Patients in group 3 were less satisfied but all comparisons NS different from each other. *These responses correspond with disease activity (DAS) – patients in Group 3 more often had low DAS while reporting not to be satisfied with their state of health*
4. **Before start of study, was there patients prefernce for a particular group?:** 44% did not have a preference. An effect of group allocation was only clear in group 3 – 22% of patients who actually received this treatment had hoped not to be assigned to group 3, whereas this percentage was much higher (>40%) in the other groups.
5. **Treatment patients would prefer if diagnosed with RA today:** 21% would choose treatment with 1 well-known anti-rheumatic drug; 19% would choose combination without prednisone; 12% would choose combination with prednisone; 44% would choose combination with the newest IV drug (Infliximab at the time)
6. **Patients feelings about taking prednisone:** 50% of patients assigned to combination therapy with prednisone (Group 3) disliked taking prednisone. In groups 1, 2 and 4, thes numbers were 15%, 20% and 9% respectively.
7. **Patients feelings about going to hospital for IV treatment:** 8% of patients treated with initial combination therapy with IFX (Group 4) disliked having to go to hospital for IV treatment. In groups 1, 2 and 3, these numbers were 2%, 3% and 2% respectively.

Authors' conclusions:
Within the limits of this retrospective study, patients clearly preferred initial combination therapy with IFX and disliked taking prednisone. After actual exposure, this preference remained, but the perception of prednisone improved. Patient perceptions need to be addressed when administering treatment.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blalock SJ, Orlando M, Mutran EJ, DeVellis RF,	Observational longitudinal study 3	N= 227 **Drop-**	**Inclusion criteria:** adults with recently diagnosed RA	45 minute telephone interview and	Nil	2 years	Psychologic wellbeing. Assessed with Positive and	NIH multipurpose Arthritis

and DeVellis BM. Effect of satisfaction with one's abilities on positive and negative affect among individuals with recently diagnosed rheumatoid arthritis. Arthritis Care & Research: 11: 158 – 165, 1998 REF ID: 379.		**outs:** 40/227 (17.6%)	**Exclusion criteria:** Nil mentioned **Baseline characteristics:** all participants had been diagnosed with RA within the previous 12 months, most were married 76.2%, female 78.9%, mean age 52.4 years (SD 15.2), education mean 12.6 years (SD 2.5).	a mailed self-administered questionnaire 6-monthly.			Negative Affect Schedule (PANAS) Satisfaction with abilities assessed via telephone interview Perceived importance of ability to do household activities, leisure activities, control pain. Assessed via telephone interview Physical limitations. Assessed using items from the following scales: Modified HAQ, AIMS, Rapid assessment of disease activity in rheumatology (RADAR), McGill pain questionnaire.	Centre grand 5-P60-AR-30701

Effect size
Greater dissatisfaction with abilities at baseline are associated with greater negative affect assessed 6 to 18 months later. The longitudinal effects of satisfaction on negative affect were observed only among patients who considered it very important to be able to do household and leisure activities, and to control their pain.

There was a lack of an association between satisfaction and positive affect.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Nagyova I, Stewart RE, Macejova Z et	Observational-correlation	Total N=160	**Inclusion criteria:** age 20 to 70 yrs	No intervention	No comparison	Follow-up:	Data collected annually over a 4 yr period. Health status data collected	Ministry of Education,

al. The impact of pain on psychological well-being in rheumatoid arthritis: the mediating effects of self-esteem and adjustment to disease. *Patient Education and Counseling.* 2005; 58(1):55-62 ID 1221	study: 3 The European Research on Incapacitating Disease and Social Support (EURODISS) Multicentre. Sample of patients from Slovakia	**Drop-outs:** (yr 1 N=9, yr 2 N=27, yr 3 N=36)	inclusive, diagnosis of RA according to ARA criteria, delay between time of establishing the RA diagnosis and inclusion in the cohort less or equal to 4 yrs Baseline characteristics: mean age 48.7 years (SD 12.0); 84.4% female; Duration of RA 22.2 months (SD 15.9); married 78.1%; RAI mean 13.3 SD 7.4), NHP mean 4.9 (SD 2.5), RSE mean 27.3 (SD 3.1), GARA mean 2.5 (SD 0.9), GHQ mean 56.7 (12.2) (no statistically significant changes over follow-up)	given.	group.	Annually	during rheumatology consultation followed by personal interview Questionnaires and interview used were: Battery of instruments included in he EURODISS protocol. Pain was assessed using the Ritchie Articular Index (RAI) (each joint rated 0 for no pain to 3 for pain, wincing or withdrawal) (total score 0 to 72 with higher score indicating more pain) and Nottingham Health Profile (NHP) (8 items with yes/no response) (the higher the score the more pain experienced) ; self-esteem was measured using the Rosenberg Self-Esteem scale (RSE) (10 items) (total score fro 0 to 40 with higher score indicating higher self-esteem); adjustment to disease measured by General Adjustment to Rheumatoid Arthritis (GARA) (1 item) (score of 1 to 5 with higher score indicating poorer adjustment); psychological well-being measured by General Health Question (GHQ-28) (4-point scale and total score 28 to 112 with a higher score indicating poorer psychological well-being)	Slovak Republic, COMAC-Health Services Research from the European Committee

Effect size

Multiple regression analysis (only the results at baseline are reported as there was very little change over time):
Step 1: Psychological well-being (GHQ) was predicted from pain:

- RAI (β= - 0.3)
- NHP (β= 0.48; p<0.001)
- Adjusted R^2 0.21 (F=19.56; p<0.001)

Step 2a: Psychological well-being predicted from pain and self-esteem:

- RAI (β= - 0.05)
- NHP (β= 0.35; p<0.001)
- RSE (β = -0.33; p<0.001)
- Adjusted R^2 0.30 (F=20.72; p<0.001)

OR Step 2b: Psychological well-being predicted from pain and adjustment to disease:

- RAI (β= - 0.11)
- NHP (β= 0.36; p<0.05)
- GARA (β = -0.27; p<0.05)
- Adjusted R^2 0.21 (F=6.42; p<0.001)

Step 3: Psychological well-being predicted from pain, self-esteem and adjustment to disease:

- RAI (β= - 0.11)
- NHP (β= 0.26)
- RSE (β= -0.28; p<0.05)
- GARA (β= 0.29 p<0.05)
- Adjusted R^2 0.30 (F=7.61; p<0.001)

At follow-ups pain explained 36% of the total variance of psychological well-being on average, and self-esteem together with pain explained 52%, where as adjustment to disease and pain explained 46%. All variables together i.e. pain, self-esteem and adjustment to disease, explained 57% of the total variance of psychological well-being on average.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. M. Smedstad, T. K. Kvien, T. Moum, and P. Vaglum. Correlates of patients' global	Observational-correlation study: 3 Single centre,	Total N=238 **Drop-outs:** 9%	**Inclusion criteria:** Aged 20-70 years, RA (ARA criteria); Duration <4 years.	No intervention given.	No comparison group.	Examinations at baseline and at 1 year and 2 years.	Participants were examined and the following measurements made: Current medication; Number of	Grants from the Research Council of Norway, Program for

assessment of arthritis impact. A 2-year study of 216 patients with RA. *Scandinavian Journal of Rheumatology* 26 (4):259-265, 1997. ID 401	Norway (patients from 2 County Departments of Rheumatology in Norway	at 2 years	**Exclusion criteria:** Presence of other incapacitating disease, stage IV (Steinbrocker's functional class). **Baseline characteristics:** mean age 52.2 years (SD 13.0); 74% female; Mean duration of RA 2.2 years (SD 1.27); mean pain (VAS) 33; 52% on DMARDs.				tender joints and degree of tenderness (Ritchie articular index); AIMS subscale of depression; Functional disability (HAQ); Pain (VAS); Patient's global assessment; ESR; CRP.	Health Services Research, Norwegian Rheumatism Association, Legacy of Grete Harbitz, Legacy of Marie and Else Mustad, Anders Jahre's Foundation and Gythfeldt's Research Foundation.

Effect size

Summary of results:

- The overall picture was that of less favourable values for women compared to men: Tender joint counts ($p<0.05$); ESR ($p<0.05$); Symptoms of depression, AIMS ($p<0.05$); Patient's global assessment ($p<0.01$) and functional disability, HAQ ($p<0.001$) were all significantly worse for women compared to men. There was NS difference between men and women for pain (VAS), hand x-ray abnormalities and CRP.

- Bivariate analysis: Strong significant correlations ($p<0.05$) were found between patient's global assessment and pain, depression, disability and tender joints. There was a weak correlation (NS) between patient's global assessment and ESR, CRP or x-ray abnormalities.

- Multiple linear regression analysis (adjusted for age, gender, disease duration): pain and depression still had a significant impact on patient's global assessments whereas disability and tender joints were no longer significant.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures[1]	Source of funding
Suurmeijer TP, Waltz M, Moum T, Guillemin F, van Sonderen FL, Briancon S, Sanderman R, and van den Heuvel WJ. Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. Arthritis & Rheumatism: 45:	Observational study 3 Multicentre, multinational study (Netherlands, France and Norway)	N= 573 **Drop-outs:**	**Inclusion criteria:** residence in sampling area, 20 -70 years of age, diagnosis of RA according to ACR criteria, disease duration of ≤4 years. **Exclusion criteria:** other serious incapacitating disorders, stage IV Steinbrocker functional grade, or probable unavailability to follow up. **Baseline characteristics:** Netherlands: age mean 54.4 (SD 11.8), female 64%, married 78%, educational level 2.9 (SD 1.0), disease duration mean 21.9 months (SD 13.9)	European Research on Incapacitating Disease and Social Support (EURIDISS) study Yearly interviews	Nil	4 years	Physical functioning measured using ASRA RAI Fatigue Pain HAQ GARS (disability measure) ESR Mental functioning measured using GHQ28 RSE	Het Nationaal Reumafonds, Ministry of Welfare, Health and Cultural Affairs, French Programme Hospitalier de Recherche Clinique Ministry of Health, Societe Francaise de Rhumatologie, Research

[1] ASRA = Appraisal of Severity of RA, RAI = Ritchie Articular Index, HAQ = Health Assessment Questionnaire, GARS = Groningen Activity Restriction Scale, GHQ28 = 28-item General Health Questionaire, RSE = Rosenberg Self-Esteem scale, SSQS = Social Support Questionnaire for Transactions, ILRA = Independent Living with RA, OEH = Overall Evaluation of Health, GARA= Global Adjustment to RA

111 – 121, 2001 REF ID: 298.			France: age mean 53.9 (SD 11.3), female 70%, married 85%, educational level 2.2 (SD 1.4), disease duration mean 30.6 months (SD 16.6) Norway: age mean 51.9 (SD 13.1), female 74%, married 69%, educational level 3.5 (SD 1.4), disease duration mean 26.5 months (SD 13.8) There were significant differences between the countries in marital status (p=0.004), educational level (p<0.001) and mean disease duration (p<0.001).				Social functioning SSQS ILRA Leisure Overall assessment of well-being OEH GARA	council of Norway, Norwegian Rheumatism Association, Legacy of Marie and Else Mustad, Legacy of Grete Harbitz, Anders Jahre's Research Foundation, COMAC-Health Services Research

Effect size

There were several significant differences between the countries:

- French patients showed significantly more tenderness, pain and fatigue, lower psychological well-being, lower self esteem and weaker feelings of independent living, less global adjustment to RA and lower health perceptions than Dutch and Norwegian patients).
- Norwegian patients showed significantly less disability, stronger feelings of independent living and more reduction in leisure activities than French and Dutch patients.
- Dutch patients showed more disability, less anxiety, more self esteem and more satisfaction with the social companionship received.
- The mean ESR scores did not differ between the countries.

When patients were divided into groups according to fatigue experienced, there were significant differences between the much vs. little fatigue groups identified for most of the quality of life and disability variables collected, across the physical, mental and social realms. [These analyses were done by country due to the differences found between them.]

Patients who experienced more fatigue were more at risk of pain, were more disabled, felt more depressed, had lower self-esteem, were less satisfied with the support provided to them, showed more reduction in leisure activities, felt less independent and adjusted, and appraised their health as markedly less well.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Thyberg I, Skogh T, Hass UAM, and Gerdle B. Recent-	Observational study 3	N= 320 **Drop-**	**Inclusion criteria:** patients in whom the first signs of arthritis (joint swelling) were observed at least 6	6 monthly follow up as part of the	Nil	12 months	ESR CRP	Research council in the south-east of

onset rheumatoid arthritis: A 1-year observational study of correlations between health-related quality of life and clinical/laboratory data. Journal of Rehabilitation Medicine: 37: 159 – 165, 2005 REF ID: 1009.	Prospective multicentre study in Sweden.	**outs:** 23/320 (7.2%)	weeks, but not more than 1 year, before inclusion, fulfilled at least 4 of 7 criteria for RA as defined by revised 1987 ACR criteria, or suffered from morning stiffness for ≥60 min, symmetrical arthritis and arthritis in small joints. **Exclusion criteria:** not mentioned **Baseline characteristics:** Female 68%, women mean age 55 years (SD 15), men mean age 58 years (SD 15), RF+ 60%, co-morbidity 33%, on DMARD 2%, on oral corticosteroids 20%, HAQ 0.9 (SD 0.6). Men were significantly older than women (p=0.02).	Swedish TIRA (Swedish acronym for 'early intervention in rheumatoid arthritis') N=297 included in analyses			Assessments of physical function 28 joint count of tender and swollen joints Physicians global assessment of disease activity (PGA) Grip force Grip ability test (GAT) Signals of functional impairment (SOFI) Walking speed HRQoL Duration f morning stiffness Pain VAS Well-being VAS HAQ (Swedish version) SF-36 (Swedish version	Sweden (FORSS), national Board of Health and Welfare, County Council of Ostergotland, Swedish Rheumatism association, King Gustav V 80-year foundation, Swedish Research Council.

Effect size

Clinical and laboratory variables:
All variables improved significantly over the first 6 months. The majority of variables remained stable over the next 6 months except PGA and walking speed which showed small but significant improvements; p=0.034 and p=0.024 respectively.

HRQoL variables:
All variables except general health improved significantly over the first 6 months (p<0.001 for all).

Relationship between HRQoL and clinical/laboratory variables:
Principal component analysis (PCA) showed that in one component five scales of the SF-36 (physical function, role function, bodily pain, general health and vitality), pain, well being and PGA were inter-correlated (loadings ≥0.25). PGA, pain and well-being correlated negatively with the 5 SF-36 scales.
A second component reflected inter-correlations between clinical/laboratory variables (ESR, CRP, swollen joint count, PGA and SOFI).

Only weak correlations existed between the clinical/laboratory variables and the HRQoL variables. Clinical/laboratory assessments explained only 18-20% of the variation in

HRQoL between diagnosis and 12 months, about 80% of the variation in HRQoL variables was unexplained at the diagnosis or the 12 month follow up.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Uhlig T, Smedstad LM, Vaglum P, Moum T, Gerard N, Kvien TK. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. Rheumatology: 39: 732-741, 2000. REF ID: 2996	Observational study Case series 3 Part of the EURIDISS study, patients recruited from 2 outpatient clinics in Norway.	N= 238 **Drop-outs:** 56/238 (23.5%) at year 5	**Inclusion criteria:** residence in the study area, age 20-70 years, diagnosis of RA according to the 1987 ARA revised criteria, disease duration <4 years. **Exclusion criteria:** presence of other incapacitating diseases, stage –IV Steinbrocker functional class or expected loss to follow up. **Baseline characteristics:** mean age 52.2 years (SD 13.0), disease duration mean 2.2 years (SD 1.27), RF+ 68% Patients completing the 5-year follow up were younger than the non-completers (p=0.01), but were comparable for other demographic and disease specific features.	Longitudinal study with follow up contact at years 1, 2 and 5.	n/a	5 years	AIMS (psychological, physical and pain scales) HAQ Modified Sharp Score ESR CRP Ritchie Articular index	Research Council of Norway, Lions Clubs International, Norwegian Rheumatism Association, Trygve Gythfeldt and Wife's Legacy, Grether Harbitz Legacy, Marie and Else Mustad's Legacy and the EURIDISS

Effect size

Physical outcomes

Health status measures of physical function were mainly unchanged from baseline to 5 year follow-up. HAQ and AIMS gave slightly divergent results of the physical function changes; HAQ scores remained stable [0.90 (0.62) at baseline, 0.91 (0.65) at 5 years; p=0.74] while AIMS physical scale increased [1.92 (1.43) at baseline to 2.16 (1.53) at 5 years; p<0.001)].

In linear regression analyses, outcomes for physical health status were best predicted by its baseline values (HAQ at baseline, p<0.001; AIMS physical at baseline, p<0.001). High age at onset (p=0.006), and psychological health status at baseline (as measured by AIMS) (p=0.02) were also significant predictors. Physical disability was not predicted

by radiographic damage at baseline, although in bivariate analyses there was an association (AIMS physical >2.0, p<0.01; HAQ >1.0, p<0.01). In separate models using either HAQ or AIMS, these variables accounted for 38% of the variance.

Psychological outcomes
There were no significant changes in psychological status over time in the group. In linear regression analyses, outcomes for psychological health status were best predicted by its baseline values (AIMS psychological at baseline, p<0.001); this accounted for 33% of the variance in the model.

Radiographic outcomes
Radiographic damage had deteriorated by the 2nd and 5th year of follow up [Modified Sharp score 9.2 (15.5) at baseline, 26.0 (31.9) at 5 years; p<0.001).
In subgroup analyses, radiographic progression differed between patients with and without RF (p<0.001), and those with and without radiographic abnormalities at baseline (p<0.001).
In linear regression analyses, radiographic damage was predicted by radiographic baseline value (p<0.001), by ESR (p<0.001) and by RF positivity (p=0.046); these variables accounted for 64% of the variance in the model.
Radiographic damage was not predicted by physical function at baseline.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
H. Lempp, D. L. Scott, and G. H. Kingsley. Patients' views on the quality of health care for rheumatoid arthritis. *Rheumatology* 45 (12):1522-1528, 2006. ID 3560	Qualitative study: 3+ UK: from 2 hospitals' Rheumatology outpatient clinics.	Total N=26 patients	**Inclusion criteria:** None mentioned. Patients were randomly selected by quota sampling (stratified by age, gender, ethnicity and duration of disease). Patients were selected on a proportional basis (RA is 3 times more common in women than men, typically develops in middle age and disease duration and ethnicity distribution are typical of the clinic. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 56 years; female 85%; Disease duration mean 10 years (established RA).	Semi-structured interviews	Immediate	Questions about patients' experiences of the quality of healthcare received in primary and secondary care.	Grants from ARC and NHS funding, UK.

Effect size

<u>OVERALL:</u> Patients highlighted 4 main factors which influenced their attitudes and approach towards hospital staff and the treatment offered: 1. Their past experiences with the NHS; 2. Their own health beliefs; 3. Professional attitudes (eg. listening to patients, receiving feedback on their disease processes) and 4. Organisational aspects (eg. good communication between healthcare professionals) which would make their visits to the outpatient clinic easier.

Main themes were:

1. Past experiences of the NHS

- Many patients had cautious attitudes about their treatment, healthcare and expectations of the NHS

2. Personal Health beliefs

- Patients described a range of hereditary and non-bodily factors which they attributed to the development of their RA.
- Most reported that when medical staff searched for new treatment options it gave them hope
- Treatments gave them physical improvement, easier movement, less/no pain, helped them get back to normal, lessened their joint swelling, or gave them better sleep.
- Biologics particularly had positive physical and emotional effects on their health and social functioning
- Many patients often resorted to making their own decisions about medication its dose and frequency, which was linked to their perception of not feeling well and knowing what was 'good for them'
- Many had tried one or more complementary therapies for their pain including acupuncture and massage. One patient mentioned they "can't do without…acupuncture and massage…and heat really helped"
- Increasing reliance on medication with the progression of RA presented a challenge to many patients health beliefs and reluctant compromises to avoid painful deterioration
- Most had been told they had no choice but to take toxic drugs to slow deterioration or alleviate their symptoms and were concerned about side-effects
- Nearly all patients hoped that new research would find a cure

3. Professional Issues

- Secondary care: most patients had expectations of their clinic visits that they would receive extra support/help when needed, and expected the staff to be understanding and have a warm approach and also wanted better feedback. A few wanted less frequent visits and were indifferent about secondary care.
- Primary care: was described in both complimentary and critical ways. Some described delays by GPs in diagnosis and early care, lack of knowledge, often were seen as prescribers of medication. Others felt they were understanding, sympathetic and had a long-term personal knowledge of the patient.
- Many patients described how they presented themselves to healthcare staff as a 'coper' or came 'just as they were' and some were undecided. Many tried to please staff 'by not being a nusiance'
- A number felt that familiarity with the staff and having access to other departments was important.

4. Interaction with different types of healthcare professional

- Many felt they had to be polite with doctors and there was a mixture of positive or negative feelings about how they interacted with them.
- All patients were positive about nurses and felt more at ease with nurses, who often got to know them better. Many patients felt nurses were a go-between them and

the doctors and nurses had positive attitudes towards them.

- Most patients gave less information about other members of the MDT which may be related to the fact that only half of them were receiving treatment from a combination of 1 to 3 of these therapists.

5. Organisational Issues

- Impact of visits and blood tests: there were mixed feelings – some felt these were non-intrusive and others felt they were inconvenient due to either working or having severe physical disability.
- Many patients preferred to have visits/consultations on their own however some preferred to have others with the for support or obtain information.
- Most were positive about the presence of medical or nursing students being present, however some felt they could not disclose personal issues (gynaecological/emotional) when they were present.
- A number of female patients preferred to talk about gynaecological/emotional issues to a female staff meber rather than male, due to perceived uncomfortable or inappropriate responses by them in the past.

Authors' conclusions:
Most patients no longer see themselves as passive recipients of care. They appreciate acknowledgement from healthcare professionals of their contribution towards management of their own disease and welcome a more equal dialogue with healthcare staff.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
H. Lempp, D. Scott, and G. Kingsley. The personal impact of rheumatoid arthritis on patients' identity: a qualitative study. *Chronic Illness* 2 (2):109-120, 2006. ID 3561	Qualitative study: 3+ UK: from 2 hospitals' Rheumatology outpatient clinics.	Total N=26 patients	**Inclusion criteria:** None mentioned. Patients were randomly selected by quota sampling (stratified by age, gender, ethnicity and duration of disease). Patients were selected on a proportional basis (RA is 3 times more common in women than men, typically develops in middle age and disease duration and ethnicity distribution are typical of the clinic. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 56 years; female 85%; Disease duration mean 10 years	Semi-structured interviews	Immediate	Questions about patients' experiences at the onset of disease; development of the illness; impact on their life, work, and family; the process when they seek medical help.	Grants from ARC and NHS funding, UK.

			(established RA).				

Effect size

Main themes were:

1. Impact upon identity in the private sphere

a) Emotional identity
- Most patients described mental distress since diagnosis, pain made them feel low.
- They were particularly affected in the initial stages following diagnosis

b) Identity as a parent/carer
- Patients' considered their role as a family member/carer as part of their social responsibility
- Role reversals had been established where family members and others now provided practical help to the patients
- Many patients did not receive help from social services feeling it was either not needed, refused it or wanted to avoid interference from agencies or those they felt incompetent

c) Identity as an independent person
- For many patients, potential loss of independence was a concern
- They did not want to become a burden for their families and wanted to remain independent
- This often meant they had to slow down and accomplish set goals each day which were seen as major achievements
- Younger patients (aged 25-45 years) were particularly concerned about independence and worried about future of family life, availability of medication and their ability to cope

d) Identity as a partner
- Many patients described frustration, especially tensions in relationships (men did not mention this)
- Tensions arose with partners' difficulties accepting the illness, sexual intimacy, limited mobility curtailing social life, growing old and accepting each others' curtailing health

e) Identity as a healthy woman
- A number of women were concerned about the feasibility of pregnancy and had concerns about passing the disease on to their children

2. Impact upon identity in the public domain

a) Identity as an employee
- Most patients had been employed in manual or administrative positions
- Some felt that if they gave up their job they were giving up and put on a brave face, kept on fighting or negotiated flexible working arrangements to pace themselves
- Some felt that bosses and colleagues were supportive or unhelpful and sometimes patients did not tell them the whole picture.

b) Identity as a friend
- A large majority of patients had an active and happy social life and had made alterations to accommodate their restricted mobility or pain.
- Some had no social life since diagnosis and were more home and family focused.

c) Public identity
- A number of patients experienced stigmatisation or discrimination, particularly among those whose RA progressed and had visible signs of the disease.
- Many of these were younger adults who had to deal with the public's outdated perceptions of disability and intolerance to their restricted mobility.

3. Impact upon identity in the private and public domains

a) Physical identity
- Many patients had changed their physical appearance to accommodate physical restrictions, or tried to hide physical deformities and expressed concern about thei physical or sexual attractiveness being affected by weight gain or loss, side-effects of medication or lack of mobility

b) Identity of established social roles
- Many described changes in their social roles in both the private and public domains due to RA – loss of identity not being able to work any more

c) Self-image and identity
- Many patients described changes in self-image and differences between their own personal sense of identity and the expectations of family, friends and members of the public.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
B. Slatkowsky-Christensen, P. Mowinckel, J. H. Loge, and T. K. Kvien. Health-related quality of life in women with symptomatic hand osteoarthritis: A comparison with rheumatoid arthritis patients, healthy controls, and normative	Cross-sectional study: 3 Norway: patients recruited from an arthritis register. Healthy controls and populataion subjects recruited from random sample drawn from National Register of Norway, persons aged 19-80.	Total N=194 RA patients; N=190 Hand OA patients; N=144 controls	**Inclusion criteria:** Adults with RA examined in the outpatient department; Adults with hand OA **Exclusion criteria:** None mentioned. **Baseline characteristics:** RA Patients: Mean age 61 years; female 100%; Disease duration mean 19 years (established RA). OA Patients: Mean age 62 years; female 100%; Disease duration mean 11 years.	Questionnaire	Immediate	Questionnaire: HRQOL (SF-36); grip strength; M-HAQ; Fatigue (VAS); Pain (VAS)	Not mentioned

data. *Arthritis Care and Research* 57 (8):1404-1409, 2007. ID 3489			Controls: Mean age 61 years; female 100%. The baseline characteristics wre similar between the groups except disease duration was significantly higher for RA patients and numver of comorbidities slightly higher in the OA group.				

Effect size

- Patients with hand OA and RA had worse scores for all health dimensions of SF-36 compared with healthy controls ($p<0.05$)
- Patients with RA had significantly worse scores than patients with hand OA for measures of physical function (M-HAQ, SF-36 physical and grip strength), fatigue and SF-36 general health ($p<0.05$)
- Patients with hand OA had significantly worse scores for SF-36 mental health than RA patients ($p<0.05$)
- There were NS differences between the groups for other measures (SF-36 role limitation physical and mental, Pain – VAS and SF36, Sf-36 vitality, SF-36 social functioning)

Authors' conclusions: This study illustrates that patients with hand OA experience a broader impact on HRQOL compared with healthy controls. Fatigue and physical function are worse in RA than hand OA.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
P. P. Katz and A. Morris. Use of accommodations for valued life activities: prevalence and effects on disability scores. *Arthritis & Rheumatism* 57 (5):730-737,	Observational study: 3 USA: patients recruited from rheumatologists (random sample)	Total N=467	**Inclusion criteria:** Adults with RA **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 60 years; female 85%; Disease duration mean 20 years (established RA)	Interview and questionnaire.	Immediate	Questionnaires: VLA disability scale: obligatory activities (those required for survival and self-sufficiency); discretionary activities (recreation and social participation) and committed activities (those associated with	Grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases

2007. ID 3484						one's principal productive social roles) Interview: patients were asked whether they had made any of 4 types of behavioural accommodations: limitations in the amount or kind of activity within the domain, taking more time to perform activities, needing help from another person and using special devices or aids.	

Effect size

Summary of overall results:

- Accommodations were widely used by individuals with RA to perform daily activities. Limits and more time were used for more activities than assistance and devices. Adjustment for accommodations produced substantial increases in disability scores (ie. the mean total VLA difficulty score increased by 84% after adjustment for all 4 accommodations).

Authors' conclusions: The accommodations included on the HAQ, the most commonly used measure of functioning for RA, include only assistive devices and personal assistance, which were not the accommodations most frequently used in our sample. If assessments are intended to estimate total disease burden, they should include use of a broader range of accommodations to develop a more complex picture of how daily function is affected.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
J. Pouchot, J. M. Le Parc, L. Queffelec, P. Sichere, A. Flinois, and des Polyarthritiques	Cross-sectional study: 3 France. Patients recruited from a French Arthritis	Total N=20,468 patients invited and N=1918 physician respondents (68%	**Inclusion criteria:** Patients with RA. **Exclusion criteria:** Not mentioned **Baseline characteristics:**	Questionnaires sent to physicians and patients.	n/a	Questionnaire on RA, pain, perceived experience of disease, activity restrictions and help received; HAQ.	Schering Plough Inc

ssociation Francaise. Perceptions in 7700 patients with rheumatoid arthritis compared to their families and physicians. *Joint, Bone, Spine: Revue du Rhumatisme* 74 (6):622-626, 2007. ID 3478	database	rheumatologists and 29% GPs) (N=7702 patients with complete data included in the analysis).	Patients: Mean age 57 years; female 81%; Disease duration mean 16 years (established RA).				

Effect size

- Main characteristics of patients' pain (strongly agree or agree responders): variabie (80%), unpredictable (68%), major interference with paid work or domestic chores (67%), underestimation of pain by the spouse (23% patients) and by the physician (14% patients), by other family members or friends (38%)
- Impact of RA on psychological well-being: negative feelings were reported more often than positive; most patients had to push themselves (89%), frustrated at being unable to do things (86%), anxiety about future disease progression (82%), depressive symptoms (75%) and inability to make plans for the future (67%).
- RA negatively affected recreational activities (84%), work-related activities (56%), sexual activities (51%), family life (51%) and intimate relationships (44%).
- Family/friends often tended to overestimate pain severity and characteristics and to underestimate negative effects of RA on the patient's life. Physicians, on the contrary, tended to underestimate pain severity and characteristics.

Authors' conclusions:
There was good overall agreement between perceptions of patients, their families, their physicians, despite differences between these last 2 groups. There was not only a major physical impact of the disease but also marked negative psychological effects.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
L. Reinseth and G. A. Espnes. Women with rheumatoid	Observational-correlation study: 3 Norway. Patients	Total N=83 invited (N=44 with	**Inclusion criteria:** women with RA (ARA criteria); diagnosis at least 3 years before the study.	Questionnaires.	n/a	SF-36; Interest checklist (non-vocational activities performed during the past 10	Sor Trondelag University and the

arthritis: non-vocational activities and quality of life. *SCAND J OCCUP THER* 14 (2):108-115, 2007. ID 3486	recruited from a rehabilitation centre	complete data included in the analysis).	**Exclusion criteria: Juvenile RA;** disease onset before the age of 16 **Baseline characteristics:** Patients: Mean age 64 years; female 100%; Disease duration mean 25 years (established RA).			years, the last year, at presnt and activities they would like to perform in the future); demographics	Norwegian Women's Public Health Association of Occupational Therapists.

Effect size

- Compared to the 10 years ago and to 1 year ago, the mean number of non-vocational activities presently performed by patients had significantly decreased by about a third (mean of 9 activities less than during last 10 years)
- Patients believed they would be able to perform more activities in the future than they were currently able to do
- A large number of activities performed correlated with a good mental health status or psychological well-being, and a low amount of activities performed correlated with a lower mental health status or more psychological distress.
- SF-36 physical function did not correlate with the number of activities patients performed during the last 10 years, the last year or at present but did not correlate with number they planned to pursue in the future
- SF-36 role physical correlated with number of activities patients performed in the last year, at present and number they planned to pursue in the future but did not correlate with during the last 10 years
- Women with RA who experienced psychological well-being participated in a high number of activities compared to those who experienced psychological distress.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
K. R. Sterba, Robert F. DeVellis, Megan A. Lewis, Brenda M. DeVellis, Joanne M. Jordan, Donald H. Baucom, and	Observational-correlation study: 3 USA: patients recruited from advertisements	Total N=190 couples	**Inclusion criteria:** Married women with RA diagnosed for at least 1 year who did not also have fibromyalgia or systemic lupus erythmatosus; husbands were also recruited. **Exclusion criteria:** women not diagnosed with RA for at least 1	Survey	at baseline and 4 months follow-up	Illness perceptions (iIlness perception Questionnaire-Revised); psychological adjustment (positive and negative); arthritis functioning (AIMS);Marital satisfaction (Kansas	Arthritis Foundation Doctoral Dissertation Grant; National Institute of Arthritis and Musculoskeletal and Skin

K. H. Sousa. Effect of couple illness perception congruence on psychological adjustment in women with rheumatoid arthritis. *Health Psychology* 27 (2):221-229, 2008. ID 3491			year due to the sometimes uncertain nature of a preliminary diagnosis and the potential for other causes of inflammatory arthritis to resolve within 1 year. **Baseline characteristics:** Mean age 49 years; female 100%; Disease duration mean 14 years (established RA)			Marital scale and Quality Marriage Index; perceptions of support over the past month	Diseases Grant; university of Texas grant.

Effect size

Summary of overall results:

- In general, wives and husbands had similar views of RA.
- It is important for husbands to understand wives' views on their control over RA and its cyclic nature. Wives may benefit when they share optimistic views with their husbands about RA and when their husbands avoid underestimating RA's consequences.

Authors' conclusions: Developing interventions to enhance partners' illness understanding may be beneficial.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. M. H. Strating, M. A. J. van Duijn, W. H. Van Schuur, T. P. B. Suurmeijer, and K. H. Sousa. The differential effects of rheumatoid arthritis on distress among patients and	Observational-correlation study: 3 The Netherlands. Patients recruited from 5 hospitals – part of the EURODISS project	Total N=94 patients and their partners (N=12 did not respond – 23%); N=61 couples gave complete data and were used for the analysis.	**Inclusion criteria:** RA patients who were married. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Patients: Mean age 60 years; female 67%; Disease duration mean 14 years (established RA).	Self-report questionnaires.	n/a	General Health Questionnaire (GHQ - distress); GARS – functional disability; Caregiver Strain Index (partner burden); Perceived negative transactions (Socail Support List); Maudsley Marital Questionnaire (MMQ – marital qualiy); demographics	Not mentioned

partners. *Psychology & Health* 22 (3):361-379, 2007. ID 3461							

Effect size

- Patients and partners mean distress score was significantly lower than that of the general population ($p \leq 0.01$)
- Patients reported significantly more distress than their partners ($p=0.02$)
- Partners received significantly more negative transactions from the patient ($p=0.01$) and significantly lower marital quality than the patient ($p=0.02$)
- Female patients reported significantly more distress than male patients ($p=0.03$)
- Female partners reported receiving significantly more negative transactions from male patients than male partners did from female patients ($p=0.01$)
- Patient's distress was significantly related to disability of the patient (p value not given)
- Patients who reported more negative transactions from their partner, reported poorer marital quality
- Patients' distress and disability were positively related to partners' perceived burden
- Negative transactions perceived by the patient and partner were positively correlated with each other as well as the marital quality perceived by both partners.
- Marital quality perceived by the partner was negatively related to patients' disability and to negative transactions perceived by the patients

Summary

- Patients' disability was a primary stressor for patients but not for partners
- Partners' burden was a primary stressor for partners but not for patients
- Interaction effects were found between patients' disability and partners' burden
- Negative transactions and marital quality were secondary stressors for partners but not for patients
- There was a weak effect of marital quality on partners' distress and its strength was moderated by negative transactions between patients and partners
- The effect of marital quality on patient's distress depended on partners' burden
- Negative transactions perceived by the partner moderated the effect of burden on his/her distress.

Author's conclusions:
More knowledge on how patient and partner influence each other's distress is needed to develop psychosocial interventions that will help patients and partners minimise their psychological distress and prevent deterioration of their marital quality.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of

							funding
P. J. Verduin, G. H. de Bock, T. P. Vliet Vlieland, A. J. Peeters, J. Verhoef, and W. Otten. Purpose in life in patients with rheumatoid arthritis. *Clinical Rheumatology* 27 (7):899-908, 2008. ID 3550	Cross-sectional study (observational-correlation): 3 The Netherlands: patients randomly selected from 2 outpatient Rheumatology departments	Total N=300 patients	**Inclusion criteria:** Adults with RA (ACR criteria). **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 60 years; female 69%; Disease duration mean 10 years (established RA).	Questionnaires	Immediate	HAQ; Coping (Coping with Rheumatic stresses questionnaire); Purpose in Life (PIL test); Psychological Wellbeing Scale (PIL subscale); Disease characteristics; RAND-36	None mentioned

Effect size

- Univariate analysis: There was NS association between Purpose in Life and gender, living status, disease duration, the VAS disease activity and the coping dimensions seeking solutions and distraction
- Multivariate analysis: Purpose in Life was significantly associated with younger age, a better mental health and an optimistic coping style were significantly associated with both measures of purpose in Life. Participation in leisure/social activities was associated with a higher Purpose in Life score.
- Purpose in Life was significantly associated to the RAND-36 Mental Health Summary Scale but not to the RAND-36 Physical Health Summary Scale

Author's conclusions:
Purpose in life pays a significant and independent contribution to the mental component of QoL.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
V. Ward, J. Hill, C. Hale, H. Bird, H. Quinn, R. Thorpe, and K. H. Sousa. Patient priorities of care in rheumatology	Qualitative study: 3+ UK: patients from an RCT comparing nurse practitioner clinic vs junior hospital doctor's	Total N=25 patients	**Inclusion criteria:** Adults with RA (ACR criteria) **Exclusion criteria:** None mentioned. **Baseline characteristics:** Median age 55 years; female 72%;	Structured interviews lasting 1.5 hours	n/a	Sociaodemographic and health data; intervies to find out perceptions of the care patients had received during the RCT. Any differences between the perceptions and experiences of	Arthritis Research Council

outpatient clinics: a qualitative study. *Musculoskeletal Care* 5 (4):216-228, 2007. ID 3477	clinic		Disease duration mean 13 years (established RA).			patients who were seen by the nurse practitioner compared with those seen by the junior doctor. **NOTE:** Patients did not restrict their comments to the 12 month RCT time-frame but discussed their experiences both prior to and following the 12-month period.	

Effect size

6 themes emerged:

- Patients want to be communicated to clearly and effectively and value positive relationships with practitioners
  - Valued wanting to lead discussions during appointments
  - Valued being listened to during appointments "it might seem minor to someone else, but when you're living with it it's a different ball game"
  - Valued empathy and approachability
- Clear communication and good relationships help to give patients confidence in the care they are receiving
  - Feel "very relaxed, I knew I was being dealt with by competent people…was at liberty to ask anything I liked, which is very reassuring"
  - " I've got a lot of confidence in him, gradually…over the years. If you see the same familiar face you feel that you're not being pushed around"
- Patients want to feel in control of their condition and tend to refuse interventions as a way of gaining control
  - Patients valued retaining control of their condition by being in control of their own medications. Pain relief medication was felt often to represent their lack of control
  - Patients recognised that interventions and medications were important to their well-being, and reported positive outcomes following appropriate treatment; however they often were "trying to reduce the drugs that I take"
- Patients want to be given clear explanations during consultations and want information in oral and written forms
  - Most discussed form of information giving was 'explanation' and patients were distressed by not receiving explanations and adequate information including self-management techniques.
  - "nobody will tell me what amount or proportion…should you push yourself or immediately rest" if you are tired when walking
  - Patients were proactive in their search for information (leaflets, talking with friends and relatives, searching written media). They appreciated receiving oral explanations from their practitioners and felt these should supplement written information.
- Patients want to be able to access practitioners between scheduled appointments as a way of gaining reassurance and felt this was important
  - Rationale for access was frustration, apprehension and fear of the future (eg. At group classes seeing others who were really disabled was very upsetting)
  - Seeing practitioners between appointments helped them to cope with such apprehensions and gain reassurance and support.
  - "if I didn't know where to turn, if I didn't know who to go to, then I think I'd have a problem"
- Patients want to feel valued by society through having their difficulties appreciated and understood by others
  - Patients were frustrated and distressed when their condition was not appreciated by others and contributed to their low sense of personal value and they felt like a social outcast
  - Importance of having their condition understood by society in general but also in clinic situations
  - Having their difficulties appreciated by practitioners would help give patients confidence in the care they receive

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
A. E. Williams, C. J. Nester, and M. I. Ravey. Rheumatoid arthritis patients'	Qualitative study (interpretive phenomenological): 3+	Total N=13 (N=14 asked to participate, N=1 declined)	**Inclusion criteria:** RA diagnosis; Listed on orthotic service records; attended a clinical appointment for footwear within last 6 months; received specialist footwear from	Semi-structured interviews	n/a	Patients' personal experiences of using therapeutic footwear.; organised into themes	Not mentioned

experiences of wearing therapeutic footwear - A qualitative investigation. *BMC Musculoskeletal Disorders* 8, 2007. ID 3488	UK. Patients recruited from orthotic services in 4 hospitals		the orthotic services; reported at their last appointment that they were satisfied with their footwear. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age 56 years; female 23%; Disease duration mean 10 years (established RA); Foot pain (Likert score) mean 8; Footwear usage: all men, 80% of women.				

Effect size

2 main themes emerged from both the female and male groups (theme 2 and 4) but the other themes were only revealed in the female group.

Theme 1: Feelings about their feet (female group)

- Women felt frustration, anger, anxiety, loss and sadness about how their feet were visibly different from other people, how they could not walk 'normally' because of the pain, and loss of femininity. Made them look and feel old and worried about what others thought. None of the men talked about the appearance of their feet.

Theme 2: Feelings about their footwear (male and female groups)

- Women's negative feelings and emotions about their feet were reinforced by the reaction of others to their footwear; they felt they were visibly different from others and worried about what others thought; they felt shame, sadness and anger associated with their feet and the footwear. Women talked about the visibility of their footwear as an item of clothing.
- Men responded differently and focused on the construction of the footwear (were positive that it was hand-made) and that it was free, comfortable and some could walk faster with them

Theme 3: Behaviour with their footwear (female group)

- Women felt a loss of femininity and impact on their sexuality. This theme was not apparent amongst the men who mentioned no change of behaviour.
- Women commented that it did improve their mobility and reduced pain but restricted social activities (some women didn't go out socially or to family events) and influenced the types of clothes they wore – particularly they felt that only trousers were suited to the shoes. They again felt shame, sadness and anger associated with the impact of the footwear.

Theme 4: Feelings about the practitioner (male and female groups)

- Women had trust in the practitioners' skills in the assessment and dispensing of footwear however they felt that the assessors were dismissive of their concerns (had little choice about the range of footwear) and had poor communication skills. They again felt shame, sadness and anger associated with the consultation as well as guilt and powerless.
- Women perceived that the practitioners lacked knowledge of RA, pain and their needs and body-language of practitioners was negative and reinforced feelings of shame.
- The men felt differently, that there was some camaraderie between them and the practitioners and they trusted the skills. They did not mention the requirement of the practitioner to have knowledge of their condition. Their main concern was lack of continuity in seeing different practitioners.

Theme 5: Feelings about what would have improved their experience (female group)

- Women felt they needed more information on which to base their choice of footwear, should be given time to consider their options before being referred for the footwear, and should be allowed to voice their opinions. Knowing that they were being listened to and feeling of trust in the practitioner was seen as important factor in the consultation.
- The men did not mention any aspect of their experience that needed improving. Acknowledgment by the practitioner that the women had a uniqe knowledge of their own disease would have made them feel important and included in the process and enhanced their experience and perhaps have avoided some of the negative emotions.

Author's conclusions:
Unlike any other intervention, specialist therapeutic footwear replaces something that is normally worn and is part of an individual's body image. It has much more of a negative

impact on the female patients' emotions and activities than previously acknowledged and this influences their behaviour with it. The patients' consultations with the referring and dispensing practitioners are pivotal; moments within the patient/practitioner relationship that have the potential to influence whether patients choose to wear their footwear or not.							
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
T. Uhlig, J. H. Loge, I. S. Kristiansen, and T. K. Kvien. Quantification of reduced health-related quality of life in patients with rheumatoid arthritis compared to the general population. *Journal of Rheumatology* 34 (6):1241-1247, 2007. ID 3485	Case-control study: 2 Norway: patients recruited from an arthritis register. Controls recruited from random sample drawn from National Register of Norway, persons aged 19-80.	Total N=1052 patients Total N=2323 general population	**Inclusion criteria:** Adults with RA **Exclusion criteria:** None mentioned. **Baseline characteristics:** Patients: Mean age 61 years; female 79%; Disease duration mean 14 years (established RA); Pain, VAS mean 38. General population sample: Mean age 45 years; female 51%. The baseline characteristics of mean age and number of women were significantly higher in the patient group than the general population sample.	Survey	Immediate	Survey: SF-36 (physical and mental components)	Not mentioned

Effect size

- RA patients had significantly poorer HRQOL (all dimensions of the SF-36) compared to the normal population ($p<0.05$)
- Women patients had worse scores than men
- The largest disease impact was in the physical functioning subscale
- Mental health subscale had low impact (in patients <50 years old) and moderate impact (in other age groups)
- There was a linear decline in HRQOL especially in the physical dimension, with increasing age in both the general population and the RA patients
- For physical functioning, standardised difference scores decreased with increasing age
- RA patients had worse overall scores for physical and mental health scores across all age groups and for mental health they were significantly different above the age of 40 years.

Authors' conclusions: RA inflicts a substantial disease burden and the disease affects all HRQOL dimensions as measured by the SF-36 in both genders and in all age groups. Physical functioning is predominantly affected, but RA has social and mental consequences.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
F. Wolfe and K. Michaud. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis & Rheumatism* 56 (7):2135-2142, 2007. ID 205	Observational-correlation study: 3 USA: patients recruited from an arthritis register of RA patients at the practices of rheumatologists.	Total N=6135 patients	**Inclusion criteria:** Adults with RA (rheumatologists diagnosis) **Exclusion criteria:** None mentioned. **Baseline characteristics:** Patients: Median age 63 years; female 80%; Disease duration mean 15 years (established RA).	Questionnaire	Immediate	Questionnaire: 11 questions on issues regarding change of therapy and satisfaction with therapy.	Not mentioned

Effect size

- 64% of patients would not want to change their therapy as long as their condition didn't get worse (included 62% of patients currently using biologics and 66% who were not)
- 73% of patients were concerned about the risk of side-effects and 68% about losing control of their arthritis.
- Patients didn't want to change therapy because:
    - they were satisfied with their current arthritis control (53%)
    - felt their doctor thought they did not need to change (72%)
    - there were no better medications than those they were currently taking (66%)
    - the hassle of new tests and insurance approval was an important problem (55%)
    - they couldn't afford new medications (43%)
    - they did not want to take medications that required IV administration or injection (36%)
- Unwillingness to change therapy (difference between those who would and would not change) – higher %, higher association with unwillingness
    - 57% - satisfaction with arthritis control
    - 40% - risk of side-effects
    - 36% - following their physicians' instructions
    - 35% - concern about loss of control
    - 27% - no availability of better medication
    - 16% - not wishing to use IV medications or injections
    - 8% - cost of medications
    - 4% - hassle factor

- Logistic multivariate regression Model – significant correlates of unwillingness to change therapy (all $p<0.05$):
    - Satisfaction with RA control (OR 7.3), risk of side-effects (OR 4.5)
    - Physician's opinion (OR 2.0) and fear of loss of control (OR 1.5)
    - The use of biologics, higher pain scores, greater income and college education were significantly associated with willingness to change therapy
    - Being married and use of MTX were significantly associated with not wanting to change therapy
    - Patients reporting side-effects were significantly more likely to be unwilling to change therapy (OR 1.8) and be concerned about the risk of side-effects (OR 1.2)

- How much more effective would new medication have to be compared with current medication to make patients switch to it:
    - 76% better - Patients who reported not wanting to change therapy vs 52% - Patients who would change therapy ($p<0.001$)
    - 67% - users of biologics vs 65% non-users of biologics (NS)

- Patient measures of disease activity/severity (HAQ and PAS) are only weakly linked to decisions about therapy
- Many patients with HAQ or PAS scores that indicate unsatisfactory function or disease activity levels, were satisfied wit their RA conreol, while others with 'good' scores for function or disease activity were dissatisfied with their RA control.
- Current users of biologics were significantly more likely to want to change therapy than those not currently taking these agents (OR 1.2) but this difference was NS once

adjusted for age, gender and RA duration (OR 1.1)

- Satisfaction with medication was significantly greater among patients not taking biologics than those not taking them ($p<0.001$) and remained significant once adjusted for age, gender HAQ score, pain score and RA duration

Authors' conclusions: There is substantial discrepancy between declared satisfaction with therapy and measured RA activity and functional status. Most RA patients are satisfied with their therapy, even many with abnormal scores. Fear of loss of control of RA and fear of side-effects are major patient concerns. Maintenance of current status, rather than future improvement, appears to be a high priority for patients.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bath J, Hooper J, Giles M, Steel D, Reed E, and Woodland J. Patient perceptions of rheumatoid arthritis. Nursing Standard: 14: 35 – 38, 1999 REF ID: 365.	Qualitative study 3+ Grounded theory No discussion of how patients were chosen No discussion of controlling for bias in interpretation of results.	N= 15	**Inclusion criteria:** none given **Exclusion criteria:** none given **Baseline characteristics:** mean age 59 (range 28-75), mean disease duration 5.4 years (range 1 month-17 years), 80% lived with partners.	Semi-structured interview conducted by nurses or a psychologist	Nil	Not applicable	Identification of psychological needs of RA patients	Not mentioned

Effect size

There were 7 categories of themes identified:

- Medication
  - Side effects of drugs, varieties of medication that patients needed to take, treatment efficacy or inefficacy
- Pain
  - This was reported to be a significant factor in reducing an individual's ability to go out, also concerns about increases in pain in the future and the inefficacy of treatments.
- Wellbeing
  - Themes included depression, loss of confidence, frustration, self-consciousness or embarrassment at the physical changes brought on by RA.
- Social support
  - A lot of social support needed, participants reported being unhappy at having to rely on partners or other family members.
- Activity and mobility
  - Concerns expressed being unable to carry out ADL, disability in the future and the possible consequences of this, inability to be sexually active.

- Information
  - Lack of clear and unambiguous information throughout their treatment, lack of general advice on services available, claiming financial benefits.
- Work
  - Financial implication of inability to work, overextending physically at work and then being unable to continue, inability to work within the home environment

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Carr A, Hewlett S, Hughes R, Mitchell H, Ryan S, Carr M, and Kirwan J. Rheumatology outcomes: the patient's perspective. Journal of Rheumatology: 30: 880 – 883, 2003 REF ID: 217.	Qualitative study 3+ Multicentre within the UK Data analysis followed 4 steps of interpretive phenomenological analysis (IPA) An independent qualitative researcher examined reports to see if themes were justified by the data. Groups facilitated by the authors	N= 39 (6-9 patients in each focus group)	**Inclusion criteria:** purposive sample from local RA population including men and women, a range of age, disease duration, functional disability and current disease activity. **Exclusion criteria:** **Baseline characteristics:** Bristol group: mean age 64 years (range 52-70), mean disease duration 12 years (range 3-24), male: female 2:4 Chertsey group: mean age 58 years (range 41-79), mean disease duration 13 years (range 3-26), male: female 3:6 London group: mean age 60 years (range 33-81), mean disease duration not reported, male: female 4:5 Nottingham group: mean age 64 years (range 48-79), mean disease duration 14 years (range 4-24), male: female 4:5 Stoke group: mean age 58 years	5 focus groups lasting 1 hour	Nil	N/a	Identification of themes and interrelationships between themes using IPA	Not mentioned

			(range 51-64), mean disease duration 9 years (range 2-20), male: female 3:3					

Effect size

Key themes were identified in 3 areas (in response to specific questions):

- Important outcomes
  - Physical (pain, disability, deformity)
  - General well-being (fatigue, feeling well), although exactly what this consisted of was unclear.
  - Independence
  - Return to normality
  - Emotional impact
  - Fear of the future
  - The relative importance of outcomes changes over time and depending on circumstances i.e. different outcomes assume primary importance at different stages of the disease and in response to specific situations like disease flares.
- Satisfaction and dissatisfaction with treatment
  - Treatment efficacy
  - Side effects
  - Patient-health professional communication
  - Access to care
- Decisions about treatment efficacy
  - Symptom reduction
  - 'forgetting you have RA'
  - Change in priorities for outcomes over time
  - Magnitude of improvement/change varies with disease duration.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Covic T, Adamson B, Hough M. The impact of passive coping on rheumatoid arthritis pain. Rheumatology: 39: 1027-1030, 2000.	Cross sectional study 3 • Convenience sample • 2 private rheumatology practices	N= 138 questionnaires distributed **Response rate:** 111/138 (86%)	**Inclusion criteria:** patients with definite or classic RA diagnosed by practicing rheumatologists **Exclusion criteria:** nil mentioned. **Baseline characteristics:** mean age 55.2 years (SD 10.9), disease duration mean 12.0 years (SD 8.7), female 77.5%, 66.7% unemployed,	Self administered questionnaire	n/a	n/a	Pain measured using: AIMS pain subscale Pain VAS Physical disability measured using: HAQ	Not mentioned

REF ID: 2997			77.5% had ≥10 years of schooling.				Psychological variables measured using: AIMS Arthiritis Helplessness Index (AHI) Vanderbilt Pain Management Inventory (VPMI)	

Effect size

Predictors of pain

The measures that correlated most with pain were passive coping (r=0.61, p<0.01), physical disability (r=0.49, p<0.01), depression (r=0.48, p <0.01) and helplessness (r=0.39, p<0.01).

In multiple regression analyses physical disability (p=0.035) and passive coping[2] (p=0.001) were the only significant predictors of pain, accounting for 40% of the variance of pain in the model. In a path analysis aimed at identifying the direct and indirect effects of the variables, helplessness was identified as a mediator between physical disability and passive coping; and passive coping mediated between physical disability and pain and depression. Depression appears to be an outcome measure independent of pain. Passive coping was a better predictor of pain and depression than helplessness.

Conclusion: passive coping was a primary psychological predictor of both pain and depression, as well as a mediator of the impact of the impact of physical disability on both pain and depression.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Heiburg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. Arthritis &	Observational-correlation study: 3	N=1552 on the register N=1024 (66%) response rate	Inclusion criteria: patients with RA who have a residential address in Oslo (Oslo RA register). Baseline characteristics: Mean (SD) age: 63.4	Patients with RA on OSLO RA register	N/A	N/A	Arthritis Impact Measurment Scales 2 (AIMS2) Modified Health Assessment Questionnaire (MHAQ) Medical Outcomes Study Short Form-36 (SF-36) Joint pain and fatigue (measured on VAS) Patient global assessment of disease	Jan A. Pahles Research Legacy

[2] Coping refers to the cognitive, emotional and behavioural strategies used in day-to-day attempts to manage the consequences of a disease. Active and passive coping refers to the degree of internal and external control, respectively, that a patient relies on to manage pain. Passive coping strategies include praying, giving up social activities and relying on health professionals for pain relief.

Rheumatism 2002; 47(4): 391-397 Ref ID: 249			(14.8) years Mean (SD) disease duration 12.7 (11.1) years Sex (% female) 78.7% Comparison to non-responders: Responders were younger (mean difference 5.4 years); had shorter disease duration (mean difference 1.9 years); no differences in distribution of sex and rheumatoid factor.				(measured on a scale of 1-5) Self efficacy for pain and other symptoms (measured on Lorig's scale; range 10-100) Current use of medication.	

Effect size

From AIMS2 (question 60), patients were allowed to report 3 areas of health in which they would like to see the most improvement.

Area of health	% reporting desire for improvement
Pain	68.6
Hand and finger function	44.6
Walking and bending	33.3
Household tasks	25.1
Mobility	23.9
Arm function	18.5
Mood	17.3
Social activity	13.2
Self care	11.9
Work	9.0
Level of tension	8.7
Support from family	5.2

- Patients with preference for improvement in pain reported:
  - More severe pain than those not having pain as a preferred area for improvement.
  - Lower scores for pain self efficacy ($p<0.001$). This association remained significant in logistic regression analyses after adjustment for pain intensity.
  - Greater use of analgesic drugs ($p=0.002$), although 1/3 of patients did not report use of pain-relieving medication.
  - Greater fatigue (VAS, $p=0.001$) and worse global health (AIMS2, $p=0.004$).

- A bivariate association between preference for improvement in pain and perceived pain intensity remained after adjusting for age, sex and level of self-efficacy.
- Preferences for improvements in different health areas differed according to age. Older patients had greater preference for improvement in physical functioning; younger patients had greater preference for improvement in pain, work and mental conditions.
- There was no difference in preference between patients in disablement benefit and those who worked full time.

Assessment of bias: 34% non-response rate, validated Norwegian version of AIMS2 used. As there were more older non-respondants, this may have influenced the results as preferences for areas of improvement differed by age.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Iaquinta ML and Larrabee JH. Phenomenological lived experience of patients with rheumatoid arthritis. Journal of Nursing Care Quality: 19: 280 – 289, 2004 REF ID: 151.	Qualitative study 3+ Purposive sampling, US study, all Caucasian female although men and women of all races were sought. Results validated by participants.	N= 6	**Inclusion criteria:** purposive sample of patients living with RA **Exclusion criteria:** not mentioned **Baseline characteristics:** age range 43-67 years, disease duration range 7-38 years, all married and all Caucasian female, all took at least 2 medications, 4/6 had college education, 4/6 were health care professionals.	In-depth interviews with open ended questions	N/A	N/A	Exploration of the lived experience of RA	Not mentioned

Effect size

There were 6 major themes that emerged:

- Grieving while growing
  - This was an ongoing emotion and concerned the loss of ability to do things while making necessary changes in one's lifestyle. Grieving enhanced personal growth.
- Persuading self and others of RA's authenticity
  - Invisibility: particularly in the early stages of the disease there are no physical signs of RA, people don't understand the disease.
  - Pretending: participants pretended to be well when they were not, reluctance to discuss disease with others because of negative reactions.
  - Validation and understanding: from family particularly was an essential form of support.
- Cultivating resistance

- Courage needed to confront daily pain and apparent losses, and develop ways of dealing with pain and disability.
- Confronting negative feelings
  - Anger was a natural response to the pain and limitations imposed by the illness
  - Fear revolved around 4 major concerns: adverse effects of medications, future outcomes of the disease process, possible physical deformity and forced dependency, inability to assume usual personal and professional responsibilities.
  - Frustration
  - Self-consciousness around visible physical deformities.
  - Depression in response to pain and disease progression
- Navigating the healthcare system
  - Limited contact with providers and lack of continuity of care
- Masterminding new lifeways
  - Finding methods of disease management, adaptation to changes, and development of new skills and reconciliation of lost abilities.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jacobi CE, Boshuizen HC, Rupp I et al. Quality of rheumatoid arthritis care: the patient's perspective. *International Journal for Quality in Health Care.* 2004; 16(1):73-81. ID 2205	Observational-correlation study: 3 Outpatients clinics Amsterdam (patients taken from outpatient clinics)	Total N=882 **Drop-outs:** Died or moved address (N=41 and these were older than responders) Non responders to questionnaire (N=158 no demographic differences to responders)	**Inclusion criteria:** aged ≥ 16yrs; and able to meet the 1987 revised American College of Rheumatology (ACR) criteria for RA Baseline characteristics: mean age 61.5 years (SD 13.8); 71% female; Duration of RA 18.4 years (SD 11.9); single 33%; mean disease duration 10.7 yrs (SD 9.3); HAQ mean score 0.73 (SD 0.67), CES-D mean 12.0 (SD 8.9), total visit score mean 1.70 (SD 0.95)	No intervention given.	No comparison group.	NA	Participants were sent a postal questionnaire Questionnaires used: Questions included health characteristics, health care utilisation and patients' views on quality of care. Health characteristics were measured using the Health Assessment Questionnaire (HAQ) (20 items with responses from 0 (no difficulty) to 3 (unable to do); Mental health assessed with Centre for Epidemiological Studies depression scale (CES-D) (score 0 to 60 with a higher score indicating more depressive symptomatology); Health care utilisation measured by interacting with 5 different health care professionals (total visit score ranging from 0 (no use of health care) to 5 (use of all five health care	The Netherlands Organisation for Health Research and Development, Medical Sciences and the Dutch Arthritis Association

			[See outcome measures for details]				providers); Quality of care assessed using the QUOTE-questionnaire (29 items rated on a 4-point scale from not important to extremely important), by rating the performance of their health care providers (dichotomised score in to inadequate/adequate performance); and to evaluate the quality of care, performance of health care providers were weighted by the importance ratings	

Effect size

Aspects of care rated as the most important (top five rankings):

- Knowledge of rheumatism
- Information about concomitant use of medication
- Explain side-effects of medication
- Keep patient's file confidential
- Open to questions

Inadequate quality of care resulting from the weighting of health care providers' performance by the importance of ranking of aspects of care (aspects of care rated as inadequate quality > 15%):

Rheumatologist (N=638)

- Allow choice of another care provider 64.9%
- Give patient access to file 51.5%
- Give information about home adjustments 44.3%
- Give information about aids 32.4%
- Giving information about concomitant use of medication 26.3%
- Never allow waiting time to exceed 15 minutes 23.6%
- Explain side-effects of medication 18.7%
- Inform on course of symptoms 18.1%

General practitioner (N=146)

- Have modified toilet in practice 65.6%
- Giving patient access to file 51.7%
- Allow choice of another care provider 48.7%
- Give information about home adjustment 48.7%
- Never allow waiting time to exceed 15 minutes 46.3%
- Give information about aids 41.7%
- Give information in plain language 32.2%
- Having enough information about rheumatism 27.2%
- Rooms accessible for physically disabled people 25.4%
- Giving information about the concomitant use of medication 16.4%

Physiotherapist (N=223)

- Allow choice of another care provider 59.5%
- Having enough information about rheumatism 54.7%
- Give information about home adjustments 42.4%
- Have modified toilet in practice 37.9%
- Giving information about aids 28.8%

- Inform on course of symptoms 18.7%

Home nurse (N=31)

- Inform on course of symptoms 67.7%
- Give information about aids 45.0%
- Give information about home adjustments 40.0%
- Be easily accessible by telephone 35.3%
- Having enough information about rheumatism 32.3%
- Be open to questions 20.0%
- Assure good care coordination 22.2%
- Make sure the patients sees the same provider as each visit 21.1%

Formal home help (N=116)

- Having enough information about rheumatism 84.4%
- Assure good care coordination 44.8%
- Be open to question 39.0%
- Arrange a replacement when the provider is absent 34.2%
- Take enough time during consultation 21.8%
- Allow patients to (co)decide about treatment/help 17.1%

Overall, patient demographics did not explain the variance in the results

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Katz PP, Morris A, Yelin EH. Prevalence and predictors of disability in valued life activities among individuals with rheumatoid arthritis. *Annals of the Rheumatic Diseases.* 2006; 65(6):763-769. ID 2206	Observational-correlation study: 3 Single centre, USA (patients taken from a panel constructed in 1982 and were from practices in Northern California)	Total N=548 **Drop-outs:** Retention from year to year on the panel average 93%; the 7% attrition includes	**Inclusion criteria:** None stated Baseline characteristics: mean age 60.1 years (SD 13.2); 83.6% female; Duration of RA 18.4 years (SD 11.9); mean pain rating 30.1 (SD 26.9); severe or very severe disease 18.7%; morning stiffness duration 1 hr or more	No intervention given.	No comparison group.	NA	Participants interviewed annually by phone Questionnaires and interview used were: Valued life activity scale(VLA) consisting of 26 items covering obligatory, committed and discretionary activities including self care and recreational and social participation. In the telephone interview, participants rate the difficulty of performing the 26 life activities on a 4-point scale (0 no difficulty to 3 unable to perform)	None reported

		deaths	20.3%; joint changes in hands 49%; joint changes in feet 37.6%, comorbidities 0 48.5%, 1 36.1%, 2 or more 15.4%; Health Assessment Questionnaire mean 1.02 (SD 0.73)				3 summary measure scores: the number of activities individuals completely unable to do due to RA (unable), the number of activities that were affected by RA (unable to do or any level of difficulty; affected), and the average difficult score (difficulty). These scores were calculated for the total VLA scale and for the obligatory, committed and discretionary subscales. Predictors of VLA disability: o No. of painful joints/joint groups (list of 17) o No. of swollen joints/joint groups (list of 14) o Rating on pain severity on day of interview (0 no pain to 100 very severe pain) o Rating of fatigue in past 2 weeks (6 point scale with rating grouped in to moderate vs severe or very severe) o Duration of morning stiffness, less than one hour vs one hour or more o Changes in the shape or appearance of hands or feet (one open ended question)	

Effect size

1 The activities most often affected by RA were in the committed and discretionary activities:

Committed

- Heavy house 85%
- Minor repairs 82%
- Paid work 73%

Discretionary

- Gardening 87%
- Physical activities (moderate 80%, rigorous 78%)
- Hobbies 75%

VLA summary scores:

All activities

- Unable to perform at least one VLA activity 49.1%
- Mean number of activities 1.65 (SD 2.75)
- 6.3% of activities queried

- At least one VLA affected 94.9%
- Mean number of activities 12.01 (SD 7.40)
- Proportion of activities queried 46.2%

Predictors of VLA disability:

- All disease measures were significant predictors of HAQ score and accounted for a substantial portion of variance in HAQ (adjusted R^2 =0.45; data not reported)

In the model including symptom and demographic measures the following were significant predictors of life activity disability (total across obligatory, committed and discretionary; p<0.0001):

Unable

- Age
- Duration of RA
- Fatigue
- AM stiffness
- Model R^2 0.28 (for all unable to do activities)

Affected

- Pain rating
- Fatigue
- Model R^2 0.38 for all affected activities)

Difficulty

- RA duration
- Pain rating
- Fatigue
- AM stiffness
- Model R^2 0.43 for all difficult activities

In the model adding HAQ to the regression model the following were significant predictors of life activity disability (total across obligatory, committed and discretionary; p<0.0001):

Unable

- HAQ
- Model R^2 0.50 (for all unable to do activities)

Affected

- Age
- HAQ
- Model R^2 0.60 for all affected activities)

Difficulty

- HAQ
- Model R^2 0.75 for all difficult activities)

The increase in R^2 for models when HAQ was entered was significant at p<0.0001 in all cases

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kjeken I, Dagfinrud H, Mowinckel P et al. Rheumatology care: Involvement in medical decisions, received information, satisfaction with care, and unmet health care needs in patients with rheumatoid arthritis	Observational -correlation study: 3 Single Centre Norway (data was obtained from two disease registries established 1994 (register	Total N=1,193 RA N=1,041 AS N=152 **Drop-outs:** NA	**Inclusion criteria:** Diagnosis of RA and resident in Oslo (all patients who attended the data collection in the registers in 2004 were included) Baseline characteristics: mean age 61.5 years (SD 15.1); 78% female; still	No intervention given.	No comparison group.	NA	Participants completed postal questionnaires Questionnaires used were: Arthritis Self-Efficacy Scale (ASES) consisting of 5 statements on pain (10 lowest level to 100); Visual analogue scale of pain, fatigue or disease activity (0 no pain, fatigue or disease activity to 100); Medical Outcomes Study Short Form 36 (SF-36) a general health measures with 8 subscales; Stanford	None reported

and ankylosing spondylitis. *Arthritis & Rheumatism.* 2006; 55(3):394-401. ID 58	assessed to hold data on 85% on all possible RA cases in the Oslo region held at one hospital, Norway)		working 35%, Arthritis Self-Efficacy Scale (ASES) pain 53.9 (SD 18.5) [see outcomes for details of questionnaires] Duration of RA 14.1 years (SD 11.3); comorbidity present 62%, Disease activity (100-mm visual analogue scale (VA) 0 is no disease activity) 38.9 (SD 25.2), VA fatigue 46.6 (SD 29.5), VA pain 35.2 (24.2), modified Stanford Health Assessment Questionnaire (MHAQ) 1.6 (SD 0.55)				Health Assessment Questionnaire (SHAQ) of 8 items to measure activities of daily living (scale 1 to 4 where 4 indicates the worse health); Data on patient involvement in medical decisions, satisfaction with care and unmet health care needs was gained from questionnaires with open and close questions – information (3-point scale none/some/much), involvement (2 questions), satisfaction with care (5-point scale 0=very dissatisfied and 4=very satisfied), unmet needs (2 questions)	

Effect size

Entire population reported

Received information, involvement in medical decisions and satisfaction with care:

- Information about diagnosis and medication:
    - 12% received no information and 50% of these reported the need for more information
    - 48% some information and 57% of these reported the need for more information
    - 40% much information and 23% of these reported the need for more information

- Information about exercise:
    - 24% received no information and 69% of these reported the need for more information
    - 50% some information and 55% of these reported the need for more information
    - 26% much information and 17% of these reported the need for more information

- Information about daily activities:
    - 35% received no information and 48% of these reported the need for more information
    - 48% some information and 44% of these reported the need for more information
    - 17% much information and 11% of these reported the need for more information

- Involvement in medical decisions:
    - 25% no involvement and 70% of these reported the need for more involvement
    - 48% some involvement and 64% of these reported the need for more involvement
    - 25% much involvement and 40% of these reported the need for more involvement

- Satisfaction with care:
    - 31% very satisfied
    - 37% somewhat satisfied
    - 24% neutral
    - 5% somewhat dissatisfied
    - 3% very dissatisfied

Factors related to low or high involvement in medical decisions (bivariate analysis):

- Low involvement (75% of patients) compared with high involvement (25% of patients) in medical decisions was significantly associated with:

Personal

- Low age ($p<0.001$)
- Living with a partner ($p=0.025$)
- Still working ($p<0.001$)
- Longer time in formal education ($p<0.001$)

- Higher ASES scores ($p < 0.001$)

Disease
- Lower comorbidity ($p=0.006$)
- Lower disease activity ($p=0.010$)
- Lower fatigue ($p=0.034$)
- Lower pain ($p=0.027$)

Health care
- Greater satisfaction with care ($p<0.001$)

Factors related to high involvement in medical decisions (multivariate analysis):
- Low age ($p=0.004$)
- High level of formal education ($p=0.019$)
- High levels of patient satisfaction ($p<0.001$)
- High levels of received patient information ($p<0.001$)

Unmet health care needs:
A total of 40 (26%) of the patients with AS and 285 (27%) of patients with RA stated that they experienced unmet health care needs due to their arthritis, where as 37 (24%) of the AS respondents and 267 (26%) of the RA respondents described specific and most commonly, multiple needs (in rank order):
- Physical symptoms or consequences of the disease related to bodily structures and functions
- Quality of care
- Heath care services
- Psycho-social consequences
- Medication
- Comorbidity
- Activity and participation
- Concerns about future
- Others

Those with unmet health care needs reported:
- Worse health status in all domains on the SF-36 ($p<0.001$ for all domains)
- Higher incidence of comorbidity ($p=0.048$)
- Greater dissatisfaction with health care provided ($p<0.001$)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Neame R, Hammond A,	Observational-correlation	Total N=600 (questionnaires	**Inclusion criteria:** Age > 18 yrs	No intervention	No comparison	None	Participants sent postal questionnaire	None reported

Deighton C. Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. *Arthritis & Rheumatism.* 2005; 53(2):249-255. ID 2208	study: 3 (Patients obtained from a disease-modifying antirheumatic drugs (DMARD) monitoring database UK)	sent) N=344 (questionnaires received) **Drop-outs:** Responses 57.3% - respondents and non-respondents similar in age and gender	Baseline characteristics: 50% age > 65 yrs; 67% women and 63% no formal education; 50% retired, median disease duration 13.3 Yrs; mean MHA 1.92 (SD 1.92), mean fatigue VAS 57.0 (SD 28.2mm), mean pain VAS 47.7 (SD 25.0mm); 91% on DMARD and 55% reported adverse reactions; median number of DMARD used 3 (IQR 2 to 5) over median duration 10 yrs (IQR 4 to 19 yrs); mean RA knowledge score 51.8 (SD 23.3)	given.	group.		Questionnaires used: Data covering information-seeking and decision-making preferences, knowledge of RA, disease features, DMARD experience and sociodemographic factors; Information-making and decision-making preferences measured using Autonomy Preference Index (8 items) and Decision-Making Preference Scale (DMPS) (15 items). Responses were made on a 5-point Likert scale (scores o to 100 with 100 strongest preferences); Knowledge of RA using Arthritis Knowledge Questionnaire RA-specific subscale (11 items); Functional status using Health Assessment Questionnaire (HAQ); Visual Analogue Scales (VAS) for pain and fatigue.	

Effect size

Level of need for information:

- There was a greater desire for information in women compared to men, median ISPS score for women was 85.0 (IQR 80.0 to 92.5) and for men 82.5 (IQR 77.5 to 90.0; Z= -1.92; p=0.05)

The % of respondents with agreement or strong agreement with the statements:

- As you become sicker you should be told more and more about your illness (n=338) 95.2%
- You should understand completely what is happening inside your body as a results of your illness (n=339) 97.0%
- Even if the news is bad you should be well informed (n=340) 96.8%
- Your doctor should explain the purpose of your laboratory tests (n=339) 97.6%
- You should be given information only when you ask for it (n=338) 19.2%
- It is important for you to know all the side effects of your medications (n=340) 97.9%
- When there is more than one way to treat a problem, you should be told about each (n=340) 98.2%
- Information about your illness is as important to you as treatment (n=340) 94.7%

Sources of information:

- Doctors and nurses were the main sources of information > 90%.
- Charities were also a common source of information >50%

Associations with the need for information (bivariate):

Women

- Age (n=215) (rs= -0.26; p<0.001)
- Education (n=215) (rs= 0.18; p=0.01)

Men

- Fatigue VAS (n=80) (rs= 0.29; p=0.01)
- Number of DMARDs (n=87) (rs= 0.28; p=0.01)
- Men who reported adverse reactions were more likely to see information than those who had not (median ISPS 83.8 vs 80.0; Z= -2.2; p=0.03)

Level of desire for involvement in decision making:

- Information preference scores were significantly higher than decision-making preference scores (Z= -15.18; p<0.001)

The % of respondents with agreement or strong agreement with the statements:

- The important medical decisions should be made by the doctor not by you (n=333) 74.8%
- You should feel free to make decisions about everyday medical problems (n=331) 77.7%
- If you were sick, as your illness became worse you would want the doctor to take greater control (n=332) 79.5%

Associations with decision making preference scores:

Women

- Age (n=212) (rs= -0.41; p<0.001)
- Education (n=205) (rs= 0.31; (p<0.001)

- o No. of DMARDs (n=182) (rs= 0.06; p<0.01)
- o RA knowledge scores (n=210) (rs= 0.46; p<0.001)

Men

- o Age (n=105) (rs= -0.25; p=0.01)
- o RA knowledge scores (n=104) (rs= 0.28; p=0.01)

Hierarchical regression of decision-making preferences:

Women

- o Age (n=212) (partial r^2= -0.41; p<0.001) (F=41.36; Model r^2= 0.17)
- o Education (n=205) (partial r^2= 0.19; p<0.01) (F=24.83; Model r^2= 0.20)
- o No. of DMARDs (n=171) (partial r^2= 0.22; p=0.001) (F=16.42; Model r^2= 0.23)
- o DMARD adverse effects (n=170) (partial r^2= 0.16; p=0.03) (F=13.52; Model r^2= 0.25)
- o RA knowledge (n=168) (partial r^2= 0.30; p<0.001) (F=11.54; Model r^2= 0.33)

Men

- o Age (n=105) (partial r^2= -0.25; p=0.01) (F=6.65 Model r^2 0.06)
- o RA knowledge (n=104) (partial r^2= 0.23; p=0.02) (F=6.14 Model r^2 0.11)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Neugebauer A, Katz PP, Pasch LA. Effect of valued activity disability, social comparisons, and satisfaction with ability on depressive symptoms in rheumatoid arthritis. *Health Psychology.* 2003; 22(3):253-262. ID 208	Observational-correlation study: 3 (Patients obtained from an RA panel USA started in 1982)	Total N=436	**Exclusion criteria:** Scoring 7 or more on the Short Form of the Geriatric Depression Scale Baseline characteristics: mean age 59.9 (SD 13.0); 82% female; mean education 13.4 yrs (SD 2.7); mean disease duration 18.1 yrs (SD 10.6), Health Assessment Scale mean 1.1 (SD 0.7), Geriatric Depression Scale mean score	No intervention given.	No comparison group.	None	Participants participated in structured telephone interviews were conducted annually (data from 4 yrs are reported here) Questionnaires used: Short Form of the Geriatric Depression Scale (S-GDS) (yes/no answers with higher values indicating more depressive symptoms); Health Assessment Questionnaire (HAQ) (scores 0 – no functional impairment to 3.0 – severe impairment); Valued activity disability with 75 activities categorised into 13 separate domains of activity; Social comparison evaluations (11 items) to assess the difficulty experienced performing a range of life activities	None reported

			2.08 (SD 2.63), No. of activities affected mean 6.05 (SD 4.36), Social comparisons score mean 4.39 (SD 3.37); Satisfaction and Well-Being Scale mean score 43.80 (SD 9.15)				compared with some one of the same age without RA; Satisfaction with Activities and Well-being Scale (SAWS)	

Effect size

Do Valued Activity Disability and Comparison Evaluations mediate the effect of physical impairment on satisfaction with physical ability?

- Individuals who experienced greater physical impairment reported a greater number of valued activities affected by their RA (β= .692; p<0.01)
- People who experience greater physical impairment engaged in more unfavourable social comparisons (β= .44; p<0.01)

The effect of valued activity disability and comparison evaluations on satisfaction:

- There was a significant effect of both valued activity disability and comparison evaluations in 1997 on reported satisfaction with abilities in 1998 (adjusted). Greater disability in valued activities in the previous year were associated with lower satisfaction with physical abilities in the following year (β= .-.461; p<0.001)
- Unfavourable social comparison evaluations were associated with lower satisfaction (β= .364; p<0.01)

The effect of physical impairment on satisfaction:

- Individuals who experienced greater physical impairment in 1997 reported lower satisfaction with abilities (adjusted) in the following year (β= -.435; p<0.01)
- Poor functional status was a significant predictor of lower satisfaction after valued activity disability and comparison evaluations were controlled (β= .-.203; p<0.01) thus failing to support the hypothesis that valued activity disability and unfavourable comparison evaluations mediated the effect of functional status on satisfaction with physical ability

Does satisfaction with physical ability mediate the effect of physical impairment, valued activity disability and comparisons evaluations on depressive symptoms?

- Lower satisfaction with abilities was found to be significantly associated with higher levels of depressive symptoms (adjusted) (β= -.495; p<0.01)

The effect of physical impairment, valued activity disability and comparison evaluations on depressive symptoms:

- Poor functional status (β= .129; p<0.05); greater disability in valued activities (β= .182; p<0.01) and more unfavourable comparison evaluations (β= .119; p<0.05)
- Lower satisfaction with abilities in 1998 was significantly associated with higher levels of depressive symptoms in that same year (β= -.532; p<0.01)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Rupp I, Boshuizen HC, Dinant HJ, Jacobi CE, Van	Observational correlation study: 3	N=330 eligible patients	Inclusion criteria: RA patients recruited into a longitudinal survey	Dutch RA patients followed	N/A	2 years	Disability: assessed with the validated Dutch questionnaire capacities of daily life (VDF) derived	Jan van Breemen Institute, the

Den Bos GAM. Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain and depressive symptoms. Scand J Rheumatology 2006; 35: 175-181 Ref ID: 61	Aim: to study the associations between disability and HRQoL respectively, and radiographic joint damage, disease activity, pain and depressive symptoms among RA patients.	N=23 (7%) excluded due to missing radiographs N=307 included in the analysis	from a rheumatology outpatient centre in Amsterdam or an affiliated outpatient clinic. Patients had to have RA according to 1987 revised ACR criteria, >16 years, having sufficient command of the Dutch language. Baseline characteristics: Mean age (range): 58.1 ± 13.4 (23.4-91.3) Sex (% female) 71% Mean disease duration 6.4 ± 7.6 years	longitudinally			from the Health Assessment questionnaire (HAQ) HRQoL: assessed with a validated Dutch version of RAND-36. Physical (PCS) and mental (MCS) component summary scores were computed according to the manual for SF-36 health summary scales. Radiographic damage: scored according to the modified Sharp/van der Heijde method (SHS) by 2 blinded readers. Disease activity: assessed by the modified Disease Activity Score (DAS28). RA-related pain: measured with VAS (0-100) Depressive symptoms: assessed with a Dutch version of the Centre for Epidemiological Study Depression Scale (CES-D). Analyses: multivariate linear regression analyses performed with disability and HRQoL as dependent variables, controlled for age, gender, disease duration and comorbidity).	Dutch Arthritis Association, the Netherlands Organisation for Health Research and Development
Effect size **Disability and HRQoL (PCS and MCS) in relation to radiographic damage, disease activity, pain and depressive symptoms**. **Results from cross-sectional analyses:** Disability: significant predictor variables included pain (β 0.359, p ≤0.001), disease activity (β 0.236, p≤0.001), depression (β 0.232, p≤0.001) and radiographic damage (β 0.216, p≤0.001). [R^2 0.453] PCS: significant predictor variables included pain (β -0.488, p≤0.001), disease activity (β -0.259, p≤0.001) and radiographic damage (β -0.124, p<0.05). [R^2 0.500] MCS: significant predictor variables included depression (β -0.707, p≤0.001) and radiographic damage (β 0.191, p≤0.001). [R^2 0.559]								

Results from longitudinal analyses:
Disability: significant predictor variables included change in disease activity (β -0.195, p≤0.001), change in pain (β -0.330, p≤0.001) and change in radiographic damage (β -0.135, p<0.05). [R^2 0.249]
PCS: significant predictor variables included change in disease activity (β -0.178, p≤0.001), change in pain (β -0.343, p≤0.001). [R^2 0.176]
MCS: significant predictor variables included change in depression (β -0.496, p≤0.001). [R^2 0.286]

In none of the multivariate models did the effects of age, gender, disease duration or comorbidity remain statistically significant for effects on disability or HRQoL.

Conclusions: pain, with respect to disability and PCS, and depressive symptoms, with respect to MCS, were more important predictors than radiographic damage and disease activity. The independent contributions of radiographic joint damage and disease activity to predicting disability and HRQoL are limited. Background variables did not show any statistically significant effects in multivariate analyses.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, Van Den Bos GAM. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis & Rheumatism 2004; 51(4): 578-585 Ref ID: 2210	Observational-correlation study: 3 Aim of the study: to elucidate fatigue in RA and evaluate the impact of fatigue on HRQoL, taking into account 2 other important potential sequelae of RA: RA-related pain and depressive symptoms.	N=841 eligible N=683 (81%) responded N=490 (58%) had complete clinical data and were used in the analyses	Inclusion criteria: RA patients recruited into a longitudinal survey from a rheumatology outpatient centre in Amsterdam or an affiliated outpatient clinic. Patients had to have RA according to 1987 revised ACR criteria, >16 years, having sufficient command of the Dutch language. Baseline characteristics: Mean age (range): 60.7±13.4 (23.4-91.3) Sex (% female) 72.7% Cohabiting (%) 65.2% Mean disease duration 10.7 ± 9.2	RA patients treated at an outpatient centre in Amsterdam.	N/A	N/A	Health related quality of life (HRQoL): measured using validated Dutch version of the RAND 36-item health survey (RAND 36). Fatigue: Global assessment of fatigue severity measured using VAS (0-100) Multidimensional Fatigue Inventory (MFI-20) Depressive symptoms: Measured using a Dutch version of the Centre for Epidemiologic Studies Depression Scale (CES-D) [An adjusted CES-D was also calculated taking into account possible criteria contamination due to RA-related items or overlap in symptomatology]. RA related pain: Measured using VAS (0-100)	Not mentioned

	They are trying to identify which aspects of fatigue are related to different aspects of HRQOL.		years Comorbidity 60% reported at least 1 comorbid condition					

Effect size

Multidimensional assessment of fatigue by MFI-20:	**Mean ± SD (range)**
General fatigue (GF)	13.4 ± 4.9 (4-20)
Physical fatigue (PF)	12.4 ± 4.6 (4.20)
Reduced activity (Rac)	11.1 ± 4.8 (4-20)
Reduced motivation (RM)	9.9 ± 4.3 (4-20)
Mental fatigue (MF)	8.2 ± 4.2 (4-20)

Correlation between fatigue, RA-related pain and depressive symptoms and HRQoL:

- Within the MFI-20
  - All aspects of fatigue (GF, PF, Rac, RM) except mental fatigue were highly correlated with each other.
  - Mental fatigue showed the weakest correlation with the other dimensions of fatigue (ρ=0.321-0.407).
  - GF and PF were strongly correlated (ρ=0.806).
- VAS for fatigue correlated highly with general fatigue (ρ=0.786) and physical fatigue (ρ=0.719) but only moderately with the other dimensions of MFI-20.
- Mental fatigue and RA-related pain were not correlated (ρ =0.173).
- Correlation between the adjusted CES-D and the original CES-D was very strong (ρ =0.938)
- All aspects of HRQoL were significantly correlated with fatigue, RA-related pain and depressive symptoms but the strength of the correlations differed between and within the different dimensions of the RAND-36.

Impact of fatigue, RA-related pain and depressive symptoms on HRQoL (results of multivariate regression analyses which controlled for sociodemographic variables, disease duration, disease activity, co-morbidity and additionally for other predicting variables in the model [i.e. MFI-20, RA-related pain and depressive symptoms]):

- Different aspects of fatigue selectively explained different dimensions of HRQoL while taking into account pain and depression.
  - Physical functioning: physical fatigue and RA-related pain had a statistically significant negative impact.
  - Social functioning: physical fatigue, reduced activity, depressive symptoms and RA-related pain had a statistically significant negative impact.
  - Role limitations physical: physical fatigue, mental fatigue, RA-related pain and depressive symptoms had a statistically significant negative impact.
  - Role limitations emotional: reduced activity, mental fatigue, RA-related pain and depressive symptoms had a statistically significant negative impact.
  - Mental health: mental fatigue and depressive symptoms had a statistically significant negative impact.
  - Vitality: physical fatigue, reduced activity, reduced motivation and depressive symptoms had a statistically significant negative impact.
  - Pain: physical fatigue, reduced activity, RA-related pain and depressive symptoms had a statistically significant negative impact.

o General health perception: physical fatigue and depressive symptoms had a statistically significant negative impact.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Rupp I, Boshuizen HC, Roorda LD, Dinant HJ, Jacobi CE, Van Den Bos GAM. Poor and good health outcomes in rheumatoid arthritis: the role of comorbidity. The Journal of Rheumatology 2006; 33: 1488-95 Ref ID: 2211	Observational-correlation study: 3	N=882 enrolled N=529 (60%) completed questionnaire in 2002. N=117 deaths N=15 moved to an unknown address	Inclusion criteria: RA patients recruited into a longitudinal survey from a rheumatology outpatient centre in Amsterdam or an affiliated outpatient clinic. Patients had to have RA according to 1987 revised ACR criteria, >16 years, having sufficient command of the Dutch language. Patients were randomly selected from strata of disease duration to cover the heterogeneity of RA within the selected group. Baseline characteristics: Mean age (range): 59.8 ± 14.8 Sex (% female) 71.9% Mean disease duration 8.9 ± 9.8 years	Dutch RA patients followed longitudinally	N/A	5 years	RA-related pain: measured with VAS (0-100) Disability: assessed with the validated Dutch questionnaire capacities of daily life (VDF) derived from the Health Assessment questionnaire (HAQ) HRQoL: assessed with a validated Dutch version of RAND-36. Physical (PCS) and mental (MCS) component summary scores were computed according to the manual for SF-36 health summary scales. **Predictive factors:** Sociodemographic factors: age, sex, marital status, having paid work, socioeconomic status (SES) as indicated by education level. RA-specific clinical factors: disease activity (assessed by the modified Disease Activity Score [DAS28]) and RF positivity. Co-morbidity: somatic co-morbidity (assessed by a self-report list adapted from the Health Interview Survey of Statistics Netherlands); psychological co-morbidity focussed	Jan van Breemen Institute, the Dutch Arthritis Association, the Netherlands Organisation for Health Research and Development

			Marital status 64% married/ cohabiting RF (% positive) 62.6% Differences between total baseline population and respondents: Respondents at baseline had better HRQoL (PCS p<0.001; MCS p<0.05), less disability (p<0.001), were younger (p<0.001) and had a more favourable SES (p<0.001). They did not have less RA-related pain (p=0.3) and did not differ with respect to gender (P=1.0).				on depressive symptoms (assessed with a Dutch version of the Centre for Epidemiological Study Depression Scale [CES-D]). Analyses: multivariate linear regression analyses performed with disability and HRQoL as dependent variables, controlled for age, gender, disease duration and co-morbidity).	
Effect size **Aim:** to investigate the predictive value of sociodemographic factors, RA-specific clinical factors, and co-morbidity in patients with RA with respect to relatively poor and good (long term) health outcomes. Patient profiles:[3] In univariate analyses, poorer outcome patients in comparison to best outcomes patients were more often women, older, had a less favourable SES, had pain work less often and were loss often married/cohabiting. They had higher disease activity assessment (except for MCS) and reported more somatic and psychological co-morbidity. RF (Rheumatoid factor) was only elevated with respect to disability among poorest outcomes patients. Factors predicting outcomes:								

[3] 10% of patients with poorest outcomes were compared with 10% of patients with best outcomes in univariate analyses in order to determine if the patient profiles obtained were different.

	Factors predicted poorer outcomes	Factors predicted better outcomes
Disability	Female sex (p<0.05) Older age (p<0.05) RF positivity (p<0.05) Disease activity (p≤0.001) Somatic co-morbidity (p<0.05) Psychological co-morbidity (p≤0.001)	Disease activity (p≤0.01) Psychological co-morbidity (p≤0.001)
Pain	Disease activity (p≤0.001) Somatic co-morbidity (p≤0.01) Psychological co-morbidity (p≤0.001)	Older age Disease activity (p≤0.001) and psychological co-morbidity (p≤0.001) reduced the risk of better outcomes
HRQoL (PCS)	Disease activity (p≤0.01) Somatic co-morbidity (p≤0.001) Psychological co-morbidity (p≤0.001) Medium SES (p<0.05) reduced the risk of poorer outcomes.	The following factors reduced the risk of better outcomes: Disease activity (p≤0.001) Somatic co-morbidity (p<0.05) Psychological co-morbidity (p≤0.001)
HRQoL (MCS)	Psychological co-morbidity (p≤0.001) Disease activity (p≤0.001)reduced the risk of poorer outcomes	Somatic co-morbidity Psychological co-morbidity (p≤0.001) reduced the risk of better outcomes

Conclusions: next to RA-specific clinical factors, co-morbidity is a major predictive factor for poor and good health outcomes.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Barlow JH, Cullen LA, and Rowe IF. Comparison of knowledge and psychological well-being between patients with a short disease duration (< or = 1 year) and patients with more established rheumatoid arthritis (> or = 10 years duration). Patient	Cross sectional study 3	N= 102 **Drop-outs:** n/a	**Inclusion criteria:** age ≥18 years, definite diagnosis of RA according to ARA criteria **Exclusion criteria:** Nil mentioned **Baseline characteristics:** the late RA group were significantly older (p<0.00), a higher proportion had co morbidity (p=0.03), fatigue (p=0.02) and higher HAQ scores (p=0.0005); fewer patients had educational qualifications (p=0.03). Early RA: Age mean 48.0 (SD 12.06),	Patients with short disease duration (≤1 year) N=33	Patients with long disease duration (≥10 years) N=69	Not applicable	Physical functioning assessed with HAQ Pain VAS Fatigue VAS Psychological wellbeing measured with Hospital Anxiety and Depression Scale (HADS) Adjustment to RA measured by the Acceptance of illness scale (AIS)	Not mentioned

Education & Counseling: 38: 195 – 203, 1999 REF ID: 366.			disease duration mean 0.03 years (SD 0.47), female 91%, educational qualifications 61%, co-morbidity 30%, fatigue 5.34 (SD 2.76), physical functioning (HAQ) 1.22 (SD 0.79). Late RA: Age mean 64.68 (SD 7.28), disease duration mean 23.52 years (SD 9.56), female 78%, educational qualifications 36%, co-morbidity 54%, fatigue 6.68 (SD 2.62), physical functioning (HAQ) 1.91 (SD 0.75).				Knowledge about RA measured using the Rheumatoid Arthritis Patient Knowledge Questionnaire. Information needs assessed with items from the Educational and Psychosocial Issues Questionnaire	
Effect size There were no statistically significant differences between the groups for RA patient knowledge. Higher pain and lower acceptance were predictors for higher anxiety levels. Higher fatigue and lower acceptance were predictors for higher depression levels. Need for information demonstrated similar patterns across the two groups, there was no statistically significant difference between the groups.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**	
F. Chilton and R. A. Collett. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. *Musculoskeletal Care* 6 (1):1-14, 2008. ID 3474	Observational study with component: 3+ UK: from a Rheumatology department	Total N=190 patients for questionnaire (had been receiving 2 or more DMARDs - combination or triple therapy but not an anti-TNF agent). N=7 patients for interview (patients who	**Inclusion criteria:** Adults with RA who had been receiving 2 or more DMARDs (combination or triple therapy but not an anti-TNF agent). **Exclusion criteria:** None mentioned. **Baseline characteristics:** Questionnaire group: Median age 65 years; female 79%; Disease duration not mentioned Interview group: Median age 52 years; female 71%; Disease	Semi-structured interview or questionnaire	Immediate	Questionnaire (Patients who had not take anti-TNFs) - Scenario questions, predominantly close-ended questions: patients read a scenario and then answered questions which involved choosing and identifying factors that influenced their treatment choice from 3 anti-TNF therapies: etanercept, adalimumab and infliximab.	Arthritis Research Care; British Health Professionals in Rheumatology	

		had changed from one anti-TNF to another) Response rate to questionnaire was 56%	duration not mentioned			Interviews (patients who had tried more than 1 anti-TNF): treatment preferences and how their current treatment had been decided	

Effect size

Patients views on who should choose medicine

- Patients who had not used anti-TNFs:
  - 41% wanted rheumatologists to decide, 33% wanted to decide themselves, 18% were unsure and 7% preferred joint decision.
  - Men were significantly more likely to want rheumatologists to make decisions (61% of men vs 36% of women, $p<0.05$)
  - There was NS difference between young and old patients for who should decide.
  - Some patients did not feel confident about making decisions without further support and discussion with healthcare staff; one patient felt internet information had 'death was quoted an awful lot'
- Patients who had used anti-TNFs:
  - Those who had been offered treatment choice from the start found shared decision-making positive and beneficial and made the patients want to choose their treatment
- All patients wanted to be involved in treatment decisions

Themes on how treatment decisions had been arrived at:

- Relinquished decision: "leave it in the hands of the doctor" as the "doctor knows best"
- Forced/informed choice: the doctor's preference maybe because he had more success with a particular drug so he "pushed it…whereas the other drug might be the one that you really want"
- Shared decision: 2allowing you to come back to another consultation…go away and thinking. You have to be sure it's the one *you* want"
- Patient choice: patients choose for themselves, "information should be provided in such a way as not pushed into it"

Summary: interviewees interpreted informed decision-making as receiving information on the treatment options, and health professionals making the final decisions. Shared decision-making was interpreted as allowing the patient to discuss options and information with a health professional, taking time out to read the information, and then returning with a decision.

Travel to the clinic for drug administration

- 37% had difficulty travelling to hospital and almost half wanted to administer their own medicine
- 52% of older patients (>61 years) had significantly more transport difficulties than younger patients ($p<0.001$).
- Convenience was a common theme…"how much hassle it is for somebody who can't walk, is crippled…*to get* into hospital. The benefits of being treated at home are brilliant…to administer the medicine myself…takes me out of the hospital environment"

Administration of drugs

- Almost half of patients preferred to administer their own treatment, but over half were not confident about self-injecting
- Older patients were significantly more likely to want hospital staff to administer treatment ($p<0.01$) whereas younger patients preferred self-administration ($p<0.05$)

Treatment preferences

- The most popular choice and choice as a first treatment for both groups was adalimumab because it was convenient to administer and allow them to regain control of their

lives.

- Patients already on anti-TNFs preferred their current treatment because of its minimal effects on their everyday lives.
- Patients felt that Sc drugs gave patients independence to continue their everyday routine, eliminated regular contact with the hospital, easier to administer and gave tem a sense of normality.
- Factors influencing coice of sc drug were: not needing to prepare the medicine, reduced potential for drug errors, use of a ready-to-use syringe with the correct dose, convenience and not needing to travel to the hospital.
- For patients who felt not needing to travel to hospital was important, they were significantly more likely to choose an sc drug over infliximab ($p<0.001$).
- Those who chose iv medication were more likely to feel it important that 'staff were available if problems arose', have 'contact with patients/meeting others' (both $p<0.001$)
- Side-effects, needle phobia or route of drug administration were not factors significantly associated with a preference for sc or iv drugs.
- Some patients felt that infliximab had restricted their lifestyles and their lives revolved around hospital appointments every 8 weeks, which was a particular problem for those who did not like hospitals.
- Patients who had not taken anti-TNFs before had anxieties about drug administration and whether they would receive enough support, whereas those who had taken anti-TNFs before were concerned with time constraints and psychological issues experienced during infusions.
- Those who had received infliximab by infusion felt that they were disempowered by events around them, and felt guilty at being in a unit where patients with cancers were also treated.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
T. Stamm, L. Lovelock, G. Stew, V. Nell, J. Smolen, H. Jonsson, G. Sadlo, and K. Machold. I have mastered the challenge of living with a chronic disease: Life stories of people with rheumatoid arthritis. *Qualitative Health Research* 18 (5):658-669, 2008.	Qualitative study: 3+ Austria: from a Rheumatology outpatient clinic. To identify the patients, the strategy of **maximum variation sampling** was applied (the principle is that if you deliberately try to interview a very different selection of people, their aggregate answers can be close to the	Total N=10 patients	**Inclusion criteria:** Paid work experience (part or full-time, but at least 20 hours per week), but no regular paid work at the time of the interviews; no history of psychiatric and/or other neuromotor disease. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Mean age not given; female 80%; Disease duration not given.	Interviews: 1. Open-ended questions 2 and 3. Topic questions asked and other questions arising from the context of the interviewee's life story which did not follow the rules for formulating topic questions could be asked.	Consecutive interviews - Immediate	Questions about patients' life stories; hypotheses built and 'typologies' emerged (types of themes – general aspects of the structure of more than one life story.	Not mentioned

ID 3558	whole population's).						

Effect size

OVERALL: some patients regarded RA as a challenge for mastery in their lives, whereas others adapted to their disease and 'made the best out of a bad situation'

2 main typologies were developed:

1. RA as a 'source of new challenges'

- For some patients, RA was viewed as a challenge and they were actively involved in mastering it
- Mastering is more than adapting – but having the upper hand, possessing skill or technique
- Patients engaged in occupations and activities which were experienced as challenging for them before and after having the disease (some replaced work with other challenging occupations and activities)
- For those unable to engage in their job, the unpaid occupations they engaged in were as challenging or more challenging than their paid work had been
- Some patients had some unresolved problems such as desire for physical activities which they were unable to fulfil
- For those brought up in sociocultural environments where there was an emphasis on cognitive success, patients felt that because of their RA that they now had a chance to experience their body and it gave them new perspectives on life.
- Some patients were different and their main challenging activity for mastering the disease was to actively negotiate with several institutions to access financial funds to help them deal with the physical limitations caused by RA.
- Some of the women had no family support and were expected to fulfil responsible tasks because family members were dependent on them – they needed the help provided by institutions to deal with RA.

2. RA as 'something to get used to' and 'to make the best out of a bad situation'

- Some patients gradually adapted to life with RA – make something out of that situation or at least accept the situation
- Learned step by step to live with the disease – they did not attribute an overall positive or negative value, nor did they view RA as a new perspective or challenge for their lives but instead they learned to accept and deal with the symptoms of RA and loss of paid work.
- One patient was initially overwhelmed by experiencing the symptoms of RA but finally got used to his role as a patient.
- One patient ignored symptoms for a long time, also ignoring fact that she might have to give up her job; they eventually found other meaningful activities, such as gardening to better adapt to their life with RA. They adapted their life by making daily activities easier for herself.
- Adaptation was a continuing process which finally led to a state of adaptation
- One patient's experience of the beginning of the disease was that their symptoms were suddenly there as they were suddenly one day unable to perform particular ADLs
- Several patients found or created for themselves eaningful occupations and activities such as gardening or adapting their home to live with RA.
- One patient had a different aspect of adapting – they accepted life with RA without having found challenging activities and adapted to being passive.
- The patient missed the social aspect of their job as they were mostly at home and was very disabled unable to walk unassisted. This patient was not receiving appropriate medical treatment and had high inflammatory activity.
- Despite staying at home and his wife going to work, this patient did not change the traditional gender roles – he still saw his role in the household as helping his wife.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of

							funding
G. J. Treharne, A. C. Lyons, D. A. Booth, and G. D. Kitas. Psychological well-being across 1 year with rheumatoid arthritis: coping resources as buffers of perceived stress. *British Journal of Health Psychology* 12 (Pt:3):3-45, 2007. ID 3483	Observational-correlation study: 3 UK: patients recruited from outpatient clinics	Total N=189 patients for questionnaire (N=154 completed, N=141 at 6 months and N=134 at 1 year) Response rate to questionnaire was 81% at baseline, 75% at 6 months and 71% at 1 year)	**Inclusion criteria:** Adults with RA (ACR criteria). Split into 3 duration groups: <6 months (early RA), 1-7 years (intermediate RA) and >7 years (long-standing RA) **Exclusion criteria:** None mentioned. **Baseline characteristics:** All: Mean age 55 years; female 75%; Disease duration mean not mentioned	Questionnaires	1 year follow-up	Questionnaires: Psychological well-being – Hospital Anxiety and Deptression scale (HADS); Life satisfaction – Quality of Life Scale (QOLS); Stress and Coping – Perceived Stress Scale (PSS); Optimism/Pessimism – Life Orientation Test (LOT); Socail support – Social support survey (SSS); Active behavioural and active cognitive coping – Coping Schedule for Stress (CSS); Physical well-being – ESR, VAS pain and fatigue; functional disability – HAQ.	Department of Rheumatology of the Dudley Group of Hospitals NHS Trust and the School of Psychology of the University of Birmingham, UK. Grants provided by ARC and Amgen, UK.

Effect size

- Employed patients had significantly lower depression than those not employed
- Disease duration, inflammation, antidepressant use and presence of comorbidity did not relate to psychological well-being
- Greater pain correlated significantly with greater depression
- Greater fatigue correlated significantly with lower life satisfaction
- Greater functional disability related significantly to higher depression and lower life satisfaction
- Optimism, pessimism and perceived stress tended to relate significantly to all psychological well-being outcomes
- General social support related significantly to lower depression and greater life satisfaction
- Healthcare social support and active cognitive and behavioural coping did not correlate significantly with any psychological well-being outcome
- At baseline, there was little effect of active behavioural coping on depression among people with lower stress; however, among those with higher stress, engaging in active behavioural coping was related to lower depression.
- There was little effect of active cognitive coping on life satisfaction at 6 months among people with lower stress, however among those with higher stress, engaging in active cognitive coping was related to higher life satisfaction at 6 months.

Authors' conclusions: Patients with RA under greater perceived stress who do not use active coping strategies appear to be at risk of psychological comorbidity and may therefore benefit from interventions teaching specific active coping strategies. Larger observational studies and interventions are required to confirm and extend these findings.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. M. Veehof, E. Taal, M. J. Willems, and DeLaarM Van. Determinants of the use of wrist working splints in rheumatoid arthritis. *Arthritis Care and Research* 59 (4):531-536, 2008. ID 3556	Qualitative descriptive study: 3+ The Netherlands: patients recruited from hospital files	Total N=18 patients	**Inclusion criteria:** Adults with RA who had recently (≤12 months earlier) received a fabric wrist working splint from their rheumatologist because of RA-relate wrist pain **Exclusion criteria:** None mentioned. **Baseline characteristics:** Patients: Mean age 56 years; female 78%; Disease duration not mentioned	Questionnaire	Immediate	In-depth Interviews (semi-structured): Splint use; prescription and knowledge; disadvantages; expectations; appearance, comfort and fit; social environment	ReumaOnderzoek Twente Foundation, The Netherlands

Effect size

1. **Prescription and knowledge**

- 2 types of splints were prescribed: Roylan D-ring and a Futuro splint (both had removable volar metal stay)
- Some patients did not receive advice from their rheumatologists on wearing the splint and others were advised to wear it when they had painful wrist – day and/or night and performing heavy activities
- Reasons and purposes for prescription: pain reduction, inflammation, swelling, rest, immobilisation, support, protection and reduction of tingling feelings.
- Few patients returned to the rheumatologists for control of their splint only Most did not need or already had to go to the hospital so many times.
- Majority were satisfied with the information they received during splint prescription.
- Some had inaccurate knowledge of washing of the splint or why the splint was prescribed

2. **Splint use**

- Many patients splint use was dependent upon the seriousness of the symptoms and were often worn only during periods of pain, swelling or tingling feelings
- If patients used their splint, they used it during heavy activities or the whole day and/or night.
- Many did not wear it during wet or dirty activities, personal care activities or at night
- Some did not wear it at parties, when visiting people or during meals

3. **Advantages**

- All patients stated that reduction of symptoms was the major reason to wear the splint; supplementary reasons were wrist support and rest/immobilisation
- The splint reduced pain, tingling feelings and swelling/inflammation
- Advantages included: sudden movements were not possible as the wrist is fixed in the splint however this may also be a disadvantage as it made it inconvenient to perform certain aspects of getting dressed due to lack of mobility.
- Other advantages were improved functional abilities, prevention of overload of the wrist, increased strength, improved sleep and less hard squeezing of oter people's hands during hand shaking.

4. **Disadvantages**

- The majority of patients also experienced decreased functional ability and almost all removed their splints when this occurred
- The splint got wet and dirty easily and had long drying time
- Other disadvantages: unpleasant physical contact with the splint due to the hard metal stay, sweating, wear and tear, difficulty wearing gloves and long-sleeved garments, inability to wear a watch, prohibited ability to drive a car and inability to remove the splint independently.
- These disadvantages were sometimes reasons for patients not to wear the splint.

5. **Expectations**

- Most patients had positive expectations with regard to the effectiveness of the splint; some did not believe it would relieve their symptoms.
- Some did not wear their splint the whole time because they did not want to become used to it and were afraid their wrist would become stiff or weak.

6. Appearance, comfort and fit

- Most patients were neutral or negative on the appearance of their splint; a few patients were positive.
- Neutral patients felt the appearance was not important and felt they would gladly wear the splint, regardless of how it looks if they had pain.
- Patients who were negative felt appearance was a reason to remove the splint during special occasions such as going out, dining or visiting people.
- Many patients were generally positive about the fit and comfort of the splint but nearly all made negative remarks about the material, metal stay and straps and/or side-effects. For some patients these complaints were reason enough to take off the splint

7. Social environment

- Almost al patients had responses from family members and acquaintances about their splint
- Most reactions were: what is wrong and why is the splint worn and many offered to help relieve the burden of work on the wrist
- Some patients received attention from unknown people such as staring or asking what is wrong.
- Many patients felt the reactions they received di not influence their splint use. Some were persuaded by their partners to wear or not wear the splint in certain situations.

- **Overall:** The majority of patients indicated that their splint use was dependent on the seriousness of the symptoms (Pain, swelling, or tingling feelings) they perceived. Important reasons to wear the splint were reduction of symptoms, wrist support, and immobilisation of the wrist. Important reasons to stop wearing the splint were reduced functional abilities using the splint and the performance of dirty or wet activities.

- **Authors' conclusions:** The reasons for patients to wear and not wear working wrist splints are related to intentional decisions of the patients, which are primarily based on perceived benefits and barriers of splint wearing. The results of this study have been used to develop educational and behavioural strategies to increase adherence to wearing wrist working splints.

5.2 Patient education (EDU)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. P. Riemsma, J. R. Kirwan, E. Taal, and J. J.	MA: 1++ RCT's of MA: 1- to 1++ SR included: N=50 trials	Total N=9026.	Inclusion criteria: RCTs; confirmed diagnosis of RA (adults >18 years	Patient education interventions that include an instructional	No intervention control group	Follow-up ranged from 8 days to 18	Pain (AIMS2, VAS); Disability (HAQ, M-HAQ); Joint counts	No external sources of

Rasker. Patient education for adults with rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (2):CD003688, 2003. ID 844	(N=9026) MA included: N=31 trials with data Trials were similar in terms of: • Study design (All RCTs) • Comparison group (no intervention) • Intervention (patient education) Trials differed with respect to: • Blinding (N=7 RCTs double blind; N=20 RCTs single blind; N=23 RCTs no blinding) • Study size (range N=18 to N=1140) • Study quality – max score of 8 (N=21 studies reasonable to good quality; N=29 poor quality) • Study duration – length of intervention (7 hours to 15 months) • Study duration – length of follow-up (8 days to 18 months) Tests for heterogeneity and quality assessment performed.		with clinical confirmation of diagnosis); studies with mixed populations but only data for RA patients were included in the analyses. Trials included were both from published and unpublished data. Search was from 1966 – 2002 (September). Exclusion criteria: cluster randomised studies (only those with the patient as the unit of randomisation were included); studies in which the intervention was only behavioural (eg. Biofeedback) without an educational component, or was only social support.	component; Intervention had to have a formal structured instruction on RA and on ways to manage arthritis symptoms. Studies were also included if they used modern psychobehavioual methods to promote changes in health behaviours. As a complement to instruction, interventions could include exercise, biofeedback or psychosocial supports.		months.	(Ritchie articular index, ACR count number of swollen and tender joints, Thompson's Articular Index); Patients and Physicians global assessment (AIMS, VAS); Psychological status, anxiety and depression (HAD, CES-D, ZSRDS); Disease Activity (ESR, CRP).	funding.

Effect size

Results: all studies, all measures pooled

- Patient education was significantly better than no intervention for:
  - Disability (N=2275; effect size SMD -0.17, 95% CI -0.25 to -0.09; p<0.001) at first follow-up;
  - Joint counts (N=1158; effect size SMD -0.13, 95% CI -0.24 to -0.01; p=0.03) at first follow-up;
  - Patient global assessment (N=358; effect size SMD -0.28, 95% CI -0.49 to -0.07; p=0.008) at first follow-up;
  - Psychological status (N=1138; effect size SMD -0.15, 95% CI -0.27 to -0.04; p=0.010) at first follow-up;
  - Depression (N=1170; effect size SMD -0.14, 95% CI -0.23 to -0.05; p=0.004) at first follow-up;

- There was NS difference between patient education and no intervention for:
  - Anxiety at first follow-up (N=1328) and at final follow-up (N=990);
  - Pain at first follow-up (N=2219) and at final follow-up (N=1073);
  - Disease Activity (N=718) at first follow-up and at final follow-up;
  - Disability (N=1308) at final follow-up;
  - Joint counts (N=974) at final follow-up;
  - Patient global assessment (N=618) at final follow-up;
  - Psychological status (N=794) at final follow-up;
  - Depression (N=1143) at final follow-up;

Results: all studies, individual measures

- Patient education was significantly better than no intervention for:
  - Pain – VAS (12 RCT's, N=1112; effect size WMD -0.38, 95% CI -0.71 to -0.05; p=0.02) at first follow-up;
  - Disability, HAQ (10 RCT's, N=375; effect size WMD -0.11, 95% CI -0.20 to -0.01; p=0.03) at final follow-up;
  - Joint counts - Ritchie Articular Index (8 RCT's, N=548; effect size WMD -1.79, 95% CI -3.29 to -0.29; p=0.02) at first follow-up; 8 RCT's, N=472; effect size WMD -1.55, 95% CI -3.08 to -0.02; p=0.05)
  - Depression – HAD depression (4 RCTs, N=375; effect size WMD -0.62, 95% CI -1.21 to -0.02; p=0.04) at first follow-up.

- There was NS difference between patient education and no intervention for:
  - Pain – VAS (12 RCT's, N=1112) at final follow-up;
  - Pain – AIMS2; AIMS-pain (6 RCT's, N=768) at first follow-up and at final follow-up;
  - Disability – HAQ (10 RCTs, N=625) at first follow-up;
  - Disability – AIMS2 Physical function (3 RCT's, N=559) at first follow-up and at final follow-up;
  - Joint counts - Ritchie Articular Index at final follow-up (8 RCT's, N=472);
  - Patient global assessment (all instruments) at first follow-up (5 RCT's, N=324) and at final follow-up (3 RCT's, N=247);
  - Psychological status – all instruments (8 RCTs) at first follow-up and at final follow-up (9 RCTs);
  - Anxiety – all instruments (13 RCTs) at first follow-up and at final follow-up;
  - Depression – HAD depression at final follow-up;
  - Depression – all other instruments (15 RCTs) at first follow-up and at second follow-up;

- Disease Activity – ESR or CRP (11 RCTs, N=662) at first follow-up and at final follow-up.

Subgroup-analysis of the 17 trials with higher quality scores (≥3) found that:

- Patient education was significantly better than no intervention for:
  - Disability (N=1586; Effect size SMD -0.20, 95% CI -0.35 to -0.05; p=0.01) at first follow-up;
  - Patient global assessment (N=190; Effect size SMD -0.32, 95% CI -0.60 to -0.03; p=0.03) at first follow-up;
  - Psychological status (N=831; Effect size SMD -0.18, 95% CI -0.31 to -0.04; p=0.01) at first follow-up;
  - Depression (N=1105; effect size SMD -0.21, 95% CI -0.32 to -0.09; p<0.001) at first follow-up;

- There was NS difference between patient education and no intervention for:
  - Pain at first follow-up and final follow-up;
  - Joint counts at first follow-up and at final follow-up;
  - Anxiety at first follow-up and at final follow-up;
  - Disease activity – ESR and CRP at first follow-up and at final follow-up;
  - Disability at final follow-up;
  - Patient global assessment at final follow-up;
  - Psychological status at final follow-up;
  - Depression at final follow-up.

Author's conclusions:
Patient education had small, short-term effects on disability, joint counts, patient global assessment, psychological status and depression. There was no evidence of long-term benefits. Patient education was provided in addition to standard medical care so the effects of education are always supplementary to the benefits of standard medical care.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hammond A, Young A, Kidao R. A randomised controlled trial of occupational therapy for people with early rheumatoid arthritis. Annals of the Rheumatic Diseases: 63: 23 – 30, 2004	RCT 1++ • Single blind (Assessor) • Randomised (computer + sealed envelopes) • Controlled • Powered study • ITT analysis	N= 326 **Drop-outs:** Total 65/326 (19.9%) OT 28/162 (17%) Control 37/164 (23%)	**Inclusion criteria:** ≥18 years, diagnosed with RA by a rheumatology consultant within the past 2.5 years, required active medical treatment, no or minimal OT previously, speak and read English adequately to complete assignments. **Exclusion criteria:** not mentioned **Baseline characteristics:** OT group: Age mean 53.9 years	OT + usual rheumatology care OT over 6-8 weeks, lasting total of 8 hours. Intervention content: comprehensive information	Usual rheumatology care only	6-8 week streatment; follow-up at 2 yeras	HAQ Arthritis Impact Measurement Scale 2 (AIMS2) DAS28 Arthritis Self Efficacy Scale (ASES) Self reported	North Thames Regional Health Authority R&D response funding programme Arthritis research campaign

REF ID: 2992			(SD 13.9); female 74.7%; Duration of RA 9.0 months (SD 7.7), on DMARD 78%, AIMS PF>3.33 in 32%. <u>Control group</u>: Age mean 57.1 years (SD 13.5); female 70%; Duration of RA 9.9 months (SD 8.8), on DMARD 72%, AIMS PF>3.33 in 38%. The control group was significantly older (p=0.04). No differences in baseline variables were found between those than completed and those that dropped out.	about RA, taught self-management methods and included advice usually provided by other staff (exercise and foot care).			adherence	

Effect size

P<0.01 considered significant due to the large number of tests conducted.

OT vs. CONTROL

- The OT group had significantly better outcomes with respect to the following:
  - Some self management methods were used significantly more than the control group particularly hand and arm exercises (p<0.001 for both), joint protection (p<0.01) and rest (p=0.05).
  - Receipt of a working splint (p=0.001), although they were not worn more often in the OT group (p=0.48).
  - Receipt of a resting splint (p=0.001)
  - Owning of assistive devices; these OT group owned on average 2.5 (SD 2.8) assistive devices vs. 1.4 (SD 2.1) in the control group (p=0.001)
  - Use of assistive devices, the OT group used these more often (p=0.002).
- There were no significant differences between the groups for any of the disease, physical, functional, psychosocial or hand measures; neither was there any trend approaching significance.
- There were no significant differences between the groups for the primary outcomes by ACR functional classes at baseline.

Conclusion: OT improved self management but not health status in early RA.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
H. L. Brus, M. A. van de Laar, E. Taal, J. J.	RCT: 1+ Single centre trial in The Netherlands	Total N=65 randomised (N=32 Education	**Inclusion criteria:** Adults with RA (ACR criteria); <3 years duration;	Education programme (taught by healthcare professionals)	Education leaflet (Dutch League against	1 year (3 months post-intervention)	Number of painful and swollen joints; Compliance with treatments; Disease	Grant from the National Committee for the

Rasker, and O. Wiegman. Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis. *Annals of the Rheumatic Diseases* 57 (3):146-151, 1998. ID 172	• Randomised (block randomisation, method not mentioned) • Single blind • No mention of ITT analysis	programme, N=33 Education leaflet). **Drop-outs:** EDU prog: N=7 (22%) EDU leaflet: N=3 (9%)	active disease (ESR >28 mm/1st hour, 6 or more painful joints, 3 or more swollen joints. **Exclusion criteria:** DMARD therapy other than hydroxychloroquine. **Baseline characteristics:** EDU programme: mean age 59.7 years (SD 15.0); Female 92%; Duration of RA = Early RA (<3 years inclusion criteria). EDU leaflet: mean age 58.7 years (SD 9.2); Female 70%; Duration of RA = Early RA (<3 years inclusion criteria). There were NS differences between the groups for any of the baseline characteristics except for gender and Dutch AIMS2 mobility scale which were significantly worse in the education programme group.	Content focused on compliance with SSZ therapy, physical exercises, endurance activities, advice on energy conservation and joint protection. 4 x 2 hour meetings during the first month with reinforcement meetings at 4 and 8 months. Healthcare professionals provided information on RA, problems and basic treatment. During group meetings patients beliefs were discussed as well as problems and possible solutions, training in physical exercises, planning of treatment and contracts of intentions. All patients in both groups were given DMARDs (SSZ, 500 mg tablets. Daily dose was increased in 4 weeks by steps of 1 tablet until a daily dose of 4 tablets was reached. Individual cases could be increased to 6 tablets/day, reduced or stopped at discretion of the rheumatologist.	Rheumatism) Content included information on RA, medication, physical and occupational therapy.		activity (DAS score – function of ESR, Ritchie score and number of swollen joints. Score 0-10 = worse activity); Physical function (Dutch M-HAQ); Dutch AIMS questionnaire; Range of Motion; CRP; ESR.	Chronically Ill, The Netherlands.

Effect size

EDUCATION PROGRAMME + DMARD (SSZ) vs EDUCATION LEAFLET + DMARD (SSZ)

- Education programme + DMARD was significantly better than the Education leaflet + DMARD for:
  - Compliance with physical exercise (min/week, change from baseline) at 3 months (30 and 5 respectively, p<0.05) at 3 months (mid-treatment);
  - Compliance with energy conservation (scale 0-4, change from baseline) at 3 months, mid-treatment (0.7 and -0.1, p.001) and 12 months, 3 months post-intervention (0.4 and -0.2 respectively, p<0.05);
  - Compliance with joint protection (scale 0-10, change from baseline) at 3 months, mid-treatment (0.9 and -0.2, p.001).

- There was NS difference between the Education programme + DMARD and the Education leaflet + DMARD for:
  - Compliance with physical exercise (min/week, change from baseline) at 6 months (mid-treatment) and 12 months (3 months post-intervention);
  - Compliance with endurance activities (min/week, change from baseline) at 3 months and 6 months (mid-treatment) and 12 months (3 months post-intervention);
  - Compliance with energy conservation (scale 0-4, change from baseline) at 6 months (mid-treatment);
  - Compliance with joint protection (scale 0-10, change from baseline) at 6 months (mid-treatment) and 12 months (3 months post-intervention);
  - DAS score (change from baseline) at 3 months and 6 months (mid-treatment) and at 12 months (3 months post-intervention);
  - M-HAQ score (change from baseline) at 3 months and 6 months (mid-treatment) and at 12 months (3 months post-intervention);
  - AIMS subscales (change from baseline) at 3 months and 6 months (mid-treatment) and at 12 months (3 months post-intervention);
  - CRP (change from baseline) at 3 months and 6 months (mid-treatment) and at 12 months (3 months post-intervention);
  - Range of Motion (exorotation of shoulders, extension and flexion of elbows and knees) at 3 months and 6 months (mid-treatment) and at 12 months (3 months post-intervention).

- Education programme + DMARD was worse than the Education leaflet + DMARD for:
  - Total number of withdrawals (N=7, 22% and N=3, 9% respectievly) over 12 months (3 months post-intervention).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
K. Freeman, A. Hammond, and N. B. Lincoln. Use of cognitive-behavioural arthritis education programmes	RCT: 1+ Single centre trial in UK • Randomised (block randomisation, method not mentioned)	Total N=64 randomised (N=30 Standard Education, N=34 Cognitive-behavioural Education).	**Inclusion criteria:** Adults 18-65 years old with newly diagnosed RA (ARA criteria). **Exclusion criteria:** Other medical condition affecting functional	Cognitive-behavioural education programme (taught by healthcare professionals) Cognitive behavioural education: Accurate information about disease and its treatment with	Standard education programme (taught by healthcare professionals) Content and presentation similar to the	3 and 6 months post intervention.	AIMS2 subscales (Physical function, pain, affect, current health); tender and swollen joints (28 joint count); Early morning stiffness; Pain (VAS); Rheumatoid Attitudes Index – higher scores = poorer sense of internal	Trent Regional Health Authority and the Hospital Savings Association (via the Chartered Society of Physiotherapy), UK.

in newly diagnosed rheumatoid arthritis. *Clinical Rehabilitation* 16 (8):828-836, 2002. ID 2190	• Single blind • No mention of ITT analysis • Sample size calculation (for self-efficacy score) • High drop-outs in the standard education group	**Drop-outs:** Std EDU: N=8 (27%) Cog-behav EDU: N=2 (5.8%)	ability. **Baseline characteristics:** mean age 51.4 years (SD 11.3); Female 85%; Duration of RA = Early RA (<2 years, mean 4.5 months). Author's state that there were NS differences between the groups for any of the baseline characteristics except for AIMS2 physical function and RAI helplessness which were significantly worse in the cognitive-behavioural education group.	emphasis on prevention of joint pain, joint deformity and loss of joint function followed by reassurance that treatment could be effective. Goal setting, modelling and persuasion were used. The programme aimed to facilitate physical coping strategies, promoting the use of positive health behaviours and concentrated on 1 aspect of behavioural change: joint protection. More than 50% of the programme was practice of positive health behaviours. Both education programmes were 8 hrs duration (afternoon or evening sessions spread over 4 weeks).	cognitive-behavioural programme. Presentations from all members of the multidisciplinary team and 3 short practical sessions on relaxation, joint protection and exercise.		control and worse learned helplessness); Total self-efficacy score (aggregate score of Arthritis Self-efficacy scale subsets of pain, function and other symptoms); ESR.	

Effect size

COGNITIVE-BEHAVIOURAL EDUCATION PROGRAMME vs STANDARD EDUCATION PROGRAMME

- Cognitive-behavioural education programmes was significantly better than the Standard Education programme for:
  - AIMS2 affect subscale (level of mood) at 3 months post-intervention (p=0.01);
  - RAI arthritis helplessness subscale at 3 months post-intervention (p=0.003);
  - AIMS2 physical function subscale at 3 months post-intervention (p=0.009)

- There was NS difference between the Cognitive-behavioural education programme and the standard education programme for:
  - Early morning joint stiffness at 3 months post-intervention
  - ESR at 3 months post-intervention
  - Pain (VAS) at 3 months post-intervention
  - AIMS2 current health subscale at 3 months post-intervention and 6 months post-intervention;
  - AIMS2 symptom subscale at 3 months post-intervention and 6 months post-intervention;
  - RAI arthritis internality subscale at 3 months post-intervention and 6 months post-intervention;
  - Total self-efficacy scale at 3 months post-intervention and 6 months post-intervention.
  - Number of tender and swollen joints (28 joint count) (p=0.03**)
  - AIMS2 physical function subscale at 6 months post-intervention(p=0.03**)

****NOTE: level of significance was set as p<0.01 by authors; at baseline AIMS2 physical function and RAI helplessness were significantly worse in the cognitive-behavioural education group.**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Hammond and K. Freeman. One-year outcomes of a randomized controlled trial of an educational-behavioural joint protection programme for people	RCT: 1+ Single centre trial in UK • Randomised (blocks of 4, method not mentioned) • Allocation concealment • Single blind • No mention of ITT analysis	Total N=139 randomised (N=67 Standard Education, N=72 Joint protection Education). **Drop-outs:** Std EDU: N=5 (8%)	**Inclusion criteria:** Adults 18-65 years old with RA (diagnosed within last 5 years); hand pain on activity; history of wrist and/or MCP joint pain and inflammation. **Exclusion criteria:** Other medical condition affecting	Joint protection education programme (taught by healthcare professionals) Joint protection education: Information pack and workbook with principles of joint protection and pictures of protection methods. Programme applied educational, behavioural, motor	Standard education programme (taught by healthcare professionals) Short talks from healthcare professionals on disease, treatments (including drugs, alternative	6 and 12 months post intervention.	Hand Pain experienced during moderate activity in the last week (VAS); Adherence with joint protection (Joint Protection Behaviour Assessment – evaluates joint protection methods while performing 20 tasks required to make a hot drink and snack meal –score 0-40 if all tasks performed correctly, score	Arthritis Research Campaign, UK.

with rheumatoid arthritis. *Rheumatology* 40 (9):1044-1051, 2001. ID 118	• Power study (for Pain, VAS; based on a previously published trial)	Joint protection EDU: N=7 (11%)	hand function. **Baseline characteristics:** Standard Education group: mean age 51.6 years (SD 9.7); Female 71%; Duration of RA = Early RA (<2 years, mean 21.3 months); Pain (VAS) 40.0 (SD 26.0). Joint protection Education group: mean age 49.5 years (SD 11.4); Female 82%; Duration of RA = Early RA (<2 years, mean 17.5 months); Pain (VAS) 38.5 (SD 23.8). There were NS differences between the groups for any of the baseline characteristics.	learning and self-efficacy enhancing strategies to increase adherence to the programme as well as a range of educational methods to match different group members' learning styles. Programme included practicing hand-joint protection methods in small groups, demonstration of various options for task performance so could select methods that worked best for them, goal setting, problem-solving methods / discussions to generate solutions. Info also given on the disease, outcomes and drug therapy. Both education programmes were 8 hrs duration (4 afternoon or evening sessions of 2 hrs each).	therapies, exercise, joint protection and other pain control methods); demonstration and practice of exercise, joint protection and relaxation; information leaflets. Programme was designed to be typical of that provided in the UK.		converted into percentage). Indicators of Disease Activity: Eular 28 tender and swollen joint count; patient and assessor's global ratings of disease severity (5 point Likert Scale); Overall Pain in the last week (VAS); number of disease flare-ups in the last 6 months. Functional assessment (AIMS2 – score 0-10 = worst function); Grip strength; Range of Movement and Deformity (Joint alignment and Motion scale); Psychological status (Self-efficacy Pain and Other Symptoms subscales – higher score = better self-efficacy; Rheumatoid Attitudes Index – higher scores = poorer sense of internal control and worse learned helplessness).	

Effect size

JOINT PROTECTION EDUCATION PROGRAMME vs STANDARD EDUCATION PROGRAMME

- Joint protection education programmes was significantly better than Standard Education programme for:
  - Joint Protection behaviour assessment (mean score 17.9 and 30.7 respectively, p=0.001) at 12 months post-intervention;
  - Hand Pain, VAS (mean score 46.6 and 33.6 respectively, p=0.02) at 12 months post-intervention;
  - Early morning stiffness (mean score 81.9 and 45.4 respectively, p=0.01) at 12 months post-intervention;
  - Assessor's global disease status (median score 3.0 and 2.0 respectively, p=0.003) at 12 months post-intervention;
  - Patient's global disease status (median score 3.0 and 2.0 respectively, p=0.03) at 12 months post-intervention;
  - AIMS2 dimension of ADLs, 0-10 (mean score 2.1 and 1.3 respectively, p=0.04) at 12 months post-intervention;
  - Number of disease flare-ups in the last 6 months (p=0.004) at 12 months post-intervention;;
  - Number of visits to doctor in previous 6 months (mean visits 1.1 and 2.0 respectively, p<0.01) at 12 months post-intervention;
  - Number of patients participating in physiotherapy (p=0.005) at 12 months post-intervention.

- There was NS difference between the joint protection education programme and the standard education programme for:
  - Change in drug therapy use at 6 months and 12 months post-intervention;
  - Pain (VAS) at 12 months post-intervention;
  - Number of tender joints, 28-joint count at 12 months post-intervention;
  - Number of swollen joints, 28-joint count at 12 months post-intervention;
  - Grip strength at 12 months post-intervention;
  - Hand joint alignment and motion (JAM scale 0-80) at 12 months post-intervention;
  - AIMS2 scores (upper and lower limbs) at 12 months post-intervention;
  - ASE dimensions of pain and other symptoms at 12 months post-intervention;
  - Rheumatoid Attitudes index (RAI) dimensions of helplessness and internality at 12 months post-intervention;
  - AIMS2 dimensions of current health status and satisfaction with health at 12 months post-intervention;
  - Numbers of deformities at 12 months post-intervention;
  - Number of patients participating in occupational therapy at 12 months post-intervention.

Info from original paper: "Whilst both groups had reduced wrist and similar MCP range of movements to baseline, the joint protection group had developed fewer dominant hand wrist radial deviation (X^2 3.72; p = 0.05), wrist anterior subluxation (X^2 = 4.47; p = 0.03) and 2-5 MCP ulnar deviation (X^2 11.39; p = 0.02) deformities."

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Hammond and K. Freeman. The long-	RCT: 1+ Single centre trial in UK • Randomised (blocks of 4,	Total N=139 randomised (N=67 Standard	**Inclusion criteria:** Adults 18-65 years old with RA (diagnosed within last 5 years); hand	Joint protection education programme (taught by healthcare professionals)	Standard education programme (taught by healthcare	4 years post intervention.	Hand Pain experienced during moderate activity in the last week (VAS); Adherence with joint protection (Joint	Arthritis Research Campaign, UK.

outcomes from a randomized controlled trial of an educational-behavioural joint protection programme for people with rheumatoid arthritis. *Clinical Rehabilitation* 18 (5):520-528, 2004. ID 66	method not mentioned) • Allocation concealment • Single blind • No mention of ITT analysis • Power study (for Pain, VAS; based on a previously published trial)	Education, N=72 Joint protection Education). **Drop-outs at 4 years:** Std EDU: 21%) Joint protection EDU: 11%	pain on activity; history of wrist and/or MCP joint pain and inflammation. **Exclusion criteria:** Other medical condition affecting hand function. **Baseline characteristics:** Standard Education group: mean age 51.6 years (SD 9.7); Female 71%; Duration of RA = Early RA (<2 years, mean 21.3 months); Pain (VAS) 40.0 (SD 26.0). Joint protection Education group: mean age 49.5 years (SD 11.4); Female 82%; Duration of RA = Early RA (<2 years, mean 17.5 months); Pain (VAS) 38.5 (SD 23.8). There were NS differences between the groups for any of the baseline characteristics.	Joint protection education: Information pack and workbook with principles of joint protection and pictures of protection methods. Programme applied educational, behavioural, motor learning and self-efficacy enhancing strategies to increase adherence to the programme as well as a range of educational methods to match different group members' learning styles. Programme included practicing hand-joint protection methods in small groups, demonstration of various options for task performance so could select methods that worked best for them, goal setting, problem-solving methods / discussions to generate solutions. Info also given on the disease, outcomes and drug therapy. Both education programmes were 8 hrs duration (4 afternoon or evening sessions of 2 hrs each).	professionals) Short talks from healthcare professionals on disease, treatments (including drugs, alternative therapies, exercise, joint protection and other pain control methods); demonstration and practice of exercise, joint protection and relaxation; information leaflets. Programme was designed to be typical of that provided in the UK.		Protection Behaviour Assessment – evaluates joint protection methods while performing 20 tasks required to make a hot drink and snack meal –score 0-40 if all tasks performed correctly, score converted into percentage). Indicators of Disease Activity: Eular 28 tender and swollen joint count; patient and assessor's global ratings of disease severity (5 point Likert Scale); Overall Pain in the last week (VAS); number of disease flare-ups in the last 6 months. Functional assessment (AIMS2 – score 0-10 = worst function); Grip strength; Range of Movement and Deformity (Joint alignment and Motion scale); Psychological status (Self-efficacy Pain and Other Symptoms subscales – higher score = better self-efficacy; Rheumatoid Attitudes Index – higher scores = poorer sense of internal control and worse learned helplessness).	

Effect size

JOINT PROTECTION EDUCATION PROGRAMME vs STANDARD EDUCATION PROGRAMME

- Joint protection education programmes was significantly better than Standard Education programme for:
  - Joint Protection behaviour assessment (p=0.001) at 4 years post-intervention;
  - Early morning stiffness (p=0.001) at 4 years post-intervention.
  - AIMS2 dimension of ADLs, 0-10 (p=0.04) at 4 years post-intervention;

- There was NS difference between the joint protection education programme and the standard education programme for:
  - Number of patients taking RA medication (DMARDs, NSAIDs or low-dose oral steroids) at 4 years post-intervention;
  - Assessor's rating of disease severity at 4 years post-intervention;
  - Number of patients participating in physiotherapy at 4 years post-intervention;
  - Number of patients participating in occupational therapy at 4 years post-intervention;
  - Hand Pain (VAS) at 4 years post-intervention;
  - Pain (VAS) at 4 years post-intervention;
  - Number of tender joints, 28-joint count at 4 years post-intervention;
  - Number of swollen joints, 28-joint count at 4 years post-intervention;
  - Grip strength at 4 years post-intervention;
  - Patient's global disease status at 4 years post-intervention;
  - AIMS2 scores (upper and lower limbs) at 4 years post-intervention;
  - ASE dimensions of pain and other symptoms at 4 years post-intervention;
  - Rheumatoid Attitudes index (RAI) dimensions of helplessness and internality at 4 years post-intervention;
  - Number of visits to doctor in previous 6 months at 4 years post-intervention;
  - Number of disease flare-ups in the last 6 months at 4 years post-intervention;
  - AIMS2 dimensions of current health status and satisfaction with health at 4 years post-intervention.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mayoux-Benhamou Giraudet-Le Quintrec JS. Effect of a collective educational program for patients with rheumatoid	RCT: 1++ Single centre trial, France • Randomised (shuffled marked cards) • Allocation concealmen	Total N=208 randomised (N=104 in each group). **Drop-outs:** EDU: N=8	**Inclusion criteria:** Adults with RA (ACR criteria) **Exclusion criteria:** Juvenile chronic arthritis, Steinbroker class IV, pregnancy, presence of RA flare.	Education programme (taught by healthcare professionals - multidisciplinary) + information leaflet weekly Sessions of 6 hrs each for 8 weeks; booster session at 6 months	Control (usual medical care + information leaflet)	1 year	HAQ; DAS28; Arthritis Helplessness Index (AHI); EMIR (QoL); AIMS2; FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue scale); Physical activity scores (Baecke questionnaire);	Grant from PHRC, France

arthritis: a prospective 12-month randomized controlled trial. *Journal of Rheumatology* 34 (8):1684-1691, 2007. ID 3460	t • Single blind • True ITT analysis • Slightly underpowered (HAQ score)	(8%) CONTROL (usual care): N=11 (11%)	**Baseline characteristics:** EDU programme: mean age 55 years; Female 86%; Duration of RA = Established RA (mean duration 12 years). Control (usual care): mean age 54 years; Female 85%; Duration of RA = Established RA (mean duration 14 years). There were NS differences between the groups for any of the baseline characteristics	Intensive education programme - Content included information on the disease and treatment, also pointed to possibilities to reduce pain and stress at home, to understand how to use non-chemical treatment, lifestyle advice, coping strategies, relaxation and physical exercise including teaching of a home exercise programme to be followed.			Knowledge of RA.	

Effect size

EDUCATION PROGRAMME + LEAFLET vs USUAL MEDICAL CARE + LEAFLET

- The Education programme + leaflet was significantly better than the Usual medical care + leaflet group for:
  - Coping (p=0.03)
  - QoL (EMIR) symtomatic dimension (p=0.03)
  - Knowledge (p<0.0001)
  - Patient satisfaction (p=0.02)

- There was NS difference between the Education programme + leaflet and the Usual medical care + leaflet for:
  - Nocturnal awakening at 1 year
  - Morning stiffness at 1 year
  - DAS28 at 1 year
  - HAQ (QoL) at 1 year
  - HADS anxiety and depression at 1 year
  - QoL (EMIR) dimensions of physical, psychological, social and work at 1 year
  - Fatigue (FACIT-F) at 1 year
  - Physical activity (Baecke questionnaire – sports activity and hobbies)
  - Behavioural changes at 1 year

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Helliwell PS, O'Hara M, Holdsworth J, Hesselden A, King T, Evans P. A 12-month randomised controlled trial of patient education on radiographic changes and quality of life in early rheumatoid	RCT 1++ UK population • Randomisation using random numbers • Allocation concealment • Single-blind (assessors) • ITT analysis	N=79 Dropout rate: N=2 deaths (not study related) N=4 did not complete education sessions but were included in	**Inclusion criteria** Patients had a diagnosis of RA (using 1987 ARA criteria) of < 5 years; able to read and speak English, had not previously participated in a group patient education programme. **Exclusion criteria** Nil mentioned **Baseline characteristics** There were no significant	N=43 Education programme (EG): In a standard recommended format education sessions took place over 4 weeks in afternoon sessions lasting 2 hrs each. The format was a talk from a non-medical health professional, a discussion period and distribution of supporting literature. Content of sessions included the pathophysiology of RA, drug treatments, local treatments, mechanisms and control of	N=34 Not specifically described ? standard care Control group (CG)	12 months	Primary outcomes: Modified Larsen radiological score of hand and writs x-rays, SF-36 QOL questionnaire Secondary outcomes: Health assessment	Not mentioned

arthritis. Rheumatology 1999; 38: 303-308 ID: 149		analyses.	differences between groups at baseline. Sex (M/F): CG 10/24 EG 16/27 Age [median(range)]: CG 56.5 (28-78) EG 55 (23-71) Disease duration [median(range)]: CG 3.5 (0-5) EG 3 (0-5) Initial Larsen score: CG 36 (4-96) EG 37 (7-87) Duration of most recent DMARD (months): CG 14 (1-60) EG 12 (1-70)	pain, stress, exercise and rest, joint protection, task allocation, splinting and assistive equipment.			questionnaire adapted for a British population (HAQ), Ritchie articular index (RAI), Patient knowledge questionnaire (PKQ), Compliance questionnaire (CQ), plasma viscosity (PV), pharmaceutical changes and consulting behaviour	

Effect size

EDUCATION PROGRAMME vs STANDARD CARE

Radiological progression: There were significant improvements in Larsen scores from baseline in both groups(CG p=0.001; EG p=0.03), but there was no significant difference between groups in radiological progression at 12 months (p=0.13).
SF-36: the 'social functioning' and 'general health perception' subscales showed a significant improvement in the education group but there was no significant difference between the groups for any of the included dimensions at 12 months.
HAQ: there was no significant difference between groups.
RAI: there was no significant difference between groups.
PKQ: patient knowledge increased significantly from baseline in both groups (CG p=0.02; EG p=0.001) with a greater increase occurring in the EG (p=0.0002 for the between group difference).
CQ: there was no significant difference between groups.
PV: there was a modest reduction in PV in the control group (p=0.05 from baseline) but no significant difference between the groups.
Consulting behaviour: appointments and admissions did not differ between the groups.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hill J, Bird H,	RCT: 1+	Total N=100	**Inclusion criteria:** ≥ 18	Experimental group (EG)	Control group	24	An independent	Arthritis

Johnson S. Effect of patient education on adherence to drug treatment for rheumatoid arthritis: arandomised controlled trial. *Ann Rheum Dis* 2001; 60: 869-875 ID: 119	Single centre trial in UK • Randomised (computer-generated randomisation) • Randomisation stratified by knowledge status • Concealed allocation • Single blind • No mention of ITT analysis • Fairly high withdrawal rates	**Drop-outs:** 37/100 CG N=19/49 (38.7%); N=3 withdrawn by the impartial observer EG N=18/51(35.3%); N=12 withdrawn by the impartial observer	years, had a positive diagnosis of RA using ARA criteria, plasma viscosity (PV) ≥1.75 mPa.s or a C-reactive protein (CRP) > 10 mg/l. In addition they should have 2 of 3 clinical features: an articular index >15, morning stiffness >45 minutes, a minimum of moderate levels of pain. **Exclusion criteria:** receipt of DPA previously, contraindications such as kidney impairment or pregnancy, receiving incompatible concomitant drugs, awaiting hospital admission as in hospital drugs are administered by nurses. **Baseline characteristics:** Age [median (range)] CG 62 (34-79) EG 63 (22-74) Sex (N female) CG 39/49 EG 34/49 Median duration of RA:	N=51 7 x 30 minute sessions of one to one patient education (PE) Nurse taught PE programme based on theory of self-efficacy. The programme comprised information about the types of drugs used for RA, the disease process physical exercise, joint protection, pain control, and coping strategies. Written information including a DPA drug information leaflet developed specially for the study was provided as back up. The leaflet provided information in a question and answer format and supplied information about DPA, how and when to take it, unwanted side effects, and described safety monitoring.	(CG) N=49 Standard management. Patients were provided with the same DPA drug information leaflet alone. Patients also met with the rheumatology nurse practitioner and were invited to talk about their social lives and families, ensuring equity of consultation time.	weeks	blind assessor carried out all clinical assessments. Adherence measured by: - phenobarbitone concentrations[4]. Poor adherence was defined as an LDR indicating patients had taken less than 85% of the drug prescribed. Therapeutic outcome measures: - CRP - articular index (AI) - morning stiffness - pain score (details not mentioned)	Research Campaign, Northern and Yorkshire R&D Directorate

[4] Phenobarbitone 2mg was encapsulated with each 125mg and 250mg of DPA in a standard capsule, resulting in a dose of 2mg daily for the first 4 weeks, and 4 mg thereafter. The ratio of phenobarbitone level in the blood to prescribed dose (LDR) was calculated for each patient for each visit.

			CG 12 (0.33-45) years EG 13 (1-37) years <u>Baseline pain</u> CG 3.49 (2-5) EG 3.40 (2-5) Morning stiffness (min) CG 187 (0-600) EG 126 (0-600) Articular index CG 25.5 (4-52) EG 28.9 (5-52)					

Effect size

EDUCATION PROGRAMME vs STANDARD CARE

<u>Adherence:</u>
EG 32 (14%) non adherent vs CG 42 (19%) non adherent. CG was adherent on fewer occasions than the EG, and this was significant ($p<0.05$).
Adherence in the EG improved over time, EG more adherent than CG after 8 weeks, peaked adherence at 95% in week 16 ($p=0.05$ for between group comparison), levelled of at 90% adherence for the remainder of the study. CG became less adherent over time, although at study end differences failed to reach significant levels ($p=0.06$)

When analysed with the inclusion of those who had been withdrawn by the independent observer, initially CG were more adherent at week 4 ($p=0.375$), but at week 8 EG were more adherent ($p=0.451$). EG became more adherent over time and the CG became less adherent over time, $p=0.01$ at week 12, $p=0.01$ at week 16, $p=0.02$ at week 20 and $p=0.01$ at week 24.

<u>Therapeutic outcomes:</u>
Despite the increased adherence in the EG, there was no additional improvement in clinical outcome.
PV: CG had significantly higher entry levels of PV than those in the EG ($p<0.05$). Levels of PV fell significantly in both groups (-1.81 CG, -1.70 EG; $p<0.01$). With the exception of week 4, PV levels remained higher in the CG throughout the study ($p<0.01$).
CRP: Levels of CRP fell significantly in both groups (-39 CG, -25 EG; $p<0.01$). There was no significant difference in CRP between groups on completion of the study ($p=0.55$).
Pain scores: Both groups showed significant within-group improvements in pain scores, but there was no significant difference in between-group scores at 24 weeks ($p=0.440$).
Articular index: Both groups showed significant within-group improvements in pain scores, but there was no significant difference in between-group scores at 24 weeks ($p=0.326$).
Morning stiffness: Both groups showed significant within-group improvements in pain scores, but there was no significant difference in between-group scores at 24 weeks ($p=0.412$).

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
W. Van	RCT: 1+	Total N=59	**Inclusion**	Spouse Included	Patient only	4 weeks	Disease activity (DAS,	Grant from

Lankveld, Helmond T. van, G. Naring, D. J. de Rooij, and Hoogen F. van den. Partner participation in cognitive-behavioral self-management group treatment for patients with rheumatoid arthritis. *Journal of Rheumatology* 31 (9):1738-1745, 2004. ID 2188	Single centre trial in The Netherlands • Randomised (poor method – consecutive admission to alternate treatments) • Single blind True ITT analysis	couples randomised (N=31 Spouse Included self-management programme, N=28 Patient only education programme). **Drop-outs:** EDU Spouse included prog: N=1 (3%) EDU patient only prog: N=1 (4%)	**criteria:** Adults with RA (ACR criteria) who were in a stable relationship for at least 1 year. **Exclusion criteria:** Psychiatric or physical comorbidity in the partner. **Baseline characteristics:** Spouse Included EDU programme: mean age 49 years (SD 12.0); Female 62%; Duration of RA = Established RA (mean duration 4.5 years). Patient only EDU programme: mean age 50 years (SD 14.1); Female 67%; Duration of RA = Established RA (mean duration 11.2 years).	Education programme (taught by healthcare professionals) 8 Sessions of 1.5 hrs each for 4 weeks (in both groups). Content same as for the Patient only programme except spouses attended the sessions and the lessons also focused on patient-partner coping and effects of the disease. All patients in both groups continued to receive their regular medical treatment. On average this included 6 hrs of physical therapy and 2 hrs of OT during the intervention.	self-management Programme (taught by healthcare professionals) Content included education and cognitive-behavioural techniques. Information on RA and its treatments by the healthcare professionals / multidisciplinary team, with emphasis on the importance of the patient's behaviour and to encourage patients to practice active coping skills. Some sessions on changing the patient's cognitions and behaviour by using RET (Rational Emotive Therapy) – taught by a psychologist.	(end of treatment) with follow-up at 2 weeks and 6 months post-intervention.	composite score of ESR, number of swollen joints and number of painful joints using 28-joint count); Physical functioning (IRGL dimensions of mobility, dexterity and pain. Higher scores + higher levels of mobility, dexterity and pain); Psychological functioning (IRGL dimensions of anxiety and depressive mood); Cognitive evaluation of disease stressors (CORS – Coping with Rheumatoid Stressors questionnaire); Marital satisfaction (MMQ - Maudsley Marital Questionnaire. Higher scores = higher satisfaction); Social support (IRGL dimensions of potential support and actual support); Spousal criticism; Communication improvement (better understanding/communication concerning the disease due to the intervention).	NOW Medical Science and the Dutch League against Rheumatism.

			There were NS differences between the groups for any of the baseline characteristics including baseline outcome measures.					

Effect size

SPOUSE INCLUDED SELF-MANAGEMENT PROGRAMME + USUAL TRATMENT vs PATIENT ONLY SELF_MANAGEMENT PROGRAMME + USUAL TREATMENT

- The Spouse Included Education programme + usual treatment was significantly better than the Patient only education programme + usual treatment for:
  - Increased Communication ($p<0.001$).

- There was NS difference between the Spouse Included Education programme + usual treatment and the Patient only education programme + usual treatment for:
  - Disease activity (DAS) at 2 weeks and 6 months post-intervention;
  - Physical functioning (IRGL dimensions of mobility, dexterity and pain) at 2 weeks and 6 months post-intervention;
  - Psychological functioning (IRGL dimensions of anxiety and depressive mood) at 2 weeks and 6 months post-intervention;
  - Disease stressors: Pain, limiatations and dependence (CORS – Coping with Rheumatoid Stressors questionnaire) at 2 weeks and 6 months post-intervention;
  - Coping (decreasing activity) at 2 weeks and 6 months post-intervention;
  - Marital satisfaction (MMQ - Maudsley Marital Questionnaire) at 2 weeks and 6 months post-intervention;
  - Social support (IRGL dimensions of potential support and actual support) at 2 weeks and 6 months post-intervention;
  - Spousal Criticism at 2 weeks and 6 months post-intervention;

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
R. P. Riemsma, E. Taal, and J. J. Rasker. Group education for patients with rheumatoid arthritis and	RCT: 1+ Single centre trial in The Netherlands • Randomised (method not mentioned) • No mention	Total N=238 randomised (N=79 Group education with significant other participation, GESO; N=80	**Inclusion criteria:** Adults aged 20-70 years with RA (showing at least 4 of the ACR criteria); significant other willing to participate. **Exclusion criteria:** Residence in a nursing home.	GESO: Group education with significant other participation + self-help guide. (Programme taught by healthcare professionals – specialised arthritis	GE: Group education for patients only + self-help guide Control: Self-help guide without	5 weeks with booster at 3, 6 and 9 months.	Self-efficacy (Dutch version of Arthritis Self-efficacy Scale); Health behaviour (how often patients performed relaxation exercises, physical	Grants from the Dutch League Against Rheumatism and the Ministry of Health, Welfare and

their partners. *Arthritis & Rheumatism* 49 (4):556-566, 2003. ID 89	of blinding • ITT analysis	Group education for patients only, GE; N=79 Control - Selfhelp guide without group session). **Drop-outs:** N=37 (17%)	**Baseline characteristics:** GESO group: mean age 57.2 years (SD 9.3); Female 58%; Duration of RA = Established RA (>2 years, mean 12.1 years); AIMS2 pain 5.4 (SD 1.7). GE group: mean age 55.1 years (SD 10.3); Female 66%; Duration of RA = Established RA (>2 years, mean 11.7 years); AIMS2 pain 5.2 (SD 2.3). Control group: mean age 57 years (SD 8.3); Female 62%; Duration of RA = Established RA (>2 years, mean 11.4 years); AIMS2 pain 5.4 (SD 2.2). There were NS differences between the groups for any of the baseline characteristics except for coping with pain and perceived problematic support.	and RA nurses) Programme consisted of 5 weekly group sessions (2 hrs each) with 3 x 2 hour booster sessions after 3, 6 and 9 months. Also received a programme book with information on the sessions, a self-help guide, various RA brochures and an audiotape with relaxation exercises. Content of programme included: Contracting, goal setting and feedback, self-management and problem solving, Information on Ra and treatments, Pain management and relaxation, physical exercises, communication skills, coping with depression.	group session.		exercises and other physical activities; Use of self-management activities; degree to which people use active coping strtegies (Dutch Coping with Rheumatoid Stressors); Disease activity (DAS28 – ESR, number of tender and swollen joints, general health status - VAS); Functional limitations (Dutch-AIMS2); AIMS2 pain scale; Psychological well being (Dutch AIMS2 affect scale); Severity of fatigue (VAS); Social interactions (perceived social support from significant other).	Sports of The Netherlands.

Effect size

GESO: Group education with significant other participation + self-help guide vs GE: Group education for patients only + self-help guide vs Control: Self-help guide without group session.

- There were NS differences between the groups for any of the outcomes at 2 months, 6 months and 12 months: (All Self-efficacy measures; All Health behaviour measures; Disease activity; DAS28 score; Effects on social interactions; Health behaviour - how often patients performed relaxation exercises, physical exercises and other physical activities; Use of self-management activities; degree to which people use active coping strategies - Dutch Coping with Rheumatoid Stressors)

- Except for:
    - Self-efficacy other symptoms dimension ($p<0.05$) at 12 months (3 months post-intervention) – does not say which group was better;
    - Fatigue (Group education with significant other programme + self-help guide was significantly better than self-help guide alone, $p=0.04$) at 12 months (3 months post-treatment)
    - Fatigue (group education with significant other programme + self-help guide was significantly worse than group education for patients only programme + self-help guide, $p=0.001$) at 12 months (3 months post-intervention);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Walker, A. Adebajo, P. Heslop, J. Hill, J. Firth, P. Bishop, and P. S. Helliwell. Patient education in rheumatoid arthritis: the effectiveness of the ARC booklet and the mind map. *Rheumatology* 46 (10):1593-1596, 2007. ID 2993	RCT: 1+ Multicentre trial: 3 centres, UK • Randomised (method not mentioned) • No mention of blinding • No mention of ITT analysis (however no drop-outs)	Total N=363 randomised (N=175 ARC booklet + mind map; N=168 ARC booklet) **Drop-outs:** None mentioned	**Inclusion criteria:** Patients with RA (rheumatologists diagnosis) **Baseline characteristics:** ARC booklet + mind map group: Age mean 62 years; Female 71%. Established RA (mean 14 years); HAQ mean 1.6. ARC booklet group: Age mean 62 years; Female	RA leaflets (ARC) + mind map	RA leaflets (ARC)	1 week post-intervention	KSQ (knowledge scale questionnaire); HAQ; REALM (test of reading fluency)	Grant from the Arthritis and Rheumatism Council (ARC), UK.

			70%. Established RA (mean 13 years); HAQ mean 1.6. There were NS differences between the groups for any of the baseline characteristics.					

Effect size

ARC booklet + mind map vs ARC booklet

- There was NS difference between the ARC booklet + mind map vs ARC booklet groups for:
  - o Increase in knowledge

- Better readers got more information from the ARC booklet + mind map than the poor readers
- Poor readers were the people with poorer educational attainment and they had poor knowledge acquisition regardless of the information given – the mind map did not solve problems for the poor readers
- Better readers benefited more from the ARC booklet + mind map than the ARC booklet alone.
- Poor readers and those who were less knowledgeable were significantly more anxious ($p<0.05$) and more depressed ($p<0.05$)
- **OVERALL: data suggests that poor reading leads to poor knowledge which associates more with more anxiety and depression**

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
S. Masiero, A. Boniolo, L. Wassermann, H. Machiedo, D. Volante, and L. Punzi. Effects of an educational-behavioral joint protection	RCT: 1+ Single centre trial: Italy • Randomised (method not mentioned) numbers) • Single blind	Total N=85 randomised **Drop-outs:** N=10 (22%) education group N=5 (13%) control group	**Inclusion criteria:** Adults aged 18-65 years; RA (ARA criteria); in treatment with a-TNF drugs (IFX); hospital outpatients; no variations in drug therapy in the previous 6 months; not have severe disability that compromised independence in ADLs.	Education (joint protection) + usual drug treatment (IFX) 4 meetings (3hrs) every 3 weeks in groups of 4-6 patients with 1 or more family members.	Usual drug treatment (IFX) Patients continued with their usual drug monitoring and medical management regimen in the	8 months	Pain (VAS); RAI; Knowledge (Halh Sevices Questionnnaire); HAQ; AIMS2	Not mentioned

program on people with moderate to severe rheumatoid arthritis: a randomized controlled trial. *Clinical Rheumatology* 26 (12):2043-2050, 2007. ID 3265	(assessor) • No ITT analysis		**Exclusion criteria:** Previous participation in educational training; variations in drug therapy at any time during the trial; rehabilitation treatment or orthopaedic surgery during the trial. **Baseline characteristics:** Education (joint protection) group: mean age 54 years; Female 81%; Duration of RA = Established RA (mean 15 years); Pain (VAS) mean 46. Control group: mean age 52 years; Female 82%; Duration of RA = Established RA (mean 16 years); Pain (VAS) mean 39. There were NS differences between the randomised groups for any of the baseline characteristics.	Programme was developed by the multidisciplinary team. Education method used: group dsiscussion, problem solving, guided practice and lectures to facilitate understanding of the programme. Content: RA; mechanisms of control of pain and stress; relaxation for pain management; home exercise programme; rest; principles of joint protection and energy conservation; finding problem activities and solutions for these; info on assistive/technical equipment designed to avoid joint overload. Follow-up phone call monthly.	follow-up months, but no physiotherapy, occupational therapy or other additional treatments were performed or permitted.			

Effect size

Education programme (joint protection) + drug treatment (IFX) vs Drug treatment (IFX)

- Education programme (joint protection) + drug treatment (IFX) was significantly better than drug treatment (IFX) alone for:
  - AIMS 2 dimensions of physical, symptoms and social interatcion at 8 months (p=0.000, p=0.049 and p=0.045 respectively);
  - HAQ at 8 months (p=0.000)
  - Pain (VAS) at 8 months (p=0.001)

- There was NS difference between the Education programme (joint protection) + drug treatment (IFX) and the drug treatment (IFX) alone for:
  - RAI at 8 months;
  - AIMS 2 dimensions psychological and work at 8 months;

- 75% of patients found the education programme very useful and only 8% found it not useful at all for ADLs.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. P. Riemsma, E. Taal, H. L. Brus, J. J. Rasker, and O. Wiegman. Coordinated individual education with an arthritis passport for patients with rheumatoid arthritis. *Arthritis Care & Research* 10 (4):238-249, 1997. ID 2192	RCT: 1-Multicentre trial: 5 centres in The Netherlands • Randomised (detailed complex method) • No blinding • No mention of ITT analysis	Total N=249 randomised (N=69 Individual coordinated Education, N=75 Standard Education, N=72 traditional care). **Drop-outs:** N=33 (13%)	**Inclusion criteria:** Adults with RA (ACR criteria). **Baseline characteristics:** Established RA (>2 years, mean 13-14 years); age 56-59 years; Female 66%. There were NS differences between the groups for any of the baseline characteristics.	Individual coordinated education programme (taught by healthcare professionals)	Standard Education (as for Individual programme but without the individualised component – arthritis passport and uninformed practitioners) Traditional care	6 months	Number of visits to members of multidisciplinary team; Health status; Behaviour; self-efficacy; clinical and laboratory tests; arthritis knowledge.	Grants from the National Reumafonds and the Ministry of Health, Welfare and Sport of The Netherlands.

Effect size There were NS differences between the groups for any of the outcome measures (treatment effect)								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. H. Barlow, D. C. Pennington, and P. E. Bishop. Patient education leaflets for people with rheumatoid arthritis: A controlled study. *Psychology Health & Medicine* 2 (3):221-235, 1997. ID 352	RCT: 1- Single centre trial: UK • Randomised (method not mentioned) • No blinding • No mention of ITT analysis	Total N=142 randomised **Drop-outs:** N=34 (24%)	**Inclusion criteria:** Adult outpatients with definite diagnosis of RA **Baseline characteristics:** Established RA (>2 years, mean 15-17 years); age 26-80 years; Female 81%. There were NS differences between the groups for any of the baseline characteristics.	RA leaflets (Arthritis and Rheumatism Council) + telephone interview at 3 weeks after leaflet given	Control – no education	3 weeks post-intervemtion	Health Assessment Questionnaire (HAQ) for physical functioning; Pain and Fatigeu (VAS); Psychological well-being (Hospital Anxiety and Depression Scale, HADS); Arthritis Self-efficacy (Pain and Other symptoms subscales); Knowledge Scale (answers to 40 statements).	Grant from the Arthritis and Rheumatism Council, UK.
Effect size There were NS differences between the groups for any of the outcome measures except for Pain (VAS) and Total Knowledge Score, which were significantly better for the education group compared top the control group (both: p<0.05; change from baseline scores at 3 weeks).								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Y. Lindroth, M. Brattstrom, I. Bellman, G.	RCT: 1- Single centre trial in Sweden	Total N=100 randomised	**Inclusion criteria:** Adults with RA (ACR criteria)	Education programme (taught by healthcare professionals) + usual medication	Usual medication	8 weeks (end of treatment) with follow-	Pain during the past week (VAS); Perceived disability (HAQ); Attitude about disease	Riksforbundet Mot Reumatism, Sweden and

Ekestaf, Y. Olofsson, B. Strombeck, B. Stenshed, I. Wikstrom, J. A. Nilsson, and F. A. Wollheim. A problem-based education program for patients with rheumatoid arthritis: evaluation after three and twelve months. *Arthritis Care & Research* 10 (5):325-332, 1997. ID 183	• Randomised (method not mentioned) • No mention of blinding • No ITT analysis	**Drop-outs:** Education: N=1 (2%) Control: N=3 (6%)	**Baseline characteristics:** EDU programme: mean age 54 years (SD 15.0); Female 88%; Duration of RA = Established RA (mean duration 11 years). Control: mean age 56 years (SD 12.0); Female 80%; Duration of RA = Established RA (mean duration 13 years). There were NS differences between the groups for any of the baseline characteristics including baseline outcome measures.	Education programme was an RA school. 8 sessions of 2.5 hrs once a week – each group had 5-7 patients. How to overcome problems associated with RA; talks about the disease and treatments; OT discussed aids and devices (sessions with demonstrations); how to live with RA and to control the crisis of being confronted with a chronic disease. Pain management and exercise also discussed. All patients in both groups continued to receive their regular medical treatment.		up at 1 year post-intervention.	(Swedish AHI); Knowledge questionnaire.	Alfred Osterlunds Stiftelse, Sweden.
Effect size **EDUCATION PROGRAMME + USUAL MEDICATION vs USUAL MEDICATION** o Education group was significantly better than the Control group for: knowledge, Joint protection, capacity to relieve pain. o There was NS difference between the groups for Practicing home exercises, Pain (VAS), Impairment (HAQ) and Attitude (AHI).								

6.1 The multidisciplinary team (MULTI)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Ahlmen, M. Sullivan, and A. Bjelle. Team versus non-team outpatient care in rheumatoid arthritis. A comprehensive outcome evaluation including an overall health measure. *Arthritis & Rheumatism* 31 (4):471-479, 1988. ID 3235	RCT: 1+ Single centre trial: Sweden • Randomised (sequential randomisation procedure) • Single blind (patients) • No mention of ITT analysis • Sample size calculation	Total N=59 randomised (N=31 team treatment; N=28 non-team treatment). **Drop-outs:** Not mentioned	**Inclusion criteria:** female patients aged 38-73 years; definite or classic RA; due for appointments at the regular outpatient clinic of the Rheumatology department. **Exclusion criteria:** current malignant, mental or ohter disease that could limit function (apart from RA); Steinbroker functional class IV; patients formerly assigned to the specialised team. **Baseline characteristics:** Team treatment: mean age 59 years; Female 100%; Duration of RA = Established RA (mean 11 years). Non-team treatment: mean age 58 years; Female 100%; Duration of RA = Established RA (mean 12 years). There were NS differences between the 2 groups for any of the baseline characteristics.	Multidisciplinary team care Patients were enrolled at the outpatient clinic for team care. All members of the team focused on educating the patient and there were five 2hr group sessions. Treatment needs were assessed, explained and discussed with the patient. The team had conference afterwards. Individualised therapeutic and education programme was drawn up. The team's capacity was 5 patients/day 2-3 days/week.	Non-team care Patients were seen by physicians in charge of the regular outpatient clinic of the Rheumatology department. Nurses and social worker attended the clinic – their services wre initiated by the doctor. PTs and Ots trained in Rheumatology were available upon referrals from the physician. Education was organised through the department of OT at the hospital on referral by the physician. Treatment decisions were made exclusively by the outpatient clinic staff. The frequency of consultations at the outpatient clinic was decided by each physician.	12 months	RAI; LAI (Lansbury Articular index – joints painful on pressure or motion); joint function; walking and stair tests (Kietel index); Grip strength; CRP; self-rated physical discomforts (Body symptoms scale, BSS); Mood Adjective Check List, (MACL); Overall health (Sickness Impact profile, SIP).	Swedish association against rheumatism and the Gothenburg Medical Society, Sweden.

Effect size

- The team-treated group was significantly better than the non-team treated group for:
  - Overall health (Sickness Impact profile – SIP; MD 3.5, p<0.05) scores at 12 weeks

- There was NS difference between the team-treated group and the non-tea treated group for:
  - Self-rated physical discomfort at 12 weeks
  - MACL (mood) scores at 12 weeks
  - Use of medication (DMARDs, NSAIDs and CS) at 12 weeks
  - LAI (Lansbury Articular index – joints painful on pressure or motion) at 12 weeks
  - RAI at 12 weeks
  - CRP at 12 weeks
  - Self-rated physical discomforts (Body symptoms scale, BSS) at 12 weeks

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
T. P. M. V. Vljeland, A. H. Zwinderman, J. P. VandenbrouckE, F. C. Breedveld, and J. M. W. Hazes. A randomized clinical trial of in-patient multidisciplinary treatment versus routine out-patient care in active rheumatoid arthritis. *Rheumatology* 35 (5):475-482, 1996.	RCT: 1+ Single centre trial: The Netherlands • Randomised (stratified by gender; assorted cards blocks of 10) • Not blinded • ITT analysis • Sample size calculation (Pain)	Total N=80 randomised (39 in-patient care; N=40 out-patient care). **Drop-outs:** None mentioned	**Inclusion criteria:** Age 18-75 years; definite RA (ARA criteria); at least 3 of the following: a modified RAI ≥9, duration of morning stiffness ≥45 mins, ESR ≥28 mm/hr. **Exclusion criteria:** Previous hospitalisation for multidisciplinary treatment; a medical need for hospitalisation; ACR functional class I or IV; presence of other major sources of disability or sever joint damage primarily requiring surgical correction.	In-patient multidisciplinary treatment 11 days (patients discharged at 2 weeks) hospitalisation in a rheumatology clinic (a referral centre with in-patient facilities for patients with rheumatic diseases). Followed by routine out-patient care Primary nursing care, prescribed bed rest and daily individual ROM and muscle strengthening exercise programme performed by the physiotherapist. The occupational therapist provided info on principles of	Routine out-patient care Prescription of drugs, paramedical treatment and splints were left to the attending physician at the out-patient clinic. In order to stay as close to daily practice as possible, no special attempts were made	2 weeks (end of in-patient care) followed by routine out-patient care – assessments at 4, 12 and 52 weeks.	Swollen joints; Radiographs (Kellgren); patient's and physician's global assessment of disease severity or activity; Pain i(VAS); morning stiffness; fatigue; HAQ score; AIMS; RAI; ESR; CRP.	Grant from the Foundation 'Vrienden van Sole Mio'

ID 3264			**Baseline characteristics:** In-patient group: mean age 56 years; Female 64%; Duration of RA = Established RA (mean 4 years); HAQ mean 1.2. Out-patient group: mean age 55 years; Female 76%; Duration of RA = Established RA (mean 3 years); HAQ mean 1.2. There were NS differences between the groups for any of the baseline disease characteristics and the 2 groups were similar for baseline demographics.	joint protection, self-care, household and work activities. Joint splints, aids and devices were arranged if necessary. Social worker discussed aspects related to coping with the disease and financial questions. Treatment goals and modalities were discussed during weekly multidisciplinary team meetings. In all study groups, DMARDs were introduced or changed shortly after study entry and during the whole study period NSAIDs were optimised, IA injections of CS were administered and DMARDs changed if necessary.	in either group to alter treatment regimens normally employed in the out-patient setting.			

Effect size

- In-patient multidisciplinary treatment was significantly better than routine out-patient care for:
  - Pain (VAS) at 2 weeks and 4 weeks, p<0.05;
  - Patient's global assessment of disease activity at 2 weeks, 4 weeks (MD 3.9, p<0.05), 12 weeks (MD 3.3, p<0.05) and 52 weeks (MD2.8, p<0.05);
  - Morning stiffness at 2 weeks, 4 weeks and 12 weeks, (MD 2.62, p<0.05);
  - Fatigue at 2 weeks and 4 weeks, p<0.05;
  - Number of swollen joints at 2 weeks and 4 weeks, p<0.05;
  - RAI at 2 weeks and 4 weeks, p<0.05;
  - Grip strength at 2 weeks, p<0.05;
  - Anxiety at 4 weeks and 12 weeks, (MD 3.3, p<0.05);
  - Depression at 12 weeks, (MD 2.4, p<0.05);
  - ACR20 at 2 weeks, 4 weeks, 12 weeks and 52 weeks, (12 weeks MD 10.0, p<0.05; 52 weeks MD 18, p<0.05).

- There was NS difference between In-patient multidisciplinary treatment and routine out-patient care for:
  - Pain (VAS) at 12 weeks and 52 weeks,
  - Morning stiffness at 52 weeks
  - Fatigue at 12 weeks and 52 weeks
  - Number of swollen joints at 12 weeks and 52 weeks
  - RAI at 12 weeks and 52 weeks
  - HAQ at 2 weeks, 4 weeks, 12 weeks and 52 weeks
  - ESR at 2 weeks, 4 weeks, 12 weeks and 52 weeks
  - CRP at 2 weeks, 4 weeks, 12 weeks and 52 weeks
  - Grip strength at 4 weeks, 12 weeks and 52 weeks
  - Anxiety at 2 weeks and 52 weeks
  - Depression at 2 weeks, 4 weeks and 52 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding
T. P. Vliet Vlieland, F. C. Breedveld, and J. M. Hazes. The two-year follow-up of a randomized comparison of	RCT: 1+ Single centre trial: The Netherlands • Randomised (stratified by	Total N=80 randomised (39 in-patient care; N=40 out-patient care). **Drop-outs:**	As for ID3264	As for ID 3264	2 year follow-up	As for ID 3264	Grant from the Foundation 'Vrienden van Sole Mio'

in-patient multidisciplinary team care and routine out-patient care for active rheumatoid arthritis. *British Journal of Rheumatology* 36 (1):82-85, 1997. ID 3233	gender; assorted cards blocks of 10) • Not blinded • ITT analysis • Sample size calculation (Pain)	None mentioned					

Effect size

- There was NS difference between In-patient multidisciplinary treatment and routine out-patient care for:
  - Pain (VAS) at 12 weeks and 52 weeks and 104 weeks
  - Morning stiffness at 52 weeks and 104 weeks
  - Fatigue at 12 weeks and 52 weeks and 104 weeks
  - Number of swollen joints at 12 weeks and 52 weeks and 104 weeks
  - RAI at 12 weeks and 52 weeks and 104 weeks
  - HAQ at 2 weeks, 4 weeks, 12 weeks and 52 weeks and 104 weeks
  - ESR at 2 weeks, 4 weeks, 12 weeks and 52 weeks and 104 weeks
  - CRP at 2 weeks, 4 weeks, 12 weeks and 52 weeks and 104 weeks
  - Grip strength at 4 weeks, 12 weeks and 52 weeks and 104 weeks
  - Anxiety at 2 weeks and 52 weeks and 104 weeks
  - Depression at 2 weeks, 4 weeks and 52 weeks and 104 weeks
  - ACR20 at 104 weeks.
  - Patient's global assessment of disease activity at 104 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Scholten C, Brodowicz T, Graninger W et al. Persistent functional and	RCT (one year follow-up) 1+ Observational (five year	N=68 (randomised) N=38 (intervention) N=30 (control)	**Inclusion criteria:** Patients with definite RA.	Multidisciplinary team care programme Compared with Waiting list control	2, 6 and 52 weeks Five years	Disability (HAQ); Coping with illness (Freiburg Questionnaire of Coping with	Major of Vienna, Austria

social benefit 5 years after a multidisciplinary arthritis training program. *Archives of Physical Medicine & Rehabilitation.* 1999; 80(10):1282-1287. REF ID: 3231	follow-up) 3	**Drop-outs:** One year N=0 Five years N=4	**Baseline characteristics:** Female: male 54:14, mean age 48 yrs, mean duration of illness 9 yrs (established RA), N=14 functional class I (Steinbrocker), N=38 II, N=17 III All patients received their ongoing rheumatologic care. Intervention group vs. waiting list control: There was NS difference between the groups either at first study entry, after training, 6 weeks later and after 1 year	Team comprised of rheumatologists, orthopedists, physiocotherapists, psychologists and social workers. The teaching professionals integrated theory with practice Nine afternoons within nine weeks. Patients could be accompanied by relatives and friends Training included remedial gymnastics, orthopaedic perspectives, psychological counselling, exercise practice sessions The training was completed by means of a supervised monthly meeting structured to establish patients' mutually interactive help by regular contact After the programme each member had the opportunity to join monthly meetings and were maintained until 1 yr after the course Five year follow-up The waiting list control underwent a training program identical to the intervention group after one year of serving as controls.		Illness (FQCI)); Depression (Beck Depression Inventory); Cognitive-behavioural and environmental impact (21-point scale to assess changes in knowledge, compliance with RA-therapy, changes in professional affairs and attitudes towards social care institutions)	
Effect size* **52 weeks** • At 52 weeks, there was a significant improvement associated with the MDT programme for: • Disability score ((mean change -0.4, p<0.001); • FQCI (mean change -1.9, p<0.01); • BDI (mean change 2.5, p<0.001);							

- Questionnaire: use of joint protection devices (mean change 68.5%, p<0.001), knowledge of treatment, regular relaxation exercises (mean change 60.5%, p<0.001) and regular remedial gymnastics (mean change 26.3, p<0.001l)

- At 52 weeks, there were NS associated with the waiting list control for:
- Disability score (NS);
- FQCI (NS);
- BDI (NS);
- Questionnaire: use of joint protection devices, knowledge of treatment, regular relaxation exercises and regular remedial gymnastics (NS for all)

At five years
At five year follow-up, there was a significant improvement compared to baseline for:
- HAQ (mean change 0.9, p<0.0001).

At five year follow-up, there was NS difference compared to baseline for:
- BDI (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
L. T. H. Jacobsson, M. Frithiof, Y. Olofsson, I. Runesson, B. Strombeck, and I. Wikstrom. Evaluation of a structured multidisciplinary day care program in rheumatoid arthritis. *Scandinavian Journal of Rheumatology* 27 (2):117-124, 1998. REF ID: 293	Case-series: 3 Single centre, Sweden Consecutive patients with RA who were referred from either the hospital clinic or a private rheumatologist	N=92 **Drop-outs:** N=5	**Inclusion criteria:** aged >16 years; RA (ACR criteria) **Exclusion criteria:** Steinbroker functional class IV **Baseline characteristics:** Age mean 55, female 84%, disease duration established RA (mean 7 years).	Multidisciplinary team care programme The rehabilitation programme (3 weeks): group of 4 patients treated daily by the team during each 3 week period. Each day of the programme included patient education, PT, OT hand training and training in various activities. Physician evaluated current disease activity, ddrug treatment and gave IA injections when necessary. Nurse, OT, PT and social-worker all intervened with support where required.	3 weeks (follow-up at 3 months)	RAI; HAQ; SOFI; DAS; EULAR and ACR criteria; patient's and physician's global assessment of disease activity; Pain (VAS); Swollen joint count; CRP; ESR; RF	Not mentioned

Effect size* • At the 3 month follow-up, significant improvements were seen in: DAS (mean change -0.59, 95% CI -0.8 to -0.38, p<0.001), HAQ (mean change -0.16, 95% CI -0.24 to -0.08, p<0.05), SOFI (mean change -2.6, 95% CI -3.5 to -1.7, p<0.05), Pain (VAS) (mean change -12, 95% CI -17 to -7, p<0.05), Swollen joints (mean change -3.3, 95% CI -5.2 to -1.4, p<0.05), RAI (mean change -1.6, 95% CI -2.5 to -0.7, p<0.05), patient's and physician's global assessment of disease activity (VAS mean change -13, 95% CI -18 to -8, p<0.05), ESR ESR (mean change -6, 95% CI -10 to -3, p<0.05). • 26% and 52% of the total study group fulfilled the ACR20 and EULAR criteria for individual response respectively • Age and disease duration (early or established RA) did not contribute to treatment effects and there was BS interaction between disease duration and administration of IA CS on the improvement of ant outcome. • 46% of patients were given IA CS, Only 13% of patients changed their DMARD treatment during the 3 week period and NSAIDs and analgesic medication remained similar.							
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Prier, F. Berenbaum, A. Karneff, S. Molcard, C. Beauvais, C. Dumontier, A. Sautet, M. P. Miralles, J. L. Peroux, and G. Kaplan. Multidisciplinary day hospital treatment of rheumatoid arthritis patients. Evaluation after two years. *Revue du Rhumatisme (English Edition)* 64 (7-9):443-450, 1997. REF ID: 3232	Case-series: 3 Single centre, France	N=70 **Drop-outs:** None mentioned	**Inclusion criteria:** Adults with RA (whatever duration and activity of disease). **Exclusion criteria:** diseases other than RA **Baseline characteristics:** Age mean 52, female 87%, disease duration early RA (mean 12 months).	Multidisciplinary team care programme (Raoul Dufy) Team care provided on a day hospital basis; patients mke their appointments on their own initiative or on advice of their usual physician. Visits take place in a room containing array of assistive devices and orthoses and books/videos. Patients are seen individually, if possible accompanied by a family member. Morning is spent evaluating the wishes and needs of the patient and starting the educational intervention. Afternoon – patients sees the specialists whose services are required by his or her specific problems. All patients are seen by a nurse, rheumatologist and a physical therapist, whereas other professionals intervene as indicated by the patient's specific needs. Patients' education is provided as interactively as possible – a detailed report is	3 months Questionnaire filled in initially then after 3 month after the visit to the programme	Patient knowledge (MCQ); QoL (AIMS)	Not mentioned

			Group 1 = initial questionnaires completed after the visit to the programme Group 2 = initial questionnaire completed before the visit to the programme	written at the end of the day and sent to the patient's own physician. The professionals participating in the programme do so as part of their normal work duties as salaried employees of the hospital and their interventions are conducted without the help of any specialised equipment. As a result the programme dose not translate in to any additional costs for the rheumatology department. The aim of the programme was not to modify the drug treatments received by the patients unless specifically requested by the referring physician – aim of programme was to provide advice about non-pharmacological interventions.			

Effect size*

Group 1 = initial questionnaire completed after the visit to the programme
Group 2 = initial questionnaires completed before the visit to the programme

- Knowledge of RA was significantly increased at the 3 month follow-up (mean increase test score 6.2, p<0.0001)
- There was NS change in QoL (AIMS) at the 3 month follow-up
- 98% of patients were satisfied with the programme the groups
- The main non-pharmacological interventions introduced within 3 months after the programme were in the areas of physical therapy, podiatry and psychology.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
B. Nordmark, P. Blomqvist, B. Andersson, M. Hagerstrom, Grate K. Nordh, R. Ronnqvist, H. Svensson, and L. Klareskog. A two-year follow-up of	Case-series: 3 Single centre, Sweden Patients with early polyarthritis referred to a rheumatology	N=110 **Drop-outs:** None mentioned	**Inclusion criteria:** RA (at least 4 ACR criteria); early disease (< 1 year). **Baseline characteristics:** Age mean 47, female	Multidisciplinary team care programme The team met patients every 3 months during the first year and every 6 months in the second year. Additional visits could be offered if needed. Meetings for planning work rehabilitation were	2 years	Tender and Swollen Joint count; Pain (VAS); Patient's global disease assessment; DAS28; HAQ; RF; ESR; CRP; employment status	Stockholm county council, Swedish Research Council, AFA insurance, Sweden

work capacity in early rheumatoid arthritis: a study of multidisciplinary team care with emphasis on vocational support. *Scandinavian Journal of Rheumatology* 35 (1):7-14, 2006. REF ID: 3230	department		75%, disease duration early RA (mean 5 months). **Patients were split into 4 groups:** 1.Patients who continued to work full time 2. Patients who were still on partial or full-time sick leave 3. Patients who had improved ability to work 4. Patients who experienced deterioration	arranged whenever needed and included participation by the patient, the team and the local insurance officer and/or the employer. Work-site inspections were performed to inform the employer about the patient's disease and provide ergonomic advice. The team encouraged patients on sick leave to go back to work at least part time and did not recommend any specific limitations of the patients' activities. The patients were advised to be aware of their symptoms and to also accept mild pain.		and sickness absence	

Effect size*

Patients were split into 4 groups:
1. Patients who continued to work full time
2. Patients who were still on partial or full-time sick leave
3. Patients who had improved ability to work
4. Patients who experienced deterioration

- There was no change in the number of patients receiving DMARDs after team treatment programme. The number of patients receiving MTX or combination therapy with MTX increased from, 8% to 41% at 2 years follow-up (end of team treatment programme)
- A similar number of patients received CS before and after team treatment programme (11% and 15% respectively).
- The number of patients working full-time increased by 14% at 2 years and 20% less people took sickness benefit. The number of patients employed remained the same
- RA patients who continued working full time or resumed working tended to be younger and living alone les often that the other patients. They also had the lowest proportion of heavy physical or mental strain in their jobs.
- CRP: the largest increase of CRP was in patients who deteriorated.
- DAS28: largest decreases were for patients who continued working and the group initially receiving sickness compensation but who went back to work
- HAQ: all groups experienced decrease in functional problems. The largest decreases were for the groups who continued working throughout the study as well as those

who resumed work

- Pain: All groups experienced significant decreases in pain (mean change in VAS: range -16 to -24, all p<0.05) except for those who stopped working and were receiving sickness benefit
- Patients who were continually on sick leave or went on sick leave during follow-up were significantly older
- There were no other significant differences for other outcomes between the groups

Authors' conclusion: active vocational support in addition to DMARD treatment may prevent or delay work disability in patients with early RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. S. Schned, M. A. Doyle, S. L. Glickstein, J. T. Schousboe, J. L. Reinertsen, A. J. Baglioni, and T. F. Tolson. Team managed outpatient care for early onset chronic inflammatory arthritis.[see comment]. *Journal of Rheumatology* 22 (6):1141-1148, 1995. ID 162	RCT: 1-Multicentre trial: 2 centres, USA • Randomised • Not blinded • Not ITT analysis • Drop-outs but number not mentioned (some analyses only used 50% of the patients)	Total N=118 **Drop-outs:** Some drop-outs but exact number not mentioned. Some analyses only used 50% of the patients	**Inclusion criteria:** RA and other arthritis patients (82% RA). **Baseline characteristics:** Early RA (mean 1.4 years)	Multidisciplinary team care	Traditional care	1 year	Beck depression score; RAI; HAQ; AIMS; Pain (VAS); morning stiffness; ACR functional class	Arthritis Foundation, USA

Effect size **Authors' conclusion:** The team-managed outpatient programme for persons with recent onset chronic inflammatory arthritis afforded no advantage to routine outpatient care.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. R. Feinberg and K. D. Brandt. Allied health team management of rheumatoid arthritis patients. *American Journal of Occupational Therapy* 38 (9):613-620, 1984. ID 3236	RCT: 1-Multicentre trial: 2 centres, USA • Not Randomised • Not blinded • Not ITT analysis • High drop-outs	Total N=40 (N=20 each group). **Drop-outs:** Control: N=7 (30%); Experimental : N=10 (50%)	**Inclusion criteria:** Definite or classical RA; functional class I or II. **Baseline characteristics:** Established RA (mean 10 and 5 years)	Experimental group (regular assessments by rheumatologists and each member of the AHP team*) *AHP team: allied health professionals	Control group (seen by rheumatologist at the same intervals but but only seen by a member of the AHP team upon referral by the rheumatologist)	2 years	ROM; Disease activity; ESR; grip strength; morning stiffness; fatigue; ADLs; psychosocial adaptation.	Arthritis Foundataion, USA
Effect size **Authors' conclusion:** Ongoing team care may be more efficacious than episodic use of allied health professionals in management of of patients with mild RA**.**								

6.2 Physiotherapy (PHYSIO)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. Harris and J. B. Millard. Paraffin-wax baths in the treatment of rheumatoid arthritis. *Annals of the Rheumatic Diseases* 14 (3):278-282, 1955. ID 3358	RCT: 1- Single centre trial: UK • Randomised (method not mentioned) • No mention of blinding • No ITT analysis	Total N=90 randomised (N=30 in each group) **Drop-outs:** N=7 (23%) no treatment (wax or exercises) N=5 (17%) wax baths + exercises for 3 weeks N=7 (23%) wax baths daily for 6 weeks	**Inclusion criteria:** RA patients. **Exclusion criteria:** none given **Baseline characteristics:** All: mean age 48 years; Female 63%; Duration of RA = Established RA (mean 8 years)	Wax baths + exercises for 3 weeks Wax baths daily for 6 weeks	Control group (no treatment (wax or exercises)	6 weeks (end of treatment)	Tenderness; Grip strength; Pain; swelling; dexterity; ESR; CRP	Not mentioned
Effect size Overall the results fail to show that the patients benefited from wax baths – the changes occurring in the 3 groups were almost identical at 3 weeks and at 6 weeks there was little comparative difference in the local condition of the hands in the treated and control group. In fact the 3-week treated patients were significantly worse than the untreated patients (subjective measures).								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**

M. J. Bell, S. C. Lineker, A. L. Wilkins, C. H. Goldsmith, and E. M. Badley. A randomized controlled trial to evaluate the efficacy of community based physical therapy in the treatment of people with rheumatoid arthritis. *Journal of Rheumatology* 25 (2):231-237, 1998. ID 179	RCT: 1++ Single centre trial: Canada • Randomised (table of random numbers) • Allocation concealment • Single blind (assessor) • ITT analysis • Higher dropouts in control group • Sample size calculation	Total N=150 randomised (N=76 PT; N=74 control) **Drop-outs:** N=7 (9%) PT N=16 (22%) Control	**Inclusion criteria:** Disease onset after age 18 years; RA (ARA criteria); referral for PT intervention; at least 6 tender and painful joints and 45 mins morning stiffness; functional class II or III. **Exclusion criteria:** Involved in the pilot study or a previous programme; require urgent care **Baseline characteristics:** PT: mean age 58 years; Female 78%; Duration of RA = Established RA (mean 8 years) Control: mean age 54 years; Female 82%; Duration of RA = Established RA (mean 7 years) There were no clinically important differences between the randomised groups for any of the baseline characteristics.	PT PT: community-based PT for 6 weeks. PT included: evaluation of disease activity, level of function, educational brochures, individual goal setting,. PTs tailored their interventions to meet these goals. Patients were given at least 3 hours of treatment or 4 therapist visits within the 6 weeks of the study.	Control group (waiting list)	6 weeks (end of treatment)	Pain (VAS); Morning stiffness; Grip strength; Joint count; Stanford Self-Efficacy Scale	Grants from the Arthritis Society, Canada and the Ontario Ministry of Health, Canada.

Effect size

PT vs Control (waiting list)

- PT was significantly better than control (waiting list) for:
  - Morning stiffness at 6 weeks, p<0.036

- There was NS difference between PT and Control (waiting list) for:
  - Pain (VAS) at 6 weeks
  - Grip strength at 6 weeks
  - Tender joint count at 6 weeks
  - Stanford Self-Efficacy Scale at 6 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. C. Lineker, M. J. Bell, A. L. Wilkins, and E. M. Badley. Improvements following short term home based physical therapy are maintained at one year in people with moderate to severe rheumatoid arthritis. *Journal of Rheumatology* 28 (1):165-168, 2001. ID 3331	RCT: 1++ Single centre trial: Canada • Randomised (table of random numbers) • Allocation concealment • Single blind (assessor) • ITT analysis • Higher dropouts in control group • Sample size calculation	Total N=150 randomised (N=76 PT; N=74 control) **Drop-outs:** N=7 (9%) PT N=16 (22%) Control	**Inclusion criteria:** As for ID 179 **Exclusion criteria:** As for ID 179 **Baseline characteristics:** As for ID 179	PT As for ID 179	Control group (waiting list) As for ID 179	52 weeks follow-up	As for ID 179	Grants from the Arthritis Society, Canada and the Ontario Ministry of Health, Canada.

Effect size

PT vs Control (waiting list)

- PT was significantly better than control (waiting list) for:
  - Morning stiffness (over 52 weeks), p<0.001
  - Pain (VAS) (over 52 weeks), p<0.001
  - Grip strength (over 52 weeks), p<0.001
  - Tender joint count (over 52 weeks), p<0.001
  - Stanford Self-Efficacy Scale (over 52 weeks), p<0.001
  - ADLs (over 52 weeks), p<0.05

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. I. Buljina, M. S. Taljanovic, D. M. Avdic, and T. B. Hunter. Physical and exercise therapy for treatment of the rheumatoid hand. *Arthritis & Rheumatism* 45 (4):392-397, 2001. ID 3329	RCT: 1+ Single centre trial: Bosnia • Randomised (table of random numbers) • Single blind (assessor) • No mention of ITT analysis, but no mention of drop-outs	Total N=100 randomised (N=50 PT; N=50 control) **Drop-outs:** Not mentioned	**Inclusion criteria:** Age 20-70 years; RA (ACR criteria); disease duration at least 6 months; 3 or more swollen joints in both hands; 5 or more tender joints in both hands; hand problem (decreased ROM and grip strength); ESR >25 mm first hour. **Exclusion criteria:** Not mentioned. **Baseline characteristics:** PT: mean age 48 years; Female 76%; Duration of RA = Established RA (mean 5 years)	PT PT: physical therapy for 3 weeks. PT included: thermal baths, therapeutic heat or cold, faradic hand baths, wax baths, exercise therapy (individualised).	Control group (waiting list) Patients in both groups continued to receive their previously prescribed medication	3 weeks (end of treatment)	ESR; joint size, RAI; Pain (VAS); ROM; ADL	Not mentioned

			Control: mean age 66 years; Female 74%; Duration of RA = Established RA (mean 5 years) There were NS differences between the randomised groups for any of the baseline characteristics.					

Effect size

PT vs Control (waiting list)

- PT was significantly better than control (waiting list) for:
  - RAI at 3 weeks, p<0.005
  - Pain (VAS) at 3 weeks, p<0.005
  - ROM at 3 weeks, p<0.01
  - ADL at 3 weeks, p<0.005
  - Grip strength (left and right hands) at 3 weeks, p<0.01
  - Pinch tests (left and right hands) at 3 weeks, p<0.05

- There was NS difference between PT and Control (waiting list) for:
  - ESR at 3 weeks
  - Joint size at 3 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Robinson V, Brosseau L, Casimiro L et al. Thermotherapy for treating rheumatoid arthritis. *Cochrane Database of Systematic*	MA: 1++ RCT's of MA: 1- to 1+ SR and MA included: N=7 trials Trials were similar in terms of: • Study design (All RCTs) • Study quality (poor /	Total N=328	**Inclusion criteria:** RCTs or CCTs, case control and cohort studies; adults with definite or classic RA	Thermotherapy Applications using any form of heat or/and cryotherapy (e.g., ice packs, cold gel	Any control including placebo, untreated or alternate interventions such as paraffin, farad baths and other form c rehabilitation interventions	Details of study duration not systematically reported	Pain OMERACT Tender joint count Swollen joint count Physician global	Ottawa Health Research Institute Institute for Population Health

Reviews. 2002;(2):CD002826. ID 867	moderate) Trials differed with respect to: • Patients (N=4 hospitalised, N=7 outpatients) • Disease duration (ranging from duration 5 yrs or less to mean 14 yrs) • Intervention (1 RCT each on ice therapy, paraffin bath plus exercise, three different thermotherapy modalities (paraffin wax bath, faradic bath and ultrasound), different temperatures of heat, 2 RCTs heat) • Comparison group (Control, exercise, cryotherapy) • Study size (N=24, N=52, N=20, N=90, N=14, N=30, N=18) Details of blinding and study duration not systematically reported Tests for heterogeneity and quality assessment performed.		(Arnett 1988) Search was up to 2001.	packs) Balneotherapy was excluded Strengthening exercises, ultrasound or medication was prescribed cocnurrentyl in combination with various application of thermotherapy	Concurrent interventions e.g., NSAIDs were accepte if they were given to both comparative groups		assessment Patients global assessment Functional status Range of motion Strength	

Effect size

Heat therapy vs heat therapy

- There were no significant differences of heat therapy compared (50°F) with heat therapy (60°F) (knee) – End of treatment 72 hrs:
  - Pain measurement (amount of morphine) (1 RCT, N=60);
  - Number of attempts per hour as monitored per hour (1 RCT, N=60);

- There were no significant differences of heat therapy compared (50°F) with heat therapy (70°F) (knee) – End of treatment 72 hrs:
  - Pain measurement (amount of morphine) (1 RCT, N=60);
  - Number of attempts per hour as monitored per hour (1 RCT, N=60);

- There were no significant differences of heat therapy compared (50°F) with heat therapy (60°F)(knee) – End of treatment 72 hrs:
  - Pain measurement (amount of morphine) (1 RCT, N=60);
  - Number of attempts per hour as monitored per hour (1 RCT, N=60);

Ice packs vs hot packs

- There were no significant differences of ice packs compared with heat packs (knee) – End of treatment 5 days:
  - Thermographic Index (1 RCT, N=30; NS);
  - Joint circumference (1 RCT, N=30; NS);

- There were no significant differences of ice packs compared with heat packs (knee) – End of treatment 5 days:
  - Number of patients preferring ice (1 RCT, N=28; NS);
  - Number of patients with improved pain grading (1 RCT, N=28; NS);
  - Number of patients with improved stiffness grading (1 RCT, N=28; NS)

- There were no significant differences of hot packs compared with ice packs (shoulder) – End of treatment 3 weeks:
  - McGill pain questionnaire (1 RCT, N=18; NS);
  - Flexion (1 RCT, N=18; NS);
  - Abduction ROM (1 RCT, N=18; NS)

Wax therapy

Wax therapy vs control

- Wax bath was significant better than control (hand) – End of treatment 4 weeks for:
  - Change in flexion of the dominant hand (1 RCT, N=28; WMD -19.10, 95% CI -37.36 to -0.84, p=0.04);
  - Change in extension of the dominant hand (1 RCT, N=28; WMD -11.90, 95% CI -23.50 to -0.30, p=0.04);
  - Change in pinch function (1 RCT, N=28; WMD -0.90, 95% CI -1.78 to -0.02, p=0.04);
  - Change in grip strength (1 RCT, N=28; WMD -9.50, -18.76 to -0.24, p=0.04);
  - Change in pain on resisted motion (1 RCT, N=28; WMD 0.10; 95% CI 0.00 to 0.20, p=0.04);

- Change in non-resisted motion (1 RCT, N=28; WMD -7.20, 95% CI -14.08 to -0.32, p=0.04);
- Change in stiffness (both hands) (1 RCT, N=28; WMD -3.20; 95% CI -6.32 to -0.08), p=0.04)

- There were no significant differences of wax baths compared with control (hand) – End of treatment 4 weeks:
  - Grip function (1 RCT, N=28)

Wax bath + exercises versus exercises (hand)

- Wax bath + exercises was significant better than exercises alone (hand) – End of treatment 4 weeks for:
  - Change in flexion of the dominant hand (1 RCT, N=24; WMD 8.30, 95% CI 0.44 to 16.16, p=0.04);
  - Change in extension of the dominant hand (1 RCT, N=24; WMD-0.60, 95% CI -1.18 to -0.02, p=0.04);
  - Change in grip function (1 RCT, N=24; WMD -1.30; 95% CI -2.55 to -0.05, p=0.04);
  - Change in grip strength (1 RCT, N=28; WMD -47.00, -92.38 to -1.62, p=0.04);
  - Change in pain on resisted motion (1 RCT, N=24; WMD -0.50, 95% CI -0.98 to -0.02, p=0.04);
  - Change in pain on non-resisted motion (1 RCT, N=24; WMD 5.10; 95% CI 0.27 to 9.93);
  - Change in stiffness (both hands) (1 RCT, N=24; WMD -6.20; 95% CI -12.19 to -0.21), p=0.04)

- There were no significant differences of wax baths + exercises compared with exercise alone (hand) – End of treatment 4 weeks:
  - Pinch function (1 RCT, N=24)

Wax bath versus exercises (hand)

- Wax bath was significant better than exercises (hand) – End of treatment 4 weeks for:
  - Change in flexion of the dominant hand (1 RCT, N=26; WMD -0.90, 95% CI -1.76 to -0.04, p=0.04);
  - Change in extension of the dominant hand (1 RCT, N=26; WMD-11.90, 95% CI -23.45 to -0.35, p=0.04);
  - Change in grip function (1 RCT, N=26; WMD -1.10; 95% CI -2.17 to -0.03, p=0.04);
  - Change in pinch function (1 RCT, N=26; WMD -1.00, 95% CI -1.97 to -0.03, p=0.04);
  - Change in grip strength (1 RCT, N=26; WMD -50.30, -87.53 to -13.07, p=0.008);
  - Change in pain on resisted motion (1 RCT, N=26; WMD 0.30, 95% CI 0.01 to 0.59, p=0.04);
  - Change in pain on non-resisted motion (1 RCT, N=26; WMD 8.90; 95% CI 0.44 to 17.36, p=p=0.04);
  - Change in stiffness (both hands) (1 RCT, N=26; WMD -4.10; 95% CI -8.80 to -0.12), p=0.04)

- There were no significant differences of wax baths compared with exercise (hand) – End of treatment 4 weeks:
  - Grip function (1 RCT, N=26)

Exercise versus control (hand)

- Exercise was significant better than control (hand) – End of treatment 4 weeks for:
  - Change in flexion of the dominant hand (1 RCT, N=24; WMD -18.20, 95% CI -28.20 to -8.20, p=0.0004);
  - Change in extension of the dominant hand (1 RCT, N=24; WMD-9.40, 95% CI -18.47 to -0.33, p=0.04);

- Change in grip function (1 RCT, N=24; WMD 1.10; 95% CI 0.04 to 2.16, p=0.04);
- Change in pinch function (1RCT, N=24; WMD 0.10, 95% CI 0.00 to 0.20, p=0.04);
- Change in grip strength (1 RCT, N=28; WMD 24.30, 0.84 to 47.76, p=0.04);
- Change in pain on resisted motion (1 RCT, N=24; WMD -0.20, 95% CI -0.39 to -0.01, p=0.04);
- Change in pain on non-resisted motion (1 RCT, N=24; WMD -16.10; 95% CI -31.35 to -0.85, p=0.04);
- Change in stiffness (both hands) (1 RCT, N=24; WMD 0.90; 95% CI 0.03 to 1.77), p=0.04)

Wax therapy versus ultrasound (hand)

- There were no significant differences of wax therapy compared with ultrasound (hand) – End of treatment 1 week, 2 weeks, 3 weeks:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular index (1 RCT, N=20);
  - Timed task (1 RCT, N=20);
  - Activity score (1 RCT, N=20)
  - ROM (1 RCT, N=20) (measured at three weeks only) ;

Faradic bath vs Control (hand)

- There were no significant differences of faradic baths compared with control (hand)– End of treatment 1 week:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular Index (1 RCT, N=20);
  - Times task (1 RCT, N=20);
  - Activity score (1 RCT, N=20)

- Faradic baths were significant better than control (hand) – End of treatment 2 weeks for:
  - Activity score (1 RCT, N=20; WMD 0.30, 95% CI 0.02 to 0.58, p=0.04);

- There were no significant differences of faradic baths compared with control (hand)– End of treatment 2 weeks:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular Index (1 RCT, N=20);
  - Times task (1 RCT, N=20);

- Control was significant better than faradic baths (hand) – End of treatment 3 weeks for:
  - Activity score (1 RCT, N=20; WMD -1.30, 95% CI -2.51 to -0.09, p=0.04);

- There were no significant differences of faradic baths compared with control (hand)– End of treatment 3 weeks:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);

- Articular Index (1 RCT, N=20);
- Times task (1 RCT, N=20);

Wax vs faradic bath + ultrasound

- There were no significant differences of wax compared with faradic baths + ultrasound – End of treatment 1 week, 2 weeks, 3 weeks::
  - Hand grip (1 RCT, N=20; NS);
  - PIP circumference (1 RCT, N=20; NS);
  - Articular Index (1 RCT, N=20; NS);
  - Times task (1 RCT, N=20; NS)

- There was a significant differences in favour of faradic baths + ultrasound compared with wax therapy – End of treatment 1 week:
  - Activity score (1 RCT, N=20; WMD -0.40; 95% CI -0.78 to -0.02)

- There was no significant difference of faradic baths + ultrasound compared with wax therapy – End of treatment 2 weeks:
  - Activity score (1 RCT, N=20)

- There was a significant differences in favour of wax therapy compared with faradic baths + ultrasound – End of treatment 3 weeks:
  - Activity score (1 RCT, N=20; RR -1.30; 95% CI -2.51 to -0.09)

Cryotherapy vs control

- There were no significant differences of cryotherapy compared with control – End of treatment 2 days, 3 days, 4 days:
  - Change in post-surgery oedema (1 RCT, N=30; NS);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hirvonen HE, Mikkelsson MK, Kautiainen H et al. Effectiveness of different cryotherapies on pain and disease activity in active	RCT: 1-Single centre trial: Finland • Randomised (method not mentioned) • Single blind (assessor) • ITT analysis	Total N=60 randomised N=20 Whole Body Cryotherapy (WBC) -110 °C N=20 WBC -60° C N=20 Local cryotherapy	**Inclusion criteria:** active seropositive RA with ≥ 5 swollen and ≥ 5 tender, ESR ≥ 20 mm/h and/or CRP > 20 mg/l, and duration of morning stiffness ≥ 30 min. Medication to be stable for at least 1 month before trial start. **Exclusion criteria:** uncontrolled hypertension (DBP > 100 mm Hg), history of cardiac arrhythmia, cardiovascular/lung disease, severe	N=20 Whole Body Cryotherapy (WBC) -110 °C N=20 WBC -60° C Procedure: People randomised to 4 groups: whole body cryotherapy at -110 °C or -60 °C. Local cryotherapy	N=20 Local cryotherapy (LC)	7 days	Pain (VAS); Grip strength; Joint count; DAS, global assessment, ESR, CRP, Adverse effects	Social Insurance institution and ministry of Social Affairs and Health Finland, European social

<table>
<tr>
<td>rheumatoid arthritis. A randomised single blinded controlled trial. Clinical & Experimental Rheumatology. 2006; 24(3):295-301.

Ref ID: 3314</td>
<td>(LOCF)
• Significant differences at baseline
• Higher dropouts in experimental group</td>
<td>(LC)

Drop-outs:
N=3 (15%) WBC -110 °C
N=3 (15%) WBC -60 °C
N=0 (0%) LC</td>
<td>Raynaud’s phenomenon, cold allergy, cold induced bronchospasm, intra-articular glucocorticoid injections

Baseline characteristics: Significant differences between groups for age, DAS, BMI, HAQ. The LC group was oldest and had the highest DAS and HAQ.
<table>
<tr><th></th><th>LC</th><th>WBC -60 °C</th><th>WBC -110 °C</th></tr>
<tr><td>N</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>female/male</td><td>16/4</td><td>18/2</td><td>17/3</td></tr>
<tr><td>Duration of disease, median, years</td><td>16</td><td>17</td><td>12</td></tr>
<tr><td>Duration morning stiffness (min), median</td><td>120</td><td>60</td><td>90</td></tr>
<tr><td>HAQ, median</td><td>1.62</td><td>1.00</td><td>1.12</td></tr>
<tr><td>Age, mean</td><td>58</td><td>52</td><td>50</td></tr>
<tr><td>DAS, mean</td><td>5.14</td><td>4.24</td><td>4.56</td></tr>
</table>
</td>
<td>involved cold packs applied locally or cold air -30 °C. The two local therapy (cold air for 1-5 min or cold packs 10-30 min) groups were combined. Cryotherapy applied 3 times/day for 7 days. All groups received physiotherapy or low impact aerobic no more than twice/day. Joint swelling/tenderness evaluated at baseline and at day 7. CRP, ESR, Pain (VAS), general well-being (VAS), DAS assessed at baseline and at day 7.. Handgrip strength assessed at baseline, 2, 4, 6, and 7 days.</td>
<td></td>
<td></td>
<td></td>
<td>fund</td>
</tr>
</table>

Effect size

Local Cold vs WBC -60 °C **vs WBC -110°C**

- WBC -110 **°C** was significantly better than LC for pain reduction (VAS) (p=0.024)
- WBC -110 **°C** was significantly better than WBC -60 **°C** for pain reduction (p=0.012)

- There was NS difference between the three groups for:
  - DAS at 7 days – significantly decreased from baseline in each group
  - Swollen joint count at 7 days
  - Tender joint count at 7 days
  - Global assessment (Patient's VAS) at 7 days - significantly decreased from baseline in each group
  - Global assessment (Physician's VAS) at 7 days- significantly decreased from baseline in each group
  - Grip strength at 7 days
  - ESR
  - CRP

  Adverse Events: N=5 LC; N=6 WBC -60 °C; N=5 WBC -110 °C
  No serious or adverse events.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brosseau L, Welch V, Wells G et al. Low level laser therapy (classes I, II and III) in the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews.* 2005;(4):CD002049. Ref ID: 1121 ID 1121	MA: 1++ RCT's of MA: 1- to 1++ SR and MA included: N=6 trials Trials were similar in terms of: • Study design (All RCTs) • Comparison (5 RCTs placebo and 1 RCT contralateral joint) • Blinding (4 RCTs double blind, 1 RCT triple blind, 1 RCT partial) Trials differed with respect to:	Total N=204 (placebo controlled trials) (N=122 laser therapy) (N=18 RCT using contralateral limb as control)	**Inclusion criteria:** RCTs; adults with clinical or radiological confirmation of RA of the hands or thumb Except one trial which did not specify joints affected Mean age range 53 to 67 yrs, baseline	Low level laser therapy (classes I, II and III) including all wavelengths from 632 nm to 1064 nm 2 to 3 sessions per week for 3 to 4 weeks Except one trial which	Standard treatment or placebo	Details of study duration not systematically reported	Pain (6 RCTs) Functional status (2 RCTs) Range of motion (4 RCTs) Swelling (3 RCTs) Grip strength (3 RCTs) Morning stiffness (4 RCTs)	University of Ottawa, Canada

	• Intervention – wavelength (1 RCT 633 nm, 1 RCT 850 nm, 1 RCT 820 nm, 1 RCT 830 nm, 1 RCT 820 nm, 1RCT 632.5 nm) • Intervention – Output power (1 RCT 10mW, 1 RCT 940 mW,, 1 RCT 40mW, 1 RCT 21 mW, 1 RCT 15 mW, 1RCT 1mW) • Study size (N=17, N=35, N=40, N=32, N=35, N=72) Tests for heterogeneity and quality assessment performed.		morning stiffness range 60 to 90 mins Search was up to 2001.	treated for 10 weeks				

Effect size

Treatment vs placebo (end of treatment)

Laser vs placebo

- There was a significant differences in favour of laser therapy compared with placebo – End of treatment 10 weeks:
  - Change in pain (VAS) (3 RCTs, N=147; WMD -1.10; 95 CI -1.82 to -0.39, p=0.003);
  - Pain (0 to 12 scale) (1 RCT, N=22; WMD -1.00; 95% CI -1.77 to -0.23, p=0.01);
  - Knee ROM (left) (1 RCT, N=35; MD -23.60; 95% CI -43.47 to -3.73, p=0.02);
  - Knee ROM (overall) (1 RCT, N=35; MD -18.03, 95% CI -31.80 to -4.27, p=0.01);
  - Flexibility – tip to palm distance (2 RCTs, N=57; WMD -1.28; 95% CI -1.72 to -0.85, p<0.00001);
  - Morning stiffness duration (3 RCTs, N=110; WMD -27.45; 95% CI -51.95 to -2.95, p=0.03);
  - Grip strength (mmHG) (2 RCTs, N=75; WMD 7.71; 95% CI 0.15 to 15.27, p=0.05);
  - Fibrinogen (1 RCT, N=35; WMD 1.50; 95% CI 0.00 to 3.00, p=0.05);
  - Leukocytes (1 RCT, N=35; WMD 1.60; 95% CI 0.62 to 2.58, p=0.001);
  - ESR (3 RCTs, N=92; WMD -10.09; 95% CI -15.04 to -5.15, p=0.00006);
  - Haemoglobin (2 RCTs, N=70; WMD 0.47; 95% CI 0.01 to 0.93, p=0.05)

- There were no significant differences of laser therapy compared with placebo – End of treatment 10 weeks:
  - McGill pain questionnaire (1 RCT, N=20);
  - Ritchie Index (1 RCT, N=40);
  - Health Assessment Questionnaire (HAQ) (2 RCTs, N=75);
  - MCP ROM (2 RCTs, N=80);
  - PIP ROM (2 RCTs, N=80);
  - Right knee ROM (1 RCT, N=35);
  - Ankle ROM (right, left overall) (1 RCT, N=35);
  - Morning stiffness (1 RCT, N=22);
  - Rheumatoid factor positive (1 RCT, N=35);
  - Grip strength (kg) (1 RCT, N=22);
  - Suprapatellar swelling (right) (1 RCT, N=35);
  - Suprapatellar swelling (left) (1 RCT, N=35);
  - MCP swelling (1 RCT, N=40);
  - PIP swelling (1 RCT, N=75);
  - Walking speed (1 RCT, N=35);
  - Lymphocytes (1 RCT, N=35);
  - CRP (1 RCT, N=57);
  - Platelets (1 RCT, N=35)

- There was a significant differences in favour of laser therapy compared with placebo – End of treatment 20 weeks:
  - Change in pain (VAS) (3 RCTs, N=147; WMD -1.10; 95 CI -1.82 to -0.39, p=0.003);

- Pain (0 to 12 scale) (1 RCT, N=22; WMD -1.00; 95% CI -1.77 to -0.23, p=0.01);
- Knee ROM (left) (1 RCT, N=35; WMD -23.60; 95% CI -43.47 to -3.73, p=0.02);
- Knee ROM (overall) (1 RCT, N=35; WMD -18.03, 95% CI -31.80 to -4.27, p=0.01);
- Flexibility – tip to palm distance (2 RCTs, N=57; WMD -1.28; 95% CI -1.72 to -0.85, p<0.00001);
- Morning stiffness duration (3 RCTs, N=110; WMD -27.45; 95% CI -51.95 to -2.95, p=0.03);
- Fibrinogen (1 RCT, N=35; WMD 1.50; 95% CI 0.00 to 3.00, p=0.05);
- Leukocytes (1 RCT, N=35; WMD 1.60; 95% CI 0.62 to 2.58, p=0.001);
- ESR (3 RCTs, N=92; WMD -10.09; 95% CI -15.04 to -5.15, p=0.00006);
- Haemoglobin (2 RCTs, N=70; WMD 0.47; 95% CI 0.01 to 0.93, p=0.05)

- There were no significant differences of laser therapy compared with placebo – End of treatment 20 weeks:
  - Pain (1 RCT, N=54);
  - McGill pain questionnaire (1 RCT, N=28);
  - Ritchie Index (1 RCT, N=26);
  - Health Assessment Questionnaire (HAQ) (2 RCTs, N=54);
  - PIP ROM (1 RCTs, N=26);
  - knee ROM (left, right, overall) (1 RCT, N=28);
  - Ankle ROM (right, left overall) (1 RCT, N=28);
  - MCP ROM (1 RCT, N=26);
  - Morning stiffness (2 RCTs, N=54);
  - Walking spend (1 RCT, N=28);;
  - Grip strength (mmHg) (1 RCT, N=26);
  - Grip strength (kg) (1 RCT, N=22);
  - Suprapatellar swelling (right, left) (1 RCT, N=28);
  - MCP swelling (1 RCT, N=26);
  - PIP swelling (1 RCT, N=26);
  - Thermographic Index (1 RCT, N=26);
  - Rheumatoid factor positive (1 RCT, N=20);
  - ESR (1 RCT, N=28);
  - CRP (2 RCTs, N=55);
  - Haemoglobin (1 RCT, N=54);
  - Platelets (1 RCT, N=54)

Subgroup analysis

- There were no significant differences according to:
  - Methodological quality;
  - Treatment duration (pain);
  - Joint compared with nerve application (pain);
  - Wavelength (pain)

Dosage

- There was a significant differences in favour of low dose laser therapy (≤3 J/cm²) compared with placebo but not high dose laser therapy compared with placebo:
  - Change in pain (VAS) (low dose SMD -0.8; 95% CI -1.2 to -0.4)

- There were no significant differences according to dosage for:
  - Grip strength;
  - Flexibility (tip to palm)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brosseau L, Judd MG, Marchand S et al. Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. *Cochrane Database of Systematic Reviews.* 2003;(2):CD004377. ID 661	MA: 1++ RCT's of MA: 1+ to 1++ SR and MA included: N=3 trials with suitable data Trials were similar in terms of: • Study design (All RCTs) • Study quality (reasonable/good) Trials differed with respect to: • Disease duration (1 RCT mean 13 yrs, 1 RCT 11, 1 RCT range 1 to 44 yrs) • Comparison group (2 RCTs placebo, 1 RCT AL-TENS) • Intervention (1 RCT 15 mins of 70 Hz, 1 RCT 20 mins of 100 Hz, 1 RCT 5 mins of 70 Hz) • Study size (1 RCT N=26, 1 RDT N=33, 1 RCT N=19) • Blinding (1 double blind, 1 single, 1 unblinded) • Follow-up (1 15 days, 2 not specified)	Total N=78	**Inclusion criteria:** RCTs or CCTs; adults > 18 yrs with clinical and/or radiological confirmation of RA of the hand (ARA 1987); treatment with TENS Search was up to 2002.	TENS	Placebo (2 RCTs) AL-TENS (1 RCT)	1 RCT 15 days 2 RCTs unspecified	Pain: Resting and grip OMERACT: Number of tender joints Number of swollen joints Physician global assessment Patient global assessment Functional status Range of motion (ROM) Strength Change in muscle power Work	University of Ottawa

	Tests for heterogeneity and quality assessment performed.							

Effect Size

Placebo versus TENS (hand); – end of treatment 3 weeks

- TENS was significantly better than placebo at end of treatment – 3 weeks for:
  - Change in resting pain (VAS) (1 RCT, N=32; effect size WMD -59.50, 95% CI -76.58 to -42.42, p<0.00001)

- There was NS difference between placebo and TENS for RA in the hand at end of treatment – 3 weeks for:
  - Change in grip pain (1 RCT, N=32);
  - Power score (1 RCT, N=32);
  - Work score (1 RCT, N=32)

C-TENS versus placebo (hand); (end of treatment – same day)

- C-TENS was significantly better than placebo at end of treatment – same for:
  - Change in joint tenderness (1 RCT, N=32; effect size WMD -20.00, 95% CI -33.79 to -6.21, p=0.004)

- There was NS difference between C-TENS and placebo at end of treatment – same day for:
  - Resting pain (VAS) (1 RCT, N=22);
  - Grip pain (VAS) (1 RCT, N=22);
  - Tender joints (1 RCT, N=30)

C-TENS versus AL-TENS (wrist); (end of treatment – 15 days)

- There was NS difference between C-TENS and AL-TENS at end of treatment – 15 days for:
  - Number of patients improved (1 RCT, N=38);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Casimiro, L. Brosseau, V. Robinson, S. Milne, M. Judd, G. Well, P. Tugwell, and B. Shea.	MA: 1++ RCT's of MA: 1- to 1+ SR and MA included: N=2 trials with suitable data Trials were similar in terms of:	Total N=80	**Inclusion criteria:** RCTs or CCTs; adults with definite or classic RA (BMI 2001); treatment with ultrasound on any joint except the	Ultrasound Applications using any combination of parameters (such as	Any control	3 weeks	Pain, OMERACT oucomes	Ottowa Health Research Institute, University of Ottowa and

Therapeutic ultrasound for the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (3):CD003787, 2002. ID 842	• Study design (All RCTs) • Study quality (poor / moderate) • Study duration – length of intervention (3 weeks) Trials differed with respect to: • Intervention (1 RCT Ultrasound combined with either exercises, electric current, wax baths or electric current and exercises; 1 RCT ultrasound alone) • Comparison group (placebo ultrasound) • Study size (1 RCT N=30, 1 RCT N=50) • Blinding (1 double blind, 1 unblinded) Tests for heterogeneity and quality assessment performed.		spine Search was up to 2001.	intensity, mode, size of the US head)				Institute of Population Health, Canada

Effect size

Treatment vs placebo (end of treatment – 10 weeks)

- Ultrasound treatment was significantly better than placebo at end of treatment – 10 weeks for:
  - Change in number of painful articulations (1 RCT, N=50; effect size RR 1.2, 95% CI 0.5 to 2.0, p=0.002);
  - Change in number of swollen articulations (1 RCT, N=50; effect size RR 1.0, 95% CI 0.5 to 1.6, p=0.0005);
  - Change in dorsal flexion of the wrist (1 RCT, N=50; effect size RR 1.9, 95% CI 0.6 to 3.2, p=0.003);
  - Change in grip strength (1 RCT, N=50; effect size RR 28.1, 95% CI 13.4 to 42.8, p=0.0002);

- There was NS difference between Ultrasound treatment and placebo at end of treatment – 10 weeks for:
  - Change in circumference of PIP joints (1 RCT, N=50);
  - Change in duration of morning stiffness (1 RCT, N=50);

Treatment vs wax (hand); (end of treatment – 1 week, 2 weeks and 3 weeks)

- There was NS difference between Ultrasound treatment and wax (hand) at end of treatment – 1 week, 2 weeks and 3 weeks for:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular index (1 RCT, N=20);
  - Timed task (1 RCT, N=20);
  - Activity score (1 RCT, N=20);

Treatment vs faradic bath + ultrasound (hand); (end of treatment – 1 week, 2 weeks and 3 weeks)

- Ultrasound treatment was significantly better than faradic bath + ultrasound (hand) at end of treatment – 1 week, 2 weeks and 3 weeks for:
  - Activity score (1 RCT, N=20; $p<0.05$);

- There was NS difference between Ultrasound treatment and faradic bath + ultrasound (hand) at end of treatment – 1 week, 2 weeks and 3 weeks for:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular Index (1 RCT, N=20);
  - Time task (1 RCT, N=20);
  - ROM at 3 weeks (1 RCT, N=20)

Faradic bath + ultrasound (hand) vs wax (hand); (end of treatment – 1 week)

- Faradic bath + Ultrasound treatment was significantly better than wax (hand) at end of treatment – 1 week, 2 weeks and 3 weeks for:
  - Activity score (1 RCT, N=20; p<0.05);

- There was NS difference betweenfaradic bath + Ultrasound treatment and wax (hand) at end of treatment – 1 week, 2 weeks and 3 weeks for:
  - Hand grip (1 RCT, N=20);
  - PIP circumference (1 RCT, N=20);
  - Articular Index (1 RCT, N=20);
  - Time task (1 RCT, N=20);
  - ROM at 3 weeks (1 RCT, N=20)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Han, V. Robinson, M. Judd, W. Taixiang, G. Wells, and P. Tugwell. Tai chi for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (3):CD004849, 2004. ID 499	MA: 1++ RCT's of MA: 1- SR and MA included: N=4 trials with suitable data Trials were similar in terms of: • Study design (All RCTs) • Study quality (poor) • Blinding (unblinded) Trials differed with respect to: • Intervention (1 RCT health education + ROM Dance and relaxation; 1 RCT oral Shan Pi Tong + education + exercise + massage + hot compress; 2 RCTs tai chi exercises) • Comparison group (1 RCT oral Lei Gong; 1 RCT oral Shan Pi Tong; 2 RCTs no exercise) • Study size (range N=28 to N=100) • Study duration – length of intervention (range 8 weeks to	Total N=206	**Inclusion criteria:** RCTs or CCTs; ambulatory adults with RA Search was up to 2002.	Exercise programmes with Tai chi instruction or incorporating Tai Chi principles	No therapy, sham therapy other active therapy	8 to 10 weeks	Pain, OMERACT outcomes; grip strength; ROM	Institute of Population Health, Canada; Paulista Centre for Health Economics, Brazil

	10 weeks) Tests for heterogeneity and quality assessment performed.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**	
L. M. Bearne, D. L. Scott, and M. V. Hurley. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. *Rheumatology* 41 (2):157-166, 2002. Ref ID: 3328	RCT: 1+ Single centre trial: UK • Randomised (method not mentioned) • Allocation concealment • No mention of blinding • ITT analysis	Total N=93 randomised (N=47 rehabilitation exercise; N=46 control group) **Drop-outs:** N=14 (30%) rehabilitation N=18 (39%) control (waiting list) Established RA (>2 years)	**Inclusion criteria:** Definite RA for >2 years; involving lower limbs; **Exclusion criteria**: acute exacerbation of disease; unstable co-existing major medical problems; started on slow-acting drugs or systematic steroids within the previous 3 months; using daily prednisolone >10 mg; wheelchair bound. **Baseline characteristics:** There were NS differences between the groups for any of the baseline characteristics**.**	Rehabilitation strengthening exercise 10 30-45 min exercise sessions (2/week for 5 weeks): individually prescribed designed to increase quadriceps strength, address each patient's disabilities and improve balance and co-ordination. Exercises were made more challenging by increasing number of repetitions, resistances and improving quality of performance of an exercise to improve muscle control. Intensity was reduced if the patient reported pain.	Control (waiting list) Continued normal activities	5 weeks (end of treatment) with follow-up at 6 months	Muscle strength; HAQ; Morning stiffness; Pain (VAS); Patient and assessor's global assessment; Swollen and tender joint counts	NHS R&D Physical and Complex Disabilities Programme, UK.	

Effect size

Strengthening exercise (rehabilitation) vs Control (waiting list)

- Strengthening exercise (rehabilitation) was significantly better than control (waiting list) for:
  - Quadriceps strength at 5 weeks (end of treatment), p<0.01
  - HAQ score at 6 months (follow-up), p<0.05

- There was NS difference between Strengthening exercise (rehabilitation) and control (waiting list) for:
  - HAQ at 5 weeks (end of treatment)
  - Morning stiffness at 5 weeks (end of treatment)
  - Pain (VAS) at 5 weeks (end of treatment)
  - Patient's and Assessor's global assessment at 5 weeks (end of treatment)
  - Swollen and Tender joints at 5 weeks (end of treatment)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. V. O'Brien, P. Jones, R. Mullis, D. Mulherin, and K. Dziedzic. Conservative hand therapy treatments in rheumatoid arthritis--a randomized controlled trial. *Rheumatology* 45 (5):577-583, 2006. ID 3272	RCT: 1++ Single centre trial: UK • Randomised (computer-generated list, permuted blocks within strata – stratified by time since diagnosis and RF status) • Single blind (assessor) • ITT analysis • Power study	Total N=67 randomised (N=21 Joint protect + both exercises; N=24 joint protection + mobilisation exercise; N=22 Control – joint protection only) **Drop-outs:** N=3 (14%) Joint protection + strengthening/mobilisation exercise N=8 (33%) Joint protection + mobilisation exercise N=4 (18%) Joint protection only	**Inclusion criteria:** Aged >18 years; RA (ACR criteria). **Exclusion criteria:** Recent changes in drug regime in the previous 3 months; oral CS therapy >7,5 mg/day; IM or IA CS treatment within previous month. Surgery to the wrist, hand or elbow or shoulder within previous 6 months; sensory impairment of the hand; uncontrolled pain affecting the joints of the wrist	Joint protection + strengthening/mobilisation exercise (hands) – 8 strengthening and mobilising (stretching) 'tendon gliding' exercises Joint protection + mobilisation exercise (hands) – 8 mobilising (stretching) exercises without any strengthening exercises All 3 groups received instruction in joint protection. The 2 treatment groups increased exercise	Control – joint protection only	6 months (end of treatment)	AIMS2; Jebsen-Taylor function test; Grip; pinch; swollen and tender joints; patients global assessment of disease activity	Promedics, UK; Birmingham branch of the Chartered Society of Physiotherapy

			or hand **Baseline characteristics:** Joint protect + both exercises: mean age 62 years; Female 71%; Duration of RA = Established RA (mean 18 years); pain (VAS) mean 3.9 Joint protect + mobilisation exercises: mean age 57 years; Female 62%; Duration of RA = Established RA (mean 13 years); Pain (VAS) mean 3.9 Control - Joint protect only: mean age 60 years; Female 73%; Duration of RA = Established RA (mean 8 years); Pain (VAS) mean 3.4 There were NS differences between the randomised	repetitions over time, as part of the home exercise programme.				

			groups for any of the baseline characteristics.					

Effect size

- Joint protection + strengthening/mobilisation exercise (hands) was significantly better than joint protection only for:
  - Dominant key grip at 6 months, p=0.007
  - AIMS2 upper limb function at 6 months, p=0.002

- Joint protection + mobilisation exercise (hands) was significantly better than joint protection only for:
  - Dominant key grip at 6 months, p=0.032

- Joint protection + mobilisation exercise was worse than Joint protection + strengthening/mobilisation exercise and control (joint protection only) for:
  - Number of drop-outs at 6 months

- There were NS differences between any of the 3 groups for:
  - AIMS (hand and finger function) at 6 months;
  - Jebsen-Taylor function score at 6 months;
  - Right index finger flexion at 6 months;
  - Dominant gross grip at 6 months;
  - Tender and swollen joint counts at 6 months
  - Patient's global assessment of disease activity at 6 months

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Eversden L. A pragmatic randomised controlled trial of hydrotherapy and land exercises on overall well being and quality of life in rheumatoid arthritis. *BMC*	RCT: 1+ Single centre trial: UK • Randomised • Allocation concealment • Single blind (assessor)	Total N=115 randomised N=58 land exercise N=57 hydrotherapy **Drop-outs:**	**Inclusion criteria:** people> 18 years old with RA functional class I, II, or III, must be on stable dose of DMARDS for 6 weeks and NSAIDS for 2 weeks before study start. **Exclusion criteria**: corticosteroid injections in previous four weeks, surgery 3 months prior to start, physiotherapy or hydrotherapy in previous 6 months, chlorine sensitivity, infected open wound,	N=57 hydrotherapy Procedure: People randomised to weekly 30-minute sessions of hydrotherapy or similar exercises on	N=58 land exercise	3 months	Primary: self-rated overall effect of treatment (asked "Please indicate how you feel after your treatment? People scored 1 = very much worse up to 7	University hospital Birmingham NHS Foundation Trust Charities

Musculoskeletal Disorders. 2007; 8:23-29. Ref ID: 865	• ITT analysis • Higher dropouts in both groups • Slightly underpowered; they needed N=60 in each arm, but recruited N=57 or N=58.	hydrotherapy = 13/57 (23%) land exercise = 17/58 (29%)	poorly controlled epilepsy, hypertension, diabetes, faecal incontinence, fear of water, pregnant women, MRSA-carriers, weight > 102 kg **Baseline characteristics:** NS differences hydrotherapy / Land exercise N: 57 / 58 % female: 68 / 72 Duration of disease, median, years: 10 / 8 Age, mean: 55 / 56	land for 6 weeks. Medication changes and corticosteroid injections permitted during trial.			= very much better) Secondary: Pain (VAS); HAQ , ten meter walk speed, EuroQol-5D Utility, EuroQol-5D VAS	

Effect size

Hydrotherapy vs land exercise

- hydrotherapy was significantly better than land exercise for the primary outcome: self-rated overall effect of treatment ($p<0.001$)
- sensitivity analysis confirmed this

- There was NS difference between hydrotherapy and land exercise groups for:
  - EQ-5D utility: decreased significantly in both groups from baseline to 3 months
  - EQ-5D VAS: NS change in both groups from baseline to 3 months
  - HAQ: NS change in both groups from baseline to 3 months
  - Pain (VAS): increased significantly in both groups from baseline to 3 months
  - 10 m walk time: decreased significantly in both groups from baseline to 3 months

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. Hall, S. M. Skevington, P. J.	RCT: 1+ Single centre trial: UK	Total N=148 randomised (N=37 each	**Inclusion criteria:** involvement of at least 6 joints; maintained on stable drug regimen for a period of	1. Hydrotherapy 2. Land exercise	3. Seated immersion	4 weeks (end of treatment)	RAI; Morning stiffness;	The Arthritis and Rheumatism

Maddison, and K. Chapman. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. *Arthritis Care & Research* 9 (3):206-215, 1996. Ref ID: 3338	• Randomised (random numbers table; blocks of 4 so equal numbers in each group – N=37) • Allocation concealment • Single blind (assessor) • No ITT analysis • Power study	group) **Drop-outs:** N=2 (5%) in each group: hydrotherapy; seated immersion; progressive relaxation. N=3 (8%) land exercise	30 days (NSAIDs) or 3 months (DMARDs). RA Steinbroker functional class I, II, or III. **Exclusion criteria**: IA CS injections or PT treatment within 30 days of assessment; joint replacement surgery within 6 months; History of any known condition contraindicating exercise therapy or immersion in water. **Baseline characteristics:** Hydrotherapy: mean age 56 years; Female 60%; Duration of RA = Established RA (mean 8 years) Seated immersion: mean age 59 years; Female 69%; Duration of RA = Established RA (mean 12 years) Progressive relaxation: mean age 60 years; Female 71%; Duration of RA = Established RA (mean 12 years) Land exercise: mean age 59 years; Female 76%; Duration of RA = Established RA (mean 12 years) The randomised groups were similar for all baseline characteristics**.**	All interventions took place in the gym or hydrotherapy pool at the same hospital in small groups of 4 or 5. Exercise sessions lasted 30 mins and all other interventions lasted the same length of time. 8 sessions – for reasons of fatigue, all interventions were limited to 2 sessions/week.. Exercises designed to increase ROM of the key joints and to improve muscle strength of the main upper and lower limb groups were used for the 2 exercise groups. The type, duration and frequency of exercises were standardised and the speed and resistance were adjusted by the therapist in response to the individual's capabilities and progress.	4. Progressive relaxation Adapted and updated version of Jacobsen's progressive relaxation technique, including some mental imagery tasks, was tailored for use with arthritis patients in the 2 non-exercise groups. Progressive relaxation group relaxed in quiet darkened room. The seated immersion group relaxed in the pool on weighted chairs with their legs dependent, water approx 36^{o}C, immersed to the suprasternal notch.	with follow-up at 3 months (2 months post-treatment)	grip strength; ROM; CRP; Pain (McGill); AIMS2	Council and the Chartered Society of Physiotherapy, UK.

Effect size

Hydrotherapy vs land exercise vs seated immersion vs progressive relaxation

- hydrotherapy was significantly better than land exercise, seated immersion and progressive relaxation for:
    - RAI (joint tenderness) at 4 weeks (end of treatment), p=0.03
    - AIMS2 (mood and tension) at 4 weeks (end of treatment), p=0.03

- There was NS difference between hydrotherapy and land exercise groups, seated immersion and progressive relaxation for:
    - Knee and wrist ROM at 4 weeks (end of treatment)
    - Morning stiffness at 4 weeks (end of treatment)
    - Grip strength at 4 weeks (end of treatment)
    - AIMS 2 (physical capacity, pain, social, work and affect) at 4 weeks (end of treatment)
    - Pain (McGill) at 4 weeks (end of treatment)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Hoenig, G. Groff, K. Pratt, E. Goldberg, and W. Franck. A randomized controlled trial of home exercise on the rheumatoid hand. *Journal of Rheumatology* 20 (5):785-789, 1993. ID 3342	RCT: 1+ Twin centre trial: USA • Randomised (blocks of 4, random numbers table) • Single blind (assessor) • No mention of ITT analysis	Total N=57 randomised (N=14 ROM; N=14 Res; N=15 Res + ROM; N=14 Control) **Drop-outs:** N=3 (21%) ROM N=5 (36%) Res N=5 (33%) Res + ROM N=3 (21%) Control	**Inclusion criteria:** RA over the preceding 5 years (ARA criteria); for definite or classical RA; functional class II or III. **Exclusion criteria:** medication changed during the previous 6 weeks **Baseline characteristics:** All: mean age 57 years; Duration of RA = Established RA (mean 11 years) The randomised	ROM:tendon gliding exercises (thumb and fingers) Res (Resistive): therapy with putty – perofmed balanced resistive hand exercises, 10 repetitions performed twice/day. Res + ROM (Resistive + ROM): both of the above combined	Control group (active lifestyle)	12 weeks (end of treatment)	RAI; MCP extension; PIP extension; dexterity	The Bassett Research Foundation and Fred Sammons Inc, USA.

			groups were similar for allof the baseline characteristics.					

Effect size

ROM exercise vs Control (active lifestyle)

- ROM exercise was significantly better than control (active lifestyle) for:
    - Painful joints in the left hand at 12 weeks, $p<0.05$

- There was NS difference between ROM exercise and Control (active lifestyle) for:
    - Painful joints in the right hand at 12 weeks
    - MCP extension in the left and right hands at 12 weeks
    - PIP extension in the left and right hands at 12 weeks
    - Dexterity in the left and right hands at 12 weeks
    - Mean grip strength in the left and right hands at 12 weeks

Resistance exercise vs Control (active lifestyle)

- Resistance exercise was significantly better than control (active lifestyle) for:
    - MCP extension in the left hand at 12 weeks, $p<0.05$

- There was NS difference between Resistance exercise and Control (active lifestyle) for:
    - Painful joints in the left and right hands at 12 weeks
    - MCP extension in the left and right hands at 12 weeks
    - PIP extension in the right hand at 12 weeks
    - Dexterity in the left and right hands at 12 weeks
    - Mean grip strength in the left and right hands at 12 weeks

Resistance + ROM exercise vs Control (active lifestyle)

- Resistance + ROM was significantly better than control (active lifestyle) for:
    - Dexterity in the left hand at 12 weeks, $p<0.05$

- There was NS difference between Resistance + ROM exercise and Control (active lifestyle) for:
    - Painful joints in the left and right hands at 12 weeks
    - MCP extension in the left and right hands at 12 weeks
    - PIP extension in the left and right hands at 12 weeks
    - Dexterity in the right hand at 12 weeks
    - Mean grip strength in the left and right hands at 12 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of

								funding
Z. De Jong, M. Munneke, A. H. Zwinderman, H. M. Kroon, A. Jansen, K. H. Ronday, Schaardenburg D. van, B. A. Dijkmans, C. H. Van den Ende, F. C. Breedveld, T. P. Vliet Vlieland, and J. M. Hazes. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial.[see comment]. *Arthritis & Rheumatism* 48 (9):2415-2424, 2003. ID 3324	RCT: 1++ Multicentre trial: 4 centres in The Netherlands • Randomised (permutated-blocked randomisation – blocks of 4, stratified for centre, age and gender, randomisation by random digit generator) • Single blind (assessors) • Allocation concealment • ITT analysis • Power study (HAQ)	Total N=309 randomised (N=151 RAPIT High intensity exercise group, N=158 Control – usual care) **Drop-outs at 2 years:** N=15 (10%) RAPIT - High intensity exercise group N=13 (8%) Control (usual care)	**Inclusion criteria:** Age 20-70 years; RA (ACR criteria); on stable medication for the last 3 months; able to cycle; ACR functional classes I-III **Exclusion criteria:** Prosthesis of a weight-bearing joint; cardiopulmonary disease excluding intensive exercise; comorbidity causing a short life-expectancy; serious psychiatric disease. **Baseline characteristics:** RAPIT exercise group: mean age 54 years; Female 79%; Duration of RA = Established RA (mean 5 years); HAQ mean 0.7 Control (usual care) group: mean age 54 years; Female 79%; Duration of RA = Established RA (mean 8 years); HAQ mean 0.6 There were NS differences between the groups for any of the baseline characteristics except for Duration of RA, DMARD use and radiographic damage of hands and feet which were significantly higher in the Control group.	RAPIT (High intensity exercise) group: Biweekly exercise programme of 1.25 hours each session. Each session had 3 parts of 20 mins each: bicycle training; exercise circuit; sport or game. During training the heart rate was kept at approx. 70-90% of the predicted MHR. If necessary the programme was adapted to individual disabilities to reach the same aims. Patients assigned to the control group were treated by a PT only if this was regarded as necessary by their attending physician. Physicians had free choice with respect to their medical prescriptions and other treatment strategies including additional PT (except for high-intensity, weight bearing exercises)	Control group (Usual care)	2 years (end of treatment)	MACTAR; HAQ; HADS (Hospital Anxiety and Depression Scale); Larsen score of large joints (LLJ), DAS4; RAI; ESR	Grant from the Dutch Health Care Insurance Board

Effect size

High intensity aerobic exercise vs control group (usual care)

- High intensity aerobic exercise was significantly better than control group (usual care) for:
  - MACTAR score at 1 year and 2 years ($p<0.05$)
  - Muscle strength at 1 year and 2 years ($p<0.05$)

- There was NS difference between High intensity aerobic exercise and control group (usual care) for:
  - HAQ score at 1 year and 2 years
  - Radiographic damage (Larsen score for large joints) at 1 year and 2 years
  - DAS 4 at 1 year and 2 years

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Z. De Jong, M. Munneke, W. F. Lems, A. H. Zwinderman, H. M. Kroon, E. K. Pauwels, A. Jansen, K. H. Ronday, B. A. Dijkmans, F. C. Breedveld, T. P. Vliet Vlieland, and J. M. Hazes. Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized,	RCT: 1++ Multicentre trial: 4 centres in The Netherlands	Total N=309 randomised (N=151 RAPIT High intensity exercise group, N=158 Control – usual care) **Drop-outs at 2 years:** N=15 (10%) RAPIT - High intensity exercise group N=13 (8%) Control (usual care)	As for ID 3324	RAPIT (High intensity exercise) group: As for ID 3324	Control group (Usual care) As for ID 3324	2 years (end of treatment)	Bone mineral density	Not mentioned

controlled trial. *Arthritis & Rheumatism* 50 (4):1066-1076, 2004. ID 3321								

Effect size

High intensity aerobic exercise vs control group (usual care)

- High intensity aerobic exercise was significantly better than control group (usual care) for:
  - Bone mineral density of the hip over 2 years

- There was NS difference between High intensity aerobic exercise and control group (usual care) for:
  - Bone mineral density of the spine over 2 years

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Z. De Jong, M. Munneke, A. H. Zwinderman, H. M. Kroon, K. H. Ronday, W. F. Lems, B. A. Dijkmans, F. C. Breedveld, T. P. Vliet Vlieland, J. M. Hazes, and T. W. Huizinga. Long term high intensity exercise and damage of small joints in rheumatoid arthritis.[see comment].	RCT: 1++ Multicentre trial: 4 centres in The Netherlands	Total N=309 randomised (N=151 RAPIT High intensity exercise group, N=158 Control – usual care) **Drop-outs at 2 years:** N=15 (10%) RAPIT - High intensity exercise group N=13 (8%) Control (usual care)	As for ID 3318	RAPIT (High intensity exercise) group: As for ID 3318	Control group (Usual care) As for ID 3318	2 years (end of treatment)	Radiological damage of the small joints (hands and feet - Larsen score)	Not mentioned

Annals of the Rheumatic Diseases 63 (11):1399-1405, 2004. ID 3318								

Effect size

High intensity aerobic exercise vs control group (usual care)

- High intensity aerobic exercise was significantly better than control group (usual care) for:
  - Radiographic damage (Larsen score for all small joints, hands and feet) over 2 years
  - Radiographic damage (Larsen score for small joints of the feet) over 2 years

- There was NS difference between High intensity aerobic exercise and control group (usual care) for:
  - Radiographic damage (Larsen score for small joints of the hands) over 2 years

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
N. Brodin, E. Eurenius, I. Jensen, R. Nisell, C. H. Opava, M. Algebrandt, I. Almin, B. Andersson, G. Bertholds, C. Forsberg, E. Haglund, A. M. Holmen-Andersson, A. Hultman, C. Lennartsson, and E.	RCT: 1++ Multicentre trial: 20 centres in Sweden	Total N=228 randomised (N=94 exercise programme, N=134 Control) **Drop-outs at 1 year:** • Randomised (rolling dice, not stratified) • No mention of blinding • Allocation	**Inclusion criteria:** Patients on the Swedish RA register; age >18 years; recently diagnosed with RA (within 12 months) **Exclusion criteria:** None – as felt that all RA patients can benefit from physical activity, regardless of comorbidities or age. **Baseline characteristics:** Physcial exercise group: mean age 54 years; female mean 72%; disease duration mean 21	Exercise programme (healthy physical activity) 1 year programme aimed at implementing healthy physical activity (moderately intensive, 30 mins/day, ≥4 days/week). They were individually coached by a PT and informed about benefits of physical activity. Goals were set (graded	Usual care	1 year	EuroQoL; HAQ; Grip strength ROM; stands test; Pain (VAS); DAS28; swollen and tender joints; patients' self-reported general health	Swedish Research Council, Swedish Rheumatism Association and several Foundations.

Norman. Coaching patients with early rheumatoid arthritis to healthy physical activity: A multicenter, randomized, controlled study. *Arthritis Care and Research* 59 (3):325-331, 2008. ID 3532		concealment • ITT analysis • Power study (EuroQoL)	months (Early RA); DAS 28 mean 3.2. Control group: mean age 56 years; female mean 75%; disease duration mean 22 months (Early RA); DAS 28 mean 3.3. There were NS differences between the groups for any of the baseline characteristics	activity training) – had continuous telephone support after 1 week then once/month. Goals were systematically evaluated and adjusted whenever required. All participants in both groups had access to, but were not specifically encouraged to participate in, ordinary physical therapy treatment including patient education, treatment with physical modalities and organised exercise a maximum of twice/week.			perception (VAS)	

Effect size

Physical exercise programme vs control group (usual care)

- Physical exercise programme was significantly better than control group (usual care) for:
  - EuroQoL (VAS) at 1 year (p=0.027)
  - Timed Stands test at 1 year (p=0.000)
  - Grip strength at 1 year (p=0.003)

- There was NS difference between the physical exercise programme and the control group (usual care) for:
  - Percentage of patients reaching healthy physical activity at 1 year
  - ROM at 1 year
  - Pain (VAS) at 1 year
  - HAQ-DI at 1 year
  - DAS28 at 1 year
  - Percentages of patients taking different types of medication at 1 year

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. H. Van den Ende, F. C. Breedveld, Cessie S. Le, B. A. Dijkmans, A. W. de Mug, and J. M. Hazes. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial.[see comment]. *Annals of the*	RCT: 1+ Single centre trial: The Netherlands • Randomised (method not mentioned) • Allocation concealment • Single blind (assessor) • No ITT analysis • Power study (Swollen joints and	Total N=64 randomised (N=32 conservative exercise; N=32 intensive exercise) **Drop-outs:** N=3 (9%) conservative exercise N=2 (6%) intensive exercise Established RA (>2 years)	**Inclusion criteria:** Patient with active RA (ARA criteria) and loss of functional ability. **Exclusion criteria**: presence of arthroplasties in the knee joints; inability to tolerate training due to serious cardiac or lung disease. **Baseline characteristics:** Conservative exercises: mean age 58 years; Female 66%; Duration of RA = Established RA (mean 7 years); HAQ mean 1.7	Intensive exercise Same exercises as the conservative group but in addition received supplemental intensive exercises. Isometric exercises, muscle strengthening and aerobic (cycling).	Conservative exercises All patients in both groups followed the usual conservative exercise programme of ROM and isometric exercises supervised 4 times/week and patients were encouraged to continue their exercise at home on their own.	24 weeks (end of treatment)	Muscle strength; DAS; HAQ; Morning stiffness; Pain (VAS); Patient and assessor's global assessment; Swollen and tender joint counts; ROM.	ZorgOnderzoek Nederland, The Netherlands.

Rheumatic Diseases 59 (8):615-621, 2000. Ref ID: 3333	DAS)		Intensive exercises: mean age 62 years; Female 59%; Duration of RA = Established RA (mean 8 years); HAQ mean 1.8 There were NS differences between the groups for any of the baseline characteristics**.**					

Effect size

Intensive exercise (rehabilitation) vs Conservative exercises

- Intensive exercise (strengthening + aerobic) was significantly better than control (strengthening) for:
  - ACR responders at 24 weeks (end of treatment), p=0.04
  - Muscle strength (isometric extension) at 24 weeks, p<0.05

- There was NS difference between Intensive exercise (strengthening + aerobic) and control (strengthening) for:
  - Swollen joints at 24 weeks (end of treatment)
  - ESR at 24 weeks (end of treatment)
  - Pain (VAS) at 24 weeks (end of treatment),
  - DAS at 24 weeks (end of treatment)
  - Joint mobility at 24 weeks (end of treatment),
  - HAQ at 24 weeks (end of treatment)
  - 50 foot walk time at 24 weeks (end of treatment)
  - Joint mobility (EPM-ROM) at 24 weeks (end of treatment)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
G. B. Neuberger, L. S. Aaronson, B. Gajewski, S. E. Embretson, P. E. Cagle, J. K. Loudon, and	RCT: 1+ Single centre trial: USA • Randomised (stratified by gender,	Total N=310 randomised (N=102 class exercise; N=103 Home exercise; N=105 Control)	**Inclusion criteria:** Aged 40-70 years; RA (ACR criteria); ambulatory; no history of fibromyalgia or COPD; not taking a beta-blocker of digitalis medication; not	Class exercise group: Low impact aerobic exercises for 1 hour, 3 times/week. Low impact = one foot is always on the ground and there are no running or	Control group (usual level of exercise; home exercise)	12 weeks (end of treatment)	Global fatigue index; Pain (SF_McGill Pain Questionnnaire); depression; total joint count; ESR; CRP; Grip strength and 50-	Grant from the NIH

P. A. Miller. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis & Rheumatism* 57 (6):943-952, 2007. ID 7	randomly generated permutations of 3 numbers) • Single blind (assessor) • ITT analysis • Power study (treatment effects) • High drop-outs	**Drop-outs at 12 weeks:** N N=34 (33%) Class exercise N=24 (23%) Home exercise N=32 (30%) Control	performing ≥30 mins of aerobic exercise ≥3 times/week; meet criteria for aerobic fitness testing. **Exclusion criteria:** Not mentioned **Baseline characteristics:** All: mean age 56 years; Duration of RA = Established RA (mean 8 years) There were no significant differences between the randomised groups for any of the baseline characteristics except race (more minorities in the Class exercise group).	jumping movements. Classes were at a fitness centre. Home exercise group: same exercise programme as the class-based group but exercises were performed at home using a videotape. In both groups patients were given their target heart rate for 60% and 80% of their MHR and were told to start exercising at 60% and progress to 80% as tolerated (being able to talk while exercising without being short of breath)			foot walk time Overall symptoms score (weighted average of the individual symptom scores)	

Effect size

Class aerobic exercise vs Control (home exercise)

- Class aerobic exercise was significantly better than control (home exercise) for:
  - Overall symptoms (adjusted for baseline) at 12 weeks, p<0.04
  - Walk time over 12 weeks, p<0.005
  - Grip strength over 12 weeks, p<0.005

Home aerobic exercise vs Control (usual exercise)

- Home aerobic exercise was significantly better than control (home exercise) for:
  - Walk time over 12 weeks, p<0.005
  - grip strength over 12 weeks, p<0.005

- There was NS difference between Home aerobic exercise and control (home exercise) for:
  - Overall symptoms (adjusted for baseline) at 12 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. M. Hansen and G. Hansen. Longterm physical training in rheumatoid arthritis. A randomized trial with different training programs and blinded observers. *Scandinavian Journal of Rheumatology* 22 (3):107-112, 1993.	RCT: 1+ Single centre trial: Denmark • Randomised (method not mentioned) • Single blind (assessor) • No ITT analysis	Total N=75 randomised (N=15 in each group) **Drop-outs at 2 years:** N=1 (7%) self-training N=1 (7%) Self-training + PT training N=4 (27%) group training N=2 (13%) group training and	**Inclusion criteria:** RA (ARA criteria); functional status I or II. **Exclusion criteria:** Aged <20 or >60 years; diseases other than RA which contraindicated or made physical training impossible; already training 3 times/week or more **Baseline characteristics:** Self-training: mean age 55 years; Female 80%; Duration of RA = Established RA (mean 7 years); HAQ mean 0.63 Self-training + PT training:	Self-training: daily exercises of training programme followed by 30 mins conditioning (aerobic) training. Self-training + PT training: As for self-training but met weekly in a PT practice to perform the exercise programme then did 15 mins conditioning (aerobic) training on bicylces Group training: weekly training in the hospital in groups of up to 5 people. Same	Control group (no training)	2 years (end of treatment)	Number of swollen joints; Pain score (VAS); Morning stiffness; HAQ score; Radiographic damage (Larsen score); Functional score; muscle strength; ESR	Grants from the Danish Arthritis Foundation and Danish Physiotherapists' Research Fund and Danish Research Council and the Fund for Medical Research in South Jutland

ID 977		pool N=2 (13%) no training	mean age 52 years; Female 47%; Duration of RA = Established RA (mean 7 years); HAQ mean 0.57 Group Training: mean age 51 years; Female 60%; Duration of RA = Established RA (mean 7 years); HAQ mean 0.50 Group Training + pool: mean age 54 years; Female 73%; Duration of RA = Established RA (mean 5 years); HAQ mean 0.75 No Training: mean age 51 years; Female 67%; Duration of RA = Established RA (mean 8 years); HAQ mean 0.50 The groups were similar for all of the baseline characteristics except morning stiffness was much lower in the group training and training in physical practice groups.	programme as Self-training + PT training group. Group training + pool: trained in hospital as for the group training group, but used the hot water pool instead of bicycles for conditioning (aerobic) training. In all groups, Minimum training should be 3 times/week with a maximum of 90 mins daily and 330 mins/week. Training intensity could be reduced if it caused severe pain or joint swelling.				

Effect size

Aerobic exercises (Self-training vs self-training + PT training vs group training vs group training and pool) vs Control (no training)

- There were NS differences between any of the groups for:
  - ESR at 2 years
  - Number of swollen joints at 2 years
  - Pain (VAS) at 2 years
  - Morning stiffness at 2 years
  - HAQ at 2 years
  - Larsen score at 2 years
  - Functional score at 2 years
  - Isometric Muscle strength of knee extensors at 2 years

- However the number of drop-outs was much higher in the aerobic group training group.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. H. van den Berg, H. K. Ronday, A. J. Peeters, Cessie S. Le, F. J. van der Giesen, F. C. Breedveld, and T. P. Vliet Vlieland. Using internet technology to deliver a home-based physical activity intervention for patients with	RCT: 1+ Single centre trial: Denmark • Randomised (random digit generator created list, block size of 4, stratified for centre and gender) • Allocation concealment • Single blind (assessor) • Not true ITT analysis	Total N=160 randomised (N=82 individualised training; N=78 general training) **Drop-outs at 1 year:** N=5 (6%) Individualised training N=3 (4%) General training	**Inclusion criteria:** RA (ACR criteria, meeting at least 4/7 criteria at least once during the course of the disease); not physically active for 30 mins in succession at a moderate intensity level on at least 5 days/week **Exclusion criteria:** cardiopulmonary conditions that would not allow moderately intensive exercise. **Baseline characteristics:** Individualised training: mean age 50 years; Female 62%; Duration of	Individualised exercise group Web pages provided weekly, personal physical activity programme consisting of muscle strengthening exercises, ROM exercises and cycling on a bicycle ergometer. Programme had to be performed 5 times/week on 5 searate days. Programme was tailor-made. Other forms of physical activity were specifically advised for the remaining 2 days of the week where the bicycle ergometer was not used and for those patients who did not like cycling on the ergometer at all. Patients received weekly,	Control group (General training) Web pages provided with general info about aerobic, muscle strengthening and ROM exercises and the promotion of physical activity. Patients were advised to perform the recommended activities on at least 5 days/week.	12 months (end of treatment)	MACTAR; HAQ; RAQoL; RAND (QoL); DAS28	Nationale Commissie Chronisch Zieken Foundation and the Health Assurance Company, Zorg en Zekerheid, The Netherlands

rheumatoid arthritis: A randomized controlled trial. *Arthritis & Rheumatism* 55 (6):935-945, 2006. ID 3313	• Power study (Dutch public health recommendation for physical activity)		RA = Established RA (mean 8 years); HAQ mean 0.8 General training: mean age 50 years; Female 60; Duration of RA = Established RA (mean 6 years); HAQ mean 0.8 There were NS differences between the groups for any of the baseline characteristics.	individual distant supervision from 2 experienced PTs and patients were invited to group meetings once every 3 months where new exercises were demonstrated and extra information given. Self-management was tailored to the patient's needs. Both groups were internet-based training programmes.				

Effect size

Individualised exercise vs General exercise

- Individualised exercise was significantly better than general exercise for:
  - Proportion of pts who were physically active at a moderate intensity level for 30 minutes in succession on at least 5 days a week (p=0.041)
  - Proportion of pts who were physically active at a vigorous intensity level for 20 minutes in succession on at least 3 days a week (p=0.005)

- There was NS difference between Individualised exercise and general exercise for:
  - MACTAR score at 12 months
  - HAQ score at 12 months
  - RAQoL at 12 months
  - RAND-36 QoL (mental and physical) at 12 months
  - DAS28 at 12 months

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Hakkinen, T. Sokka, A. Kotaniemi, and P. Hannonen. A randomized two-year study	RCT: 1-Single centre trial: Finland • Randomised (clusters of	Total N=70 randomised (N=35 in each group) **Drop-outs at 1**	**Inclusion criteria:** RA (ACR criteria); <2 years symptoms; not been treated with prednisolone or DMARDs before inclusion. **Exclusion criteria:** Not	Strength training group	Control group (Conventional training group)	2 years (end of treatment)	Morning stiffness; DAS28; Walk speed	Grants from Central Finland Healthcare District

of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis.[see comment]. *Arthritis & Rheumatism* 44 (3):515-522, 2001. ID 3330	4 patients stratified according to age and gender) • No mention of blinding • No ITT analysis	**year:** N=4 in each group (11% each)	mentioned **Baseline characteristics:** All: mean age 49 years; Female range 58 to 62%; Duration of RA = Established RA (mean range 8 to 10 years) There groups were similar for all of the baseline characteristics.					
Effect size **Author's conclusion:** Regular dynamic strength training combined with endurance type physical activities improves muscle strength and physical function, but not BMD, in patients with early RA, without detrimental effects on disease activity.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Hakkinen, T. Sokka, A. M. Lietsalmi, H. Kautiainen, and P. Hannonen. Effects of	RCT: 1-Single centre trial: Finland • As for ID 3330	Total N=70 randomised (N=35 in each group) As for ID 3330	**Inclusion criteria:** As for ID 3330	Strength training group	Control group (Conventional training group)	2 years (end of treatment)	ESR; RAI; Larsen score; Pain (VAS); HAQ; Muscle strength;	Grants from Central Finland Healthcare District

dynamic strength training on physical function, Valpar 9 work sample test, and working capacity in patients with recent-onset rheumatoid arthritis. *Arthritis & Rheumatism* 49 (1):71-77, 2003. ID 3325							work capacity	
Effect size **Author's conclusion:** The patients' exercise induced muscle strength gains during a 2 year training period were maintained throughout a subsequent self-monitored training period of 3 years. Despite substantial training effects in muscle strength, BMD values remained relatively constant. Radiographic damage remained low even at 5 years.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Hakkinen, T. Sokka, and P. Hannonen. A home-based two-year strength training period in early rheumatoid arthritis led to good long-	RCT: 1-Single centre trial: Finland • As for ID 3330	Total N=70 randomised (N=35 in each group) **Drop-outs at 5 years:** N=6 (17%) Training group N=5 (15%) Control group	**Inclusion criteria:** As for ID 3330	Strength training group	Control group (Conventional training group)	5 years (3 years post-intervention follow-up)	Extension and flexion; Larsen Score	Grants from Central Finland Healthcare District

term compliance: a five-year followup. *Arthritis & Rheumatism* 51 (1):56-62, 2004. ID 3322								
Effect size **Author's conclusion:** The improvements achieved during the 2-year strength training period were sustained for 3 years in patients with early RA.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Hakkinen, T. Sokka, H. Kautiainen, A. Kotaniemi, and P. Hannonen. Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up.	RCT: 1-Single centre trial: Finland • As for ID 3330	Total N=70 randomised (N=35 in each group) **Drop-outs at 5 years:** N=6 (17%) Training group N=5 (15%) Control group	**Inclusion criteria:** As for ID 3330	Strength training group	Control group (Conventional training group)	5 years (follow-up)	Extension and flexion; Larsen Score	Grants from Central Finland Healthcare District

Annals of the Rheumatic Diseases 63 (8):910-916, 2004. ID 3320								

Effect size

Author's conclusion: Strength training led to increased muscle strength, but this increase did not correlate with improved physical function (Valpar 9 work sample test). The increased muscle performance did not prevent a substantial proportion of patients from retiring preterm. The 2 items of the Valpar 9 test that were applied were not sensitive enough to differentiate the patients according to their working status.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. H. Van den Ende, J. M. Hazes, Cessie S. Le, W. J. Mulder, D. G. Belfor, F. C. Breedveld, and B. A. Dijkmans. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. *Annals of the Rheumatic*	RCT: 1-Single centre trial: The Netherlands • Randomised (method not mentioned) • No blinding • Not true ITT analysis • Power study (Improvement in physical condition)	Total N=100 randomised (N=25 in each group) **Drop-outs at 24 weeks:** N=3 (12%) High intensity exercise group N=5 (20%) Low intensity group exercise group N=2 (8%) Low intensity individual exercise group N=0 (0%) Home	**Inclusion criteria:** Age 20-70 years; RA (ACR criteria); on stble medication for the last 3 months; able to cycle **Exclusion criteria:** High disease activity such that starting or changing DMARD was necessary; inability to tolerate physical fitness training due to serious cardiac or lung disease; presence of one or more arthroplasties of the weight-bearing joints. **Baseline characteristics:** All: mean age range 48 to 56 years; Female range 52 to 72%; Duration of RA = Established RA (mean range 8 to 12 years); HAQ mean range 0.7 to 0.83	High intensity exercise group Low intensity group exercise group Low intensity individual exercise group	Control group (Home individual exercise group)	12 weeks (end of treatment) with follow-up at 24 weeks	Joint mobility, muscle strength; HAQ; Walk test; flexion and extension (ROM); Swollen joints; Pain (VAS); RAI; Patient's global assessment of disease activity; ESR	Nationale Commissie Chronisch Zieken Foundation and the Health Assurance Company, Zorg en Zekerheid, The Netherlands

Diseases 55 (11):798-805, 1996. ID 3337		individual exercise group	There were NS differences between the groups for any of the baseline characteristics.					
Effect size **Author's conclusion:** Intensive dynamic training is more effective in increasing aerobic capacity, joint mobility and muscle strength than ROM exercises and isometric training in RA patients with controlled disease.								

6.3 Occupational therapy (OCCU)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. A. Astin, W. Beckner, K. Soeken, M. C. Hochberg, and B. Berman. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis &*	MA: 1++ RCT's of MA: 1- to 1++ SR and MA included: N=25 trials with suitable data Trials were similar in terms of: • Study design (All RCTs) Trials differed with respect to: • Study size (range N=8 to N=141) • Study quality – max score of 10 (some poor and some reasonable-good quality) • Study duration – length of	Total N=1676.	**Inclusion criteria:** RCTs; Active treatment that included some psychological/psychosocial component beyond simply providing information (eg. patient education) about the disease; patients diagnosed with RA; mixed populations had to have data for RA patients reported separately. Search was up to June 2001. **Exclusion criteria:** Inadequate control;	Psychological interventions . Interventions typically involved some combination of relaxation, imagery, stress management or teaching cognitive coping skills.	Placebo; usua care, waiting li	Treatment ranged from 3 days to 9 months (mean 9.8 weeks)	Pain (VAS); Functional disability (HAQ; AIMS, disability); tender joints; psychological status (Depression; AIMS); Coping; Self-efficacy)	Grant from NIH

Rheumatism 47 (3):291-302, 2002. ID 849	intervention (range 3 days to 9 months with follow-up range from 2 to 18 months) • Comparison group (placebo; usual care; waiting list) • Intervention (N=13 multimodal cognitive-behavioural interventions; N=5 included biofeedback; N=5 more traditional psychotherapeutic interventions; N=2 intervention involved patients expressing difficult emotions or stressful experiences) Tests for heterogeneity and quality assessment performed.		predominantly informational / educational intervention					

Effect size

Psychological interventions vs control

- Psychological interventions were significantly better than control for:
  - Pain (13 RCTs, effect size 0.22, 95% CI 0.07 to 0.37, p=0.003) at end of treatment
  - Disability (5 RCTs, effect size 0.30, 95% CI 0.04 to 0.56, p=0.005) at end of treatment
  - Tender joints (5 RCTs, effect size 0.30, 95% CI 0.04 to 0.56, p=0.005) at follow-up
  - Psychological status at end of treatment (12 RCTs, effect size 0.15, 95% CI -0.01 to -0.31, p=0.03) and at follow-up (5 RCTs, effect size 0.33, 95% CI -0.07 to -0.59, p=0.01)
  - Coping (4 RCTs, effect size 0.46, 95% CI 0.09 to 0.83, p=0.007) at end of treatment and (3 RCTs, effect size 0.52, 95% CI -0.07 to -1.11, p=0.04) at follow-up
  - Self-efficacy (5 RCTs, effect size 0.35, 95% CI 0.11 to 0.59, p=0.017) at end of treatment

- There was NS difference between Psychological interventions and control for:
  - Pain (6 RCTs) at follow-up
  - Disability (7 RCTs) at follow-up
  - Tender joints (7 RCTs) at end of treatment
  - Self-efficacy (3 RCTs) at follow-up

NOTE: Studies using waiting list or treatment as a control, had larger effect sizes than those using an attention, education, or placebo control for: psychological status but significantly smaller for tender joints and were comparable for pain and disability.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Egan, L. Brosseau, M. Farmer, M. A. Ouimet, S. Rees, G. Wells, and P. Tugwell. Splints and orthoses in the treatment of rheumatoid arthritis. *Cochrane Database of*	MA: 1++ RCT's of MA: 1- to 1++ SR and MA included: N=10 trials (12 papers) with suitable data (N= 7 trials on wrist or hand orthoses) Trials were similar in terms of: • Study design (All RCTs) • Intervention (working wrist splints) Trials differed with respect to:	Total N=449.	**Inclusion criteria:** All trial types; patients aged 18 years or older, diagnosed with RA; mixed populations had to have 50% or more of RA. Search was up to 2002. **Exclusion criteria:** Joints of the neck	Orthoses – rigid, semi-rigid or soft orthotics designed to provide support and/or pain relief at all joints	Placebo; active intervention or regular treatment	Treatment ranged from 1 week to 6 months for wrist/hand orthoses	OMERACT; number of tender and swollen joints; Pain; physician's and patient's global assessment; functional status; radiological damage (OMERACT); morning stiffness; muscle strength; endurance; ROM;	None

Systematic Reviews (4):CD004018, 2001. ID 741	• Comparison group (3 RCTs no splint, 2 RCTs other splints) • Study size (range N=10 to N=110 for wrist splints) • Study quality – max score of 5 (some poor and some reasonable-good quality for wrist splints) • Study duration – length of intervention (range 1 week to 6 months for wrist splints) Tests for heterogeneity and quality assessment performed.		or back				postural status; gait status; walking speed; walking distance; cadence; stride length; QoL; AEs.	

Effect size

ONLY DATA FOR WRIST OR HAND ORTHOSES

Working wrist gauntlet vs no splint (immediate follow-up)

- Working wrist gauntlets were significantly better than no splints at immediate follow-up for:
  - Grip strength of non-dominant hand forpalmar splint and elastic with metal stay ready made gauntlet (1 RCT, N=38; $p<0.05$);

- There was NS difference between Working wrist gauntlets and no splints at immediate follow-up for:
  - Grip strength of dominant hand (1 RCT, N=37);
  - Grip strength of non-dominant hand for dorsal working splint, plastazote and polythene sheeting custom-made gauntlet (1 RCT, N=37)

Working wrist gauntlet (elastic with metal insert) vs no splint (1 week)

- Working wrist gauntlets (elastic with metal insert) were significantly better than no splints at 1 week for:
  - Passive joint motion (1 RCT, N=55; $p<0.05$);

- There was NS difference between Working wrist gauntlets (elastic with metal insert) and no splints at 1 week for:
  - Work perfomance using screwdriver or shears (1 RCT, N=80);
  - Dexterity (1 RCT, N=80);
  - Pain using screwdriver or shears (1 RCT, N=80)
  - Pain on motion (1 RCT, N=55)
  - Pain at rest (1 RCT, N=55)
  - Activity Pain (1 RCT, N=55)
  - Wrist Pain on motion(1 RCT, N=55)
  - Grip strength (1 RCT, N=55)
  - Morning stiffness (1 RCT, N=55)
  - Active joint motion (1 RCT, N=55)
  - Active pronation and supination (1 RCT, N=55)
  - Pinch grip (1 RCT, N=55)
  - Joint and forearm circumferance (1 RCT, N=55)
  - HAQ (1 RCT, N=55)

Futuro wrist gauntlet vs Thermolyn custom-made wrist gauntlet (2 weeks)

- There was NS difference between Futuro wrist gauntlets and Thermolyn custom-made wrist gauntlets at 2 weeks for:
  - Pain in wrist (1 RCT, N=20);
  - Tender and swollen joints (1 RCT, N=20);
  - Total passive wrist ROM (1 RCT, N=20);

- Grip strength with and without orthosis (1 RCT, N=20);

Futuro wrist gauntlet vs Alimed wrist gauntlet (1 week)

- There was NS difference between Futuro wrist gauntlets and Alimed wrist gauntlets at 1 week for:
  - Dexterity (1 RCT, N=84);
  - Grip strength without orthosis (1 RCT, N=84);

Alimed wrist gauntlet vs Rolyan wrist gauntlet (1 week)

- There was NS difference between Alimed wrist gauntlets and Rolyan wrist gauntlets at 1 week for:
  - Dexterity (1 RCT, N=84);
  - Grip strength (1 RCT, N=72);

Futuro wrist gauntlet vs Rolyan wrist gauntlet (1 week)

- There was NS difference between Futuro wrist gauntlets and Rolyan wrist gauntlets at 1 week for:
  - Dexterity (1 RCT, N=84);
  - Grip strength (1 RCT, N=84);

Resting hand and wrist splint vs no splint (1-6 months)

- Resting hand and wrist splints were significantly better than no splints at 1-6 months for:
  - Patient preference of splint vs no splint (1 RCT, N=78; p<0.001);

- There was NS difference between Resting hand and wrist splints and no splints at 1-6 months for:
  - Grip strength (1 RCT, N=29);
  - Swollen joints (1 RCT, N=29);
  - RAI (1 RCT, N=29);

Circumferential cotton-padded splint vs pan-type hard thermoplastic splint (1 month)

- There was NS difference between circumferential cotton-padded splint and pan-type hard thermoplastic splint at 1 month for:
  - Patient preference of splint vs no splint (1 RCT, N=78);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hammond A, Young A, Kidao R. A randomised	RCT 1++	N= 326 **Drop-**	**Inclusion criteria:** ≥18 years, diagnosed with RA by a rheumatology consultant within the	OT + usual rheumatology care	Usual rheumatology care only	6-8 weeks treatment;	HAQ Arthritis Impact	North Thames Regional

controlled trial of occupational therapy for people with early rheumatoid arthritis. Annals of the Rheumatic Diseases: 63: 23 – 30, 2004 REF ID: 2992	• Single blind (Assessor) • Randomised (computer + sealed envelopes) • Controlled • Powered study • ITT analysis	**outs:** Total 65/326 (19.9%) OT 28/162 (17%) Control 37/164 (23%)	past 2.5 years, required active medical treatment, no or minimal OT previously, speak and read English adequately to complete assignments. **Exclusion criteria:** not mentioned **Baseline characteristics:** OT group: Age mean 53.9 years (SD 13.9); female 74.7%; Duration of RA 9.0 months (SD 7.7), on DMARD 78%, AIMS PF>3.33 in 32%. Control group: Age mean 57.1 years (SD 13.5); female 70%; Duration of RA 9.9 months (SD 8.8), on DMARD 72%, AIMS PF>3.33 in 38%. The control group was significantly older (p=0.04). No differences in baseline variables were found between those than completed and those that dropped out.	OT over 6-8 weeks, lasting total of 8 hours. Intervention content: comprehensive information about RA, taught self-management methods and included advice usually provided by other staff (exercise and foot care).		follow-up at 2 yeras	Measurement Scale 2 (AIMS2) DAS28 Arthritis Self Efficacy Scale (ASES) Self reported adherence	Health Authority R&D response funding programme Arthritis research campaign

Effect size
P<0.01 considered significant due to the large number of tests conducted.

OT vs. CONTROL

- The OT group had significantly better outcomes with respect to the following:
  - Some self management methods were used significantly more than the control group particularly hand and arm exercises (p<0.001 for both), joint protection (p<0.01) and rest (p=0.05).
  - Receipt of a working splint (p=0.001), although they were not worn more often in the OT group (p=0.48).
  - Receipt of a resting splint (p=0.001)
  - Owning of assistive devices; these OT group owned on average 2.5 (SD 2.8) assistive devices vs. 1.4 (SD 2.1) in the control group (p=0.001)
  - Use of assistive devices, the OT group used these more often (p=0.002).
- There were no significant differences between the groups for any of the disease, physical, functional, psychosocial or hand measures; neither was there any trend approaching significance.
- There were no significant differences between the groups for the primary outcomes by ACR functional classes at baseline.

Conclusion: OT improved self management but not health status in early RA.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. Helewa, C. H. Goldsmith, P. Lee, C. Bombardier, B. Hanes, H. A. Smythe, and P. Tugwell. Effects of occupational therapy home service on patients with rheumatoid arthritis. *Lancet* 337 (8755):1453-1456, 1991. ID 3298	RCT: 1++ Single centre trial: Canada • Randomised (stratified; block size 4; random number lists) • Double blind (assessor and data evaluator; but not possible for patient blinding) • ITT analysis • Sample size calculation	Total N=105 randomised (N=53 OT; N=52 control) **Drop-outs:** N=2 (4%) in each group	**Inclusion criteria:** Adults aged 18-70 years; RA diagnosis (ARA criteria) for definite or classical RA; limitations in physical function; no other sources of disability; stable clinical status and on stable drug therapy for RA; had no IA treatment in previous 2 months and no joint surgery for RA in previous 3 months. **Exclusion criteria:** Disease onset before 16 years of age. **Baseline characteristics:** OT group: mean age 53 years; Female 89%; Duration of RA = Established RA (mean 164 months); HAQ mean 17.2. Control group: mean age 55 years; Female 85%; Duration of RA = Established RA (mean 174 months); HAQ mean 17.2. There were NS differences	OT OT treatment was given by 4 OTs – evaluation of disease activity and level of function, physical examination, functional evaluation while performing ADLs. A problem list was formulated and treatment plans were drawn up. Specific hand and wrist management help was given. ADLs were enhanced by the provision of aids and devices, home adaptations etc, and joint protection and energy conservation techniques. If required vocational, leisure and psychosocial counselling and help was given as well as advice about stress and socialising.	Control (no treatment)	6 weeks treatment	Function: AIMS; HAQ; Beck depression score; Pooled index (active joints, grip strength, ESR, morning stiffness, functional change); pain	Ontario Ministry of Health and the Conn Smythe Foundation, Canada.

			between the randomised groups for any of the baseline characteristics.					

Effect size

OT vs Control (no treatment)

- OT was significantly better than control (no treatment) for:
  - Functional score (AIMS, change from baseline) at 6 weeks (end of treatment), p=0.006;
  - Pooled index (symptoms and function) at 6 weeks (end of treatment), p=0.04;

- There was NS difference between OT and Control (no treatment) for:
  - Beck Depression scale at 6 weeks (end of treatment);
  - HAQ score at 6 weeks (end of treatment);
  - Pain (VAS) at 6 weeks (end of treatment).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. J. Zautra, M. C. Davis, J. W. Reich, P. Nicassario, H. Tennen, P. Finan, A. Kratz, B. Parrish, and M. R. Irwin. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without	RCT: 1++ Single centre trial: USA • Clusters of patients assigned using a random number's table • Single blind (data collection) • ITT (All patients included in analysis) • Power	Total N=144 **Drop-outs:** N=7 lost to follow-up at 6 months	Patients with RA who varied in depression history assessed using the Structured Clinical Interview for DSM-IV (SCID) **Inclusion criteria:** Adults aged 18-70 years; RA diagnosis (ARA criteria) for definite or classical RA; limitations in physical function; no other sources of disability; stable clinical status and on stable drug therapy for RA; had no IA treatment in previous 2 months and no joint surgery for RA in previous 3 months. **Exclusion criteria:**	**1. Mindfulness-based emotion regulation therapeutic program (M)** N=48 Based on emotion regulation and adaptation to chronic pain. Developed to a) reduce the negative impact of stressful life events and illness burdens b) enhance positive social engagements despite pain and stress Interventions were given to group of 5 to	**Education control group (E)** N=44 Provided a control for the nonspecific therapeutic elements that were alternative explanations for treatment effectiveness (M and P). Included general information about RA but not on coping.	6 months	Diary measures: Pain, positive and negative affect, depressive symptoms, coping efficacy for pain, pain catastrophizing, pain control Physicians' assessment: Disease Activity Score-28 (DAS-28) to measure joint swelling and tenderness	None reported

history of recurrent depression. *Journal of Consulting & Clinical Psychology* 76 (3):408-421, 2008. ID 3549	calculation		**Baseline characteristics:** History of recurrent depression RD+ Mindfulness (N=6) Female 5/6, age 46 yrs, disease duration 6 yrs CBT for pain (N=17) Female 15/17, age 51 yrs, disease duration 17 yrs Education (N=14) Female 11/14, age 51 yrs, disease duration 12 yrs No history of recurrent depression (RD-) M (N=41) Female 22/41, age 57 yrs, disease duration 10 yrs P (N=35) Female 21/35, age 56 yrs, disease duration 14 yrs E (N=30) Female 23/30, age 52 yrs, disease duration 12 yrs The groups were well matched at baseline	8 people over an 8 week period in weekly 2 hr sessions. **2. Cognitive Behaviour Therapy (CBT) for pain** N=52 Therapy followed standard CBT format including relaxation, coping, problem solving				

Effect size

Diary analyses
Treatment (Mindfulness (M) or CBT for pain (P)) vs Control (education (E)):

- Treatment (M and P) were significantly better than control (E) on:
  - Positive affect (change scores) at 30 days, $p<0.01$;
  - Coping efficacy for pain (change scores) at 30 days, $p<0.01$;
  - Catastrophizing (change scores) at 30 days, $p<0.001$;

- **Treatment (M) for patients with recurrent depression (RD+) were significantly better than P and E on:**
  - Positive affect (change scores) at 30 days, $p<0.001$;
  - Negative affect (change scores) at 30 days, $p<0.01$;
  - Coping efficacy for pain (change scores) at 30 days, $p<0.001$);
  - Catastrophizing (change scores) at 30 days, $p<0.001$)

- **Treatment (P) and control (E) were significantly worse than Treatment (M) on:**
  - Pain control (change scores) at 30 days, $p<0.05$

- **There was NS interaction between Treatment (mindfulness or CBT for pain) and Control (education) for:**
  - Daily pain (change scores) at 30 days;
  - Daily pain (change scores) at 30 days as a function of R;
  - Negative affect (change scores) at 30 days;
  - Daily depression symptoms (change scores) at 30 days;

Laboratory analyses

- Treatment (M) for patients with recurrent depression (RD+) were significantly better than P and E on:
  - Physicians' ratings of tenderness, $p<0.001$
  - Physicians' ratings of joint swelling, $p<0.001$)

Summary

- Patients receiving CBT for pain showed the greatest pre and post improvement in self reported pain control.
- Both CBT for pain and mindfulness groups showed more improvement in coping efficacy than the educational control group
- The relative value of the treatments varied as a function of depression history
- RA patients with recurrent depression benefited most from the mindfulness therapy across several measures, including negative and positive affect and physicians' ratings of joint tenderness.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of	Outcome measures	Source of

						follow-up		**funding**
S. Haskett, C. Backman, B. Porter, J. Goyert, and G. Palejko. A crossover trial of custom-made and commercially available wrist splints in adults with inflammatory arthritis. *Arthritis & Rheumatism* 51 (5):792-799, 2004. ID 3276	RCT (cross-over): 1+ Single centre trial: Canada • Randomised (table of numbers) • Single blind (assessor) • No ITT analysis • Power study (Pain, VAS) • Wash-out period included	Total N=47 randomised **Drop-outs:** Varied from N=7 (15%) to N=5 (11%)	**Inclusion criteria:** Adults aged ≥20 years; Inflammatory arthritis (78% patients had RA) affecting the wrist; with any 2 of the following: palpable swelling, pain on direct pressure, pain on motion, wrist ROM restricted by ≥20%. **Exclusion criteria:** if they were obtaining a replacement wrist splint and not willing to participate in a 2-week washout period with no splint use prior to commencement of the trial; required a combination wrist splint with thumb post or other custom design feature; were referred for a postoperative splint following wrist joint fusion; had excessive subluxation of the wrist joint requiring a specially adapted splint or treatment protocol; in the process of or planning to adjust their medication. **Baseline characteristics:** mean age 49 years; Female 87%; Duration of RA = Established RA (mean 9 years); Pain (VAS) mean 4.1.	Customised Splint (LWS – leather wrist splint) LWS was custom fabricated on a plaster mould of the patient's hand and forearm. In all groups, if adjustments were required, participants returned to the clinic after 1 week.	Commercially available splints 1. RWS – Rolyan Wrist extensor orthoses. Circumferential fabric gauntlet with removable forearm stay, fastened with 3-D ring straps. 2. AWS – Anatech elastic wrist support. Elasticised fabric splint that opens dorsally and fastens with 4 flat straps. The most appropriately sized RWS and AWS was used for each patient and the metal stays in the RWS and AWS were adjusted to the same degree of wrist extension as the plaster cast and contoured to fitr the forearm. No further custom	4 weeks treatment with follow-up at 6 months	Pain (VAS); ROM; Morning stiffnes; AHFT (Arthritis hand function test); MACTAR score	Grants from the British Columbia Health Research Foundation, Canada.

			There were NS differences between the randomised groups for any of the baseline characteristics.		modifications were done to the commercial splints. Washout period of 1 week between treatments			

Effect size

Customised leather wrist splint vs Commercially available wrist splints

- There was NS difference between the Customised leather wrist splint (LWS) and the commercially available wrist splints (RWS and AWS) for:
  - Pain (VAS) at 4 weeks (end of treatment);
  - AHFT (Arthritis hand function test - all items) at 4 weeks (end of treatment);
  - MACTAR score at 4 weeks (end of treatment);

Commercially available wrist splint vs Commercially available wrist splint

- The Rolyan Wrist extensor orthoses was significantly better than the Anatech elastic wrist support for:
  - Grip at 4 weeks (end of treatment), p=0.03;

- There was NS difference between the Rolyan Wrist extensor orthoses and the Anatech elastic wrist support for:
  - Pain (VAS) at 4 weeks (end of treatment);
  - AHFT (Arthritis hand function test - all items) at 4 weeks (end of treatment);
  - MACTAR score at 4 weeks (end of treatment);

- The Rolyan Wrist extensor orthoses was significantly worse than the Anatech elastic wrist support for:
  - Dexterity at 4 weeks (end of treatment), p=0.04;

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. W. Evers, F. W. Kraaimaat, P. L. van Riel,	RCT: 1+ Multicentre trial: 3 centres in The Netherlands	Total N=64 randomised (N=32 CBT group; N=32	**Inclusion criteria:** Age >18 years; RA (ACR criteria); disease duration <8 years;	CBT group (Cognitive-behavioural therapy)	Control group (standard medical care)	6 months treatment with follow-up	Disease activity (DAS; ESR; swollen and painful joints);	Grants from Dutch Arthritis Association

and A. J. de Jong. Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 100 (1-2):141-153, 2002. ID 2994	• Randomised (pattern of random numbers) • No mention of blinding • ITT analysis	control group) **Drop-outs:** N=3 (9%) in control group N=2 (6%) in CBT groups	patients classified as 'at risk' (heightened anxiety and negative mood levels and dysfunctional cognitive-behavioural factors of illness cognitions, coping and social support. **Exclusion criteria:** Comorbid conditions that might interfere with the CBT treatment **Baseline characteristics:** CBT: mean age 54 years; Female 70%; Duration of RA = Established RA (mean 3 years) Control: mean age 54 years; Female 72%; Duration of RA = Established RA (mean 4 years) There were NS differences between the randomised groups for any of the baseline characteristics.	CBT group received tailor-made CBT treatment within 6 months – 10 bi-weekly, 1 hour sessions and one final booster session scheduled 4 weeks later. CBT was individual treatment with 2 out of the 4 possible treatment modules that targeted the most frequently experienced problems with which RA patients have to cope: pain and functional disability, fatigue, negative mood and social relationships. Choice of modules was determined on the basis of patient priorities. Patients in both groups received standard medical care from the rheumatologist as well as quarterly consultations from the rheumatology consultant.	standard medical care from the rheumatologist as well as quarterly consultations from the rheumatology consultant.	at 12 months	AIMS; Pain (IRGL pain scale); Fatigue (fatigue scale); IRGL anxiety and negative mood; Beck depression score; coping with stress and pain (UCL – Utrechtse Coping List and PCI – Pain Coping Inventory)	

Effect size

CBT vs Control (routine care)

- CBT was significantly better than control (routine care) for:
  - Physical functioning (functional disability, pain, fatigue) over time, p<0.05;
  - Psychological functioning (depression, negative mood, anxiety) over time, p<0.05;

- There was NS difference between CBT and Control (routine care) for:
  - Disease Activity over time
  - Social functioning over time

- CBT was similar to control (routine care) for:
  - Illness cognition, Coping with stress and coping with pain over time

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. C. Parker, R. G. Frank, N. C. Beck, K. L. Smarr, K. L. Buescher, L. R. Phillips, E. I. Smith, S. K. Anderson, and S. E. Walker. Pain management in rheumatoid arthritis patients. A cognitive-behavioral approach. *Arthritis & Rheumatism* 31 (5):593-	RCT: 1+ Single centre trial: Canada • Randomised (table of random numbers) • No mention of blinding • ITT analysis not mentioned (but only 1 drop-out)	Total N=83 randomised (N=29 CBT group; N=26 AP group; N=28 CN group) **Drop-outs:** N=1 (3%) in CB group N=0 in all other groups	**Inclusion criteria:** RA (ARA criteria) for definite or classical RA **Exclusion criteria:** Uncontrolled medical problems, organic brain syndrome, major psychiatric disturbances, functional class IV. **Baseline characteristics:** All patients: mean age 61 years; Female 4%; Duration of RA = Established RA	CBT group (Cognitive-behavioural therapy) CB group received comprehensive pain management programme which began with 1-week hospital stay. Included education overview of RA, gate control theory of pain, info about acute vs chronic pain and about medical management of RA. Coping strategies were also addressed (problem-solving	AP group (attention-placebo) Basic RA education programme also began with 1-week inpatient stay. Same amount of time was spent as with the CB group. Films and written materials from the Arthritis Foundation were presented and discussed in small groups but no specific recommendations for behavioural or attitudinal changes were made. Support groups were same	6 weeks treatment	Pain (VAS); McGill Pain questionnaire; coping strategies questionnaire; AIMS; Beck depression score; Ways of coping questionnaire; Arthritis Helplessness index (AHI); Disease activity measures (walking speed; grip strength; morning stiffness; joint counts)	Grants from the Medical Research Service of the Veterans Administration and from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, USA.

601, 1988. ID 3299			(mean 11 years) There were NS differences between the randomised groups for any of the baseline characteristics.	techniques, relaxation training, diverting attention, awareness of pain, family dynamics and communication). After this phase, the patients participated in an extensive support group programme designed to maintain treatment gains (once/month – once/three months).	schedule as the CB group. CN group (control, routine care Routine care provided by the Rheumatology team but patients not exposed to the programmes and received no foloow-up treatment beyond their routine Rheumatology clinic visits.			

Effect size

CBT vs Control (routine care)

- CBT was significantly better than control (routine care) for:
    - Coping strategies questionnaire at 6 months and 12 months (p=0.0017 and p=0.0001);

- There was NS difference between CBT and Control (routine care) for:
    - AIMS at 6 months and 12 months
    - Ways of coping scale at 6 months and 12 months
    - AHI at 6 months and 12 months
    - Beck Depression scale at 6 months and 12 months
    - Pain (VAS and McGill) at 6 months and 12 months

CBT vs Control (attention-placebo)

- CBT was significantly better than control (attention-placebo) for:
    - Coping strategies questionnaire at 6 months and 12 months (p=0.0017 and p=0.0001);

- There was NS difference between CBT and Control (attention-placebo) for:
    - AIMS at 6 months and 12 months
    - Ways of coping scale at 6 months and 12 months
    - AHI at 6 months and 12 months
    - Beck Depression scale at 6 months and 12 months
    - Pain (VAS and McGill) at 6 months and 12 months

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. K. Pradhan, M. Baumgarten, P. Langenberg, B. Handwerger, A. K. Gilpin, T. Magyari, M. C. Hochberg, and B. M.	RCT: 1+ Single centre trial: USA • Randomised (computer randomisation, stratified on anti-depressant	Total N=63 randomised (N=31 MBSR group; N=32 control group) **Drop-outs:** N=2 (6%) in control group	**Inclusion criteria:** Age ≥18 years; not in remission with RA (ACR criteria). **Exclusion criteria:** Major psychiatric illness; active alcohol or drug dependency; fibromyalgia; participation in another	MBSR group (Mindfulness-Based Stress Reduction programme) MBSR: Participants met once/week for 2.5 hours and also attended a full-day retreat. Classes	Control group (waiting list) Patients received their prescribed medications and were under the regular care of their rheumatologist throughout the study	8 weeks (end of treatment)	DAS28; Psychological well-being.	Grant from the NIH

Berman. Effect of Mindfulness-Based Stress Reduction in rheumatoid arthritis patients. *Arthritis & Rheumatism* 57 (7):1134-1142, 2007. ID 3266	medication with randomly selected block sizes) • Single blind • ITT analysis • Sample size calculation (underpowered)	N=3 (10%) in CBT groups	trial; scheduled major surgery. **Baseline characteristics:** MBSR: mean age 56 years; Female 84%; Duration of RA = Established RA (mean 6 years) Control: mean age 53 years; Female 91%; Duration of RA = Established RA (mean 11 years) There were NS differences between the randomised groups for any of the baseline characteristics except for history of clinical depression and therefore this was adjusted for in the analysis..	consisted of conceptual training in mindfulness, discussions of its application in daily life and experiential training in medication and gentle yoga. Participants were asked to practice at home for 45-minutes/day, 6 days/week. Patients in both groups received their prescribed medications and were under the regular care of their rheumatologist throughout the study.	and joined the MBSR programme at the end of the trial.			

Effect size

Mindfulness-Based Stress Reduction programme (MBSR) vs Control (waiting list)

- MBSR was significantly better than control (waiting list) for:
  - Psychological distress over time (6 months), p=0.04
  - Well-being over time (6 months), p=0.03

- There was NS difference between MBSR and Control (waiting list) for:
  - Depressive symptoms at 2 months (end of treatment) and over time (6 months)
  - Psychological distress at 2 months (end of treatment)
  - Well-being at 2 months (end of treatment)
  - DAS28 at 2 months (end of treatment) and over time (6 months)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Sharpe, T. Sensky, N. Timberlake, B. Ryan, and S. Allard. Long-term efficacy of a cognitive behavioural treatment from a randomized controlled trial for patients recently diagnosed with rheumatoid arthritis. *Rheumatology* 42 (3):435-441, 2003.	RCT: 1++ Multicentre trial: 3 centres UK • Randomised (table of random numbers) • Allocation concealment • Single blind (assessor) • ITT analysis • Power study (Tender joints and pain)	Total N=53 randomised (N=27 CBT; N=26 control) **Drop-outs:** N=0 in control group N=1 (4%) in CBT group	**Inclusion criteria:** Age 18 to 75 years; RA (ARA criteria); seropositive for RA. **Exclusion criteria:** History of psychotic illness; alcohol or drug abuse. **Baseline characteristics:** All: mean age 55 years; Female 70%; Duration of RA = Early RA (mean 13 months) Control: mean age 53 years; Female 91%; Duration of RA = Established RA (mean	CBT CBT: 8 individual 1 hr sessions, once/week. CBT intervention was developed from standard pain management approaches and self-help educational material. Aims to help learn to cope. Included education, relaxation training, goal setting, balance of rest and exercise, attention diversion training, cognitive restructuring, management of disease.	Control group (standard care) Standard care	18 months follow-up	HAD (depression and anxiety); CSQ (coping strategies questionnaire); Pain (11-point scale); HAQ; RAI; ESR; CRP	Grant from the North Thames Regional Research Programme, UK.

ID 3280			11 years) There were NS differences between the randomised groups for any of the baseline characteristics except for CRP.					

Effect size

CBT vs Control (standard care)

- CBT was significantly better than control (standard care) for:
  - HAD depression and anxiety (over time, 18 months), $p<0.05$
  - HAQ (over time, 18 months), $p<0.05$

- There was NS difference between CBT and Control (standard care) for:
  - Coping Strategies Questionnaire (CSQ) over time (18 months)
  - Pain (11-point scale) over time (18 months)
  - RAI over time (18 months)
  - ESR and CRP over time (18 months)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Sharpe, S. Allard, and T. Sensky. Five-year followup of a cognitive-behavioral intervention for patients with recently-diagnosed rheumatoid arthritis: Effects on	RCT: 1++ Multicentre trial: 3 centres UK • Randomised (table of random numbers) • Allocation concealmen t	Total N=53 randomised (N=27 CBT; N=26 control) **Drop-outs at 5 years:** N=6	As for ID 3280	As for ID 3280	As for ID 3280	5-year follow-up	Healthcare utilisation	Grant from the North Thames Regional Research Programme, UK.

health care utilization. *Arthritis Care and Research* 59 (3):311-316, 2008. ID 3535	• Single blind (assessor) • ITT analysis • Power study (Tender joints and pain)							

Effect size

CBT vs Control (standard care)

- CBT was significantly better than control (standard care) at 5 years for:
  - Lower use of healthcare resources overall (over time, 5 years), p=0.02
  - Number of inpatient nights (p=0.039), number of physiotherapy referrals (p=0.029), number of injections (p=0.007) and total occasions of care (p=0.032)

- There was NS difference between CBT and control (standard care) at 5 years for:
  - Number of Rheumatology consultations
  - Number of psychiatric referrals
  - Number of patients discharged as improved
  - Number of orthopaedic referrals
  - Number of surgeries

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Rapoliene and A. Krisciunas. The effectiveness of occupational therapy in restoring the functional state of hands in rheumatoid	RCT: 1-Single centre trial: Lithuania • Not properly randomised (divided into 2 groups) • No	Total N=120 randomised (N=60 OT; N=60 control) **Drop-outs:** Not mentioned	**Inclusion criteria:** patients with RA treated at the rheumatology department at 1 hospital in Lithuania. **Exclusion criteria:** Not mentioned. **Baseline characteristics:** OT group: mean age 53 years; Duration of RA = Established RA (mean 12	OT programme	Control (no treatment)	10 days treatment	ROM; pinch strength and grasp strength; functional independence measures	Not mentioned

arthritis patients. *Medicina (Kaunas)* 42 (10):823-828, 2006. ID 3378	mention of blinding • No mention of ITT analysis		years). Control group: mean age 52 years; Duration of RA = Established RA (mean 12 years). There were NS differences between the groups for baseline characteristics.					
Effect size **Authors' conclusions:** hand function significantly improved in patients with RA after completion of a course of OT and led to a significant increase in functional independence.								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
L. C. Li, A. M. Davis, S. C. Lineker, P. C. Coyte, and C. Bombardier. Effectiveness of the primary therapist model for rheumatoid arthritis rehabilitation: a randomized controlled trial. *Arthritis & Rheumatism* 55 (1):42-52, 2006. ID 3381	RCT: 1-Multicentre trial: Canada • Randomised (computer generated list; stratified by ACR functional status; block sizes of 6) • No mention of blinding • No mention of ITT analysis • High drop-outs in one	Total N=144 randomised (N=73 PTM; N=71 TTM) **Drop-outs:** N=10 (14%) PTM; N=23 (32.4%) TTM	**Inclusion criteria:** patients with RA (ACR criteria) who required pT/OT and had not received rehabilitation treatment for RA in the previous 2 years. **Exclusion criteria:** joint replacement surgery in past 3 months or scheduled to occur in the next 3 months **Baseline characteristics:** PTM group: mean age 54 years; 87% female; Duration of RA =	PTM (Primary therapist Model) All primary therapists were PTs and OTs who completed the Arthritis Society Training programme in the assessment of Polyarthritis.	TTM (Traditional therapist model) Traditional PTs and OTs were generalists practicing in hospital outpatient departments, publicly funded clinics or home care agencies.	6 weeks treatment with 6 month foloow-up	HAQ; Pain (VAS); ACR20	PhD grant from Canadian institute of Health Research

	of the groups and these		Established RA (mean 11 years). TTM: mean age 57 years; 79% female; Duration of RA = Established RA (mean 13 years). There were NS differences between the groups for baseline characteristics.					
Effect size **Authors' conclusions:** At 6 months 44% of patients in the PTM group were clinical responders bs 19% in the TTM group. Compared with TTM, the PTM was associated with better outcomes in patients with RA. The results however, should be interpreted with caution due to the high drop-out rate in the TTM group.								

6.4 Podiatry (POD)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Egan, L. Brosseau, M. Farmer, M. A. Ouimet, S. Rees, G. Wells, and P. Tugwell. Splints and orthoses in the treatment of	MA: 1++ RCT's of MA: 1- to 1++ SR and MA included: N=10 trials (12 papers) with suitable data (N=3 trials, 4 papers, on foot orthoses) Trials were similar in terms of: • Study design (All RCTs for	Total N=449. N=160 for foot orthoses	**Inclusion criteria:** All trial types; patients aged 18 years or older, diagnosed with RA; mixed populations had to have 50% or more of RA. Search was up to	Orthoses – rigid, semi-rigid or soft orthotics designed to provide support and/or pain relief at all joints	Placebo; active intervention or regular treatment …	Treatment ranged from 2 months to 3 years for foot orthoses	OMERACT; number of tender and swollen joints; Pain; physician's and patient's global assessment; functional status; radiological damage	None

rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (4):CD004018, 2001. ID 741	foot orthoses) Trials differed with respect to: • Intervention (supporting insoles, extra depth shoes and insoles in extra depth shoes) • Comparison group (regular footwear, extra depth shoes, placebo insoles) • Study size (range N=28 to N=102 for foot orthosis) • Study quality – max score of 5 (All studies reasonable to good quality for foot orthoses) • Study duration – length of intervention (2 months to 3 years for foot orthoses) Tests for heterogeneity and quality assessment performed.		2002. **Exclusion criteria:** Joints of the neck or back				(OMERACT); morning stiffness; muscle strength; endurance; ROM; postural status; gait status; walking speed; walking distance; cadence; stride length; QoL; AEs.	

Effect size

ONLY DO DATA ON FOOT ORTHOSES

Extra depth shoes vs regular footwear (2 months)

- Extra depth shoes were significantly better than regular footwear at 2 months for:
  - HAQ (change from baseline) (1 RCT, N=30; effect size WMD –0.20, 95% CI –0.35 to –0.05; p=0.01);
  - Pain on walking (change from baseline) (1 RCT, N=30; effect size WMD –18.7, 95% CI –28.5 to –8.9; p=0.0002);
  - Pain on climbing stairs(change from baseline) (1 RCT, N=30; effect size WMD –27.0, 95% CI –37.8 to –16.2; p<0.00001);
  - Pain-free walking time (change from baseline) (1 RCT, N=30; effect size WMD 18.2, 95% CI 8.2 to 28.2; p=0.0004);

- There was NS difference between Extra depth shoes and regular footwear at 2 months for:
  - Fatigue (change from baseline) (1 RCT, N=30);
  - Subjective well-being (change from baseline) (1 RCT, N=30);

Semi-rigid insoles vs extra-depth shoes (12 weeks)

- Semi-rigid insoles were significantly better than extra-depth shoes at 12 weeks for:
  - Pain, VAS (1 RCT, N=48; effect size WMD –1.9, 95% CI –3.3 to –0.51; p=0.007);

- There was NS difference between Semi-rigid insoles and Extra depth shoes at 12 weeks for:
  - RB walking (1 RCT, N=48);
  - RB stairs (1 RCT, N=48);
  - RB stand (1 RCT, N=48);
  - Toronto ADL – walking dimension (1 RCT, N=48);
  - Toronto ADL – stairs dimension (1 RCT, N=48);
  - Walking (1 RCT, N=48);
  - Lower extremity joint counts (1 RCT, N=48);
  - MTP joint count, number of painful joints (1 RCT, N=48);

Soft insoles vs extra-depth shoes (12 weeks)

- There was NS difference between Soft insoles and Extra depth shoes at 12 weeks for:
  - Pain, VAS (1 RCT, N=48);
  - RB Walking (1 RCT, N=48);
  - RB stairs (1 RCT, N=48);
  - RB stand (1 RCT, N=48);

- Toronto ADL – walking (1 RCT, N=48);
- Toronto ADL – stairs (1 RCT, N=48);
- 50 foot walk time (1 RCT, N=48);
- Lower extremity joint counts (1 RCT, N=48);
- MTP joint count, number of painful joints (1 RCT, N=48);

Semi-rigid insoles vs extra-depth shoes (12 weeks)

- Supporting insoles (Rohadar posted foot orthoses) were significantly better than placebo insoles at 3 years for:
  - Hallux abductus angle remained < 21 degrees (1 RCT, N=98; effect size WMD RR 3.6, 95% CI 2.2 to 5.9; p<0.00001);

- There was NS difference between Supporting insoles (Rohadar posted foot orthoses) and placebo insoles at 3 years for:
  - Painful foot joint count (1 RCT, N=88);
  - Foot function index (1 RCT, N=88);
  - Foot pain (1 RCT, N=88).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. J. Davys, D. E. Turner, P. S. Helliwell, P. G. Conaghan, P. Emery, and J. Woodburn. Debridement of plantar callosities in rheumatoid arthritis: a randomized controlled trial. *Rheumatology* 44 (2):207-210, 2005. ID 3244	RCT: 1++ Single centre trial: UK • Randomised (random number codes and bock size of 4) • Allocation concealment • Single blind (patients) – second phase unblinded • ITT analysis	Total N=38 randomised (N=19 each group). **Drop-outs:** Treatment: N=1	**Inclusion criteria:** RA; symptomatic skin callosities overlying the plantar metatarsal heads that would have been routinely debrided by a podiatrist as part of normal foot care. **Exclusion criteria:** Diabetes mellitius, neurological disease with lower limb symptoms or symptomatic peripheral vascular disease of the lower extremities. **Baseline characteristics:** Normal treatment: mean age 60 years; Female 84%; Duration of RA =	Normal callus treatment Sharp scalpel debridement of the callosity Patients n both groups continued to use their normal orthopaedic footwear or orthoses during the study period	Sham callus treatment Simulated normal callus treatment using blunt scalpel so that no callus material was debrided	Immediately after treatment, then follow-up at 7 days and once/week for 4 weeks (5 weeks post-treatment)	Pain (VAS); radiographs (modified Larsen score); Plantar pressure measures; Spatial temporal gait measures; AEs	MRC and ARC, UK

	• Power study (VAS)		Established RA (mean 21 years). Sham treatment: mean age 58 years; Female 89%; Duration of RA = Established RA (mean 19 years). The 2 groups were similar for all baseline characteristics.					

Effect size

- There was NS difference between Normal callus debridement and sham callus debridement for:
  - Forefoot pain (VAS) at 5 weeks post-intervention
  - Plantar pressure measures at 5 weeks post-intervention
  - Spatial temporal gait measures at 5 weeks post-intervention

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Woodburn, S. Barker, and P. S. Helliwell. A randomized controlled trial of foot orthoses in rheumatoid arthritis. *Journal of Rheumatology* 29 (7):1377-1383, 2002.	RCT: 1++ Single centre trial: UK • Randomised (blocks of 4, method not mentioned) • Single blind (physicians) • True ITT analysis • Slightly underpower	Total N=101 randomised (50 – foot orthosis programme; N=51 control programme). **Drop-outs:** Control: 21% Intervention: 14%	**Inclusion criteria:** Definite RA (ARA criteria); history of bilateral subtalar and/or ankle and/or talonavicular pain and valgus heel deformity. Normal range of motions testing was used to ensure the valgus heel deformity was correctable with ≥10 degrees of subtalar joint inversion past neutral. **Exclusion criteria:** Concomitant endocrine disorders, especially diabetes	Rigid foot orthoses under podiatry supervision Orthoses were custom-designed and manufactured to a standardised protocol from impression casts. Inbuilt correction was customised for each patient, according to the degree of valgus heel deformity	Control group No prescribed foot orthoses at baseline; over 30 months these patients were permitted orthoses if prescribed at any	30 months	Foot function Index (FFI) – pain and disability; DAS; HAQ; Radiographs (Larsen Index); ESR and CRP; AEs	Grant from the ARC, UK and Yorkshire NHS R&D, UK.

ID 3260	ed (Pain and disability)		mellitus; history of orthopaedic foot surgery; those currently using foot orthoses and those with inappropriate footwear. **Baseline characteristics:** Foot orthosis programme: mean age 54 years; Female 68%; Duration of RA = Established RA (mean 3 years); HAQ mean 1.0. Foot orthosis programme: mean age 53 years; Female 65%; Duration of RA = Established RA (mean 3 years); HAQ mean 1.0. There were NS differences between the groups for any of the baseline characteristics	present and usedintrinsic posting in the rearfoot and maximum forefoot balancing techniques.	subsequent outpatient medical consultation.			
Effect size • The customised foot orthosis was significantly better than the control group (no orthosis) for: o Foot function Index (total) at 30 weeks, p=0.026 o Foot function Index (pain) at 30 weeks, p=0.014 o Foot function Index (disability) at 30 weeks, p=0.016 • There was NS difference between customised foot orthosis and the control group (no orthosis) for: o Foot function Index (functional limitation) at 30 weeks o Global pain at 30 weeks o DAS at 30 weeks o HAQ at 30 weeks o Larsen score (hands) at 30 weeks o Larsen score (feet) at 30 weeks								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-**	**Outcome measures**	**Source of funding**

						up		
J. Woodburn, P. S. Helliwell, and S. Barker. Changes in 3D joint kinematics support the continuous use of orthoses in the management of painful rearfoot deformity in rheumatoid arthritis. *Journal of Rheumatology* 30 (11):2356-2364, 2003. ID 3261	RCT: 1++ Single centre trial: UK • Randomised (blocks of 4, method not mentioned) • Single blind (physicians) • True ITT analysis • Slightly underpowered (Pain and disability)	Total N=101 randomised (50 – foot orthosis programme; N=51 control programme). **Drop-outs:** Control: 21% Intervention: 14%	**As for ID 3260**	Rigid foot orthoses under podiatry supervision **As for ID 3260**	Control group (no orthosis) **As for ID 3260**	30 months	3D Joint kinematic measures	Grant from the ARC, UK and Yorkshire NHS R&D, UK.

Effect size

- The customised foot orthosis was significantly better than the control group (no orthosis) for:
  - Dorsioflexion/plantarflexion motion at 30 weeks, p=0.005
  - Inversion/eversion motion at 30 weeks, p=0.0001
  - Internal/external AJC rotation at 30 weeks, p=0.006
  - Internal rotation at 30 weeks, p=0.007

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
C. Moncur and J. R. Ward. Heat-moldable shoes for	Case-series: 3 Single centre, USA.	N=25 **Drop-outs:**	**Inclusion criteria:** RA with metatarsalgria (RA - classic adult onset);	Heat-mouldable extra-depth and extra-width shoe (Thermold, USA)	3 months	Walking ability; satisfaction with footwear	Not mentioned

management of forefoot problems in rheumatoid arthritis. *Arthritis Care and Research* 3 (4):222-226, 1990. REF ID: 3256	RA patients from out-patient clinic	None mentioned	forefoot pain not ameliorated by current footwear; ACR functional class II or III; most common lesions occurring in the forefoot were hallusx valgus, overlapping toes, cock-up toe deformities with dorsal callus formation, and prominent metatarsal heads on the plantar surface of the foot; patients could not find footwear which alleviated their pain. **Baseline characteristics:** Age mean 57, female 100%, disease duration NOT MENTIONED.	Mouldable inlay that can be removed to insert an orthosis. Light-weight and heat-mouldable to accommodate prominences that are painful; on the sides and top of the foot. Patients asked t wear the shoes in place of their usual shoes; if they had been wearing orthoses they placed these into their heat-mouldable shoes. Patients who had previously required medial or lateral stabilisation of their shoes had this same procedure done to their heat-mouldable shoes. Patients were followed as needed to modify the shoes and orthoses. Patients were asked to walk 5-10mins to identify painful areas where the foot touched the shoe. The shoe was then placed in a small oven to heat the mouldable lining for about 3-5 mins. Once removed from the oven, a shoe-stretching device was placed in the shoe to mould it to accommodate the patient's forefoot deformities. Stretching of the upper shoe was continued until the patient was satisfied that the shoes were comfortable.			
Effect size* **Heat-mouldable shoes** • 80% wore their shoes all the time during the day and 20% sometime during the day. • 72% wore their custom-made semi-rigid foot orthoses in their shoes and 28% did not • 20% had their shoes modified to control hindfoot vagus • 50% of those who had foot orthoses stated that they always wore their inserts in their shoes.							

• 80% of patients felt they walked better with the heat-mouldable shoes. 20% were not walking better • Significantly more patients found that they walked better with the heat-mouldable shoes compared to previous shoes ($p<0.01$) • Patients found that their heat-mouldable shoes were significantly better than previous shoes and were significantly more comfortable ($p<0.001$)								
Reference	**Study type Evidence level**	**Number of patients**	**1.6 Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
A. E. Williams, K. Rome, and C. J. Nester. A clinical trial of specialist footwear for patients with rheumatoid arthritis. *Rheumatology* 46 (2):302-307, 2007. ID 3258	RCT: 1-Single centre trial: UK • Randomised (computer generated) • Single blind (patients) • No ITT analysis • Very high drop-outs (high bias due to no ITT analysis) Power study (VAS) but with drop-outs is very underpowered	Total N=80 randomised (N=40 each group). **Drop-outs:** Traditional: N=31 (78%) New: N=12 (30%)	**Inclusion criteria:** RA patients with established RA (>5 years duration) with foot deformity.	New shoe design (based on patients' opinions)	Traditional shoe design	12 weeks	Foot health status questionnaire - FHSQ dimensions (Foot pain function, health; general health; physical activity; social capacity); SF-36; FFI	MRC and ARC, UK

Effect size
Authors' conclusion: Improvement in pain and patient satisfaction with the new design of footwear over the old design for patients with RA, indicates the importance of patients' involvement in the design process and throughout the process of supplying and monitoring the footwear

7. Pharmacological management

7.1 DMARDS

7.1.1 Introducing DMARDs (DMARD)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Finckh, M. H. Liang, C. M. van Herckenrode, and Pablo P. de. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis & Rheumatism* 55 (6):864-	MA: 1++ MA included: N=12 trials Trials included: • Six follow-up studies of RCTS • Six cohort studies Trials were similar in terms of: • Mean age – 44 to 57 yrs Trials differed with respect to: • Study size (range N=23 to N=189) • Study quality (max score of 6) - (N=6 score of 2 or 3; N=6	Total N=1133	Inclusion criteria: Diagnosis of RA according to the ACR criteria; disease duration < 2 yrs at enrolment (early RA) Cohort studies that had data on the time delay between disease onset and DMARD initiation, and follow-up studies of at least 1 yr after termination of RCTs; duration of	Follow-up studies: Level 2 vs. level 1 Level 2 vs. placebo Level 1 vs. placebo Level 3 vs. level 2 (2 studies) Early level 1 to 2 vs. delayed level 1 to 2 Cohort studies (all early vs. delayed): Level 1 to 2 (N=2 studies) Level 2 (N=2 studies) Level 2 to 3 (N=2 studies)	See intervention	Follow-up ranged from 1 to 5.6 yrs Median 3 yrs	Rate of radiographic progression. When studies reported mean change scores, the average difference in the individual radiographic scores between the baseline and the final assessment was divided by the mean duration of follow up to obtain a yearly rate of radiographic progression. Standard mean difference. Calculated	No external sources of funding.

872, 2006. ID 57	score of 4 or 5) • Delay in DMARD initiation (difference in months in mean disease duration at DMARD initiation between the two treatment arms) – 6 to 14 months • Study duration – length of follow-up (1 to 5.6 yrs) Tests for heterogeneity and quality assessment performed		3 to 24 months between early DMARD group and delayed DMARD group; comparable efficacy of DMARD regimen in treatment arms over follow up period; and documentation of radiographic evidence Exclusion criteria: Duplicated data and DMARD regimen not comparable during follow-up	Level 1 = hydroxychloroquine, oral gold, or penicillamine Level 2 = methotrexate, sulfasalazine, or parental gold Level 3 = combination therapy			as the difference in the mean rate of radiographic progression between the intervention and the comparator groups divided by the standard deviation of the difference. The SMDs were transformed into percentage reduction of radiographic progression rates. The difference in mean progression rates between the delayed treatment group and the early treatment group divided by the progression rate in the delayed treatment group.	

Effect size

Patients in the delayed DMARD group stared effective therapy an average of 9 months later than patients in the early DMARD group.

Results: all studies, all measures pooled

- Rate of radiographic reduction for early vs. delayed DMARD therapy (standard mean difference (95%CI):
  - Follow-up studies -0.18 (-0.39 to 0.02)
  - Cohort studies -0.21 (-0.48 to 0.06)
  - Combined follow-up and cohort studies -0.19 (-0.34 to -0.04). This corresponds to a -33% (-50 to -16%) in long-term radiographic progression rates in patients received early compared with late DMARD therapy.

Sensitivity analysis

- Sensitivity analysis for potential sources of bias showed no statistical differences for:
  - Study design, radiographic scoring systems, study quality, disease duration at enrolment, delay in DMARD initiation between treatment

- There was a significant difference for low initial rates of progression (≤ 1.5%/year) vs. high level rates of progression (>1.5%/year) (standard mean difference -0.04 (95%CI -0.23 to 0.16) vs -0.33 (95%CI -0.53 to -0.13); p=0.04) indicating that patients with more aggressive disease seemed to benefit from early DMARD therapy. Standardised differential rates of progression (95%CI) (positive score indicates a protective effect) -1.17 (-1.84 to -0.50) to 0.15 (-0.20 to 0.50)

Author's conclusions:
These results support the existence of a critical period to initiate antirheumatic therapy, a therapeutic window of opportunity early in the course of RA associated with sustained benefit in radiographic progression for up to 5 years. Prompt initiation of antirheumatic therapy in persons with RA may alter the long-term course of the disease.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Anonymous. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study.[see comment]. *American Journal of Medicine* 98 (2):156-168, 1995. ID 3054	RCT: 1++ Multicentre, 6 centres in Canada • Randomised (computer generated numbers, stratified by centre and allocated in blocks of 4) • Allocation concealment • Double blind • ITT analysis • Power study (for composite scores)	Total N=120 randomised (N=60 early treatment - hydroxychlorpquine; N=60 delayed treatment - placebo). **Withdrawals:** N=2, 3.3% (early DMARD treatment) N=3, 5% (delayed treatment – placebo)	**Inclusion criteria:** Age ≥18 years; RA (ARA criteria); Disease duration < 2 years (Early RA); persistent synovitis despite therapeutic doses of aspirin or other NSAIDs for at least 6 weeks; presence of 6 or more actively inflamed joints; 45 mins morning stiffness or ESR ≥25 mm/hr. **Exclusion criteria:** ARA functional class IV disease; prior therapy with second-line agent or anti-malarial drug; use of IA or systemic corticosteroids within 1 month of entry; ophthalmologic abnormality; any major surgery within 2 months of entry. **Baseline characteristics:** Early treatment (hydroxychloroquine) group: age mean 53 years; Female 76%; duration of RA mean 9 months; HAQ pain mean 1.46. Delayed treatment (placebo) group: age	Early treatment - hydroxychlorpquine Hydroxychloroquine (maximum 400 mg/day). Initial dose was half the maximum and of after 2 weeks of treatment there were no side-effects then the full dose was prescribed Protocol permitted decreasing or stopping the dose for a maximum of 4 weeks if there were AEs or was intercurrent illness. **Concomitant use of NASIDs** current use of aspirin or other NSAIDs was maintained. Changes in NSAIDs or new ancillary treatments were initiated only when clinically essential. **Other medication** Physiotherapy and use of orthotics initiated prior to the study could be continued.	Delayed treatment - placebo Other medication allowed as for intervention Mean dose of HCQ and equivalent placebo was similar between the 2 groups (385 mg/day and 383 mg/day respectively); there were NS differences between the groups for alterations in use of NSAIDs, use of analgesics or use of corticosteroids.	36 weeks (end of treatment) and assessments every 4 weeks before this.	Composite scores (indexes) were established and each component of an index was given equal weighting: Pain and physical functioning: (more than 1 measure was available and these were combined); Joint index (combined tender and swollen joint counts, grip strength and duration of morning stiffness); Pain index (combined AIMS pain dimension and HAQ pain – VAS); physical function index (combined physical disability scores from AIMS, HAQ	Grants from the MRC and Arthritis Society of Canada.

			mean 53 years; Female 76%; duration of RA mean 9 months; HAQ pain mean 1.46. There was NS difference between the groups for any of the baseline characteristics.	Analgesics premitetd were: paracetamol, propoxyphene and codeine. Injections of IA corticosteroids were permitted from weeks 2 to 24 inclusive.			and MACTAR); psychological function (AIMS psychological dimension); patient and physician global assessment of efficacy; ESR; AEs.	

Effect size

EARLY TREATMENT (HCQ) vs. DELAYED TREATMENT (PLACEBO)

- There were NS differences between the early treatment (hydroxychloroquine, HCQ) and delayed treatment (placebo) groups for:
    - AIMS psychological scale (change from baseline 36 weeks, end of treatment)
    - AIMS psychological scale (average treatment effect over all assessment times)
    - ESR (change from baseline 36 weeks, end of treatment)
    - Number of clinically significant AEs (N=25 and N=19 respectively)
    - Withdrawals due to AEs (both: N=2)

- The early treatment group (HCQ) was significantly better than the delayed treatment (placebo) group for:
    - Composite joint index score (symptoms), MD 0.33, p=0.004 (change from baseline 36 weeks, end of treatment)
    - Composite pain index score (symptoms), MD 0.55, p=0.007 (change from baseline 36 weeks, end of treatment)
    - Composite physical function index score, p=0.004 (change from baseline 36 weeks, end of treatment)
    - Composite joint index score (symptoms), p=0.034 (average treatment effect over all assessment times)
    - Composite pain index score (symptoms), p=0.001 (average treatment effect over all assessment times)
    - Composite physical function index score, MD 0.23, p=0.011 (average treatment effect over all assessment times)
    - Patient's and physician's global assessment of therapeutic benefit (change from baseline 36 weeks, end of treatment), MD 0.67 and 0.57, p=0.01 and 0.032 respectively.
    - Clinically significant improvement at 36 weeks (Paulus criteria improvement ≥20%), p=0.02

- The 2 groups were similar for:
    - Discontinuing study drug due to AEs (N=1 and N=2; HCQ and placebo respectively)
    - Total number of AEs (N=39 and N=38; HCQ and placebo respectively)

- The early treatment group (HCQ) was better than the delayed treatment (placebo) group for:
    - Discontinuing study drug due to lack of efficacy (N=4 7% and N=10 17% respectively).

- The time at which significant persistent benefit was detected varied among primary outcomes: Joint index (from 24 weeks); pain index and physical function index (from 12 weeks)

NOTE: the high response rate in both groups probably results from restricting enrolment to subjects with recent-onset RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

E. Tsakona and A. A. Fitzgerald. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. *Journal of Rheumatology* 27 (3):623-629, 2000. ID 954	RCT: 1++ Multicentre, 6 centres in Canada • Randomised (computer generated numbers, stratified by centre and allocated in blocks of 4) • Allocation concealment • Double blind • ITT analysis • Power study (for composite scores) but not for the extension period	Total N=120 randomised (N=60 early treatment - hydroxychlorpquine; N=60 delayed treatment - placebo). **Withdrawals:** N=4 (3%) of original 119 did not participate in the extension phase; additional 9% contributed only partial data.	**Inclusion criteria: PARTICIPANTS FROM THE ORIGINAL HERA STUDY** Age ≥18 years; RA (ARA criteria); Disease duration < 2 years (Early RA); persistent synovitis despite therapeutic doses of aspirin or other NSAIDs for at least 6 weeks; presence of 6 or more actively inflamed joints; 45 mins morning stiffness or ESR ≥25 mm/hr. **Exclusion criteria:** ARA functional class IV disease; prior therapy with second-line agent or anti-malarial drug; use of IA or systemic corticosteroids within 1 month of entry; ophthalmologic abnormality; any major surgery within 2 months of entry. **Baseline characteristics:** Early treatment (hydroxychloroquine) group: age mean 53 years; Female 76%; duration of RA mean 9 months; HAQ pain mean 1.46. Delayed treatment (placebo) group: age mean 53 years; Female 76%; duration of RA mean 9 months; HAQ pain mean 1.46. There was NS difference	1) Early treatment - hydroxychlorpquine Hydroxychloroquine (maximum 400 mg/day). Initial dose was half the maximum and of after 2 weeks of treatment there were no side-effects then the full dose was prescribed 2) Delayed treatment - placebo (9 months) then allowed to take DMARDs for the extension study (see below) In this extension study, no attempt was made to constrain the treatment that study participants received after the completion of the 9 month double blind portion of the HERA study. Data were obtained at each follow-up assessment on all medications used. There were NS differences in the use of corticosteroids, MTX, IM gold or other second-line agents.	Extended follow-up: assessments at 3 annual intervals after completion of the trial (1.75, 2.75 and 3.75 years after randomisation).	Pain (AIMS and HAQ); Physical disability 9AIMS and HAQ); RA global well-being scale (AIMS, VAS); probability that the 2 groups are equivalent / clinically immaterial difference.	Grants from Sanofi Winthrop Canada, the MRC and Arthritis Society of Canada.

			between the groups for any of the baseline characteristics.				

Effect size

EARLY TREATMENT (HCQ) vs. DELAYED TREATMENT (PLACEBO)

- For pain index and physical function index the probability is at least 50% that the difference between the early and delayed treatment groups was more than clinically immaterial throughout the followup.
- For global well-being the probability was < 50% of the difference being greater than clinically immaterial
- A clinically substantial difference in the pain index persisted for at least 33 months and for the global well-being scale it persisted for at least 21 months.

VALUES NOT GIVEN

Authors' conclusion: These findings show that a delay in instituting therapy with second-line agents, even a 9-month delay in instituting a moderately powerful second-line agaent such as HCQ, has significant effects on long-term patient utcome, and provides strong evidence in support of early therapy in RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
G. Borg, E. Allander, B. Lund, E. Berg, U. Brodin, H. Pettersson, and L. Trang. Auranofin improves outcome in	RCT: 1+ Multicentre, 11 centers in Scandanavia • Randomised (blocks for 4 within each centre)	Total N=138 randomised (N=69 early treatment – gold; N=69 delayed treatment – placebo).	**Inclusion criteria:** Disease duration ≤2 years (Early RA); active or definite RA (ACR criteria); no previous treatment with 2nd line drugs. **Exclusion criteria:** Age < 18 yrs; known hypersensitivity or skin reactions to heavy metals and previous treatment with	Early DMARD therapy Auranofin 6 mg daily **Concomitant**	Delayed DMARD therapy (placebo) In cases of intolerable side-effects or lack of efficacy, patients	2 years follow-up	Number of swollen joints, Ritchie articular index, duration of morning stiffness, grip strength, general health (VAS), Pain (VAS), disability (HAQ), Kietel functional	Not mentioned

early rheumatoid arthritis. Results from a 2-year, double blind placebo controlled study. *J Rheumatol* 15 (12):1747-1754, 1988. ID 23	• Double Blind for 1st part of trial (up to 2 years) then open trial for 2-5 year follow-up • Not true ITT analysis	**Drop-outs at 2 years:** N=5, 7% early treatment; N=10, 14% delayed treatment.	immunosuppressive drugs, gold salts, penicillamine or levimasole; taken steroids or antimalarials within the last month; steinbroker functional class 4; clinical or biochemical evidence of severe disease. **Baseline characteristics:** Early group: age mean 58 years; Female 57%; disease duration mean 10 months (early RA); Disability score (HAQ) mean 0.6; Pain (VAS) mean 46 mm. Early group: age mean 56 years; Female 68%; disease duration mean 12 months (early RA); disability score (HAQ) mean 0.6; Pain (VAS) mean 51 mm. The groups were well matched at baseline for all characteristics except Larsen score which was higher in the delayed group. **NOTE:** Mean duration of therapy was 48 months (early group) and 42 months (delayed group. Mean delay to SAARD therapy was 8 months in the delayed group.	**medication:** NSAIDs given to all patients in both groups and use of corticosteroids or analgesics was allowed if needed.	could be switched to an open DMARD.		index, Beck depression inventory scale. Radiologic outcomes: Larsen score, erosion score, number of engaged joints and eroded joints.	

Effect size

EFFICACY There were NS differences between the groups for:
- Pain, VAS(change from baseline) at 2 years

- The early group was significantly better than the delayed group for:
  - Number of patients withdrawn from treatment due to lack of response (19% and 49% respectively; p<0.001)
  - Disability (HAQ) score (change from baseline) at 2 years
  - Kietel Functional score (change from baseline) at 2 years
  - Beck depression score (change from baseline) at 2 years

- The early group was better than the delayed group for:
  - Number of patients still continuing on the original treatment (52% and 37% respectively) at 2 years
  - Larsen score (change from baseline) at 2 years

- The early group was significantly worse than the delayed group for:
  - Number of patients withdrawn from treatment due to AEs (28% and 3% respectively; p<0.01)

- The early group was clinically significantly better than the delayed group for:
  - Number of swollen joints

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Egsmose, B. Lund, G. Borg, H. Pettersson, E. Berg, U. Brodin, and L. Trang. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup	RCT: 1+ Multicentre, Sweden, Denmark • Randomised (method not mentioned) • Double Blind for 1st part of trial (up to 2 years) then	Total N=137 randomised (N=69 early treatment – gold; N=69 delayed treatment – placebo). Total included at 5 years N=75 (N=40 early	**Inclusion criteria:** Disease duration ≤2 years (Early RA); active or definite RA (ACR criteria); no previous treatment with 2nd line drugs. **Exclusion criteria:** Age < 18 yrs; known hypersensitivity or skin reactions to heavy metals and previous treatment with immunosuppressive drugs, gold salts, penicillamine or levimasole; taken steroids or antimalarials within the last	Early DMARD therapy Auranofin 6 mg daily **Concomitant medication:** NSAIDs given to all patients in both groups and	Delayed DMARD therapy (placebo) Patients began on placebo and then gold therapy (SAARD) – treatment was delayed by 8 months????	5 years follow-up	Changes over time (AUC) for numer of swollen joints, Ritchie articular index, duration of morning stiffness, grip strength, general health (VAS), Pain (VAS), disability (HAQ), Kietel functional index, Beck depression inventory scale.	Not mentioned.

of a prospective double blind placebo controlled study. *Journal of Rheumatology* 22 (12):2208-2213, 1995. ID 3000	open trial for 2-5 year follow-up • Not ITT analysis • High number lost-to follow-up but this is over 5 years	treatment; N=35 delayed treatment) **Lost to follow-up/ withdrawals at 5 years:** N=48, 35%.	month; steinbroker functional class 4; clinical or biochemical evidence of severe disease. **Baseline characteristics:** Early group: age mean 58 years; Female 53%; Disability score (HAQ) mean 0.6; Pain (VAS) mean 44 mm; Larsen score mean 6. Early group: age mean 55 years; Female 54%; Disability score (HAQ) mean 0.6; Pain (VAS) mean 51 mm; Larsen score mean 10. The groups were well matched at baseline for all characteristics except Larsen score which was higher in the delayed group. **NOTE:** Mean duration of therapy was 48 months (early group) and 42 months (delayed group. Mean delay to SAARD therapy was 8 months in the delayed group.	use of corticosteroids or analgesics was allowed if needed.			Radiologic outcomes: Larsen score, erosion score, number of engaged joints and eroded joints.	

Effect size

EFFICACY (VALUES NOT GIVEN)

- There were NS differences between the groups for:
  - Morning stiffness, grip strength, general health, Pain (VAS) and HAQ score.

- The early group was significantly better than the delayed group for:
  - Number of swollen joints (AUC) and Ritchie Articluar index (AUC) over 5 years
  - Kietel functional index and Beck Depression Inventory scale
  - Larsen score and erosion score (P=0.004 and p<0.002 respectively) at 5 years. If patients with early damage (Larsen score >12) were excluded, then the early group was still significantly better than the delayed group (p<0.01).
  - Number of engaged joints (p=0.01) and number of eroded joints (p<0.004) at 5 years.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
T. Mottonen, P. Hannonen, M. Korpela, M. Nissila, H. Kautiainen, J. Ilonen, L. Laasonen, et al, and RACo Trial Group. FIN. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early	RCT: 1+ Multicentre trial 18 centres in Finland. • Randomised (blocks of 10, stratified by RF status) • Unblinded (except for radiological assessments the assessor was blind) • True ITT analysis • Power study (remission rate)	Total N=199 randomised: (N=99 combination; N=100 single drug therapy) **Drop-outs/lost to follow-up:** Combination: 12% Single: 9%	**Inclusion criteria:** Adults aged 18-65 years with RA (ARA criteria); disease duration <2 years; active disease. **Exclusion criteria:** Previous use of DMARDs or undergone glucocorticoid therapy within previous 2 weeks; serious comorbidity; hypersensitivity to any of the study drugs or serious disease. **Baseline characteristics:** Combination group: Age mean 47, female	Combination: 3 DMARDs + prednisolone Single: DMARD with or without prednisolone Combination group started with SSZ (500 mg twice/day), MTX (7.5 mg/week) and HCQ (300 mg/day) and prednisolone 5 mg/day. If tolerated this combination was continued for 3 months. If clinical improvement at 3 months was <50%, the respective doses of MTX and prednisolone were increased to 10 mg/week and 7.5 mg/day. The protocol allowed flexible subsequent dose adjustments to mimic clinical practice. If patient reached remission during the first year with initial combination, the drug doses were tapered and prednisolone and MTX could be discontinued at 9 mths and 18 mths respectively. However SSZ and HCQ had to be continued until the end of the study. Patients who reached remission during 1st year but not with initial combination, drug doses were gradually tapered to those of the 2nd year. If the induced remission was lost, the DMARD doses were increased with intention of reaching	2 years (end of treatment) with assessments every 3-6 months.	Remission; Joint damage; long and short delay to therapy (subgroup analysis)	Finnish Society for Rheumatology; Rheumatism Research Foundation; Medical Research Foundation and Finnish Office of Health Care Technology Assessment, Finland.

rheumatoid arthritis. *Arthritis & Rheumatism* 46 (4):894-898, 2002. ID 3008			mean 58%, duration of RA mean 7.3 months. Single group: Age mean 48, female mean 66%, duration of RA mean 8.6 months. The groups were similar for all baseline characteristics.	remission. If one or several of the combination components had to be discontinued, the 3 DMARDs was restarted by replacing SSZ and HCQ with auranofin and MTX with AZA. Other DMARDs could be used as substitutes. Single group were treated continuously with 1 DMARD alone, with or without prednisolone and if a more beneficial effect was needed, the dose was increased or the DMARD was changed. SSZ (2 g/day) was used as the initial drug in all patients and the dose was increased to 3 g/day at 3 months if clinically indicated. If an AE occurred or clinical response was <25% at 6 months, SSZ was replaced by MTX (7.5-15 mg/week). As the 3rd DMARD, the protocol recommended AZA (2 mg/kg/day), auranofin, HCQ, injectable gold, penicillamine or podophyllotoxin could be used alternatively after AZA. The use of NSAIDs and IA corticosteroids was allowed in both treatment groups.			

Effect size

- Combination therapy was significantly better than single DMARD therapy for:
  - Number of patients in remission at 2 years (42% and 17% respectively, p=0.001)
  - Joint damage - increase in median Larsen score (p<0.001)

- Combination therapy was similar to single DMARD therapy for:
  - Median delay to institution of DMARD therapy (6 months and 7 months respectively)

- In logistic regression analysis, for the single-treatment group, delay to therapy was the only variable that significantly predicted remission at 2 years.
- In logistic regression analysis, for the combination-treatment group, no variable significantly predicted remission at 2 years.
- The frequency of patients with remission of their disease were similar in the long- and short- delay groups treated with the combination therapy (42% in each group)
- However, in the single-therapy group the frequency of patients with remission of their disease was significantly lower in the long-delay group compared to the short-delay group (11% and 35%, p=0.021) even when adjusting for other variables.
- There was NS difference between the long- and short- delay groups treated with the combination therapy or with the single therapy for Joint damage - increase in Larsen score
- Increase in joint damage (Larsen score) was significantly less in the combination –treated patients whose disease was in remission than in the other combination-treated patients (p=0.005).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Van der Heide, J. W. Jacobs, J. W. Bijlsma, A. H. Heurkens, Frankfort C. van Booma, der van, V, H. C. Haanen, D. M. Hofman, Kuipers GA van Albada, E. J. ter Borg, H. L.	RCT: 1+ Multicentre, Netherlands • Randomised (Blocks of 100 with equal number of patients for each of the four treatments per hospital)	Total N=238 randomised (N=57 non-SAARD strategy group – pyramid; delayed DMARD treatment; N=181 SAARD strategy group – early DMARD treatment).	**Inclusion criteria:** Disease duration less than one year (Early RA). **Exclusion criteria:** Age < 17 yrs; co-morbid conditions that might interfere with therapeutic strategies; previous or current treatment with SAARDs, glucorticosteroids, or cytotoxic or immunosuppressive therapy; pregnancy or breast-feeding; psychiatric or mental disturbances likely to interfere with adherence to protocol	SAARD (early DMARD therapy) 12 months duration Three groups. Initial therapy followed by other DMARD therapy initiated in the event of adverse reaction necessitating discontinuation: 1)	Non-SAARD (Delayed DMARD therapy – pyramid group) Patients started on NSAID therapy, the dose and type modified at any time (no DMARDs	12 months (at three monthly intervals)	Radiographic progression (hads and feet) using modified verision of the Sharp and coworkers method. Erosions and joint space narrowing in hand and foot joints were scored and added together to	Dutch League Against Rheumatism

Brus, H. J. Dinant, A. A. Kruize, and Y. Schenk. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Annals of Internal Medicine* 124 (8):699-707, 1996. ID 3014	• Blinding – radiographic abnormalities and ESR performed blind to treatment; functional disability and pain were not assessed blind to treatment • ITT analysis	**Lost to follow-up:** N=18 (N=3 non-SAARD; N=15 SAARD) statistical analysis showed they were similar to those patients who completed except for more likely to be male and older)	**Baseline characteristics:** Non-SAARD group: age mean 56 years; Female 70%; Rheumatoid factor-positive 59%; Disability score mean 1.3; pain score mean 45 mm; ESR mean 42 mm/hr; Radiologic damage score mean 5 SAARD group: age mean 57 years; Female 68%; Rheumatoid factor-positive 63%; Disability score mean 1.3; pain score mean 44 mm; ESR mean 41 mm/hr; Radiologic damage score mean 4 The groups were well matched at baseline.	Hydroxychloroquine 400 mg/day followed by auranofin 6 to 9 mg/day 2) Intramuscular gold (aurothioglucose 50 mg/week) followed by D-pencillamine 500 to 750 mg/day 3) Oral methotrexate 7.5 to 15 mg/week followed by sulfasalazine 2000 to 3000 mg/day **Concomitant use of NASIDs** allowed, the dose and type could be changed at any time **Other medication** Use of analgesics allowed; use of glucocorticosteroids avoided if possible; and intraarticular injections were not allowed within two months of a scheduled visit	given for the first year) Initiation of SAARD treatment = discontinuation of the therapeutic strategy Other medication allowed as for intervention		obtain a total radiologic damage score (range 0 to 448); Functional disability measured using Dutch version of the Health Assessment Questionnaire Disability Score (items score from 0 no problems to 3 worst); Pain measured on VAS of 100 mm; Joint scores measured using method of Thompson and coworkers to assess simultaneous presence of joint tenderness and swelling in a selection of joints weighted for joint size (range 0 to 534); ESR; AEs. Secondary end points: grip strength; duration of morning stiffness (maximum 720 min) ; general well-being (VAS	

							of 100 mm); serum level of C-reactive protein; hemoglobin concentration; and platelet counts	

Effect size

DISCONTINUATION of THERAPEUTIC STRATEGIES

- In both six-month periods, discontinuation occurred more frequently in the delayed DMARD (pyramid, non-SAARD) group - statistical analyses not reported:
    - 16 of 57 (29%) patients who completed follow-up could not continue to receive the pyramid therapeutic strategy for one year. Discontinuation was usually due to insufficient effectiveness (15/16 patients)
    - 15 of 181 (8%) patients discontinued with the early DMARD treatment (SAARD strategy - with the second SAARD). 12 of the 15 discontinued due to adverse reactions
    - 81% of patients were still using the first SAARD strategy at the end of the first year

CORTICOSTEROID USE

- At 12 months, 7/57 (12%) of patients in the delayed DMARD (pyramid, non-SAARD) group and 11/181 (6%) of patients in the early DMARD treatment (SAARD) group had been prescribed oral corticosteroids
- At 12 months, 23/57 (40%) of patients in the delayed DMARD (pyramid, non-SAARD) group and 35/181 (19%) of patients in the early DMARD treatment (SAARD) group had been prescribed intra-articular corticosteroids

CHANGES IN BASELINE IN THE DELAYED DMARD (PYRAMID, NON-SAARD) GROUP VS. THE EARLY DMARD TREATMENT (SAARD) GROUP (MEAN, SD). NEGATIVE VALUES INDICATE IMPROVEMENT

- The SAARD strategy was significantly better than the delayed DMARD (pyramid, non-SAARD strategy) group for:
    - Disability (HAQ), Pain, joint score and ESR at 12 months
    - % of patients showing clinical improvement (≥33% of baseline value) for disability (HAQ) at 6 months (44% and 27% respectively) and at 12 months (67% and 51% respectively).
    - % of patients showing clinical improvement (≥33% of baseline value) for joint scoreat 6 months (54% and 28% respectively) and at 12 months (78% and 57% respectively)

- There was NS difference between the groups for:
    - Increase in radiologic damage at 12 months

<u>ALL END-POINTS FAVOURED THE SAARD STRATEGY AT 6 AND 12 MONTHS:</u>

- At six months:
    - Disability 0.0 (-0.7 to 0.7) vs. -0.3 (-0.9 to 0.3); difference 0.3 (0.1 to 0.5)
    - Pain score, mm -0.15 (-44 to 14) vs. -20 (-47 to 7), difference 5 (-0.3 to 14)
    - Joint score -34 (-178 to 110) vs. -74 (-184 to 37), difference 40 (-2 to 82)
    - ESR, mm/h -5 (-33 to 23) vs. (-16 (-39 to 7), difference 11 (4 to 19)

- At twelve months:

- Disability, HAQ -0.1 (-0.8 to 0.6) vs. -0.4 (-1.0 to 0.2); difference 0.3 (0.2 to 0.6)
- Pain score, mm -0.11 (-43 to 21) vs. -21 (-49 to 7), difference 10 (1 to 19)
- Joint score -50 (-185 to 85) vs. -89 (-199 to 21), difference 39 (4 to 74)
- ESR, mm/h -5 (-32 to 22) vs. (-16 (-41 to 9), difference 11 (3 to 19)
- Radiologic damage score (N=43 non-SAARD; N=128 SAARD) +8 (0 to 21) vs. +7 (0 to 18), difference 1 (-3 to 5)

SECONDARY ENDPOINTS CHANGES IN BASELINE IN THE DELAYED DMARD (PYRAMID, NON-SAARD) GROUP VS. THE EARLY DMARD TREATMENT (SAARD) GROUP (MEAN, SD). NEGATIVE VALUES INDICATE IMPROVEMENT

- At six months:
  - Grip strength kpa +1 (-17 to 19) vs. +8 (-11 to 25), difference -7 (-12 to -2)
  - Well-being mm -17 (-47 to 13) vs. -21 (-52 to 10), difference 4 (-6 to 13)
  - Morning stiffness, min -17 (-186 to 152) vs. -68 (-225 to 89), difference 51 (1 to 102)
  - C-reactive protein level (N=39 non-SAARD; N=107 SAARD) mg/L -7 (-36 to 22) vs. -20 (-60 to 20), difference 13 (-2 to 28)
  - Hemoglobin concentration mmol/L -0.1 (-0.9 to 0.7) vs. +0.2 (-0.5 to 0.9), difference -0.3 (-0.5 to 0.0)
  - Platelet count -13 (-101 to 75) vs. -49 (-138 to 40), difference 36 (7 to 66)

- At twelve months:
  - Grip strength kpa +3 (-17 to 23) vs. +9 (-10 to 28), difference -6 (-12 to 0)
  - Well-being mm -12 (-42 to 18) vs. -21 (-52 to 10), difference 9 (-1 to 18)
  - Morning stiffness, min -37 (-159 to 85) vs. -66 (-211 to 79), difference 29 (-13 to 72)
  - C-reactive protein level (N=39 non-SAARD; N=107 SAARD mg/L -5 (-42 to 32) vs. -23 (-63 to 17), difference 18 (3 to 32)
  - Hemoglobin concentration mmol/L 0.0 (-0.8 to 0.8) vs. +0.3 (-0.5 to 1.1), difference -0.3 (-0.5 to 0.0)
  - Platelet count -15 (-110 to 80) vs. -50 (-139 to 39), difference 35 (7 to 64)

ADVERSE REACTIONS (ARs)

- Delayed DMARD treatment (pyramid, Non-SAARD) group:
  - 16/57 (28%) reported serious GI symptoms. Other ARs were rare

- In the Early DMARD treatment (SAARD) group discontinuation was due to:
  - 9/181 (16%) GI symptoms
  - 7/151 (12%) skin reactions
  - 4/151 anxiety about ARs
  - 2/151 increased aminotransferase levels
  - 2/151 headache or concentration problems
  - 1/151 proteinuria
  - 1/151 herpes zoster infection
  - 1/151 pneumonitis
  - 1/151 mouth ulcer
- In the Early DMARD treatment (SAARD) group, mild toxicity not leading to discontinuation (64 patients in total):

- 37/151 related to the NSAIDs
- 17/151 skin reactions
- 15/151 headache or dizziness (4 due to NSAIDs)
- 10/151 oral mucosal erosions
- 9/151 increased transaminase
- 8/151 upper respiratory tract infection
- 6/151 hair loss
- 5/151 thrombopenia or leukopenia
- 4/151 dyspnea
- 3/151 proteinuria
- 2/151 increase serum creatinine concentrations (1 due to NSAIDs)

SAME TRIAL AS VAN DER HEIGJE ID 3014 – but 5 year results

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. M. Verstappen, J. W. Jacobs, J. W. Bijlsma, A. H. Heurkens, Frankfort C. van Booma, E. J. Borg, D. M. Hofman, der van, V, and Utrecht Arthritis Cohort Study Group. Five-year followup of rheumatoid arthritis patients after early treatment	RCT: 1+ Multicentre, Netherlands • Randomised (Blocks of 100 with equal number of patients for each of the four treatments per hospital) • Blinding – radiographic abnormalities and ESR performed blind to	Total N=238 randomised (N=57 non-SAARD strategy group – pyramid; delayed DMARD treatment; N=181 SAARD strategy group – early DMARD treatment). **Lost to follow-up/ withdrawals at 5 years:** N=49, 21%.	As for ID 3014	As for ID 3014	As for ID 3014	12 months (at three monthly intervals)	Radiographic progression (hads and feet) using modified verision of the Sharp and coworkers method. Erosions and joint space narrowing in hand and foot joints were scored and added together to obtain a total radiologic damage score (range 0 to 448); Functional disability measured using Dutch version of the Health	Dutch League Against Rheumatism

with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. *Arthritis & Rheumatism* 48 (7):1797-1807, 2003. ID 154	treatment; functional disability and pain were not assessed blind to treatment • ITT analysis	Similar percentage in each group: 20% in early DMARD group vs 21% in pyramid group (delayed DMARD treatment).					Assessment Questionnaire Disability Score (items score from 0 no problems to 3 worst); Pain measured on VAS of 100 mm; Joint scores measured using method of Thompson and coworkers to assess simultaneous presence of joint tenderness and swelling in a selection of joints weighted for joint size (range 0 to 534); ESR; AEs. Secondary end points: grip strength; duration of morning stiffness (maximum 720 min) ; general well-being (VAS of 100 mm); serum level of C-reactive protein; hemoglobin concentration; and platelet counts	

Effect size

CORTICOSTEROID USE

- There was NS difference between the 2 groups for use of oral or IA corticosteroids.

EFFICACY

- There were NS differences between the groups for:
  - Median AUC values over 5 years for all clinical variables: ESR, Thompson joint score, Pain (VAS), General well-being (VAS), Morning stiffness (mins), Grip strength. However, all these clinical variables tended to favour early DMARD treatment.
  - Functional disability (HAQ, median change from baseline)
  - Number of patients achieving complete response (remission)
  - Radiographic scores - change from baseline (JSN, erosion and total radiographic damage score).

- The early DMARD group was significantly better than the delayed DMARD (pyramid) group for:
  - Median lag time until first complete response (12 months and 20 months respectively, $p<0.05$)
  - number of patients showing clinically relevant individual improvement (≥20% improvement) at 3 months, 6 months, 9 months, 12months and 21 months; $p<0.05$ However, there were NS differences in percentages.

- The delayed DMARD (pyramid) group was significantly better than the early DMARD group for:
  - Shorter median lag time between administration of the 1st DMARD and complete response (6 months and 12 months, p-value not given).

- ESR and morning stiffness (median AUC) was significantly better for patients who received more aggressive DMARDs (IM gold or MTX) at study start than for patients who did not take any DMARD or used less aggressive DMARD (hydroxychloroquine) at study start (p-values not given).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. R. Lard, H. Visser, I. Speyer, Bruinsma IE vander Horst, A. H. Zwinderman, F. C. Breedveld, and J. M. Hazes. Early	Cohort study (prospective): 2+ Single centre, The Netherlands • All patients included in analysis	Total N=206 (N=97 early treatment), N=109 delayed treatment) **Lost to follow-up/ withdrawals:** N=16, 15%	**Inclusion criteria:** RA 'definite RA' diagnosis (ACR criteria), early RA; active disease (at least 3 of the following: morning stiffness >30 mins, >5 swollen joints, Ritchie score >15 or ESR >28 mm/hr. The delayed treatment group were patients who visited the clinic 1993-1995 at which time patients with RA were treated consistently	Early treatment: prompt treatment with DMARDs + NSAIDs. Time to start DMARD treatment from 1st visit: mean 15 days	Delayed treatment: NSAIDs then DMARDs if still had active disease after several months. DMRADS were: chloroquine (300mg, 200 mg then 100mg per day at months 1, 2 and 3 and	2 years	Progression of radiographic joint damage (modified Sharp score); functional capacity (HAQ); modified DAS; Ritchie articular index	Not mentioned.

versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies.[see comment]. *American Journal of Medicine* 111 (6):446-451, 2001. ID 3005	(even drop-outs)	(delayed treatment), N=4, 4% (early treatment)	according to delayed therapy strategy. Early treatment group visited the clinic 1996-1998 in which time standard treatment was to give all patients with RA DMARDs as soon as possible. Only patients with diagnosis of probable or definite RA were included. **Baseline characteristics:** Early treatment group: mean age 54 years; Female 72%; disease duration mean 128 days (early RA); Sharp score mean 1. Delayed treatment group: mean age 58 years; Female 79%; disease duration mean 162 days (early RA); Sharp score mean 0. There were NS differences between the groups for any of the baseline characteristics except for time to start DMARD treatment.		thereafter respectively) or salazopyrine (2000 mg/day). Chloroquine was used preferentially. Time to start DMARD treatment from 1st visit: mean 123 days (approx 4 months).		score; CRP; AEs.	

Effect size

EARLY TREATMENT vs DELAYED TREATMENT

- Early treatment was significantly better than delayed treatment for:
    - Number of patients with progressive joint destruction (Sharp score >5) over the 2 years (38% vs 58%, p=0.01)
    - Radiographic joint damage (modified Sharp score) at 2 years, p<0.05
    - DAS score at 1 year (values not given, p<0.05)
    - CRP level at 3 months (values not given, p<0.05)
    - AUC for DAS score (median difference 64 units, 95% CI 59 to 69, p=0.002)
    - AUC for HAQ score
    - AUC for CRP level

- The early treatment group was better than the delayed treatment group for:
    - Number of withdrawals/lost-to follow-up (4% and 15% respectively);

- There was NS difference between the early treatment group and the delayed treatment group for:
    - Functional disability (HAQ score) at 2 years
    - DAS score at 2 years
    - CRP level at 1 year and 2 years (both: p<0.05, median difference 9 units)

- The early treatment group and the delayed treatment group were similar for:
    - Radiographic joint damage (modified Sharp score) at 6 months

- The early treatment group was worse than the delayed treatment group for:
    - Change in initial DMARD therapy due to AEs (12% vs 3% respectively);
    - Change in initial DMARD therapy due to lack of efficacy (22% vs 9% respectively)
    - Discontinuation of DMARD therapy (N=8 and N=4 respectively

Subgroup analysis

- In patients with definite RA, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with probable RA, the median change in joint damage was NS different in the early treatment group compared to the delayed treatment group.
- In patients with RF+, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with RF-, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.
- In patients with Sharp score >0 at baseline, the median change in joint damage was significantly less in the early treatment group compared to the delayed treatment group.

Authors' conclusion: early introduction of DMARDs was associated with better disease outcome after 2 years.

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length	Outcome	Source

	Evidence level	patients				of follow-up	measures	of funding
van Aken J., L. R. Lard, Cessie S. Le, J. M. Hazes, F. C. Breedveld, and T. W. Huizinga. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Annals of the Rheumatic Diseases* 63 (3):274-279, 2004. ID 127	Cohort study (prospective): 2+ Single centre, The Netherlands • Completers only included in the analysis	Total N=206 (N=97 early treatment), N=109 delayed treatment) **Lost to follow-up/ withdrawals:** 25%	As for ID 3005	As for ID 3005	As for ID 3005	4 years	Progression of radiographic joint damage (modified Sharp score); functional capacity (HAQ); modified DAS; Ritchie articular index score; CRP; AEs.	Dutch Arthritis Foundation

Effect size

EARLY TREATMENT vs DELAYED TREATMENT

- Early treatment was significantly better than delayed treatment for:
    - Number of patients with progressive joint destruction (Sharp score) at 1 year, 2 years and at 4 years (p=0.005, p=0.001 and p=0.032 respectively)

- There was NS difference between the early treatment group and the delayed treatment group for:
    - Rate of radiographic progression from 1-4 years and from 2-4 years,. However rate of progression was higher (worse) in the delayed group at years 1, 2 and 3 years (3 years: median difference 1.3 points/year, p=0.032) but equal rate at year 4.

Subgroup analysis:

- In patients with definite RA, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years and from 0-4 years but there was NS difference from 1-4 years.
- In patients with probable RA, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years but there was NS difference from 0-4 years and from 1-4 years.
- In patients with Sharp score >0 at baseline, the median change in joint damage (modified Sharp progression rate) was significantly better in the early treatment group compared to the delayed treatment group from 0-2 years and from 0-4 years but there was NS difference from 1-4 years.
- In patients with Sharp score 0 at baseline, the median change in joint damage (modified Sharp progression rate) was NS different in the early treatment group compared to the delayed treatment group from 0-2 years, from 0-4 years and from 1-4 years.

Authors' conclusion: early introduction of DMARDs was associated with better disease outcome after 2 years.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. Peltomaa, L. Paimela, T. Helve, and Repo M. Leirisalo. Effect of treatment on the outcome of very early rheumatoid arthritis. *Scandinavian Journal of*	Cohort study (prospective): 2+ Two centres, Finland	Total N=149 (N=83 cohort 1 & N=66 cohort 2) There were no differences between the cohorts in the duration of symptoms before the	**Inclusion criteria - cohort 1 1986-1989):** RA 'definite or classical RA' diagnosis (ARA criteria) and symptom duration ≤ 12 months **Cohort 2 1991-1993:** 1987 revised ACR criteria and duration of symptoms ≤ 24 months **Baseline characteristics:** Very early treatment group: mean age 55 years; Female 78%; disease duration mean 3.1 months*	Very Early RA (VERA) N=27 Duration of symptoms less than four months before the diagnosis No patients had been treated previously with	Early RA (ERA) N=122 Duration of symptoms for four to 24 months	3 years	Progression of radiographic joint damage (Larsen score); number of swollen joints and joint tenderness (Ritchie	Helsinki University Central Hospital Research Funds and Academy of Finland

Rheumatology 30 (3):143-148, 2001. ID 207		first medical encounter or delays in diagnosis **Lost to follow-up/ withdrawals:** Not reported	Early treatment group: mean age 50 years; Female 76%; disease duration mean 9.2 months* * denotes significant difference between the very early and early RA Time between symptom onset and first medical encounter: 1 month vs 2.5 months (VERA vs ERA p<0.001) Time from first physician treatment before referring to a rheumatologist: 1 month vs 1.5 months (VERA vs ERA p<0.001) The very early treatment group had a more acute disease onset (acute 59% and subacute 41%) compared with the early treatment group (acute 12%, subacute 62% and insidious 25%; p<0.001). Patients in the large joints affected (either alone or in association with arthritis of small joints) were over represented in the very early compared with the early group (p=0.019). Only small joint involvement at the onset was observed in 18% of the patients in the very early group and 48% in the early group (p<0.01).	DMARDs or oral corticosteroids, only NSAIDs. Intramuscular gold, sulphasalazine or hydroxychloroquine was started as soon as the diagnosis was made. If the initial medication had to be changed either due to side effecs or inefficacy, DMARDs were initiated (methotrexate, oral gold, azathioprine, d-penicillamine, cyclosporine, podophyllotoxine, wither single or in combinations) Low-dose corticosteroids were prescribed when necessary			index); morning stiffness, grip strength, VAS; functional capacity (HAQ); modified DAS; CRP	

Effect size (values not given)

VERY EARLY TREATMENT vs EARLY TREATMENT
BASELINE:

- The clinical picture at the time of diagnosis was more active in the very early compared with the early RA group:
    - Median CRP 34 vs 14 mg/l (p=0.004)
    - Median number of swollen joints 7 vs 4 (p=0.002)
    - Median Ritchie articular index 14 vs 9 (p<0.001)
    - Median Health Assessment Questionnaire score 0.6 vs 0.3 (p=0.003)

- There was NS difference between the very early treatment group and the early treatment group for:
    - ESR, erosive disease, duration of morning stiffness, Larsen score or VAS (NS)

THROUGHOUT THE THREE YEAR STUDY PERIOD:

- The differences between very early treatment compared with early treatment remained significant for:
    - CRP (p<0.05)
    - Ritchie index (p<0.05)
    - At the three year period only for the number of swollen joints (p<0.05)

- The differences between very early treatment compared with early treatment were not significant for:
    - ESR, erosive disease or Larsen scores (NS)

CHANGES FROM BASELINE AND FINAL VALUES:

- Within each group the differences were significant for (all p<0.01):
    - CRP
    - ESR
    - Number of swollen joints for the very early treatment group only, early treatment group (NS)
    - Ritchie Index

Duration of symptoms before the initiation of the DMARD therapy:

- When analysed with respect to the duration of symptoms before the initiation of DMARD therapy, the patients in the very early treatment group had a statistically higher Larsen score/month (median, IQR) compared with those in the early treatment group (1.2 [0.3 to 3.8] vs. 0.5 [0.0 to 1.3]; p=0.0044). In the whole group the initial Larsen score/month before treatment correlated also with the final three-year Larsen score (r=0.601; p<0.001)

Time from first visit to a primary care physician and a referral to a specialist (median one month):

- There was NS difference between the groups in the clinical picture or radiological progression (data not shown). However, on the HAQ those patients with a short time lag had a statistically higher score than those with a long time lag at entry (0.56 vs 0.36; p=0.004) and three-year follow-up (0.37 vs 0.18; p=0.04)

HAQ:

- The HAQ-score at onset was worse in the very early treatment group compared with the early treatment group mean 0.74 (SD 0.62) vs 0.39 (0.39) (p=0.0026)
- Over the three year follow-up, the HAQ-score significantly improved in the early treatment group only (0.39 (0.39) vs 0.22 (0.34); p=0.0001) but not the very early treatment group (NS)

DMARDs:

- The use of DMARDs did not statistically differ between the two groups
- The cumulative number of DMARDs used was significantly higher in the very early treatment group compared with the early treatment group at two year follow-up only (p=0.046)

Other analysis:

- The use of corticosteroids was significantly more frequent in the very early treatment group compared with the early treatment group (70% on permanent or intermittent therapy vs 38%; p=0.0005). The number of patients on permanent therapy was significantly higher in the very early treatment group compared with the early treatment group (56 vs 20%; p<0.001).
- There were no statistical differences between the two groups on:
- Annual radiological progression (Larsen score), with equal progression by the end of the third year
- Number of patients in remission at any time point

Authors' conclusion: Patients with very early RA (symptoms less than 4 months before diagnosis) was more aggressive from the onset onwards compared to RA patients with longer duration of symptoms.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
V. P. Nell, K. P. Machold, G. Eberl, T. A. Stamm, M. Uffmann, and J. S. Smolen. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with	Cohort study 2+ Single centre, Austria • Observer blind • Power analysis • Last-observation carried forward analysis	Total N=40 (N=20 early treatment), N=20 delayed treatment) Plus N=20 validation cohort Lost to follow-up: At 3 yrs, N=1 early	**Inclusion criteria:** RA diagnosed by rheumatologist based on clinical signs and symptoms and on laboratory tests, and ascertained by chart review during their first year of follow-up Fulfilled ACR criteria at baseline and/or cumulatively during the first year **Baseline characteristics:** Early treatment group: mean age 54 years; Female 75%; disease duration until DMARDs mean 3 months; Larsen ≥ 2 25%,	Early treatment group DMARD started median 3 months after symptom onset As soon as RA diagnosed patients were treated with DMARDs Validation cohort N=20 The same as above but	Delayed treatment group Age- and gender-matched controls DMARDs started median 12 months after symptom onset Presented to clinic for the first time with a symptom duration 9 months	3 years	Disease activity (DAS28; radiological progression (Larsen score); Quality of life (Health Assessment Questionaire HAQ), ACR and European League Against Rheumatism	None reported

early rheumatoid arthritis. *Rheumatology* 43 (7):906-914, 2004. ID 3009		treatment and N=2 delayed treatment	receiving NSAIDs 85%, receiving corticosteroids 60% Delayed treatment group: mean age 53 years; Female 75%; disease duration until DMARDs mean 12 months; Larsen ≥ 2 50%, receiving NSAIDs 95%, receiving corticosteroids 55% There were NS differences between the groups for any of the baseline characteristics except for time to start DMARD treatment. And 25% in the early group versus 50% in the delayed early group had erosions at the start of DMARD treatment	recruited at a subsequent time point	to 3.5 years and had never received DMARDs before DMARDs prescribed as soon as RA diagnosed		(EULAR) response rates	

Effect size

EARLY TREATMENT vs LATE DELAYED TREATMENT
DAS28:

- At three months, there was a significant difference in favour of early versus delayed treatment on the DAS28 (decrease from baseline approx. 40% vs. 12%; $p<0.05$)
- At three years, a significantly higher proportion of patients in the early compared with the delayed treatment group had a DAS28 of ≤ 3.2 (75 vs 25%; $p<0.05$)

EULAR:

- There were no statistical differences between the groups in the EULAR response rates (NS), however the number of good responders was significantly higher in the early compared with the late treatment group (8 vs 2; $p<0.05$)

Radiographic progression:

- At baseline (8 vs 2; $p<0.05$) and at 12, 24 and 36 month follow-up there was a significant difference in the mean Larsen scores when comparing the early with the delayed treatment group. Changes from baseline were significantly higher (more than four-fold) in the delayed compared with the early treatment group ($p<0.05$)
- Significantly more patients in the early treatment compared with the delayed treatment group had erosions (Larsen score ≥ 2) at baseline (5 vs 10; $p<0.05$) and at 36 months (7 vs 15; $p<0.05$).

Functional outcome, joint counts and acute phase response:

- There was a significant difference in favour of early compared with delayed treatment on the change from baseline on the HAQ score at three months (-0.5 vs -0.1) and at 36 months (-0.7 vs -0.4) (both $p<0.05$)
- There was a significant difference in favour of early compared with delayed treatment on the change from baseline on the patients' pain assessment (VAS) at three months (-29.3 vs -7.2 mm) and at 36 months (-40.4 vs -24.9 mm) (both $p<0.05$)
- There was a significant difference in favour of early compared with delayed treatment on the change from baseline on the patient's global assessment (VAS) at three months (-22.3 vs -6.7 mm) and at 36 months (-35.8 vs -24.2 mm) (both $p<0.05$)
- There was a significant difference in favour of early compared with delayed treatment on the change from baseline on the physicians' global assessment (VAS) score at three months (-30.5 vs -6.6 mm) and at 36 months (-38.0 vs -19.5 mm) (both $p<0.05$)
- There was no statistical difference between the early and delayed treatment groups at three (NS) or 36 months (NS) on the swollen joint count
- There was a statistical difference in favour of early treatment compared with delayed treatment on the tender joint count at 36 months (-8.0 vs -4.5; $p<0.05$) but not at three months (NS)
- A decrease in the acute phase response measured by ESP and CRP was demonstrated after only three months of DMARD therapy in both groups but with no statistical differences between the two groups at three or 36 months.

ACR response criteria:

- At three months, significantly more patients in the early treatment compared with the delayed treatment had achieved an ACR 20% response (65 vs 20%; $p<0.05$). A similar result was reported for an ACR 50% (50 vs 15%; $p<0.05$) and an ACR 70% (35 vs 0%; $p<0.05$).
- At 36 months, an ACR 20% response was achieved in significantly more patients in the early compared with the late treatment group (70 vs 40;; $0.1>p>0.05$). A similar finding was reported for an ACR 50% (60 vs 25%; $p<0.05$) and ACR 70% (55 vs 20%; $p<0.05$).

Switches of DMARD therapy:

- The initial distribution of DMARDS was similar at baseline. However, DMARDs of four patients in the early treatment group subsequently switched once, and twice or three times in each one additional patient (total number of regimen changes nine). In contrast, among patients in the delayed treatment group, switching of DMARD was necessary once in six patients, twice in two and three times in one patient (total changes 13). Of the nine switches in the early treatment group, six were due to adverse events and three due to inefficacy. This contrasts with four switches due to adverse events and nine due to inefficacy in the delayed treatment group. Thus, DMARD switching due to lack of inefficacy was three-fold ($p<0.05$) more frequent in the early versus the delayed treatment group.

Validation sample:
The demographics and outcomes for the original sample and validation sample (early treatment) were similar with no statistical differences.

Authors' conclusion: Early DMARD therapy is associated with improve outcome related to function, quality of life and joint destruction.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. H. Choy, D. L. Scott, G. H. Kingsley, P. Williams, J. Wojtulewski, G. Papasavvas, E. Henderson, D. Macfarlane, C. Erhardt, A. Young, M. J. Plant, and G. S. Panayi. Treating rheumatoid arthritis early with disease modifying drugs reduces joint damage: a randomised double blind trial of sulphasalazine vs diclofenac sodium. *Clinical & Experimental*	RCT: 1-Multicentre, UK • Very Large number of patients discontinued treatment and withdrew (53% and 75% from each arm) • Randomised (by centre) • Double blind, double dummy • ITT analysis	Total N=118 randomised (N=64 SSZ; N=55 NSAIDs). **Withdrawals:** N=46, 72% (early treatment - SSZ); N=29, 53% (delayed treatment – NSAIDs)	**Inclusion criteria:** Adults with early RA <1 year duration (ACR criteria); Active disease (≥6 swollen and tender joints, DAS ≥3.0). **Exclusion criteria:** previous DMARD therapy, hypersensitivity to sulphonamides; risk of serious diseases. **Baseline characteristics:** Early treatment (SSZ) group: age mean 57 years; Female 76%; DAS mean 5.0; Pain (VAS) 63.5. Delayed treatment (NSAIDs) group: age mean 58 years; Female 74%; DAS mean 5.3; Pain	SSZ (early DMARD therapy) + placebo 1 g/day for 2 weeks followed by 2 g/day **Other medication** In both groups use of analgesia (paracetamol, dextropropoxyphene or dihydrocodeine) was allowed; use of other anti-rheumatics or NSAIDs was not permitted.	NSAIDs (Delayed DMARD therapy) + placebo 100 mg/day	12 months (assessments at 26 and 52 weeks)	EULAR core data set of outcomes (number of tender and swollen joints, Ritchie Articular index, Pain - VAS, patient global assessment of disease activity, HAQ, ESR); Radiographic progression (Sharps method for hands, wrists and feet); AEs.	Not mentioned

Rheumatology 20 (3):351-358, 2002. ID 2999			(VAS) 63.5. The groups were similar for all baseline characteristics except the delayed group had greater morning stiffness.					

Effect size

- **Authors' conclusions:** Accelerated dosing schedule of SSZ has identical effects to diclofenac in reducing symptoms; indicating that it is a rapidly effective DMARD. ITT analysis also shows that early treatment with SSZ significantly reduces the extent of radiological progression in active RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wright JC Buckland, G. S. Clarke, I. C. Chikanza, and R. Grahame. Quantitative microfocal radiography detects changes in erosion area in patients with early rheumatoid arthritis treated with myocrisine. *Journal of*	RCT: 1-Single centre, UK • Randomised (method not mentioned) • No mention of blinding • No mention of ITT analysis • Small trial	Total N=29 randomised (N=13 early treatment – gold; N=16 delayed treatment - gold). **Lost to follow-up/ withdrawals:** 15% early gold 6% delayed gold	**Inclusion criteria:** Disease duration early RA (<2 years); not previously been treated with SAARDs. **Exclusion criteria:** Not given **Baseline characteristics:** Age mean 56 years, disease duration mean 8 years, female 85%. The groups were well matched at baseline except much higher % female in the delayed treatment group..	Early treatment: gold 50 mg/week of gold sodium thiomalate (GSTM) changing to 50 mg/month after 5 months. **Concomitant use of NASIDs**: both groups remained on their previously established NSAIDs	Delayed treatment: gold Patients started on their usual NSAID therapy, then after 6 months (delay) were treated with GSTM as for the early treatment group.	18 months (assessments every 6 months)	Radiographic damage (wrist and hands); Functional disability measured using (HAQ); Pain (VAS); Ritchie Articular index; Number of active joints; grip strength; patient's assessment of duration of early morning stiffness; overall stiffness (VAS); well-being (VAS); CRP; ESR.	Rhone-Poulenc Rorer Ltd.

Rheumatology 20 (2):243-247, 1993. ID 3055								
Effect size **EFFICACY** • In the first 6 months mean erosion increased significantly in both the early and delayed treatment arms. In the second 6 months, the early treatment group showed no increase and an insignificant increase in the delayed treatment group. By the third 6 months both groups showed a decrease.								

7.1.7 Optimal sequencing of DMARDs (DRUG1)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Boers. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine	RCT: 1++ Multicentre trial 10 centres in The Netherlands and Belgium (follow-up of the COBRA trial). • Randomised (stratified by centre,	Total N=156 randomised (N=77 CS+SSZ; N=79 SSZ). **Drop-outs:** SSZ + CS:	**Inclusion criteria:** Adults 18-70 years with RA (ACR criteria) with symptoms <2 years; active disease; of the joints and inadequate control w (due to lack of efficacy or toxicity of treatment); presence of 6 or more actively inflamed joints located at 3 or more different sites. **Exclusion criteria:** previous or current treatment with any DMARDs	SSZ + prednisolone + MTX All patients in both groups were given SSZ (500 mg/day) increased to 2000 mg/day over 3 weeks.	SSZ + placebo	Assessments at 28 weeks and 56 weeks and 80 weeks (end of treatment)	HAQ score; ACR remission; Disease activity index (Ritchie tender joint index, swollen joint count, ESR and patient's	Not mentioned

alone in early rheumatoid arthritis. *Lancet* 350 (9074):309-318, 1997. REF ID: 829	computer generated numebrs) • Allocation concealment • Double blind • ITT analysis	9% SSZ: 29%	except antimalarials; serious comorbidities or recent major surgery; hypersensitivity to study medication, SSZ containing compounds or aspirin; serious diseases; use of any experimental drug <2 months before inclusion. **Baseline characteristics:** SSZ + CS group: mean age 50 years; Female 66%; Duration of RA = Early RA (<2 years, mean 4 months); HAQ score 1.5. SSZ group: mean age 50 years; Female 52%; Duration of RA = Early RA (<2 years, mean 4 months); HAQ score 1.4. The groups were similar for all baseline characteristics. Concomitant treatment with NSAIDs and analgesics was permitted and maximum of two IA steroid injections were allowed in 2 periods after week 38 of the protocol, except during the 6 weeks preceding a clinical evaluation.	Prednisolone (tapered dose: 60 mg/day, 40 mg/day; 25 mg/day, 10 mg/day and 7 mg/day for weeks 1-6 and thereafter respectively). MTX: at 40 weeks tapered dose 5 mg/week for 3 weeks, 2.5 mg/week for 3 weeks then stopped. Prednisolone and MTX were stopped after 28 weeks and 40 weeks respectively If there was flare of disease then the last drug stopped was reintroduced.			overall assessment); Pooled index (tender joint count; assessor's overall assessment, VAS; grip strength; ESR; MACTAR score); tender and swollen joint counts; assessor's overall assessment; Pain (VAS); ACR20 and ACR50; Radiographic damage score (total, erosion and JSN – Sharp/van der Heijde score, SHS); ESR; CRP level; AEs.	

Effect size

SEQUENCES: Group 1 = SSZ then SSZ + CS + MTX
Group 2 = SSZ then continue SSZ

SSZ then SSZ + CS + MTX vs. SSZ then continue SSZ

- SSZ then SSZ + CS + MTX was significantly better than SSZ then continue SSZ for:
  - Pooled index (change from baseline) at 28 weeks, (MD 0.6, 95% CI 0.4 to 0.8, p<0.0001)
  - Tender joint count (change from baseline) at 28 weeks, (MD 8, 95% CI 4 to 13, p=0.0004)
  - Swollen joint count (change from baseline) at 28 weeks, (MD 5, 95% CI 2 to 7, p=0.00)
  - Grip strength (change from baseline) at 28 weeks, (MD 14, 95% CI 9 to 19, p<0.0001)
  - ESR (change from baseline) at 28 weeks, (MD 13, 95% CI 5 to 22, p=0.002)
  - Assessor's global assessment (change from baseline) at 28 weeks, (MD 16, 95% CI 8 to 24, p=0.0001)
  - MACTAR score (change from baseline) at 28 weeks, (MD 3, 95% CI 1 to 5, p=0.0007)
  - Pain, VAS (change from baseline) at 28 weeks, (MD 14, 95% CI 5 to 23, p=0.002)
  - HAQ score (change from baseline) at 28 weeks, (MD 0.5, 95% CI 0.3 to 0.7, p<0.0001)
  - DAS (change from baseline) at 28 weeks, (change 0.1 /year, p<0.0001)
  - Total number of withdrawals at 56 weeks, (8% vs 29%, p=0.0008)
  - Erosion score (change from baseline) at 28 weeks, 56 weeks and 80 weeks (p<0.0001, p=0.001 and p=0.004 respectively)
  - JSN score (change from baseline) at 28 weeks (median difference 28 weeks: 1.0, p=0.04)
  - Total radiographic damage (SHS) score (change from baseline) at 28 weeks, 56 weeks and 80 weeks (p<0.0001, p=0.004 and p=0.01 respectively)

- SSZ then SSZ + CS + MTX was better than SSZ then continue SSZ for:
  - Withdrawals due to AEs (3% and 8% respectively)
  - Withdrawals due to lack of efficacy (5% and 15% respectively)

- There was NS difference between SSZ then SSZ + CS + MTX and SSZ then continue SSZ for:
  - Patient's global assessment (change from baseline) at 28 weeks and 56 weeks
  - Pooled index (change from baseline) at 56 weeks
  - Tender joint count (change from baseline) at 56 weeks
  - Swollen joint count (change from baseline) at 56 weeks
  - Grip strength (change from baseline) at 56 weeks
  - ESR (change from baseline) at 56 weeks
  - Assessor's global assessment (change from baseline) at 56 weeks
  - MACTAR score (change from baseline) at 56 weeks
  - Pain, VAS (change from baseline) at 56 weeks

o HAQ score (change from baseline) at 56 weeks o DAS (change from baseline) at 56 weeks o JSN score (change from baseline) at 56 weeks and 80 weeks								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
R. B. Landewe, M. Boers, A. C. Verhoeven, R. Westhovens, M. A. van de Laar, H. M. Markusse, J. C. van Denderen, M. L. Westedt, A. J. Peeters, B. A. Dijkmans, P. Jacobs, A. Boonen, D. M. van der Heijde, and Linden S. van der. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural	RCT: 1++ Multicentre trial 10 centres in The Netherlands and Belgium (COBRA trial). • Randomised (stratified by centre, computer generated numebrs) • Allocation concealmen t • Double blind • ITT analysis	Total N=156 randomised (N=77 CS+SSZ; N=79 SSZ). **Drop-outs:** SSZ + CS: 9% SSZ: 29%	As for ID 829	As for ID 829	As for ID 829	Assessments at 28 weeks, 56 weeks and 80 weeks (end of treatment)	HAQ score; ACR remission; Disease activity index (Ritchie tender joint index, swollen joint count, ESR and patient's overall assessment); Pooled index (tender joint count; assessor's overall assessment, VAS; grip strength; ESR; MACTAR score); tender and swollen joint counts; assessor's overall assessment; Pain (VAS);	Grant from Ontwikkelingsgeneeskunde, The Netherlands..

benefits of a brief intervention. *Arthritis & Rheumatism* 46 (2):347-356, 2002. REF ID: 2170							ACR20 and ACR50; Radiographic damage score (total, erosion and JSN – Sharp/van der Heijde score, SHS); ESR; CRP level; AEs.	

Effect size

SEQUENCES: Group 1 = SSZ then SSZ + CS + MTX
Group 2 = SSZ then continue SSZ

- The COBRA group was significantly better (35% lower) than the SSZ group for Sharp damage score over time (median difference 8.0, change from 1-5 years; p=0.03)
- The COBRA group was better (30% reduction)than the SSZ group for Erosion score over time (median difference 3.0, change from 1-5 years)
- The COBRA group was better (42% reduction) than the SSZ group for JSN score over time (mean change from 1-5 years)
- Radiologic progression did not resume in the COBRA group after the 1 year trial
- The COBRA group was better than the SSZ group for DAS28 score reduction over time (mean change from 1-5 years)
- The HAQ score remained stable in both groups over time (mean change from 1-5 years)
- DMARD use at 5 years was the same in both groups (both: N=96 patients)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
M. L. Hetland and K. Stengaard-Pedersen. Combination treatment with methotrexate, cyclosporine, and	RCT: 1++ Multicentre trial, 5 centres in Denmark. • Randomised (Computer generated	Total N=163 (N=80 MTX + CyS + betameth; N=80 MTX + placebo +	**Inclusion criteria:** Adults aged 18-75 years with RA (ACR criteria); disease duration <6 months; at least 2 swollen joints at baseline. **Exclusion criteria:** Treatment with glucocorticoids in the preceding 4 weeks, previous use of DMARDs, serious disease, any condition	MTX + CyS + betameth MTX 7.5 mg/week; cyclosporine (CyS) 2.5 mg/kg/day. IM	MTX + placebo + betameth Same doses as for intervention group	52 weeks	Remission (ACR criteria and DAS28); ACR 20, 50 and 70; Overall ACR response (ACR-N, AUC); disability (HAQ); Pain score	Grant from Danish Rheumatism Association; drugs provided by Novartis, MSD and Schering-

intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. *Arthritis & Rheumatism* 54 (5):1401-1409, 2006. REF ID: 763	numbers, blocks of 4) • Allocation concealment • Double blind • ITT analysis • Power study (response rate)	betameth). **Drop-outs:** MTX + CyS + betameth: 14% MTX + placebo + betameth: 15%	contraindicated for the study medication. **Baseline characteristics:** MTX + CyS + betameth group: mean age 53 years; Female 64%; Duration of RA = Early RA (mean 3.2 months); DAS28 score mean 5.3; HAQ score mean 1.0. MTX + placebo + betameth group: mean age 51 years; Female 70%; Duration of RA = Early RA (mean 3.9 months); DAS28 score mean 5.5; HAQ score mean 0.9. There were NS differences between the groups for any of the baseline characteristics except % of ant-CCP positive patients was significantly higher in the MTX + Placebo + betameth group.	betamethasone 7 mg/ml was given in all swollen joints every 2 weeks for 8 weeks then every 4 weeks thereafter up to week 52. For both groups, doses were changed if there were AEs (hypertension or increased serum creatinine).			(VAS); joint damage (Larsen score); AEs.	Plough, Denmark.

Effect size

There was NS difference between the groups for dose of MTX, however cumulative dose of betamethasone was significantly higher in the non-aggressive group.

AGGRESSIVE (MTX + CyS + BETHAMETHASONE) vs NON-AGGRESSIVE (MTX + BETAMETHASONE)

- Aggressive treatment was significantly better than non-aggressive treatment for:
  - Proportion of patients achieving ACR20 response at 52 weeks (MD 17, OR 2.61, 95% CI 1.14 to 6.25, p=0.02)
  - Proportion of patients achieving overall ACR-N response at 52 weeks (p=0.03)
  - Radiographic progression at 2 years (p=0.03)
  - Rate of radiographic progression (% destruction per year), p<0.025

- There was NS difference between aggressive treatment and non-aggressive treatment for:
  - Proportion of patients achieving ACR50 and ACR70 responses at 52 weeks
  - Proportion of patients achieving remission (ACR) at 48 weeks and at 52 weeks
  - Proportion of patients achieving remission (DAS28) at 48 weeks and at 52 weeks
  - Reduction in median HAQ score
  - Number of patients with no swollen joints at 52 weeks
  - Number of patients with HAQ score ≤0.25 at 52 weeks
  - Number of patients with Pain scores ≤10 mm (VAS) at 52 weeks
  - Larsen score at 52 weeks
  - Development of bone erosions at 52 weeks

- Aggressive treatment was similar to non-aggressive treatment for:
  - SAEs leading to study withdrawal (N=1 and N=3 respectively)

- Aggressive treatment was worse than non-aggressive treatment for:
  - AEs (median increase in serum creatinine level), p<0.001
  - AEs – number of patients starting anti-hypertensive treatment (N=17 and N=9 respectively)
  - AEs – number of AEs rthat occurred in >10% of patients (N=89 and N=63 respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. L. Hetland, K. Stengaard-Pedersen, P. Junker, T.	RCT: 1++ Multicentre trial, 5 centres in Denmark.	Total N=160 (N=80 MTX +	As for ID 763	As for ID 763	2 years	Remission (ACR criteria and	Grant from Danish Rheumatism Association;

Lottenburger, I. Hansen, L. S. Andersen, U. Tarp, A. Svendsen, J. K. Pedersen, et al. Aggressive combination therapy with intraarticular glucocorticoid injections and conventional DMARDs in early rheumatoid arthritis Two Year Clinical and Radiographic Results From The CIMESTRA Study. *Annals of the Rheumatic Diseases* 66, 2007. REF ID: 3050	• Randomised (Computer generated numbers, blocks of 4) • Allocation concealment • Double blind • ITT analysis • Power study (response rate) • High dropouts	CyS + betameth; N=80 MTX + placebo + betameth). **Drop-outs at 2 years:** MTX + CyS + betameth: 40% MTX + placebo + betameth: 30%				DAS28); ACR 20, 50 and 70; Overall ACR response (ACR-N, AUC); disability (HAQ); Pain score (VAS); joint damage (Larsen score); AEs.	drugs provided by Novartis, MSD and Schering-Plough, Denmark.

Effect size

- Median dose of MTX at 2 years: 17.5 mg/week in both treatment groups.
- CyS / placebo-CyS had been withdrawn in all patients at week 104 (in accordance with protocol)
- There was NS difference between the groups in the cumulated dose of betamethasone during year 2 (1.5 ml and 2ml respectively)

AGGRESSIVE (MTX + CyS + BETHAMETHASONE) vs NON-AGGRESSIVE (MTX + BETAMETHASONE)

YEAR 1 vs YEAR 2

- Significantly more patients in the combination therapy group achieved ACR50 after 2 years than after 1 year (p=0.04)
- Significantly more patients in the monotherapy therapy group achieved ACR50, ACR70 and DAS-remission after 2 years than after 1 year (all: p<0.05)

- Aggressive treatment was significantly better than non-aggressive treatment for:
  - ACR20 and ACR50 (% of patients) at 2 years (MD 15 and 17, p=0.04 and 0.03 respectively)

- There was NS difference between aggressive treatment and non-aggressive treatment for:
  - Number of tender and swollen joints at 2 years
  - Pain (VAS) at 2 years
  - Patient's and Physician's global assessment at 2 years
  - CRP level at 2 years
  - ESR at 2 years
  - DAS28 score at 2 years
  - HAQ score at 2 years
  - ACR70 (% of patients) at 2 years
  - EULAR remission (% of patients) at 2 years
  - ACR remission (% of patients) at 2 years
  - Total Sharp Score at 2 years
  - Erosion score at 2 years
  - JSN at 2 years
  - Progression since baseline at 2 years
  - Number or type of AEs during the 2nd year

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
H. Makinen, H. Kautiainen, P. Hannonen,	RCT: 1+ Multicentre trial 18 centres in	Total N=199 randomised: (N=99	**Inclusion criteria:** Adults aged 18-65 years with RA	Combination: 3 DMARDs + prednisolone Single: DMARD with or without prednisolone	2 years with assessments every 3-6	Remission (ACR criteria);	Finnish Society for Rheumatology;

T. Mottonen, Repo M. Leirisalo, L. Laasonen, M. Korpela, H. Blafield, M. Hakola, and T. Sokka. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *Journal of Rheumatology* 34 (2):316-321, 2007. ID 2968	Finland. • Randomised (blocks of 10, stratified by RF status) • Unblinded (except for radiological assessments the assessor was blind) • True ITT analysis • Power study (remission rate)	combination; N=100 single drug therapy) **Drop-outs/lost to follow-up:** Combination: 12% Single: 9%	(ARA criteria); disease duration <2 years; active disease. **Exclusion criteria:** Previous use of DMARDs or undergone glucocorticoid therapy within previous 2 weeks; serious comorbidity; hypersensitivity to any of the study drugs or serious disease. **Baseline characteristics:** Combination group: Age mean 47, female mean 58%, duration of RA mean 7.3 months. Single group: Age mean 48, female mean 66%, duration of RA mean 8.6 months. The groups were similar for all baseline characteristics.	Combination group started with SSZ (500 mg twice/day), MTX (7.5 mg/week) and HCQ (300 mg/day) and prednisolone 5 mg/day. If tolerated this combination was continued for 3 months. If clinical improvement at 3 months was <50%, the respective doses of MTX and prednisolone were increased to 10 mg/week and 7.5 mg/day. The protocol allowed flexible subsequent dose adjustments to mimic clinical practice. If patient reached remission during the first year with initial combination, the drug doses were tapered and prednisolone and MTX could be discontinued at 9 mths and 18 mths respectively. However SSZ and HCQ had to be continued until the end of the study. Patients who reached remission during 1st year but not with initial combination, drug doses were gradually tapered to those of the 2nd year. If the induced remission was lost, the DMARD doses were increased with intention of reaching remission. If one or several of the combination components had to be discontinued, the 3 DMARDs was restarted by replacing SSZ and HCQ with auranofin and MTX with AZA. Other DMARDs could be used as substitutes. Single group were treated continuously with 1 DMARD alone, with or without prednisolone and if a more beneficial effect was needed, the dose was increased or the DMARD was changed. SSZ (2 g/day) was used as the initial drug in all patients and the dose was increased to 3 g/day at 3 months if clinically indicated. If an AE occurred or clinical response was <25% at 6 months, SSZ was replaced by MTX (7.5-15 mg/week). As the 3rd DMARD, the protocol recommended AZA (2 mg/kg/day), auranofin, HCQ, injectable gold, penicillamine or podophyllotoxin could be used alternatively after AZA.	months.	ACR20, ACR50 and ACR70; Swollen and tender joint count; Pain (VAS); Patient's and Physician's global assessment; morning stiffness; HAQ; ESR; CRP levels; radiographic joint damage (Larsen score); AEs;.	Rheumatism Research Foundation; Medical Research Foundation and Finnish Office of Health Care Technology Assessment, Finland.

				The use of NSAIDs and IA corticosteroids was allowed in both treatment groups.			

Effect size

- Aggressive (combination) therapy was significantly better than non-aggressive (single DMARD) therapy for:
  - Number of patients with sustained ACR remission over 2 years (14% and 3% respectively, p=0.013; OR 4.6, 95% CI 1.2 to 17.0)
  - Number of patients with sustained DAS28 remission over 2 years (51% and 16% respectively, p<0.001; OR 5.6, 95% CI 2.6 to 11.6)
  - Number of patients with sustained EULAR good treatment response over 2 years (67% and 27% respectively, p<0.001; OR 5.4, 95% CI 2.7 to 10.6)

- Aggressive (combination) therapy was better than non-aggressive (single DMARD) therapy for:
  - Number of patients in ACR remission at 6 months (25% and 12% respectively), 1 year (16% and 3% respectively), 2 years (14% and 3% respectively)
  - Number of patients with DAS28 remission at 6 months (66% and 37% respectively), 1 year (57% and 23% respectively), 2 years (51% and 16% respectively)
  - Number of patients with good EULAR treatment response at 6 months (75% and 52% respectively)
  - Number of patients not achieving good EULAR treatment response between 6 months and 2 years (7.5% and 26% respectively)

- In patients with sustained ACR remission, median increase of Larsen score over 2 years was 0 (95% CI 0 to 2), whereas in patients with ACR remission at 6 months but not in sustained remission, the Larsen score increased with median of 4 points (95% CI 0 to 10, p=0.017), and in patients who were not in ACR remission at 6 months the Larsen score increased with median of 4 points (95% CI 2 to 8, p=0.07 NS difference).
- In patients with sustained DAS28 remission, increase of Larsen score over 2 years was 1 (95% CI 0 to 2), whereas in patients with DAS28 remission at 6 months but losing it later, the median Larsen score increased by 4 points (95% CI 2 to 16, p<0.001).
- In patients achieving good EULAR response at all 3 visits, increase of Larsen score over 2 years was 1 (95% CI 0 to 6), whereas in patients with good EULARD response at 6 months but losing it later, the median Larsen score increased by 6 points (95% CI 2 to 10, p<0.001).

Authors' conclusions: A remarkable proportion of patients with early RA treated with combinations of DMARD were in remission at 2 years, and remission was more often sustained compared to patients treated with a single DMARD. Sustained remission protects against radiographic joint damage. Patients in sustained remission had less radiographic progression over 2 years compared with patients who were in remission at 6 months and lost it later; and that sustainability of remission and good treatment response was better in patients who were treated with a combination of DMARD + low dose prednisolone compared to the monotherapy with or without prednisolone, although treatment was targeted towards remission in both groups.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
T. Mottonen, P. Hannonen, M. LeirisaloRepo, M. Nissila, H.	RCT: 1+ Multicentre trial 18 centres in Finland.	Total N=199 randomised: (N=99 combination; N=100 single	As for ID 2968	As for ID 2968	2 years (end of treatment) with assessments every 3-6	Remission (ACR criteria); ACR20, ACR50 and	Finnish Society for Rheumatology; Rheumatism Research

Kautiainen, M. Korpela, L. Laasonen, H. et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. *Lancet* 353 (9164):1568-1573, 1999. ID 409	• Randomised (blocks of 10, stratified by RF status) • Unblinded (except for radiological assessments the assessor was blind) • True ITT analysis • Power study (remission rate)	drug therapy) **Drop-outs/lost to follow-up:** Combination: 12% Single: 9%			months.	ACR70; Swollen and tender joint count; Pain (VAS); Patient's and Physician's global assessment; morning stiffness; HAQ; ESR; CRP levels; radiographic joint damage (Larsen score); AEs;.	Foundation; Medical Research Foundation and Finnish Office of Health Care Technology Assessment, Finland.

Effect size

- Aggressive (combination) therapy was significantly better than non-aggressive (single DMARD) therapy for:
  - Number of patients in remission at 2 years (37% and 18% respectively, p=0.003)
  - Proportion of patients reaching ACR50 response at 2 years (values not given)
  - Swollen joint count at 2 years (values not given, p<0.05)
  - ESR at 2 years (p<0.05)
  - Joint damage (increase in Larsen score) at 2 years (p=0.002)
  - Number of eroded joints at 2 years (p=0.006)

- Aggressive (combination) therapy was similar to non-aggressive (single DMARD) therapy for:
  - Proportion of patients reaching ACR20 response at 6 months (80% and 78% respectively) and at 2 years (78% and 84% respectively)
  - Number of tender joints at 2 years
  - Patient's and Physician's overall assessments at 2 years
  - Physical function at 2 years

- There was NS difference between aggressive (combination) therapy and non-aggressive (single DMARD) therapy for:
  - Number of patients with AEs over 2 years
  - Number of patients with SAEs over 2 years
  - Number of patients with GI AEs over 2 years

- Patients in the single treatment group who were treated with prednisolone during the study developed more joint damage than the rest of the patients in that group (median change in Larsen score 7.5 and 4.0 respectively)
- The median dose of MTX was higher in the single-treatment patients who received it than in the combination group
- More patients in the single-treatment group received oral prednisolone than in the combination group
- More patients in the single-treatment group received glucocorticoid injections than in the combination group
- In logistic regression analysis, combination treatment was the only variable that significantly predicted remission at 2 years.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
M. Korpela, L. Laasonen, P. Hannonen, H. Kautiainen, Repo M. Leirisalo, M et al, and RACo	RCT: 1+ Multicentre trial 18 centres in Finland. • Randomised	Total N=199 randomised: (N=99 combination; N=100 single drug therapy)	As for ID 2968	As for ID 2968	5 years (end of treatment)	Remission (ACR criteria); ACR20, ACR50 and ACR70; Swollen and	Finnish Office of Health Care Technology Assessment, Finland.

Trial Group FIN. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis & Rheumatism* 50 (7):2072-2081, 2004. ID 3004	(blocks of 10, stratified by RF status) • Unblinded (except for radiological assessments the assessor was blind) • True ITT analysis • Power study (remission rate)	**Drop-outs/lost to follow-up at 5 years:** Combination: 20% Single: 16%				tender joint count; Pain (VAS); Patient's and Physician's global assessment; morning stiffness; HAQ; ESR; CRP levels; radiographic joint damage (Larsen score); AEs;.	

Effect size

- The median number of DMARDs taken during the 5-year follow-up period was the same in both the single and combination therapy groups (N=3)
- In logistic regression analysis, the extent of joint damage in the hands and feet at 5 years was predicted by: RF+ at baseline, single-treatment strategy for the first 2 years, disease duration before diagnosis and ESR at baseline.

- Aggressive (combination) therapy was significantly better than non-aggressive (single DMARD) therapy for:
  - Median DAS score at 5 years (median difference 0.52, p=0.048)
  - Time-weighted mean DAS28 (AUC) up to 5 years (mean difference 0.70, p<0.001)
  - Number of eroded joints (median) at 5 years (median difference 3.0, p=0.008)
  - Joint damage - Larsen score at 5 years (median difference 6.0, p=0.001)
  - Joint damage progression – increase in Larsen score over 5 years (MD 33%, 95% CI 15 to 50, p=0.004)

- There was NS difference between aggressive (combination) therapy and non-aggressive (single DMARD) therapy for:
  - Number of patients in remission at 5 years (28% and 22% respectively)

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention and Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
K. Puolakka. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis & Rheumatism* 50 (1):55-62, 2004. ID 1818	RCT: 1+ Multicentre trial 18 centres in Finland. • Randomised (blocks of 10, stratified by RF status) • Unblinded (except for radiological assessments the assessor was blind) • True ITT analysis • Power study (remission rate)	Total N=199 randomised: (N=99 combination; N=100 single drug therapy) **Drop-outs/lost to follow-up at 5 years:** Combination: 20% Single: 22%	As for ID 2968	As for ID 2968	5 years	Work disability (period of tiome patients was on sick leave, receiving sickness allowance or disability pension due to RA); Cumulative duration of sick leaves.	Medical Research Foundations of of Lappeenranta Central hospital and the Rheumatism foundation Hospital, Finland.

Effect size

- Aggressive (combination) therapy was significantly better than non-aggressive (single DMARD) therapy for:
  - Cumulative duration of work disability per patient observation year (12.4 days and 32.2 days respectively; p=0.008)
  - Sick-leave - work disability periods ≤300 days (11.7 days and 30.0 days respectively; p=0.002)

Authors' conclusions: Aggressive initial treatment of RA with a combination of DMARDs improves 5-year outcome in terms of lost productivity in patients with a recent onset of RA.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Grigor, H. Capell, A. Stirling, A. D. McMahon, P. Lock, R. Vallance, W. Kincaid, and D. Porter. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial. *Lancet* 364 (9430):263-269, 2004.	RCT: 1++ Multicentre: 2 centres in the UK • Randomised (randomisation software) • Allocation concealment • Single blind (assessors) • ITT analysis • Power study (responders)	Total N=111 randomised (N=55 each group). **Drop-outs:** Intensive: N=2 (4%) Routine: N=5 (9%)	**Inclusion criteria:** Adults (aged 18 to 75 years) with RA; duration <5 years; active disease (Disease activity score >2.4). **Exclusion criteria:** previously received combination DMARD treatment or had concurrent liver, renal or haematological disease. **Baseline characteristics:** Intensive group: mean age 51 years; Female 71%; Duration of RA = Early RA (19 months); Pain (VAS) mean 62. Routine group: mean age 54 years; Female 69%; Duration of RA = Early RA (20 months); Pain (VAS) mean 59. There was no clinically significant difference between the two groups for any of the baseline characteristics.	Intensive strategy Patients were seen every month by the same rheumatologist and their disease activity score was calculated. Any swollen joint was injected with IA CS unless had been injected within the previous 3 months – up to total dose of 120 mg triamcinolone acetonide per visit, After month 3, at every	Routine care Patients were also reviewed every 3 months with no formal composite measure of disease activity used in clinical decision-making. DMARD monotherapy was given to patients with active synovitis and failure of treatment resulted in change in monotherapy or addition of a second or third drug at the discretion of the rheumatologists. IA CS was given as for those in the intensive group.	18 months (end of treatment); assessments every 3 months	Fall in disease activity score (RAI, ESR, swollen joints and patients' assessment of disease activity); Good response (EULAR disease activity score <2.4); remission (EULAR); ACR20, 50 and 70;Pain (VAS); HAQ; patient's and physician's assessment of disease	Scottish Executive

ID 2168				assessment, patients with disease activity score of >2.4 received an escalation of their DMARD treatment. **START:** SSZ 500 mg/day increased every week to 40 mg/kg/day (or max tolerated dose). If DAS >2.4 at 3 months then go to triple therapy SSZ + MTX + HCQ. If DAS >2.4 then still triple therapy but increase MTX dose; if DAS >2.4 then4 then still triple therapy but increase SSZ dose; if DAS >2.4 then change triple therapy to Ciclosporin + MTX; if DAS >2.4 then			activity; ESR; radiographic progression (Sharp-van der Heijde score); SF-12 (QoL).	

				change DMARD to leflunomide or sodium aurothiomalate				

Effect size

Intensive: SSZ monotherapy increasing dose then triple therapy SSZ + MTX + HCQ then increase doses
Routine: SSZ monotherapy then alternative monotherapy or step-up

Intensive strategy reatment adjustment based on disease activity measures of response) vs Routine strategy (rheumatologist's criteria for treatment adjustment)

- The Intensive strategy was significantly better than the routine strategy for:
  - EULAR good response at 18 months (p<0.0001)
  - EULAR remission at 18 months (p<0.0001)
  - ACR20 (OR 5.7, 95% CI 1.9 to 16.7), ACR50 (OR 6.1, 95% CI 2.5 to 14.9) and ACR70 (OR 11, 95% CI 4.5 to 27) at 18 months (p<0.0001)
  - Disease activity score at 18 months (MD 1.6, 95% CI 1.1 to 2.1, p<0.0001)
  - Joint swelling at 18 months (MD 3, 95% CI 1 to 5, p=0.0028)
  - Joint tenderness at 18 months (MD 8, 95% CI 4 to 12, p=0.0003)
  - Patient's and assessor's global assessment of disease activity at 18 months (MD 30, 95% CI 17 to 42 and MD 24, 95% CI 14 to 34, both: p<0.0001)
  - Pain (VAS) at 18 months (MD 25, 95% CI 14 to 36, p<0.0001)
  - ESR at 18 months (MD 18, 95% CI 8 to 28, p=0.0007)
  - HAQ at 18 months (MD 0.5, 95% CI 0.2 to 0.8, p=0.0025)
  - SF-12 physical domain at 18 months (MD 5.3, 95% CI 0.8 to 9.8, p=0.021)
  - Erosion score at 18 months (MD 2.5, p=0.002)
  - Total sharp score at 18 months (MD 4.0, p=0.02)

- The Intensive strategy was better than the conventional strategy for:
  - Number of AEs (N=46 vs N=85) over 18 months
  - Higher prescription of IM and IA CS over 18 months
  - Higher prescription of combination DMARDs over 18 months
  - Higher doses of MTX over 18 months

- There was NS difference between the Intensive strategy and the routine strategy for:
  - CRP at 18 months
  - SF-12 mental domain at 18 months
  - JSN at 18 months
  - Doses of SSZ over 18 months

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. H. Van Jaarsveld, J. W. Jacobs, M. J. Van der Veen, and A. A. Blaauw. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. *Annals of the Rheumatic Diseases* 59 (6):468-477, 2000. ID 959	RCT: 1-Multicentre trial: 6 centres in Netherlands • Randomised (blocks of 100 patients within each centre, method not mentioned) • Open label • Not true ITT analysis • low number of dropouts • no statistical power calculation	Total N=344 randomised (analysis restricted to N=313) **Drop-outs:** Strategy I N=11 (9%) Strategy II N=12 (11%) Strategy III N=8 (7%)	**Inclusion criteria:** Adults with RA <1 yr duration **Exclusion criteria**: age < 17 years, interfering comorbid conditions, previous/current treatments with SAARD, corticosteroids, cytotoxic, immunosuppressive drugs, pregnancy/breastfeeding, mental disturbances making protocol adherence difficult **Baseline characteristics:** There were NS differences between the groups (data from only the patients included in the analysis) for all baseline characteristics.	Strategy 1: mild SAARD with a long lag time (hydroxychloroquine 400 mg/day, if necessary replaced by auranofin 6-9 mg./day) N=107 Strategy 2: potent SAARD with a long lag time (intramuscular gold 1M gold at 50 mg/week, if necessary replaced by D-penicillamine at 500-750 mg/day) N=101 Strategy 3: potent SAARD with a short lag time (oral methotrexate at 7.5 to 15 mg/week, if necessary replaced by sulfasalazine at 2 to 3 g/day) N=105 Protocol: Physicians managing each patient were free to prescribe NSAIDS, analgesics, but corticosteroids were avoided. Patients randomised to one of 3 strategies. SAARD therapy continued if improvement of 50% from baseline to 1 year in ¾ primary outcomes. If not, initial SAARD was discontinued and the alternate SAARD (same category) started. Outcomes measured at baseline, and every 3 months,	Groups compared with each other	2 years	**Primary Endpoints:** Pain; Functional disability; Joint score; ESR; Radiological Damage **Secondary Endpoints**: Morning stiffness duration; General well-being; Grip strength; CRP; Discontinuation of drugs; Clinical remission	Dutch League against Rheumatism.

				except for radiological damage which was assessed annually.				

Effect size

99% of participants took NSAIDS throughout study.
Authors conclude that strategy 2 or 3 are more effective than strategy 1, and strategy 2 was more toxic than strategy 3.
PRIMARY ENDPOINTS:
Changes from baseline were all significant for all 3 strategies for all primary endpoints after 1 year and after 2 years. (95% CI).
NS differences between any groups for disability score, pain score, joint score, ESR.
Radiological damage was significantly greater in Strategy 1 (median +12, N=107) than in Strategy 2 (median +9, N=101, p<0.05) and also significantly greater in Strategy 1 (median +12, N=107) than in Strategy 3 (median +8, N=105, p<0.05).

Primary Endpoint (change from baseline after 2 years)	Strategy 1: mild SAARD with a long lag time N=107	Strategy 2: potent SAARD with a long lag time N=101	Strategy 3: potent SAARD with a short lag time N=105	P between groups
Disability score	-0.3 (-0.5 to -0.2)	-0.4 (-0.6 to -0.2)	-0.3 (-0.4 to -0.2)	NS between any groups
Pain score, mm	-22 (-27 to -16)	-25 (-31 to -19)	-21 (-27 to -16)	NS between any groups
Joint score	-89 (-111 to -67)	-104 (-128 to -80)	-86 (-106 to -66)	NS between any groups
ESR, mm/1st h	-19 (-24 to -14)	-21 (-27 to -16)	-20 (-24 to -15)	NS between any groups
Radiological damage, median	+12	+9	+8	P<0.05 1 versus 2 P<0.05 1 versus 3 NS 2 versus 3

SECONDARY ENDPOINTS:

Secondary Endpoint (change from baseline after 2 years)	Strategy 1: mild SAARD with a long lag time N=107	Strategy 2: potent SAARD with a long lag time N=101	Strategy 3: potent SAARD with a short lag time N=105	P between groups
Well-being score, mm	- 17 (-23 to -11)	-24 (-30 to -17)	-18 (-24 to -12)	NS between any groups
Grip strength, kPa	+ 12 (+8 to +15)	+ 13 (+8 to +17)	+ 15 (+11 to +20)	NS between any groups
Morning stiffness, min median (10-90 centiles)	-45 (-309 to + 36)	-45 (-150 to + 30)	-30 (-216 to + 45)	NS between any groups
CRP, mg/l median (10-90 centiles)	-18 (-74 to +5)	-11 (-95 to +6)	-5 (-55 to +5)	NS between any groups

After 1 year, only grip strength was significantly higher in strategy 3 [+14 (95% CI 10 to 18)] than in strategy 1 [+9 (95%CI 6 to 12)]. Mean difference was 5 (95%CI 0.2 to 10.0) between groups 1 and 3. NS difference between strategy 2 and 3 [mean difference 5 (95% CI -0.2 to 10.0), NS]

Clinical remission: defined as morning stiffness≤ 15 minutes, pain score ≤ 10 mm, joint score ≤ 1, and ESR ≤ 30 mm/1 st h at 1 and 2 years
After 1 year, significantly more people randomised to strategy 2 (31%) experienced clinical remission than those randomised to strategy 1 (16%), p=0.01. NS difference between strategy 1 versus 3. NS difference for strategy 2 versus 3.

After 2 years, NS differences between any group for clinical remission.

Toxicity
Strategy 1: subjective GI complaints (N=52), anaemia (N=21), rash (N=17)
Strategy 2: mucocutanaeous reaction (N=62)
Strategy 3: subjective GI (N=32), hepatotoxicity (N=23)
Mean number of adverse events was higher in strategy 2 (2.1) compared with strategy 1 (1.6) and strategy 3 (1.7)
Events that lead to drug discontinuation was significantly higher in strategy 2 (46 events) than strategy 1 (17 events) or strategy 3 (16 events).
Discontinuation of drugs:
NS different between each of the three strategies: 27% in Strategy 1, 30% in strategy 2, and 20% strategy 3 from 0-2 years.
Main reasons for discontinuation were insufficient effectiveness in strategy 1 and 2 and adverse reactions in strategy 3.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
J. Braun, P. Kastner, P. Flaxenberg, J. Wahrisch, P. Hanke, W. Demary, Hinuber U. von, K. Rockwitz, W. Heitz, U. Pichlmeier, Schmolck C. Guimbal, A. Brandt, and M. T. X. MC. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active	RCT: 1++ Multicentre trial 29 centres in Germany. • Randomised (permuted block randomisation, stratified by centre) • Allocation concealment • Triple blind (double dummy) • Not true ITT analysis • Power study (ACR20)	Total N=384 randomised (N=194 SC MTX group; N=190 oral MTX group). **Drop-outs at 6 months:** SC MTX: N=6 (3%) Oral MTX: N=3 (2%)	**Inclusion criteria:** Adults 18 -75 years of age; active disease; RA (ACR criteria); never been treated with MTX prior to randomisation. Treatment with other DMARDs had to be discontinued for ≥2 weeks prior to randomisation and during the study period. **Exclusion criteria:** Treatment with biologics before or during the study. Serious diseases; ulcers of the GI tract within 6 months; current or recent alcohol or drug abuse; extensive consumption of coffee. **Baseline characteristics:** SC MTX: mean age 58 years; Female 79%; Duration of RA = Early RA (mean 2.5 months); HAQ score mean 1.3. Oral MTX: mean age 59 years; Female 74%; Duration of RA = Early RA (mean 2.1 months); HAQ score mean 1.4.	SC (subcutaneous) MTX 15 mg (pre-filled syringe + 2 placebo tablets) Oral MTX 15 mg (2 x 7.5mg tablets + 1 pre-filled syringe placebo) For all groups at week 16, patients who did not meet the ARC20 criteria were switched from their initial treatment to the following: from 15mg oral MTX to 15mg SC MTX; from 15mg SC MTX to 20mg SC MTX. This regimen was continued for the remaining 8 weeks and study blinding was maintained.	6 months (24 weeks)	ACR20; ACR50; ACR70; DAS28; CRP; ESR; Physicans' and Patients' global assessment of disease activity; Pain (VAS); HAQ; AEs and SAEs	Medac, Germany

rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis & Rheumatism* 58 (1):73-81, 2008. REF ID: 3504			There was NS difference between the groups for any of the baseline characteristics. IA CS and propyhlaxis against possible AEs were not allowed during the study.				

Effect size

NOTE: 75% of patients had not previously received DMARDs

SC MTX vs ORAL MTX

- SC MTX was significantly better than Oral MTX for:
  - Percentage of patients with an ACR20 response (78% vs 70%, $p<0.05$) at week 24
  - Percentage of patients with an ACR70 response (41% vs 33%, $p<0.05$) at week 24
  - Number of swollen joints

- There was NS difference between SC MTX and Oral MTX for:
  - Percentage of patients with an ACR50 response at week 24
  - Number of tender joints at week 24
  - HAQ score at week 24
  - DAS28 at week 24
  - Percentage of patients with at least 1 moderate AE
  - And similar for percentage of patients with SAEs

- Subgroup analysis of patients with ≥1 year who had received prior DMARDs or steroids showed an even greater significant difference in percentage of ACR20 responders in the SC vs oral MTX groups (89% vs 63% respectively, $p<0.05$)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding
E. H. Choy, C. M. Smith, V.	RCT: 1++ Multicentre trial:	Total N=467 randomised	**Inclusion criteria:** Age ≥18 years; RA (ACR criteria); active disease;	Group 1: MTX (starting 7.5 mg/week increasing	2 years	HAQ; DAS28; SF-36;	Medical Research

Farewell, D. Walker, A. Hassell, L. Chau, D. L. Scott, and Rheumatic Drugs in Early Rheumatoid Arhritis Trial Group CARDERA (Combination Anti. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Annals of the Rheumatic Diseases* 67 (5):656-663, 2008. ID 3505	42 centres UK. • Randomised (stratified by region, blocks of 16) • Double blind (double dummy) • Allocation concealment • ITT analysis • Power study (40% reduction in cases developing erosions)	(N=117 MTX, N=119 MTX + ciclo, N=115 MTX + pred, N=116 MTX + ciclo + pred). **Drop-outs/lost to follow-up at 2 years:** N=25 (21%) MTX N=26 (22%) MTX + ciclosporin N=19 (17%) MTX + prednisolone N=18 (16%) MTX + ciclosporin + prednisolone	duration <24 months with 3 of the following: ≥3 swollen joints, ≥6 tender joints, ≥45 mins morning stiffness, ESR ≥28 mm/hr. **Exclusion criteria:** Other inflammatory arthropathies; current oral glucocorticoids; serious medical disorders; contraindications for trial drugs. **Baseline characteristics:** MTX group: mean age 54 years; Female 67%; Duration of RA = Early RA (2.7 months); HAQ mean 1.5 MTX + ciclo group: mean age 53 years; Female 66%; Duration of RA = Early RA (4.2 months); HAQ mean 1.7 MTX + pred group: mean age 54 years; Female 78%; Duration of RA = Early RA (5.1 months); HAQ mean 1.6 MTX + ciclo + pred group: mean age 55 years; Female 67%; Duration of RA = Early RA (3.9 months); HAQ mean 1.6 The groups were similar for all baseline characteristics.	incrementally to 15 mg/week) Group 2: Step-down prednisolone started with MTX (60 mg/day initially, reduced to 7.5 mg at 6 weeks, 7.5 mg/day from 6-8 weeks, stopped by 34 weeks) Group 3: ciclosporin started 3 months after MTX (initial dose 100 mg/day, increased gradually to target dose of 3 mg/kg daily) Group 4: all treatments **Concomitant NSAIDs/other treatment**: Analgesics and NSAIDs were used at standard dosages. Other drugs were continued as needed. IA glucocorticoids (40 mg methylprednisolone with lignocaine) were given as required. IM glucocorticoids were allowed but only 3 doses of 120 mg of depot methylprednisolone could be given in a year.		clinically relevant reduction (40% fewer patients developing new erosions); ACR20, 50 and 70; DAS28 <2.6.	Council Wyeth Research

Effect size

SEQUENCES: Group 1 = MTX increasing dose = sequence
Group 2 = MTX + prednisolone (decrease dose)
Group 3 = MTX , add ciclosporin after 3 months
Group 4 = MTX + prednis + ciclo

MTX increasing dose vs MTX + prednisolne (decrease dose)

- MTX increasing dose was better than MTX + prednisolone (decrease dose) at 2 years for:
  - Change in HAQ score (MD 0.01)
  - Change in SF-36 score (MD 2.4)
  - Change in DAS28 score (MD 0.05)

- MTX increasing dose was worse than MTX + prednisolone (decrease dose) at 2 years for:
  - Cases of new erosions (28% vs 16%)
  - Change in Larsen score (MD 3.71)

MTX increasing dose vs MTX , add ciclosporin after 3 months

- MTX increasing dose was better than MTX , add ciclosporin after 3 months at 2 years for:
  - Change in DAS28 score (MD 0.08)
  - Change in Larsen score (MD 2.88)
  - Cases with erosions (28% vs 17%)
  - Change in SF-36 score (MD 1.9)

- MTX increasing dose was similar to MTX , add ciclosporin after 3 months at 2 years for:
  - Change in HAQ score (MD 0.09)

MTX + prednisolone (decrease dose) vs MTX then add ciclosporin after 3 months

- MTX + prednisolone (decrease dose) was better than MTX , add ciclosporin after 3 months at 2 years for:
  - Change in Larsen score

- MTX + prednisolone (decrease dose) was worse than MTX , add ciclosporin after 3 months at 2 years for:
  - Change in HAQ score (MD 0.08)
  - Change in SF-36 score (MD 0.4)
  - Change in DAS28 score (MD 0.03)
  - Cases of new erosions (MD 0.17)

MTX + prednis + ciclo vs all groups

- MTX + prednis + ciclo was better than all the other groups at 2 years for:
  - Cases with new erosions (13% vs 28% and 17%)
  - Change in Larsen score (MD 4.42 and 1.54 and 1.71)
  - HAQ score (MD 0.21 and 0.30 and 0.22)
  - Change in SF-36 (MD 2.2 and 4.1 and 4.5)
  - Change in DAS28 (MD 0.25 and 0.33 and 0.30)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. A. Capell, R. Madhok, D. R. Porter, R. A. Munro, I. B. McInnes, J. A. Hunter, M. Steven, A et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from	RCT: 1++ Multicentre trial – 8 sites in UK. • Randomised (computer generated numbers, stratified by RF status) • Double blind • ITT analysis • Power study (DAS) Fairly high drop-outs	Total N=166 randomised (N=56 combination SSZ + MTX, N=55 SSZ, N=54 MTX). **Drop-outs:** Combination: 30% SSZ: 25% MTX: 30%	**Inclusion criteria:** Adults 18-80 years with RA ;disease duration <10 years; active disease (DAS >2.4). **Exclusion criteria:** Prior exposure to MTX or SSZ; known sulphonamide allergy; significant renal or liver disease; abnormal white cell count; pulmonary fibrosis; use of oral steroids >7.5 mg/day. **Baseline characteristics:** Combination (SSZ + MTX) group: mean age 56 years; Female 75%; Duration of RA = Early RA (1.9 years); DAS mean 3.6. SSZ group: mean age 55 years; Female 75%; Duration of RA = Early RA (1.6 years); DAS mean 3.7.	**Phase I** (0-6 months) all patients given SSZ **Phase II** patients randomised into 3 groups: 1) SSZ + MTX 2) SSZ + placebo 3) Placebo + MTX Phase I: SSZ dose 500 mg daily increasing by 500 mg/week until target dose of 40 mg/kg/day (or maximum tolerated dose) to a maximum dose of 4 g/day was reached. Phase II: Combination group 1 - SSZ continued at dose achieved at 6 months, MTX added 7.5 mg/week increasing by 2.5 mg/month until maximum dose of 25 mg or toxicity occurred. SSZ group 2 - SSZ continued at dose achieved at 6 months, addition of placebo MTX (as for schedule		18 months (end of treatment) with assessments every 3 months. At 6 months Phase II of the study was started (patients were randomised into their second treatment group).	DAS; ACR 20, 50 and 70; HAQ; Ritchie Articular Index; Swollen joint count; Pain (VAS); Patient's and Physician's global assessment;EULAR response; disease progression: modified Sharp score; total erosions (hands and feet); JSN; ESR; CRP levels; AEs.	Grants from the Arthritis Research Council, UK. Drugs supplied by Wyeth and Pharmacia.

the double-blind placebo-controlled MASCOT study. *Annals of the Rheumatic Diseases* 66 (2):235-241, 2007. ID 19			MTX group: mean age 53 years; Female 79%; Duration of RA = Early RA (1.8 years); DAS mean 3.5. Both groups were similar for all baseline characteristics.	above). MTX group 3 – Placebo SSZ at the previously achieved number of tablets by 6 months, MTX added (as for schedule above). **Concomitant NSAIDs/other treatment**: NSAID and other treatment was continued; IA or IM corticosteroids was permitted, but not within 1 month of the assessments. Oral CS were not used in any group and similar for all study drugs between each group.			

Effect size

SEQUENCES: Group 1 = SSZ then SSZ + MTX
Group 2 = SSZ
Group 3 = SSZ then MTX

SSZ then SSZ + MTX vs. SSZ continuous

- SSZ then SSZ + MTX was significantly better than continuous SSZ for:
  - DAS score (change from 6 - 18 months when sequence of drug was changed), median difference 0.37, p=0.039

- SSZ then SSZ + MTX was better than continuous SSZ for:
  - % of patients with EULAR good response (18% and 7% respectively) at 18 months
  - % of patients in remission (10% and 5% respectively) at 18 months

- There was NS difference between SSZ then SSZ + MTX and continuous SSZ for:
  - HAQ score (change from 6 - 18 months when sequence of drug was changed)
  - Ritchie Articular Index (change from 6 - 18 months when sequence of drug was changed)
  - Swollen joint count (change from 6 - 18 months when sequence of drug was changed)
  - Pain, VAS (change from 6 - 18 months when sequence of drug was changed)
  - Patient's and physician's global assessment (change from 6 - 18 months when sequence of drug was changed)
  - ESR (change from 6 - 18 months when sequence of drug was changed)
  - CRP level (change from 6 - 18 months when sequence of drug was changed)
  - ACR20, ACR50 and ACR70 (change from 6 - 18 months when sequence of drug was changed)
  - Total Sharp score, total erosions (hands and feet) and JSN (change from 6 - 18 months when sequence of drug was changed)

- SSZ then SSZ + MTX was similar to continuous SSZ for:
  - Number of withdrawals (30% and 25% respectively)
  - Number of withdrawals due to AEs (21% and 18% respectively)
  - Number of withdrawals due to lack of efficacy (4% and 7% respectively)

SSZ then SSZ + MTX vs. SSZ then MTX

- SSZ then SSZ + MTX was significantly better than SSZ then MTX for:
  - DAS score (change from 6 - 18 months when sequence of drug was changed), median difference 0.41, p=0.023
  - Ritchie Articular Index (change from 6 - 18 months when sequence of drug was changed), median difference 4.0, p=0.019
  - ESR (change from 6 - 18 months when sequence of drug was changed), median difference 1.0, p=0.033

- SSZ then SSZ + MTX was better than SSZ then MTX for:
  - % of patients with EULAR good response (18% and 5% respectively) at 18 months

- % of patients with EULAR remission (10% and 3% respectively) at 18 months

- There was NS difference between SSZ then SSZ + MTX and SSZ then MTX for:
  - HAQ score (change from 6 - 18 months when sequence of drug was changed)
  - Swollen joint count (change from 6 - 18 months when sequence of drug was changed)
  - Pain, VAS (change from 6 - 18 months when sequence of drug was changed)
  - Patient's and physician's global assessment (change from 6 - 18 months when sequence of drug was changed)
  - CRP level (change from 6 - 18 months when sequence of drug was changed)
  - ACR20, ACR50 and ACR70 (change from 6 - 18 months when sequence of drug was changed)
  - Total Sharp score, total erosions (hands and feet) and JSN (change from 6 - 18 months when sequence of drug was changed)
  - Number of withdrawals (both: 30%)

- SSZ then SSZ + MTX was similar to SSZ then MTX for:
  - Number of withdrawals (both: 30%)
  - Number of withdrawals due to AEs (21% and 26% respectively)
  - Number of withdrawals due to lack of efficacy (both: 4%)

SSZ then MTX vs. SSZ continuous

- There was NS difference between SSZ then MTX and continuous SSZ for:
  - DAS score (change from 6 - 18 months when sequence of drug was changed)
  - HAQ score (change from 6 - 18 months when sequence of drug was changed)
  - Ritchie Articular Index (change from 6 - 18 months when sequence of drug was changed)
  - Swollen joint count (change from 6 - 18 months when sequence of drug was changed)
  - Pain, VAS (change from 6 - 18 months when sequence of drug was changed)
  - Patient's and physician's global assessment (change from 6 - 18 months when sequence of drug was changed)
  - ESR (change from 6 - 18 months when sequence of drug was changed)
  - CRP level (change from 6 - 18 months when sequence of drug was changed)
  - ACR20, ACR50 and ACR70 (change from 6 - 18 months when sequence of drug was changed)
  - Total Sharp score, total erosions (hands and feet) and JSN (change from 6 - 18 months when sequence of drug was changed)

- SSZ then MTX was similar to continuous SSZ for:
  - % of patients with EULAR good response (5% and 7% respectively) at 18 months
  - % of patients with EULAR remission (3% and 5% respectively) at 18 months
  - Number of withdrawals (30% and 25% respectively)
  - Number of withdrawals due to AEs (26% and 18% respectively)
  - Number of withdrawals due to lack of efficacy (7% and 4% respectively)

Reference	Study type	Number of	Patient	Intervention	Comparison	Length of	Outcome	Source

	Evidence level	patients	characteristics			follow-up	measures	of funding
E. H. Choy, C. Smith, C. J. Dore, and D. L. Scott. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology* 44 (11):1414-1421, 2005. ID 248	MA: 1++ RCT's of MA: 1+ to 1++ SR included: N=36 trials (N=1867) MA included: N=36 trials (N=1867) Trials were similar in terms of: • Study design (All RCTs/quasi-randomised CTs) • Intervention (DMARD) • Comparison group (combination therapy with 2 or more DMARDs or 1 DMARD + 1 biological agent) • Blinding (double blind assessment was performed) • Allocation concealment • ITT analysis was performed • Study size (all fairly small, N <100) Trials differed with respect to: • Study size (range N=11 to N=89) • Study quality – max Jadad score of 5 (N=30 studies good quality; N=6 poor quality) • Study duration – variable, (exact lengths not mentioned) Tests for heterogeneity and quality assessment performed.	Total N=1867.	**Inclusion criteria**: RCTs or quasi-randomised CTs; confirmed diagnosis of RA (ARA or ACR criteria); established RA (>3years) or early RA (<3 years); DMARDs or biologicals were those currently used in routine clinical practice; publications written in English. Search was from 1975 – 2004 (April). **Exclusion criteria**: inadequate concealment; not double blind assessment; not ITT analysis.	DMARD monotherapy	DMARD combination therapy (2 or more DMARDs or1 DMARD + 1 biological agent)	Not mentioned	**Primary endpoint for efficacy:** Patients withdrawn due to lack of efficacy **Secondary endpoints for efficacy:** number of patients who achieved ACR20 response; major clinical response (ACR70 or remission); number of patients withdrawn due to AEs.	No external sources of funding.

Effect size

NOTE: There was a moderate but NS degree of heterogeneity between the trials; further analysis showed that the combination of DMARDs involved was the main contributor to this.

EFFICACY

- Combining MTX with a-TNF inhibitors was significantly more effective than MTX monotherapy (RR 0.22, 95% CI 0.14 to 0.32; p=0.00001)
- MTX + SSZ and/or a-malarials was a common combination and was significantly more effective than monotherapy (8 studies: RR 0.41, 95% CI 0.24 to 0.7; p=0.00001)
- CS added to single DMARD as bridging therapy was NS different to monotherapy (7 studies)
- Other non-biological DMARD combinations were significantly more effective than monotherapy (RR 0.37, 95% CI 0.25 to 0.51; p=0.00001)

ESTABLISHED AND EARLY RA

- Combination therapy was significantly more effective than monotherapy in established RA (RR 0.31, 95% CI 0.24 to 0.4; p=0.00001) even after removing studies involving TNF inhibitors (RR 0.4, 95% CI 0.28 to 0.56; p=0.00001)
- Combination therapy was significantly more effective than monotherapy in early RA (9 studies: RR 0.56, 95% CI 0.35 to 0.91; p=0.02)

TRIAL DESIGN

- Combination therapy was significantly more effective in parallel (RR 0.45, 95% CI 0.32 to 0.62; p=0.02), step-up (RR 0.28, 95% CI 0.2 to 0.4; p=0.00001) designed trials and step-down trials (RR 0.32, 95% CI 0.16 to 0.62; p=0.001)

TRIAL QUALITY

- When poor quality studies were removed, combination therapy was still significantly more effective than monotherapy (RR 0.31, 95% CI 0.24 to 0.41; p<0.05)

DOUBLE and TRIPLE THERAPY

- Combination therapy with 2 therapies was significantly more effective than monotherapy (RR 0.35, 95% CI 0.27 to 0.44; p=0.00001)

OTHER OUTCOMES

- Combination therapy was significantly more effective than monotherapy for patient withdrawals (18 studies: p values not given)
- Combination therapy was significantly more effective than monotherapy for ACR20 response (18 studies: p values not given)
- Combination therapy was more effective than monotherapy for major clinical improvement (14 studies: data not given)
- Combination therapy was more effective than monotherapy for reduction in joint counts (Effect size 1.12 vs 0.85 – 31% benefit favouring combination)
- Combination therapy was worse than monotherapy for withdrawals due to toxicity (RR 1.37, 95% CI 1.16 to 1.62; p=0.0001)
- There was NS difference between monotherapy and combining MTX with SSZ or a-malarials or both
- Combination therapy was significantly better than monotherapy for withdrawals due to lack of efficacy (RR 0.89, 95% CI 0.80 to 0.99; p=0.033)

Author's conclusions:
DMARD combinations vary in their efficacy/toxicity ratio. MTX + SSZ or a-malarials and MTX + TNF inhibitors have particularly favourable benefit/risk ratios.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Y. P. M. Goekoop-Ruiterman, J. K. De Vries-Bouwstra, C. F. Allaart, Zeben D. van, P. J. S. M. Kerstens, J. M. W. Hazes, A. H. Zwinderman, H. K. Ronday, K. H. Han, M. L. Westedt, A. H. Gerards, J. H. L. M. Van Groenendael, W. F. Lems, M. V. Van Krugten, F. C. Breedveld, and B. A. C. Dijkmans. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the best study): A	RCT: 1+ Multicentre trial 20 centres in The Netherlands (BEST study). • Randomised (variable block sizes, stratified by centre) • Allocation concealment • Single blind • Not true ITT analysis • Power study (D-HAQ)	Total N=508 randomised (N=126 sequential monotherapy group 1; N=121 step-up combination therapy group 2; N=133 initial combination therapy with CS group 3; N=128 initial combination therapy with infliximab). **Drop-outs:** Group 1: 3% Group 2: 5% Group 3: 4% Group 4: 1.5%	**Inclusion criteria:** Adults ≥ 18 years with early RA (ACR criteria); disease duration ≤2 years; active disease. **Exclusion criteria:** Previous treatment with DMARDs other than anti-malarials; concomitant treatment with an experimental drug; malignancy within the last 5 years; serious disease; serious or opportunistic infections within last 3 and 6 months; known allergy to murine proteins.. **Baseline characteristics:** Group 1: mean age 54 years; Female 68%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. Group 2: mean age 54 years; Female 71%; Duration of RA = Early RA (mean 26 weeks);	Group 1: sequential monotherapy Group 2: step-up combination therapy Group 3: initial combination therapy with CS Group 4: initial combination therapy with infliximab For all groups the protocol described a number of subsequent treatment steps for patients whose medication failed. The decision whether to adjust medication was made every 3 months based on the DAS44 score. Gp1: started 15 mg/week MTX, increased to 25-30 mg/week if DAS44 >2.4. Subsequent steps for insufficient response: SSZ monotherapy, leflunomide monotherapy, MTX + infliximab, gold + methylprednisolone and finally MTX + CyA and prednisolone. Gp2: started 15 mg/week MTX, increased to 25-30 mg/week if DAS44 >2.4. Subsequent steps for insufficient response: add SSZ, followed by add HCQ then prednisolone. If failed to respond to combination of these 4 they were switched to MTX + infliximab, MTX + CyA + prednisolone and finally to leflunomide. Gp3: started 7.5 mg/week MTX + 2000 mg/day SSZ and 60 mg/day prednisolone (pred was tapered in 7 weeks to 7.5 mg/day). If DAS44 >2.4 MTX was augmented to 25-30 mg/week .Subsequent steps for insufficient response: combination was replaced by combination of MTX	1 year of treatment (assessments every 3 months).	D-HAQ score; joint damage (modified Sharp/Van der Heijde score, SHS – total, erosion score and joint space narrowing score; ACR 20, 50 and 70; clinical remission (DAS44 of <1.6); Smallest detectable difference (SDD for several scores; ESR; AEs.	Dutch College of Health Insurances; grant from Schering-Plough BV and Centocor Inc., The Netherlands.

randomized, controlled trial. *Arthritis & Rheumatism* 52 (11):3381-3390, 2005. REF ID: 2186			D-HAQ score mean 1.4. Group 3: mean age 55 years; Female 65%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. Group 4: mean age 54 years; Female 66%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. There was NS difference between the groups for any of the baseline characteristics. Concomitant treatment with NSAIDs and IA corticosteroid injections were allowed.	+ CyA + prednisolone, followed by MTX + infliximab, leflunomide monotherapy, gold + methylprednisolone and finally by AZA + prednisolone. If persistent good response (DAS44 ≤2.4), first prednisolone was tapered to 0 after 38 weeks, then mTX tapered to after 40 weeks. Gp4: started 25-30 mg/week MTX + infliximab 3mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter. If DAS44 >2.4, dose of infliximab increased after 3 months to 6 mg/kg/every 8 weeks. Every 8 weeks dose was reassessed and adjusted if DAS44 >2.4, to 7.5 mg/kg/every 8 weeks and finally every 10 mg/kg/every 8 weeks. If still had DAS44 >2.4 while on MTX + 10 mg/kg infliximab, medication was switched to SSZ, then to leflunomide, then to combination of MTX, CyA and prednisolone then to gold + prednisolone and finally to AZA + prednisolone. If persistent good response (DAS44 ≤2.4 for at least 6 months), infliximab dose was reduced (from 10 to 7.5, 6 then 3 mg/kg) every next infusion until stopped.			

Effect size

Group 1: sequential monotherapy
Group 2: step-up combination therapy
Group 3: initial combination therapy with CS
Group 4: initial combination therapy with infliximab

- Clinical improvement (ACR response criteria) was achieved earlier and by more patients in Groups 3 and 4 than Groups 1 and 2
- The number of patients without progression of radiographic joint damage was higher in groups 3 and 4 than Groups 1 and 2
- Progression of radiographic joint damage was less in groups 3 and 4 than Groups 1 and 2

GROUP 1 vs GROUP 2

- Group 2 was significantly better than Group 1 for:
    - Number of patients reaching DAS44 of ≤2.4 at 1 year (p=0.004)

- There was NS difference between Group 2 and Group 1 for:
    - D-HAQ at 1 year (values not given)
    - Total SHS at 1 year
    - Number of patients with no progression of total SHS (> SDD) at 1 year
    - Number of patients with improvement of total SHS (> SDD) at 1 year
    - Erosion score at 1 year
    - JSN score at 1 year
    - Number of patients with ≥1 AEs
    - Number of patients with SAEs

GROUP 1 vs GROUP 3

- Group 3 was significantly better than Group 1 for:
    - D-HAQ at 1 year (values not given, p=0.01)
    - Total SHS at 1 year (p=0.003)
    - Number of patients with no progression of total SHS (> SDD) at 1 year (p<0.001)
    - Erosion score at 1 year (p<0.05)
    - JSN score at 1 year (MD 1.0, p<0.05)

- There was NS difference between Group 1 and Group 3 for:
    - Number of patients reaching DAS44 of ≤2.4 at 1 year
    - Number of patients with improvement of total SHS (> SDD) at 1 year

- Number of patients with ≥1 AEs
- Number of patients with SAEs

GROUP 1 vs GROUP 4

- Group 4 was significantly better than Group 1 for:
  - Number of patients reaching DAS44 of ≤2.4 at 1 year (≤74% vs 53%, p=0.001)
  - D-HAQ at 1 year (values not given, p=0.01)
  - Total SHS at 1 year (p=0.003)
  - Number of patients with no progression of total SHS (> SDD) at 1 year (p<0.001)
  - Erosion score at 1 year (p<0.05)
  - JSN score at 1 year (MD 1.0, p<0.05)

- There was NS difference between Group 1 and Group 4 for:
  - Number of patients with improvement of total SHS (> SDD) at 1 year
  - Number of patients with ≥1 AEs
  - Number of patients with SAEs

GROUP 2 vs GROUP 3

- Group 3 was significantly better than Group 2 for:
  - Total SHS at 1 year (p=0.007)
  - Number of patients with no progression of total SHS (> SDD) at 1 year (p=0.01)
  - Erosion score at 1 year (p<0.05)

- There was NS difference between Group 3 and Group 2 for:
  - Number of patients reaching DAS44 of ≤2.4 at 1 year
  - D-HAQ at 1 year
  - Number of patients with improvement of total SHS (> SDD) at 1 year
  - JSN score at 1 year
  - Number of patients with ≥1 AEs
  - Number of patients with SAEs

GROUP 2 vs GROUP 4

- Group 4 was significantly better than Group 2 for:
  - Total SHS at 1 year (93% vs 73%, p<0.001)
  - Number of patients with no progression of total SHS (> SDD) at 1 year (p<0.001)
  - Number of patients with improvement of total SHS (> SDD) at 1 year (p=0.001)

- Erosion score at 1 year (p<0.05)
- JSN score at 1 year (MD 0, p<0.05)

- There was NS difference between Group 4 and Group 5 for:
  - Number of patients reaching DAS44 of ≤2.4 at 1 year
  - D-HAQ at 1 year
  - Number of patients with ≥1 AEs
  - Number of patients with SAEs

GROUP 3 vs GROUP 4

- Group 3 was significantly better than Group 4 for:
  - Number of patients with improvement of total SHS (> SDD) at 1 year (p=0.028)

- There was NS difference between Group 3 and Group 4 for:
  - Number of patients reaching DAS44 of ≤2.4 at 1 year
  - D-HAQ at 1 year
  - Total SHS at 1 year
  - Number of patients with no progression of total SHS (> SDD) at 1 year
  - Erosion score at 1 year
  - JSN score at 1 year
  - Number of patients with ≥1 AEs
  - Number of patients with SAEs

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
C. F. Allaart, Y. P. Goekoop-Ruiterman, J. K. De Vries-Bouwstra, F. C. Breedveld, B. A. Dijkmans, and FARR study group. Aiming at low disease	RCT: 1+ Multicentre trial 20 centres in The Netherlands (BEST study). • Randomised (variable block sizes, stratified by centre) • Allocation	Total N=508 randomised (N=126 sequential monotherapy group 1; N=121 step-up combination therapy group 2; N=133 initial	As for ID 2186	As for ID 2186	2 years of treatment (assessments every 3 months).	D-HAQ score; joint damage (modified Sharp/Van der Heijde score, SHS – total, erosion score and joint space narrowing	Not mentioned

activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. *Clinical & Experimental Rheumatology* 24 (6 suppl 43):1-77, 2006. REF ID: 6	concealment • Single blind • Not true ITT analysis • Power study (D-HAQ)	combination therapy with CS group 3; N=128 initial combination therapy with infliximab). **Drop-outs at 2 years:** Not mentioned				score; ACR 20, 50 and 70; clinical remission (DAS44 of <2.4); Smallest detectable difference (SDD); ESR; AEs.	

Effect size

Group 1: sequential monotherapy
Group 2: step-up combination therapy
Group 3: initial combination therapy with CS
Group 4: initial combination therapy with infliximab

- More patients in Group 1 and Group 2 changed from the initial treatment step to subsequent therapy adjustments than in Group 3 and Group 4
- More patients in Group 3 and Group 4 were able to taper and discontinue drugs of the initial combination therapy because of continuous low disease activity.
- At the end of 2 years 33% of patients in group 1 and 31% of patients in group 2 were still treated with monotherapy (MTX) as initially started, compared to 36% in group 3 and 54% in group 4 who were able to taper their treatment to monotherapy (SSA in group 3 and MTX in group 4).
- N=77 (67%) of patients in Group 4 were able to discontinue initial infliximab (IFX) because of DAS ≤2.4 for ≥6 months. N=10 of these patients experienced flare after discontinuation however the remaining N=67 patients had continuous DAS ≤2.4 after discontinuation of IFX and were also able to taper MTX to maintenance dose.
- In patients who had continuous good response (DAS ≤ 2.4) on MTX monotherapy and those who had failed on MTX monotherapy: 32% were initial MTX responders. After 2 years SHS progression was significantly lower in initial MTX responders compared to initial MTX failures, p=0.008.
- Patients with continuous clinical remission to initial therapy (DAS <1.6 from 6 months to 2 years) – continuous remission occurred significantly (twice) more often in patients who started with initial combination therapy with either prednisolone or infliximab than in patients who started with initial monotherapy (p=0.034).
- Of patients who achieved continuous remission after initial monotherapy, 25% still had joint damage progression (SHS progression >SDD) compared to 3% of patients who achieved continuous remission after initial combination therapy.
- NS differences were seen in % of patients with continuous failure, but patients with continuous failure in groups 3 and 4 (initial combination therapy) had significantly more improvement in functional ability (HAQ AUC) than patients with continuous failure in groups 1 and 2 (sequential monotherapy and step-up therapy), p=0.037.
- Linear regression analyses showed that after adjusting for baseline characteristics, RF status and a-CCP status for all groups except for Group 1 where positive RF abd a-CCp were significantly associated with SHS progression.

GROUP 1 vs GROUP 2

- There was NS difference between Group 2 and Group 1 for:
    - D-HAQ at 2 years
    - Total SHS at 2 years
    - Erosion score at 2 years
    - JSN score at 2 years
    - Number of patients reaching DAS44 of ≤2.4 at 2 years
    - Number of patients with AEs
    - Number of patients with SAEs

GROUP 1 vs GROUP 3

- Group 3 was significantly better than Group 1 for:
    - Total SHS at 2 years (median difference 6.4, p<0.001)
    - Erosion score at 2 years (median difference, 1.0, p<0.001)

- There was NS difference between Group 1 and Group 3 for:
    - Number of patients reaching DAS44 of ≤2.4 at 2 years
    - D-HAQ at 2 years
    - JSN score at 2 years
    - Number of patients with AEs
    - Number of patients with SAEs

GROUP 1 vs GROUP 4

- Group 4 was significantly better than Group 1 for:
    - Total SHS at 2 years (median difference 6.5, p<0.001)
    - Erosion score at 2 years (median difference 1.0, p<0.001)

- There was NS difference between Group 1 and Group 4 for:
    - D-HAQ at 2 years
    - JSN score at 2 years
    - Number of patients reaching DAS44 of ≤2.4 at 2 years
    - Number of patients with AEs
    - Number of patients with SAEs

GROUP 2 vs GROUP 3

- Group 3 was significantly better than Group 2 for:
    - Total SHS at 2 years (median difference 1.0, p<0.001)
    - Erosion score at 2 years (median difference 0.5, p<0.001)

- There was NS difference between Group 3 and Group 2 for:
    - Number of patients reaching DAS44 of ≤2.4 at 2 years
    - D-HAQ at 2 years
    - JSN score at 2 years
    - Number of patients with AEs
    - Number of patients with SAEs

GROUP 2 vs GROUP 4

- Group 4 was significantly better than Group 2 for:
  - Total SHS at 2 years (median difference 1.0, p<0.001)
  - Erosion score at 2 years (median difference 0.5, p<0.001)

- There was NS difference between Group 4 and Group 2 for:
  - Number of patients reaching DAS44 of ≤2.4 at 2 years
  - D-HAQ at 2 years
  - JSN score at 2 years
  - Number of patients with AEs
  - Number of patients with SAEs

GROUP 3 vs GROUP 4

- There was NS difference between Group 3 and Group 4 for:
  - Number of patients reaching DAS44 of ≤2.4 at 2 years
  - D-HAQ at 2 years
  - Total SHS at 2 years
  - Erosion score at 2 years
  - JSN score at 2 years
  - Number of patients with AEs at 2 years
  - Number of patients with SAEs at 2 years

Author's conclusions: Treatment is the main determinant of disease outcome – all patients are likely to benefit more from initial combination therapy than from initial monotherapy with MTX. In patients with early active RA, clinical improvement and suppression of joint damage progression can be achieved with frequent, objectively steered treatment adjustments. The best chance for an early clinical and radiologic response lies with initial combination treatment with either MTX, SSZ and prednisolone or with MTX and infliximab, which can be tapered to DMARD monotherapy once low disease activity is achieved.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Y. P. Goekoop-Ruiterman, Bouwstra J. K. de Vries, C. F. Allaart, D. Van Zeben, P. J. Kerstens, J.	RCT: 1+ Multicentre trial 20 centres in The Netherlands (BEST study). • Randomised (variable	Total N=508 randomised (N=126 sequential monotherapy group 1; N=121 step-up	As for ID 2186	As for ID 2186	2 years of treatment (assessments every 3 months).	D-HAQ score; joint damage (modified Sharp/Van der Heijde score, SHS – total,	Not mentioned

M. Hazes, A. H. Zwinderman, A. J. Peeters, Bok JM de Jonge, C. Mallee, W. M. de Beus, P. B. de Sonnaville, J. A. Ewals, F. C. Breedveld, and B. A. Dijkmans. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Annals of Internal Medicine* 146 (6):406-415, 2007. REF ID: 14	block sizes, stratified by centre) • Allocation concealment • Single blind • Not true ITT analysis • Power study (D-HAQ)	combination therapy group 2; N=133 initial combination therapy with CS group 3; N=128 initial combination therapy with infliximab). **Drop-outs at 2 years:** Group 1: N=6 (5%) Group 2: N=9 (7%) Group 3: N=8 (6%) Group 4: N=4 (3%)				erosion score and joint space narrowing score; ACR 20, 50 and 70; clinical remission (DAS44 of <2.4); Smallest detectable difference (SDD); ESR; AEs.	

Effect size

Group 1: sequential monotherapy GI: 12%, CV: 4%
Group 2: step-up combination therapy GI: 9%, CV: 4%
Group 3: initial combination therapy with CS GI: 9%, CV: 7%
Group 4: initial combination therapy with infliximab GI: 12%, CV: 6%

GROUP 1 vs GROUP 2

- Group 2 was significantly better than Group 1 for:
  - SHS score (radiographic progression) over time (values not given, p=0.044)

- Group 2 was similar to Group 1 for:
  - Number of withdrawals (7% and 5% respectively)
  - Number of patients with GI AEs (9% and 12% respectively)
  - Number of patients with CV AEs (both: 4%)

- There was NS difference between Group 2 and Group 1 for:
  - HAQ score over time

GROUP 1 vs GROUP 3

- Group 3 was similar to Group 1 for:
  - Number of withdrawals (6% and 5% respectively)
  - Number of patients with GI AEs (9% and 12% respectively)
  - Number of patients with CV AEs (7% and 4% respectively)

- Group 3 was significantly better than Group 1 for:
  - HAQ score over time ($p<0.001$)
  - SHS score (radiographic progression) over time ($p<0.001$)

GROUP 1 vs GROUP 4

- Group 4 was similar to Group 1 for:
  - Number of withdrawals (6% and 5% respectively)
  - Number of patients with GI AEs (both: 12%)
  - Number of patients with CV AEs (6% and 4% respectively)

- Group 4 was significantly better than Group 1 for:
    - HAQ score over time (p<0.001)
    - SHS score (radiographic progression) over time (p<0.001)

GROUP 2 vs GROUP 3

- Group 3 was similar to Group 2 for:
    - Number of withdrawals (7% and 6% respectively)
    - Number of patients with GI AEs (both: 9%)
    - Number of patients with CV AEs (7% and 4% respectively)

- Group 3 was significantly better than Group 2 for:
    - HAQ score over time (p<0.001)
    - SHS score (radiographic progression) over time (values not given, p<0.001)

GROUP 2 vs GROUP 4

- Group 4 was similar to Group 2 for:
    - Number of withdrawals (3% and 7% respectively)
    - Number of patients with GI AEs (12% and 9% respectively)
    - Number of patients with CV AEs (6% and 4% respectively)

- Group 4 was significantly better than Group 2 for:
    - HAQ score over time (p<0.001)
    - SHS score (radiographic progression) over time (values not given, p<0.001)

GROUP 3 vs GROUP 4

- Group 4 was similar to Group 3 for:
    - Number of withdrawals (3% and 6% respectively)
    - SHS score (radiographic progression) over time (values not given)
    - Number of patients with GI AEs (12% and 9% respectively)
    - Number of patients with CV AEs (6% and 7% respectively)

- Group 4 was significantly better than Group 3 for:
    - HAQ score over time (p<0.001)

Reference	Study type	Number of	Patient characteristics	Intervention and	Length of	Outcome	Source

	Evidence level	patients		Comparison	follow-up	measures	of funding
S. M. van der Kooij, J. K. De Vries-Bouwstra, Y. P. Goekoop-Ruiterman, Zeben D. van, P. J. Kerstens, A. H. Gerards, J. H. van Groenendael, J. M. Hazes, F. C. Breedveld, C. F. Allaart, and B. A. Dijkmans. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Annals of the Rheumatic Diseases* 66 (10):1356-1362, 2007.	RCT: 1+ Multicentre trial 20 centres in The Netherlands (BEST study). • Randomised (variable block sizes, stratified by centre) • Allocation concealment • Single blind • Not true ITT analysis • Power study (D-HAQ)	Total N=508 randomised (N=126 sequential monotherapy group 1; N=121 step-up combination therapy group 2; N=133 initial combination therapy with CS group 3; N=128 initial combination therapy with infliximab). **Drop-outs at 2 years:** Group 1: N=6 (5%) Group 2: N=9 (7%)	**Inclusion criteria:** Adults ≥ 18 years with early RA (ACR criteria); disease duration ≤2 years; active disease. **Exclusion criteria:** Previous treatment with DMARDs other than anti-malarials; concomitant treatment with an experimental drug; malignancy within the last 5 years; serious disease; serious or opportunistic infections within last 3 and 6 months; known allergy to murine proteins.. **Baseline characteristics:** Group 1: mean age 54 years; Female 68%; Duration of RA = Early RA (mean 23 weeks); D-HAQ score mean 1.4. Group 2: mean age 54 years; Female 71%; Duration of RA = Early RA (mean 26 weeks); D-HAQ score mean 1.4. There were significant differences between the 'MTX successes' and MTX failures' groups for baseline characteristics. Concomitant treatment with NSAIDs and IA corticosteroid injections were allowed.	MTX successes and failures in groups 1 and 2 SSZ successes and failures in groups 1 and 2 MTX successes (DAS<2.4) and MTX failures (DAS>2.4); Group 1: sequential monotherapy Group 2: step-up combination therapy For all groups the protocol described a number of subsequent treatment steps for patients whose medication failed. The decision whether to adjust medication was made every 3 months based on the DAS44 score. MTX failures: In group 1 these switched to SSZ then leflunomide and finally to MTX + IFX. In group 2 these added SSZ to MTX then HCQ, then prednisolone and eventually switched to MTX + IFX. MTX successes: patients who achieved DAS≤2.4 after 2 years while still on mMTX monotherapy.	2 years of treatment (assessments every 3 months).	Progression (Sharp/Van der Heijde score, SHS – total score, TSS) from years 0-2 in MTX failures vs MTX successes.	Dutch College of Health Insurance Companies; Schering-Plough and Centocor.

REF ID: 3049							

Effect size

NOTE: There were significant differences between the 'MTX successes' and MTX failures' groups for baseline characteristics. Higher DAS at baseline and female gender were predictors for 'MTX failures'

MTX SUCCESSES

- 21% of patients achieved DAS ≤2.4 on MTX 15 mg/week after 3 months; 44% on MTX 15-25 mg/week after 6 months. After 2 years 32% were MTX successes (DAS ≤2.4 while still on MTX monotherapy).
- After 2 years 66% of patients had discontinued MTX.
- Significantly more MTX failures than MTX successes received IA steroids at least once, 34% and 20% respectively, p=0.029 (but there was NS difference between Groups 1 and 2)
- After 2 years 'MTX successes' showed significantly less TSS progression than 'MTX failures' regardless of the success of subsequent treatment steps. There was NS difference in TSS progression between groups 1 and 2 in 'MTX failures' nor between patients in 'MTX successes' who remained on MTX <15 mg/week and those on 25 mg/week.

SSZ SUCCESSES

- During 2 years of follow-up, 85% of 'MTX' failures proceeded to SSZ; 22% in group 1 achieved DAS <2.4 on SSZ monotherapy (successes); 22% in group 2 achieved sustained DAS <2.4 by adding SSZ to MTX.
- In both groups 1 and 2 'SSZ failures' had significantly higher DAS, higher HAQ and more tender joints at the start of SSZ treatment and comprised more females than 'SSZ successes'. Female gender and higher DAS were significant predictors of 'SSZ failure'.

SUCCESS ON STEP 3

- During 2 years of follow-up, N=98 'SSZ failures' proceeded to the next treatment step. 13% of those in group 1 achieved DAS <2.4 on LEF monotherapy, 87% discontinued LEF. 36% in group 2 achieved sustained DAS <2.4 by adding HCQ to MTX + SSZ. 64% failed on HCQ + SSZ + MTX.
- Significantly more patients achieved DAS <2.4 on HCQ + SSZ + MTX than LEF (p=0.028).
- Prednisolone was added to the treatment of 24 failures on HCQ + SSZ + MTX. 50% of these achieved DAS <2.4 with HCQ + SSZ + MTX + prednisolone abd te other 50-% retained DAS >2.4, 83% of these proceeded to treatment with MTX + IFX.
- After 2 years, 59% of all patients achieved DAS <2.4 with conventional therapy, 20% proceeded to MTX + IFX and subsequent treatment steps, 9% were treated outside the protocol and 12% dropped out/had missing DAS.

SUCCESS ON MTX + IFX

- During 2 years, n=48 failures on ≥3 DMARDs (N=38 from group 1 and N=10 from group 2) proceeded to MTX + IFX. 71% of these achieved DAS <2.4 on IFX and began tapering IFX to zero. N=14 discontinued IFX.

AUTHORS' CONCLUSIONS: 44% of patients achieved DAS ≤2.4 on MTX after 6 months and after 2 years 33% still exhibited sufficient clinical response on MTX monotherapy. After failure on MTX, consecutive treatments steps with other conventional DMARDs in monotherapy or an add-on setting seldom resulted in a DAS ≤2.4.

Patients who do not achieve and maintain DAS ≤2.4 with MTX, regardless of the success of consecutive treatment steps, developsignificantly more radiographic joint damage compared to patients with DAS ≤2.4 on initial MTX(MD 6 units of TSS, p=0.007). To what account this damage progression may be caused by ineffective MTX therapy in the first 6 months is speculative. However, overall it seems that adequate, early suppression of disease activity is paramount for the suppression of joint damage progression. Patients show improved outcomes if treatment is adjusted to achieve low disease activity by monitoring of the DAS.

After 2 years, 66% of patients had discontinued MTX because of insufficient response or toxicity. Of these, 78% also failed on SSZ (adding or switching), 87% subsequently failed on LEF (in group 1) and 64% on MTX + SSZ + HCQ (in group 2). 71% in groups 1 and 2 were successfully treated with MTX + IFX. After 2 years, regardless of the 'success' on subsequent DMARDs, 'MTX failures' had a significantly higher TSS progression than 'MTX successes'.

SUMMARY: After failure on initial MTX, treatment with subsequent conventional DMARDs is unlikely to result in a DAS≤2.4 and allows progression of joint damage.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
G. F. Ferraccioli, E. Gremese, P. Tomietto, G. Favret, R. Damato, and Poi E. Di. Analysis of improvements, full responses, remission and toxicity in rheumatoid patients treated with step-up combination therapy (methotrexate, cyclosporin A, sulphasalazine) or monotherapy for three years. *Rheumatology* 41 (8):892-898,	RCT: 1+ Single centre trial in Italy. • Randomised (method not mentioned) • Unblinded • ITT analysis • Power study (ACR50) • Fairly high drop-outs for SSZ group	Total N=126 randomised (N=42 randomised to each of 3 groups). **Drop-outs/lost to follow-up:** MTX: 12% CsA: 17% SSZ: 48%	**Inclusion criteria:** Age 17-70 years; RA (ACR criteria); all patients had already been on DMARDs (anti-malarials for at least 4 months and most were receiving prednisolone as a previous DMARD); active disease and at least 1 erosion on X-rays of hands and feet. **Exclusion criteria:** comorbidities that might preclude any of the therapeutic approaches; previous treatment with immune suppressants; psychiatric or neurological disease; hypertension under treatment. **Baseline characteristics:** MTX group 1: mean age 59 years; Female 86%; Duration of RA = Early RA (1.2 years); Pain (VAS) mean 6.1 CsA group 2: mean age 54 years;	Patients had already been on DMARDs (anti-malarials for at least 4 months and most were receiving prednisolone as a previous DMARD) Patients were then randomised to 3 groups: MTX, CsA or SSZ. Patients in groups 1 and 2 if showed no ACR50 clinical improvement at 6 months were put onto combination therapy (CsA + MTX) and if no ACR50 at 12 months were given SSZ. Group 1: MTX 10 mg/week, dose increased after 8 weeks by 5 mg/month up to 20 mg/week. Group 2: CsA 3 mg/kg/day with possible increase after 12 weeks, up to 5 mg/kg/day, according to clinical response. Group 3: SSZ starting at 1 g/day		18 months (end of treatment) with assessments every 6 months. Follow-up at 36 months. Also assessed at 3 years (after 2 months of stopping all treatment except NSAIDs)	Full response (Magnusson criteria: no steroids + fulfilment of 4 of the following 6 criteria – morning stiffness <30 mins, no fatigue, no joint pain, no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, ESR <30 mm/h in women and <20 mm/hr on men whilst on DMARDs and/or full remission according to	Grants from the Arthritis Research Council, UK. Drugs supplied by Wyeth and Pharmacia.

2002. ID 3021			Female 83%; Duration of RA = Early RA (1.0 years); Pain (VAS) mean 5.9 SSZ group 3: mean age 59 years; Female 86%; Duration of RA = Early RA (2.0 years); Pain (VAS) mean 6.3 Both groups were similar for all baseline characteristics.	and increased by 500 mg/week for 5 weeks to reach 3 g/day. **Concomitant NSAIDs/other treatment**: NSAIDs and paracetamol were allowed concurrently.		ACR criteria); ACR20, ACR50 and ACR70; Swollen and tender joint count; Pain (VAS); Patient's and Physician's global assessment; ESR; CRP levels; AEs.	

Effect size

SEQUENCES: Group 1 = DMARD then add MTX
Group 2 = DMARD then add CsA
Group 3 = DMARD then add SSZ

DMARD then DMARD + MTX vs. DMARD then DMARD + SSZ

- DMARD then DMARD + MTX was significantly better than DMARD then DMARD + SSZ for:
  - Swollen joint count at 18 months, (MD 2.6, p=0.04)
  - Tender joint count at 18 months, (MD 3.6, p=0.001) and between 18 and 36 months, (MD 1.1, p=0.02)
  - Patient's and Physician's global assessment at 18 months, (MD 2.9 and 2.8, p=0.001)
  - Pain (VAS) at 18 months, p=0.001 and between 18 and 36 months, (MD 1.9, p=0.001)
  - ESR at 18 months, (MD 30.2, p=0.01) and between 18 and 36 months, (MD 5.5, p=0.02)
  - CRP at 18 months, (MD 11.2, p=0.001) and between 18 and 36 months,(MD 0.9, p=0.001)
  - Withdrawals due to toxicity (7% and 48% respectively), p=0.0001

- DMARD then DMARD + MTX was the better than as DMARD then DMARD + SSZ for:
  - Number of patients with persistence of Magnusson criteria (full response): 40% and 21% respectively at 3 years (2 months after treatment cessation)
  - Number of drop-outs/lost to follow-up (12% and 48% respectively) at 18 months

- There was NS difference between DMARD then DMARD + MTX and DMARD then DMARD + SSZ for:
  - Swollen joint count between 18 and 36 months
  - Patient's and Physician's global assessment between 18 and 36 months
  - Number of patients with AEs at 18 month

- DMARD then DMARD + MTX was similar to DMARD then DMARD + SSZ for:
  - Number of patients in full remission (ACR criteria): 9% and 7% respectively at 3 years (2 months after treatment cessation)

- DMARD then DMARD + MTX was worse than DMARD then DMARD + SSZ for:
  - Number of patients with AEs at 36 months (88% and 47% respectively)

DMARD then DMARD + CsA vs. DMARD then DMARD + SSZ

- DMARD then DMARD + CsA was significantly better than DMARD then DMARD + SSZ for:
  - Tender joint count at 18 months, (MD 3.5, p=0.001)
  - Pain (VAS) at 18 months, (MD 2.1, p=0.001)
  - Patient's and Physician's global assessment at 18 months, (MD 1.5 and 2.7, p=0.001)
  - CRP between 18 and 36 months, (MD 8.1, p=0.03)

- Withdrawals due to toxicity (12% and 48% respectively), p=0.0001

- DMARD then DMARD + CsA was the better than as DMARD then DMARD + SSZ for:
  - Number of patients with persistence of Magnusson criteria (full response): 40% and 21% respectively at 3 years (2 months after treatment cessation)
  - Number of drop-outs/lost to follow-up (17% and 48% respectively) at 18 months

- There was NS difference between DMARD then DMARD + CsA and DMARD then DMARD + SSZ for:
  - Swollen joint count at 18 months and between 18 and 36 months
  - Tender joint count between 18 and 36 months
  - Pain (VAS) between 18 and 36 months
  - Patient's and Physician's global assessment between 18 and 36 months
  - ESR at 18 months between 18 and 36 months
  - CRP at 18 months
  - Number of patients with AEs at 18 months

- DMARD then DMARD + CsA was similar to DMARD then DMARD + SSZ for:
  - Number of patients in full remission (ACR criteria): 9% and 7% respectively at 3 years (2 months after treatment cessation)

- DMARD then DMARD + CsA was worse than DMARD then DMARD + SSZ for:
  - Number of patients with AEs at 36 months (95% and 47% respectively)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. L. Hider, A. Silman, D. Bunn, S. Manning, D. Symmons, and M. Lunt. Comparing the long-term clinical outcome of treatment with methotrexate or sulfasalazine prescribed as the first disease-modifying antirheumatic	Cohort study (prospective): 2+ Patients recruited from the Norfolk Arthritis register (NOAR) – a primary care-based group of patients with early inflammatory	Total N=439 (N=108 MTX; N=331 SSZ). **Drop-outs at 2 years** MTX: 21% SSZ: 22% **5 years** MTX: 20% SSZ: 18%	**Inclusion criteria:** Adults age ≥16 years with swelling of 2 or more joints lasting at least 4 weeks is notified by GP to NOAR. Between 1990 and 1999 2659 patients recruited by NOAR and had baseline assessment within 2 weeks of receiving notification. Some patients would have been on DMARD treatment before notification. This study is restricted to patients on MTX or SSZ as their 1st DMARD within 3 months of their baseline visit and had been followed up for at least 2 years.	MTX (1st DMARD) 7.5 mg/week	SSZ (1st DMARD) 2 g/day	2 years and 5 years	Swollen and tender joint count; DAS28; HAQ; erosions; radiographic damages (Larsen score); remission (no swollen or tender joints in patients not currently taking DMARDs); proportion of patients still on	Arthritis Research Campaign, UK.

drug in patients with inflammatory polyarthritis. *Annals of the Rheumatic Diseases* 65 (11):1449-1455, 2006. REF ID: 3052	polyarthritis **NOTE:** higher number of patients in the SSZ group than the MTX group		**Baseline characteristics:** MTX group: median age 58 years; Female 64%; Duration of RA = Early RA (<2 years, mean 5.8 months); HAQ score 1.3. SSZ group: median age 53 years; Female 60%; Duration of RA = Early RA (<2 years, mean 7.1 months); HAQ score 1.3. There were NS differences between the groups for any of the baseline characteristics.				their original treatment; CRP levels.	

Effect size

SEQUENCES: Group 1 = MTX 1st
Group 2 = SSZ 1st

- There was NS difference between the patients starting on SSZ and patients starting on MTX for:
  - Proportion of patients with no change in treatment over the 2 years (50% and 56% respectively);
  - Tender and swollen joint count at 2 years (median difference 2 and 3 respectively)
  - HAQ at 2 years and at 5 years
  - % of patients in remission at 2 years and at 5 years
  - CRP at 5 years
  - DAS28 at 5 years
  - Larsen score at 5 years
  - % of patients with erosions

- Patients starting on SSZ were significantly better than patients starting on MTX for:
  - Number of swollen and tender joints at 5 years (p=0.01 and 0.02 respectively);
  - % of patients with erosions (OR adjusted for propensity)*

Authors' conclusion: Long-term clinical outcome is similar in patients prescribed MTX and SSZ, although it would seem that MTX has greater potential to suppres erosions, which supports it being the first DMARD of choice.

* propensity is the probability of patients in each group receiving MTX rather than SSZ as their first treatment (as this is an observational study, there may have been confounding in allocation between the 2 treatments).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. T. Felson, J. J. Anderson, and R. F. Meenan. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis.	MA: 1- RCT's of MA: not known SR included: N=5 trials (N=749) MA included: N=5 trials (N=749) Trials were similar in terms of: • Study design (All RCTs) • Comparison group (single DMARD)	Total N=749.	Inclusion criteria: RCTs; diagnosis of RA ; adults >18 years; Search was from 1966 – 1992 (December).	Combination of at least 2 full-dose second-line drugs started concurrently (at the MCID).	Single second-lir drug.	Follow-up: range not mentioned.	All components of the ACR core set of outcome measures for RA.	Grant from the NIH.

Arthritis & Rheumatism 37 (10):1487-1491, 1994. ID 1600	• Intervention (combination DMARDs) Trials differed with respect to: • Study size (range N=32 to N=335) • Study duration • Types of DMARDs used Tests for heterogeneity and quality assessment were NOT performed. Basic search – could have been more thorough.							
Effect size **Author's conclusions:** Combination therapy, as it has been used in recent trials, does not offer a substantial improvement in efficacy, but does have higher toxicity than single drug therapy. These combination therapy regimens are not recommended for widespread use. Other more aggressive regimens with additional drugs or higher drug doses than have been studied might be more efficacious, but with an even higher rate of toxicity.								

7.1.14 DMARDs: when to withdraw them (DRUG2)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

M. J. Ahern, N. D. Hall, K. Case, and P. J. Maddison. D-penicillamine withdrawal in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 43 (2):213-217, 1984. ID 447	RCT [5] 1+ • Randomised (method not mentioned) • Single Blind • No mention of ITT analysis, however no dropouts	N=38	Inclusion criteria: 440 consecutive patients with RA on penicillamine for a minimum of 12 months were reviewed. Of these 440 patients only 40 (9%) with definite or classical RA were found to be in remission. These 40 patients were then followed up prospectively for a further 6 months to confirm the presence of remission. At six months 38 patients remained in remission, 2 patients being excluded because of recurrence of active joint disease. Patients were selected because they were in remission for at least 18 months (12 months retrospectively and 6 months prospectively). **Baseline characteristics:** Both groups were closely matched with respect to age, sex, duration, and type of disease, duration of penicillamine therapy, and dosage. NSAIDs and analgesic medications were continued unchanged throughout the study. Disease duration Same dose: 10.9 yrs Reducing dose: 11.6 yrs	GRADUAL DECREASE D-pen Reducing dose N= 19 Drug dose was decreased by 125 mg/month by substituting dummy tablets.	D-pen Same dose N= 19	12 months	Morning stiffness Grip strength patient's and observer's impression on a 5-point scale CRP	Not reported

[5] Remission was defined as the absence of clinically active joint disease. Joints were considered active if they were tender to palpation or at extremes of motion, or if there were soft tissue swelling or effusion. Conversely, we defined relapse as recurrence of active joint disease even if only one
joint became involved.

			Duration of DPA therapy Same dose: 3.7 yrs Reducing dose: 3.3 yrs					

Effect size
Remission
Of the 19 patients continuing the same dose of D-penicillamine (control group) 17 remained in remission (89% vs 21%). Of 19 who reduced dosage 15 flared from 2 to 7 months (mean 3.3) after beginning withdrawal and 4 remained in remission 9 to 12 months after complete withdrawal.

Ten of the 15 patients who flared developed polyarticular synovitis, while
only five had a relapse affecting only one joint.

CRP
The mean CRP level increased in the withdrawal group one month before relapse, but this only became statistically significant one month and 3 months after clinical relapse.

Reintroduction of D-pen
All patients who had a recurrence of disease activity on withdrawal were asked to resume their former dose of penicillamine. Thirteen of the 15 responded to their former dose within 4 months, having achieved a complete clinical remission. Two required an increased dose but eventually responded
to the higher dose.

Drop-outs
None

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Silva M. De and B. L. Hazleman. Long-term azathioprine in rheumatoid arthritis: A double-blind study. *Annals of the Rheumatic Diseases* 40 (6):560-563,	RCT 1+ • Randomised (method not mentioned) • Double blind • No mention of ITT analysis • High	N= 32	Baseline characteristics: the two groups were well matched for age, sex, disease duration, serology, and functional capacity. Most patients required anti-inflammatory agents and analgesics in addition to azathioprine. Twenty-one patients, 12 in the placebo group and 9 in the azathioprine group, had been on a combination of gold and azathioprine. Patients were stabilised on	Azathioprine N= 14	SUDDEN WITHDRAWAL Placebo N= 18	8 months	Day and night pain Morning stiffness Patient's and clinician's general evaluation of the response to	Wellcome research lab

1981. ID 460	number of drop-outs		the minimum effective dosages of their drugs for several months before the study began. Changes only in analgesic requirement were allowed, and these were note. Disease duration (yrs): Placebo: Mean 13.8 Range 5-38 Azathioprine: Mean 18.2 Range 5-50 The mean dose of azathioprine was 2.4 and 2.7 mg/kg/day in the placebo and azathioprine groups respectively. The mean duration of treatment with azathioprine was 6.6 and 6.1 years in the placebo and azathioprine groups respectively.				therapy Articular index (modified Ritchie, ESR Adverse events	

Effect size
Pain score (scale 0-4)

Week	*AZA*	*Placebo*	*p*
0	1.4	1.8	NS
8	1.4	1.8	<0.05
16	1.3	1.9	<0.05
24	0.9	1.9	<0.01
32	1.2	1.9	<0.03

Morning stiffness (minutes)

Week	*AZA*	*Placebo*	*p*
0	43.9	40.0	NS
8	34.3	82.9	NS
16	18.8	100.3	<0.03
24	16.4	70.7	<0.05
32	25.9	100.9	<0.05

Response to therapy
The Patient's and clinician's general evaluation of the response to therapy at the time of withdrawal or at the end of 32 weeks showed that only 1 patient in the azathioprine group deteriorated compared with 12 in the placebo group.

ESR
NS differences observed

Drop-outs
Azathioprine 3/14 (21%)
1 carcinoma of tonsil
1 major surgery (hip replacement)
1 pancytopenia

Placebo 7/18 (39%)
6 clinical deterioration
1 uncontrolled itching

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Gotzsche PC, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang KL, Wangel M, Rydgren L, Halberg P, Juncker P, Andersen V, Hansen TM, and Endahl L. Randomized, placebo controlled trial of withdrawal of slow-acting antirheumatic drugs and of observer bias in rheumatoid arthritis. Scandinavian Journal of Rheumatology: 25: 194 – 199, 1996 REF ID: 169.	RCT 1++ • Withdrawal study • Computer randomisation • Allocation concealment • Double blind • Audited trial	N= 112 **Drop-outs:** 26/112 (23%) at 2 months	**Inclusion criteria:** patients with RA who had been treated with methotrexate, penicillamine, or sulphasalazine during the previous 12 months, insufficient effect of NSAIDs, or who had 3 of the following: ≥6 tender joints, ESR ≥ 20 mm/hr or morning stiffness ≥ 30 minutes. **Exclusion criteria:** patients confined to a bed or wheelchair, patients treated with >1 slow-acting drug, or who are known to be poor compliers. **Baseline characteristics:** Drug group: Age median 61 (IQR 50-70), disease duration median 12 (IQR 7-24), HAQ median 0.8 (IQR 0.3-1.2), Number on methotrexate 26. Placebo group: Age median 62 (IQR 52-70), disease duration median 12 (IQR 7-19), HAQ median 0.8 (IQR 0.4-1.2), Number on methotrexate 27.	Usual drug	SUDDEN WITHDRAWAL Placebo	6 months	Primary outcomes: Treatment failure[6] Patients well-being (5-point scale) Number of tender joints on palpation (Physician assessed) Number of tender joints on palpation (Patient assessed) Secondary outcomes: Activity index (HAQ score) Pain (5 point scale) Number of swollen joints CRP	Danish Arthritis foundation, GEA, Lederle, and Pharmacia
Effect size Treatment failure Significantly more patients on placebo experienced treatment failure [33 (60%) vs. 9 (15.8%); p=0.000001]. The relative risk of treatment failure when patients received placebo compared with drug was 5.2 (95% CI 2.5-11.0). There were significantly better outcomes in the drug vs. placebo group for the following: Patients perception of well being (p=0.002 for the difference between the groups). Decrease in the number of swollen joints from baseline; mean difference 2.2 (SE 1.0; p=0.03).								

[6] Treatment failure was defined as withdrawal irrespective of cause, open treatment with a slow-acting drug, or increase in the dose of prednisolone.

There was no difference between the groups with respect to the following: Decrease in the number of tender joints from baseline; mean difference 2.4 (SE 1.4; p=0.08) Patients evaluation of the number of painful joints; mean difference 3.0 (SE 1.9; p=0.12). Severity of the reported side-effects (p=0.91).								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Rynes RI Bartholomew LE Kremer JM. Severe flare of rheumatoid arthritis after discontinuation of long-term methotrexate therapy. Double-blind study. *American Journal of Medicine* 82 (4):781-786, 1987. ID 876	RCT[7] 1+ • Randomised (method not mentioned) • Double blind • No mention of ITT analysis	N= 10	Inclusion criteria: Ten patients with definite or classic RA who were part of larger cohort of 29 patients being prospectively followed to determine the long-term safety and efficacy of MTX in RA were studied. These patients have been receiving continuous weekly oral MTX for at least 36 months (mean 40.1 months; range 36-52) Baseline characteristics: At entry, the data of the two groups were comparable. Baseline number of tender and swollen joints was similar in each group, although the baseline mean number of tender joint was higher in the group receiving MTX, largely due to increased joint counts in one patient in this group. Duration of MTX therapy was 10.4 months in the placebo group versus 39.8 months in the patients who continued to receive MTX.	Methotrexate N= 5	Placebo N=5	One month	Morning stiffness (mins) ARAFC Evening fatigue (mins) Grip (mm Hg) Pain Global disease activity (GDA) Tender joints Swollen joints ESR	Lederle laboratories and NIH

[7] Patients were randomly assigned to receive MTX or identical-appearing placebo tablets on the basis of the relative activity of their disease. They were placed into one of three categories of disease activity (mildly active, moderately active, or active) by a clinical investigator who had been following prospectively. Equal number of patients in each of the three categories were then placed in each of the two study groups (two with mildly active disease, tow with moderately active disease, and one with active disease in each group). However, a sub-analysis by category was not performed

			Mean weekly MTX dosage was identical in each group (14mg). All 10 patients had received prior gold therapy, and eight of 10 and nine of 10 had received had received hydroxychloroquine and penicillamine, respectively.					

Effect size

Results after one month

Overall
After one month, mean values for physician and patient evaluation of pain and global disease activity , American Rheumatism Association Functional Class (ARAFC), and number of tender and swollen joints all worsened significantly in the placebo group when compared with that in the patients continuing to receive MTX (all p values < 0.04)

All of these same values except ARAFC also showed statistically significant worsening when compared with the baseline evaluations (all p values <0.04)

At the one-month visit, physician evaluators judged that all five patients in the placebo group were undergoing a significant flare (100% vs 20%) and asked that they be informed of the identity of the tablets (active drug of placebo) these patients have been receiving. → At this time, the previous dose of MTX was reinstituted in all the placebo-treated patients.

Results after two months

There was a significant improvement (all p values <0.04) in morning stiffness, patient evaluation of pain and global disease activity (GDA) after patients receiving placebo resumed taking MTX for one month.

Drop-outs
Not withdrawals were reported

Baseline data

Outcome	***MTX***	***placebo***
Morning stiffness (mins)	45.0	51.4
Evening fatigue (mins)	902	900
Grip (mm Hg)	98.0	168.0
ARAFC	2.4	1.8
Pain (0-4) Patient	2.2	1.6

Physician	2.0	1.2
GDA		
Patient	2.0	1.8
Physician	2.6	1.2
Tender joints	14.8	7.2
Swollen joints	11.6	10.4
ESR	11.6	25.6

After one month

Outcome	***MTX***	***placebo***
Morning stiffness (mins)	153.0	270.0

Change in placebo b/w baseline and one month → NS

Change in placebo vs MTX at one month → NS

Evening fatigue (mins)	858.0	914.0

Change in placebo b/w baseline and one month → NS

Change in placebo vs MTX at one month → NS

Grip (mm Hg)	94.0	135.0

Change in placebo b/w baseline and one month → NS

Change in placebo vs MTX at one month → NS

ARAFC 2.2 2.8

Change in placebo b/w baseline and one month → p= 0.07

Change in placebo vs MTX at one month → p= 0.02

Pain (0-4)
Patient 2.2 3.3
Physician 1.8 2.8

Change in placebo b/w baseline and one month → p= <0.01 and 0.03 respectively

Change in placebo vs MTX at one month → p= 0.004 and 0.01 respectively

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GDA
Patient 2.4 3.3
Physician 2.4 2.8
Change in placebo b/w baseline and one month → p= <0.01 and 0.03 respectively

Change in placebo vs MTX at one month → p= <0.01 and 0.001 respectively

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Tender joints 16.4 15.6

Change in placebo b/w baseline and one month → p= 0.03

Change in placebo vs MTX at one month → p= 0.04

Swollen joints 11.8 17.8

Change in placebo b/w baseline and one month → p= 0.04

Change in placebo vs MTX at one month → p= 0.02

ESR 45.0 30.3

Change in placebo b/w baseline and one month → NS

Change in placebo vs MTX at one month → NS

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Ten Wolde, F. C. Breedveld, J. Hermans, J. P. Vandenbroucke, M. A. F. J. van de Laar, H. M. Markusse, M. Janssen, H. R. van den Brink, B. A. C. Dijkmans. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet*; 347: 347-52,	RCT: 1+ Multi centre trial, all in the Netherlands • Randomised using block randomisation (stratified by drug and sex) • Double blind • Placebo controlled • Not mentioned if ITT analysis • Power study (flares)	Total N= 285 **Drop-outs:** 14/285 (4.9%) 9/285 withdrew 5/285 were given incorrect doses of medication Protocol was discontinued in the event of a flare or a recurrence of synovitis as judged by the rheumatologist. NB:	**Inclusion criteria:** patients between 18 and 85 years with RA (as defined by 1987 criteria) who met the following criteria: a good therapeutic response to long-term treatment with second-line drugs according to ARA criteria for clinical remission[8], stable for at least the past year according to the patients chart, treatment with one of the following second-line drugs for at least the past 2 years: chloroquine, hydroxychloroquine, parenteral gold (aurothioglucose in oil), d-penicillamine, sulphasalazine, azathioprine, or methotrexate. **Exclusion criteria:** use of prednisone or a previous unsuccessful attempt to discontinue the second-line drug.	Continue customary dose of second-line drug	Placebo	52 weeks	Occurrence of a flare (mild or severe)[9]	Het Nationaal Reumafonds (Netherlands)

[8] According to the ARA criteria for clinical remission five of the following six requirements had to be fulfilled: (1) duration of morning stiffness not exceeding 15 min; (2) no fatigue; (3) no joint pain; (4) no joint tenderness or pain on motion; (5) no soft tissue swelling in joints or tendon sheaths; (6) ESR <30 mm/hr for a female or 20 mm/hr for a male.

[9] A study flare was defined according to the following generally accepted criteria: firstly three or more swollen joints, secondly tow or more of the following three criteria (a) Ritchie articular index of >9 points, (b) duration of morning stiffness >45 min, (c) ESR > 28 mm/hr for men and >38 mm/hr for women.

<table>
<tr>
<td>1996
ID 2941</td>
<td>• Low dropouts</td>
<td>recruitment was discontinued when N=285 due to predefined safety monitoring criteria.</td>
<td>Baseline characteristics:
<table>
<tr><th></th><th>Continued treatment</th><th>Placebo</th></tr>
<tr><td>Age mean (SD)</td><td>61.8 (11.9)</td><td>60.4 (11.3)</td></tr>
<tr><td>Sex (% female)</td><td>58</td><td>58</td></tr>
<tr><td>RA duration, median (range)</td><td>8 (2-43)</td><td>9 (2-48)</td></tr>
<tr><td>Median duration of 2nd line therapy (yr)</td><td>5 (2-27)</td><td>6(2-33)</td></tr>
<tr><td>Erosive change on x-ray (%)</td><td>78</td><td>75</td></tr>
</table>
Baseline mean annual dose of parenteral gold was distinctly lower in the placebo group (p=0.01), although the mean serum gold concentrations at baseline did not differ between the groups.</td>
<td></td><td></td><td></td><td></td><td></td>
</tr>
</table>

Effect size

CONTINUED 2ND LINE DRUG vs. DISCONTINUED 2ND LINE DRUG

	Continued 2nd line drug		Discontinued 2nd line drug			
	No. with flare/ No. of patients	Cumulative incidence of flare at 52 weeks (%)	No. with flare/ No. of patients	Cumulative incidence of flare at 52 weeks (%)	RR	p
All 2nd line drugs All flares Severe flare	 30/142 15/142	 22 12	 53/143 24/143	 38 20	 2.0	 0.002 0.04
Antimalarials	14/74	20	26/78	35	2.0	0.034
Parenteral gold	8/34	26	11/33	34	1.5	0.407
Sulphasalazine	3/17	18	8/17	49	3.8	0.038
Penicillamine	4/10	40	4/10	40	1.0	1.000

Azathioprine and methotrexate: numbers of patients treated in each group were too small for statistical analysis.

The group that discontinued 2nd line therapy fared significantly worse than the continued treatment group (measured by differences in the mean change from baseline)with respect to the following disease activity indices: pain at rest (MD 0.2, p=0.031), morning stiffness (MD 27, p=0.005), grip strength right hand and left hand (MD -5.2 and -5.0, p=0.024 and p=0.019), HAQ score (MD 0.14, p=0.014), Ritchie articular index (MD 1.9, p=0.000), ESR (MD 5, p=0.000), CRP (MD 2 p=0.008), IgM rheumatoid factor (p=0.000).

Risk factors for rheumatoid flare:
In a logistic regression model the following variables were significantly related to the risk for a flare: high maintenance dose of second-line drugs (RR 2.3, 95% CI 1.3-4.2), presence of painless swollen joints (RR 1.8, 95% CI 1.0-3.3), ever-positive RF (RR 1.9, 95% CI 1.0-3.6).

Adverse events

Side effects were similar in the two groups. Possible adverse events were registered for 37% (52/142) of those who continued treatment and 34% (50/143) of those who discontinued treatment.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Leeden H. Van der, B. A. Dijkmans, J. Hermans, and	RCT 1+ • Randomised	N= 24	Inclusion criteria: Patients visiting the out-patients clinic who had definite or classical RA according to the ARA criteria and had received at least 6 g	Gold therapy[10] N= 11	Placebo N= 13	24 months	Morning stiffness Ritchie index	Not reported

[10] Patients were randomized into two groups: one of them called the gold group, comprising patients given the same dosage schedule as before the study and the other, called the placebo group, comprising patients given the same dosage schedule as before the study and the other, called the placebo group, comprising patients who received gold in a suspension diluted 1/100

A. Cats. A double-blind study on the effect of discontinuation of gold therapy in patients with rheumatoid arthritis. *Clinical Rheumatology* 5 (1):56-61, 1986. ID 2973	(method not mentioned) • Double blind • No mention of ITT analysis		gold (Auromyose®) Intramuscular injections The previous gold dosage ranged between 50mg every six weeks to 100 mg every two weeks. No exclusion criteria reported Baseline characteristics: At entry, the data of the two groups were comparable except for the radiological findings, the patients in the placebo group showing significantly (p=0.02) less destruction than those in the gold group. The total amount of gold administered up to the start of the study ranged from 6,260 to 36,750 mg and the duration of gold therapy varied from almost 4 to 32 years.				Number of swollen joints EST Rx Abnormalities Adverse events	

Effect size

Overall
Comparison of the entry and 24-month values of each patient showed no significant differences between the two groups with respect to the clinical, laboratory, and radiological data except for the gold concentrations, which were significantly lower in the placebo group.

Adverse events
No AEs were observed during this study

Drop-outs
At 24 months, 5 patients had dropped out of the gold group and 4 out of the placebo group.

The reasons for drop outs in the gold group were exacerbation of RA, admission to an elderly centre, death due to carcinoma of the lung, death due to sepsis, and refusal to cooperate further.

The reasons for drop outs in the placebo group were refusal to cooperate further, sudden death (N=2), and exacerbation of RA

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-	Outcome measures	Source of funding

						up		
B. Tengstrand, E. Larsson, L. Klareskog, and I. Hafstrom. Randomized withdrawal of long-term prednisolone treatment in rheumatoid arthritis: effects on inflammation and bone mineral density. *Scandinavian Journal of Rheumatology* 36 (5):351-358, 2007. REF ID: 3463.	RCT 1- • Randomised (minimisation method – balanced groups for age and presence or absence of osteoporosis) • No mention of blinding • No mention of ITT analysis	N=58 Randomised **Drop-outs at 2 years:** Withdrawal group: N=2 (7%) Continue group: N=4 (13%)	**Inclusion criteria:** RA (ACR criteria); prednisolone treatment for at least 2 years with stable disease activity as well as unchanged dose of GC for at least 3 months and stable treatment with DMARDs. **Exclusion criteria:** Patients with high disease activity. **Baseline characteristics:** All: Age median 62; female 73%; disease duration median 9 years (established RA); HAQ median 1.05.	Usual drug	Gradual withdrawal (tapering of prednisolone)	2 years	DAS28; HAQ; Bone minderal density; radiological damage (erosions)	Danish Arthritis foundation, GEA, Lederle, and Pharmacia
Effect size N=15 (57%) of patients randomised to withdraw prednisolone treatment failed withdrawal and had flare (increased) joint symptoms								

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Bacon PA Myles AB Beardwell CG Daly JR. Corticosteroid withdrawal in rheumatoid arthritis. *Lancet* 2 (7470):935-	Case series 3	N= 38	Inclusion criteria: patients who had RA for periods ranging from 2 to 30 years (average 14 years) and who were treated with corticosteroids for a period from 6 months to 16 years (average 7.5 years). In all the patients selected for the trial RA appeared to have been adequately suppressed for at least 3 months, so there seemed to be a	The study perform a slow phased withdrawal, decreasing the prednisolone by 1mg per month.[11] GRADUAL WITHDRAWAL		Not stated		Ciba laboratories supplied the drug

[11] The corticosteroid withdrawal was covered, if necessary, by supplementary treatment with aspirin and other analgesics.

937, 1966. ID 821			reasonable chance that the symptoms could be controlled by a lower dose or that the drug was no longer necessary.				

Effect size

Successful withdrawal
In 10 patients corticosteroid therapy was successfully withdrawn. Three of them had taken the drug for 12 years or more and had received over 30g of prednisolone. The other 7 were mostly included in the group with the shortest period of treatment, but there was no close relation between total dosage, duration of therapy, and successful withdrawal.

The actual rate of withdrawal varied considerably from patient to patient and only one patient was able to follow the original plan of a regular 1mg a month reduction (this patient was using corticosteroids for the shortest time)

The average rate of withdrawal was 1mg in 3.5 months

Withdrawal failure
In 23 patients withdrawal of corticosteroids had to be stopped on account of active arthritis.

Drop-out
Two patients stopped attending to the clinic and one emigrated.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Tishler, D. Caspi, and M. Yaron. Methotrexate treatment of rheumatoid arthritis: is a fortnightly maintenance schedule enough? *Annals of the*	Case series 3	N= 15	Inclusion criteria: The study group comprised 15 patients with RA, all fulfilling the criteria of the ACR, who were treated with methotrexate. Patients chosen for this study were those in whom the disease was stable for the six months before the start of the trial (a stable methotrexate	The dose of methotrexate was kept unchanged but the schedule was changed from a weekly oral dose to a fortnightly one.		12 months		Not reported

Rheumatic Diseases 51 (12):1330-1331, 1992. ID 2972			weekly dosage, up to four tender joints, NSAIDs or steroid adjunct treatment). All patients had radiographic erosions but none had any signs of extra-articular disease				

Effect size

Thirteen of the 15 patients completed the 12 month trial. In two patients a flare of arthritis activity, consisting of joint pain and a rise in the ESR, occurred at two and four months respectively after changing the methotrexate schedule to a fortnightly dose. Reinstitution of weekly methotrexate treatment resulted in control of disease activity.

In the 13 patients who were followed up for 12 months
there was no deterioration in the beneficial effect of methotrexate after changing the schedule of the drug.

No differences in laboratory and clinical parameters were noted 12 months after changing methotrexate to a
fortnightly schedule. There was no increase in the use of analgesics or NSAIDs during the study period and all 13 patients sustained a stable disease course.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fleischmann RM, Cohen SB, Moreland LW, Schiff M, Mease PJ, Smith DB, Keenan G, Kremer JM, and iRAMT Study Group. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis	Case series 3 • Open label study • Multisite	N= 210 **Drop-outs:** 36/210 (17.1%)	**Inclusion criteria:** infliximab naïve patients with an established diagnosis of RA according to the revised criteria of the ARA at least 3 months prior to screening, a minimum of 8 tender and 4 swollen joints, oral or parenteral methotrexate was prescribed for at least 3 months prior to the study with a stable dosage of 7.5 to 25 mg per week for at least the previous month. **Exclusion criteria:** investigational drugs and drugs other than infliximab that act to reduce TNF were not permitted, patients with a history or risk of serious infection or lymphoproliferative diseases, active	Infliximab infusion at a minimum dosage of 3 mg/kg at 8-week intervals. At week 22 or later infliximab dose could be could be increased until a clinically important improvement[12] was achieved.	n/a	1 year	Primary outcomes: number of patients on a maintenance dose of infliximab who achieved a clinically important improvement (≥40%)and who tolerated any reduction in methotrexate dosage at or beyond week 22. Secondary efficacy endpoints: Proportion of	Centocor Inc.

[12] The clinically important improvement was a≥ 40% improvement from baseline in the combined swollen and tender joint count.

Methotrexate Tapering (iRAMT) trial. Current Medical Research & Opinion: 21: 1181 – 1190, 2005 REF ID: 43.			or untreated latent tuberculosis. **Baseline characteristics:** Age mean 53.2 (range 18-80), female 73.8%, disease duration mean 10.4 years (range 0.3-56), duration of methotrexate treatment mean 4.7 (SD 5.1), previous DMARD use 15%, HAQ 1.28 (SD 0.619)	Methotrexate dose could be tapered once a clinically important improvement was seen (after week 22) to a lowest methotrexate dose of 5 mg/week			patients achieving a clinically important improvement Proportion reaching ACR20 Proportion experiencing changes in ACR core components (pain VAS, patients global assessment of disease activity, physicians global assessment of disease activity, HAQ) CRP ESR	

Effect size

Improvements from baseline in signs and symptoms of RA:
Proportion of patients achieving at least a 40% reduction in total joint count at week 22 or later and tapered methotrexate dose: 75.7% (159/210).
ACR20 response at week 22 or later 75% (158/210).

Of the responders (those achieving ≥40% improvement):

- 57.8% (92/159) achieved response by week 22 and did not relapse [median week 46 infliximab dose 4.4 (4.7 ± 1.4) mg/kg, median week 54 methotrexate dose 5.0 (6.4 ± 3.2) mg/week]
- 20.1% (32/159) achieved the response, relapsed but regained the response [median week 46 infliximab dose 5.6 (5.5 ± 1.2) mg/kg, median week 54 methotrexate dose 5.0 (7.9 ± 4.5) mg/week]
- 22% (35/159) achieved the response, relapsed and did not regain it [median week 46 infliximab dose 5.3 (5.7 ± 1.6) mg/kg, median week 54 methotrexate dose 5.0 (8.2 ± 4.8) mg/week]
- When MTX was tapered, significant improvements from baseline were seen for tender and swollen joints (median improvement 73%, $p<0.001$), ESR and CRP levels (median improvement 23% and 50%, both $p\leq0.001$) and HAQ score (median improvement 40%, $p<0.001$) at week 54.

Non-responders:
7% (15/210) never achieved a clinically important response or achieved it only at week 54, despite a median dose of infliximab of 8.1 (8.0 ± 1.2) mg/kg at week 46.
In non-responders, tender and swollen joint count worsened by 10.6% and HAQ remained stable ate week 54.

Adverse events Among the responders: incidence of AE during the initial 22 weeks 78.0% (124/159); incidence of AE during the methotrexate tapering phase 79.9% (127/159). Specific AEs were not specified but included infection and infusion reactions.

7.2 GLUCOCORTICOIDS (CORTICO)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. A. Capell, R. Madhok, J. A. Hunter, D. Porter, E. Morrison, J. Larkin, E. A. Thomson, R. Hampson, and F. W. Poon. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial.[see	RCT: 1++ Single centre trial in UK. • Randomised (stratified by age, gender, rheumatoid factor status, presence/absence of erosions by minimisation method) • Double blind • ITT analysis • Power study (Progression of erosions)	Total N=167 randomised (N=84 CS prednisolone, N=83 placebo). **Drop-outs:** CS: 27% Placebo: N=20%	**Inclusion criteria:** Adults 18-75 years with RA (ACR criteria) with symptoms <3 years; at least 3 of the following: ≥6 painful joints, 3 swollen joints, ≥20 mins early morning stiffness, ESR ≥28 mm in the first hour, CRP ≥10 mg/l. **Exclusion criteria:** Peptic ulcer disease and not on gastroprotection;; received DMARD treatment other than hydroxychloroquine in previous 4 weeks. **Baseline characteristics:** Prednisolone group: mean age 55 years; Female 65%; Duration of RA = Early RA (<2 years mean 12 months, <3 years inclusion criteria); Pain (VAS) 54. Placebo group: mean age 56 years; Female 64%; Duration of	Oral Prednisolone 7 mg daily + DMARD (sulphasalazine) All patients in both groups were given DMARD (sulphasalazine treatment). Patients wer tsrated on 500 mg/day and the dose was increased weekly by 500 mg/day to a target dose of 40 mg/kg unless toxicity limited increments.	Placebo + DMARD (sulphasalazine)	1 year and 2 years (end of treatment)	Pain (VAS); Patient and Physican's global assessment of activity (VAS); Ritchie Articular index; HAQ (British modification); Progression of joint erosions (hand and feet) assessed by SHS (Sharp/van der Heijde score – 44 joints of hands and feet graded for erosions, range 0-280, 42 joints for JSN, range 0-448). Both scores added to	Grants from the Arthritis Research Council, UK and The Sir Hugh Fraser Foundation (Glasgow, UK).

comment]. *Annals of the Rheumatic Diseases* 63 (7):797-803, 2004. ID 2182			RA = Early RA (<2 years mean months, <3 years inclusion criteria); Pain (VAS) 56. There were NS differences between the groups for any of the baseline characteristics. NSAIDs treatment wa at the discretion of the individual physician as was further DMARD use if sulphasalazine failed.				yield total score range 0-448); ESR; CRP; ACR 20% response; AEs.	

Effect size

ORAL CS (PREDNISOLONE) + DMARD (SULPHASALAZINE) vs ORAL PLACEBO + DMARD (SULPHASALAZINE)

- The CS prednisolone + DMARD was significantly better than placebo + DMARD for:
  - ESR, median change from baseline (12.0 and 18.0 respectively, p<0.05) at 1 year (mid-treatment).

- There was NS difference between the CS prednisolone + DMARD and placebo + DMARD for:
  - Radiological damage – total score (SHS erosions and JSN score, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Pain (VAS, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - HAQ (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Patient's global assessment of activity (VAS, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Physician's global assessment of activity (VAS, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Ritchie Articluar Index (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - CRP (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - ESR (change from baseline) at 2 years (end of treatment).

- The CS prednisolone + DMARD was worse than placebo + DMARD for:
  - Withdrawals due to AEs due to CS or placebo (N=6, 7% and N=2% respectively) during 2 years (end of treatment).

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. R. Kirwan, M. Byron, P. Dieppe, C. Eastmond, J. Halsey, P.	RCT: 1+ Multicentre trial: 13 centres in UK • Randomised	Total N=128 randomised (N=61 CS prednisolone, N=67	**Inclusion criteria:** Adults 18-69 years, with RA <2 yrs duration and currently active (6 or more painful joints, 3 or more joints wit active synovitis, early morning stiffness for > 20 mins and	YEARs 1 and 2 Prednisolone 7.5 mg daily + routine	Placebo + routine medication	Year 1 abd year 2 (end of treatment)	Progression of radiological damage for each finger or rist joint (Larsen scale: 0-	Grant from the Arthritis and Rheumatism Council, UK.

Hickling, P. Hollingworth, R. Jacoby, A. Kirk, C. Moran, D. Reid, T. Swannell, D. Yates, C. Cooper, E. George, D. Forbes, J. Jessop, and I. Watt. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *New England Journal of Medicine* 333 (3):142-146, 1995. ID 2162	(blocks of 6 patients within each centre, method not mentioned) • Double blind • Allocation concealment • Not true ITT analysis	placebo). **Drop-outs:** Year 0: N=8 (13%) prednisolone, N=6 (9%) placebo. Year 1: N=8 (13%) prednisolone, N=10 (15%) placebo. Year 2: N=10 (16%) prednisolone, N=9 (13%) placebo.	ESR > 28mm/h, plasma viscosity > 1.72 or CRP > 10mg/l). **Baseline characteristics:** Prednisolone group: mean age 48.2 years (SD 10.0); Female 62%; Weight 71.1 kg (SD 11.1); Duration of RA = Early RA (<2 years inclusion criteria); Pain score (VAS) 1.36 (SD 0.71). Placebo group: mean age 50.3 years (SD 10.1); Female 66%; Weight 67.4 kg (SD 15.4); Duration of RA = Early RA (<2 years inclusion criteria); Pain score (VAS) 1.54 (SD 0.8). There were NS differences between the groups (data from only the patients included in the analysis) for all baseline characteristics.	medication Physicians managing each patient were free to prescribe any treatment except systemic CS.			5, 0=normal, 5=maximum joint destruction. Larsen score is a summation of all the finger and wrist joint scores in both hands taken together) and the appearance of erosions in hands which had no erosions at baseline (hand radiographs); Changes in disability (HAQ); joint inflammation (articular index of tender and swollen peripheral joints weighted for joint size); Pain over previous 24 hrs (VAS); Acute phase response (ESR, CRP or plasma viscosity); AEs.	

Effect size

ORAL CS (PREDNISOLONE) + USUAL TREATMENT vs ORAL PLACEBO + USUAL TREATMENT

- The CS prednisolone (+ usual treatment) was significantly better than placebo (+ usual treatment) for:
  - Progression of radiological damage, Larsen score, change from baseline, (mean difference 4.65, p=0.04) at 2 years (end of treatment);
  - Proportion of erosive hands at 1 year, mid-treatment (26% and 38% respectively; mean difference 18.9%, 95% CI 1.7 to 35.7, p=0.018) and at 2 years end of treatment (22% and 46% respectively; mean difference 23.5%, 95% CI 5.9 to 40.7, p=0.007).

- There was NS difference between the CS prednisolone (+ usual treatment) and placebo (+ usual treatment) for:
  - Progression of radiological damage (Larsen score, change from baseline) at 1 year (mid-treatment);
  - Pain (VAS) at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Acute phase response at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Disability score (HAQ) at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Joint Inflammation (articular index score) at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Proportion of patients treated with NSAIDs at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Proportion of patients treated with specific anti-Rheumatoid drugs at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Number of patients with AEs at 1 year (mid-treatment) and at 2 years (end of treatment).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. A. Van Everdingen, D. R. Siewertsz van Reesema, J. W. Jacobs, and J. W. Bijlsma. The clinical effect of glucocorticoids in patients with rheumatoid arthritis may be masked by decreased use of additional therapies. *Arthritis &*	RCT: 1++ Single centre trial in The Netherlands • Randomised (computer-generated randomisation, blocks of 10) • Double blind • ITT analysis	Total N=81 randomised (N=40 CS prednisolone, N=41 placebo). **Drop-outs:** CS: N=4, 10% Placebo: N=6, 15%	**Inclusion criteria:** Adults ≥18 years with active, early and previously untreated RA (at least 2 of the following: ≥30 mins early morning stiffness, 28-joint score for tenderness and 28-joint score for swelling ≥3, ESR ≥28 mm in the first hour); RA duration <1 year. **Exclusion criteria:** Contraindications to prednisone or NSAIDs; active GI problems; serious complicating diseases; serious hypertension; haemorrhagic diathesis; treatment with cytotoxic or immunosuppressive drugs; alcohol or drug abuse; psychiatric or mental problems.	Oral Prednisolone 5 mg daily at breakfast All patients in both groups were given 500 mg of elementary calcium in the evening.	Placebo	1 year and 2 years (end of treatment)	Impact of Rheumatic Diseases on General Health and lifestyle Questionnaire (IRGL – based on AIMS1 assesses physical, psychological and social functioning as well as impact of disease on daily life); Early morning pain (VAS).	Grant from the Dutch League against Rheumatism.

Rheumatism 51 (2):233-238, 2004. ID 73			**Baseline characteristics:** Prednisolone group: mean age 60 years (SD 14); Female 56%; Duration of RA = Early RA (<1 year inclusion criteria); Pain (VAS) 28 (SD 20).. Placebo group: mean age 64 years (SD 12); Female 71%; Duration of RA = Early RA (<1 year inclusion criteria); Pain (VAS) 34 (SD 25). There were NS differences between the groups for any of the baseline characteristics. Use of NSAIDs was not regulated. Local glucocorticoid injections were permitted only when absolutely necessary. Physical therapy and additional use of paracetamol were allowed. After 6 months, use of SSZ (2 g/day) was permitted as rescue medication based on clinical RA activity.					

Effect size

ORAL CS (PREDNISOLONE) vs ORAL PLACEBO

- The CS prednisolone was significantly better than placebo for:
  - IRGL dimension of potential support (range 5-20) at 1 year, mid-treatment (p=0.04) and 2 years, end of treatment (p=0.004).

- There was NS difference between the CS prednisolone and placebo for:
  - IRGL dimension of potential support (range 5-20) at 6 months (mid-treatment);
  - All other 16 dimensions of IRGL at 6 months (mid-treatment) 12 months (mid-treatment) and 24 months (end of treatment);
  - Early morning pain (VAS) at 1 year (mid-treatment) and at 2 years (end of treatment).

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**

A. A. Van Everdingen, J. W. Jacobs, D. R. Siewertsz van Reesema, and J. W. Bijlsma. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Annals of Internal Medicine* 136 (1):1-12, 2002. ID 112	RCT: 1++ Single centre trial in The Netherlands • Randomised (computer-generated randomisation, blocks of 10) • Double blind • ITT analysis	Total N=81 randomised (N=40 CS prednisolone, N=41 placebo). **Drop-outs:** CS: N=4, 10% Placebo: N=6, 15%	As for ID 73	As for ID 73	As for ID 73	1 year and 2 years (end of treatment)	Disability (Dutch version of HAQ, 0=best score to 3=worst score); Early morning stiffness (mins); Morning pain (VAS); General well-being (VAS, 0- no problems, 100=worst score); Swelling and tenderness (28-joint score); Grip strength (kPa); Progression of joint erosions (hand and feet) assessed by SHS (Sharp/van der Heijde score – 44 joints of hands and feet graded for erosions, range 0-280, 42 joints for JSN, range 0-448). Both scores added to yield total score range 0-448); Number of patients with erosive disease; number of radiologically affected joints per patient; Clinically relevant improvement (20% improvement in the 28-joint scores for swelling and tenderness and at	Grant from the Dutch League against Rheumatism.

							least 2 of the following: pain, general well-being, HAQ score and CRP level); use of concomittant medication and treatments; CRP; AEs.	

Effect size

ORAL CS (PREDNISOLONE) vs ORAL PLACEBO

- The CS prednisolone was significantly better than placebo for:
    - Grip strength, kPA (change from baseline) at 1 year, mid-treatment (13.0 and -1.0 respectively, p=0.002);
    - Radiologic damage (SHS score, change from baseline) at 1 year, mid-treatment (8.0 and 15.0 respectively, p=0.008)and at 2 years, end of treatment (16.0 and 29.0 respectively, p=0.007);
    - Radiologic score (Total) at 1 year, mid-treatment (19 and 30 respectively, p=0.04) and at 2 years, end of treatment (27 and 44 respectively, p=0.02);
    - Radiologic score (Total) at 2 years, end of treatment (16 and 29 respectively, p=0.04);
    - Radiologic score (Joint space narrowing) at 2 years, end of treatment (11 and 15 respectively, p=0.02);
    - Total numbers of affected joints per patient at 2 years, end of treatment (12 and 16 respectively, p=0.047);
    - 28-joint score for tenderness (change in AUC from baseline) at 2 years, end of treatment (-2.0 and 0 respectively, p=0.01);
    - Number of patients receiving concomitant IA CS injections at 6 months, mid-treatment (5% and 27% respectively, p=0.01).

- There was NS difference between the CS prednisolone and placebo for:
    - Functional disability (Dutch HAQ), change from baseline, at 1 year (mid-treatment) and at 2 years (end of treatment);
    - Grip strength, kPA (change from baseline) at 2 years (end of treatment);
    - Early morning stiffness, mins (change in AUC from baseline) at 2 years (end of treatment);
    - Morning pain, VAS (change in AUC from baseline) at 2 years (end of treatment);
    - General well-being, VAS (change in AUC from baseline) at 2 years (end of treatment);
    - 28-joint score for swelling (change in AUC from baseline) at 2 years (end of treatment);
    - CRP level, g/L (change in AUC from baseline) at 2 years (end of treatment);
    - Individual patient improvement, % (change from baseline) at 1 year (mid-treatment) and at 2 years (end of treatment);
    - Use of additional physiotherapy (number of patients) at 6 months (mid-treatment) and at 2 years (end of treatment);
    - Use of additional IA corticosteroid injections (number of patients) at 2 years (end of treatment);
    - Use of paracetamol (number of patients) at 6 months (mid-treatment) and at 2 years (end of treatment);
    - Withdrawals due to AEs related to study medication (both N=0) during the 2 years (end of treatment);
    - Radiologic score (erosions) at 1 year, mid-treatment;
    - Radiologic score (joint space narrowing) at 1 year, mid-treatment;
    - Total numbers of affected joints per patient at 1 year, mid-treatment;

- The CS prednisolone was similar to placebo for:
    - Total number of AEs (N=61 and N=67 respectively) during the 2 years (end of treatment);

- The CS prednisolone was worse than placebo for:
    - Total number of withdrawals (N=4, 10% and N=6, 15% respectively) during the 2 years (end of treatment);

AUC =area under curve

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. Hickling, R. K. Jacoby, J. R. Kirwan, M. Byron, I. Watt, P. A. Dieppe, A. Kirk, C. J. Eastmond, J. R. Kirwan, P. Hollingworth, C. Moran, D. M. Reid, J. Halsey, A. J. Swannell, D. Yates, C. Cooper, E. George, J. Jessop, and D. Forbes. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *British Journal of Rheumatology* 37 (9):930-936, 1998. ID 2167	RCT: 1+ Multicentre trial: 13 centres in UK • Randomised (blocks of 6 patients within each centre, method not mentioned) • Double blind • Allocation concealment • Not true ITT analysis • High number of dropouts	Total N=128 randomised (N=114 CS prednisolone, N=114 placebo). **Drop-outs:** Year 3: N=17 (28%) prednisolone, N=15 (22%) placebo.	**Inclusion criteria:** Adults 18-69 years, with RA <2 yrs duration and currently active (6 or more painful joints, 3 or more joints wit active synovitis, early morning stiffness for > 20 mins and ESR > 28mm/h, plasma viscosity > 1.72 or CRP > 10mg/l). **Baseline characteristics:** Prednisolone group: mean age 48.3 years (SD 9.4); Female 61%; Weight 69.9 kg (SD 10.3); Duration of RA = Early RA (<2 years inclusion criteria); Pain score (VAS) 1.35 (SD 0.7). Placebo group: mean age 50.1 years (SD 10.1); Female 77%; Weight 66.8 kg (SD 15.9); Duration of RA = Early RA (<2 years inclusion criteria); Pain score (VAS) 1.56 (SD 0.8). There were NS differences between the groups (data from only the patients included in the analysis) for all baseline characteristics.	YEAR 2-3: Prednisolone 7.5 mg (alternate-day treatment for 2 weeks then every 3rd day treatment for 2 weeks then discontinued) + routine medication Physicians managing each patient were free to prescribe any treatment except systemic CS.	Placebo + routine medication	Year 3 (approx. 1 year post-treatment - this is a follow-up study looking at effects after withdrawal of CS)	Progression of radiological damage for each finger or rist joint (Larsen scale: 0-5, 0=normal, 5=maximum joint destruction. Larsen score is a summation of all the finger and wrist joint scores in both hands taken together) and the appearance of erosions in hands which had no erosions at baseline (hand radiographs); Changes in disability (HAQ); joint inflammation (articular index of tender and swollen peripheral joints weighted for joint size); Pain over previous 24 hrs (VAS); Acute phase response (ESR, CRP or	Grant from the Arthritis and Rheumatism Council, UK.

							plasma viscosity); AEs.	

Effect size

CS (PREDNISOLONE) + USUAL TREATMENT vs PLACEBO + USUAL TREATMENT

- The CS prednisolone (+ usual treatment) was significantly better than placebo (+ usual treatment) for:
  - Proportion of erosive hands (38% and 67% respectively, p=0.000) at 3 years (1 year post-treatment).

- There was NS difference between the CS prednisolone (+ usual treatment) and placebo (+ usual treatment) for:
  - Progression of radiological damage (Larsen score, change from baseline) at 3 years (1 year post-treatment);
  - Pain (VAS) at 3 years (1 year post-treatment);
  - Acute phase response at 3 years (1 year post-treatment);
  - Disability score (HAQ) at 24-27 months (immediately after treatment withdrawal).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
B. Svensson, A. Boonen, K. Albertsson, Heijde D. Van Der, C. Keller, and I. Hafstrom. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction	RCT: 1+ Multicentre trial 6 centres in Sweden (BARFOOT study). • Randomised (block randomisation stratified by gender) • Allocation concealment • Not blinded • ITT analysis • Basic sample size calculation based on	Total N=259 randomised (N=119 CS prednisolone + DMARD, N=131 DMARD). **Drop-outs:** CS + DMARD: 3 (2.5%) DMARD: N=5 (3.8%)	**Inclusion criteria:** Adults 18-80 years with RA (ACR criteria) with symptoms ≤1 year; active disease (DAS 28 score >3.0); started by the treating rheumatologist on their first DMARD. **Exclusion criteria:** Earlier treatment with glucocorticoids for RA or other diseases; previous treatment with DMARDs; contraindication for glucocorticoid therapy; previous fragility fractures; patients aged <65 years with a T score < -2.5 and those aged ≥65 years with Z score < -1 on bone mineral densitometry.. **Baseline characteristics:** Prednisolone + DMARD group: mean age 51 years (SD 14); Female 65%; Duration of RA =	Oral Prednisolone 7 mg daily + DMARD (50% started on MTX and 35% SSZ) All patients in both groups were given DMARDs (choice was left to the treating physicians who followed the recommended treatment strategy in Sweden at the time of the	DMARD (53% started on MTX and 37% SSZ)	3 and 6 months, 1 year, 18 months and at 2 years (end of treatment)	Disease activity (DAS28 – a patient's disease considered in remission with score <2.6); Functional disability (Swedish version of HAQ – range 0-3 higher score = worse disability); Signals of Functional impairment (SOFI index: performance test for hand function, upper	Grants from: the Swedish Rheumatism Association; The Foundation of King Gusatv V; the Ugglas Foundation; the Borje Dahlins Foundation; the Gorthon Foundation in Helsing borg and Stiftelsen for Rorelsehindrade I Skane.

and increases the remission rate: A two-year randomized trial. *Arthritis & Rheumatism* 52 (11):3360-3370, 2005. ID 2165	another published trial		Early RA (<2 years, mean 6.5 months, <1 year inclusion criteria); HAQ score (range 0-3) 1.01 (SD 0.59). DMARD group: mean age 59 years (SD 14); Female 63%; Duration of RA = Early RA (<2 years, mean 5.8 months, <1 year inclusion criteria); HAQ score (range 0-3) 0.98 (SD 0.65). The groups were similar for all baseline characteristics. Concomitant treatment with NSAIDs twas permitted and IA steroid injections were allowed except during the 2 weeks preceding a clinical evaluation.	study). All patients were given 1000 mg/day calcium carbonate or calcium gluconate.			limb function and lower limb function. Each item scored on scale 0-3, max score of 44. Higher score = worse function); Radiographic damage score (total, erosion and JSN – Sharp/van der Heijde score, SHS); CRP level; AEs.	

Effect size

ORAL CS (PREDNISOLONE) + DMARD vs DMARD

- The CS prednisolone + DMARD was significantly better than DMARD alone for:
  - Number of patients taking concomitant NSAID treatment (44% and 65% respectively, p=0.001) at 2 years (end of treatment);
  - Mean dose of concomitant IA corticosteroid (23 mg and 38 mg respectively, p=0.017) at 2 years (end of treatment);
  - Radiographic damage – total score (SHS, median change from baseline) at 1 year mid-treatment (1.0 and 2.0 respectively, p=0.035) and at 2 years, end of treatment (1.8 and 3.5 respectively, p=0.019);
  - Radiographic damage – erosion score (SHS, median change from baseline) at 1 year mid-treatment (0.0 and 0.5 respectively, p=0.005) and at 2 years, end of treatment (0.5 and 1.5 respectively, p=0.019);
  - Proportion of patients with radiographic preogression greater than the SDD, smallest detectable difference 5.8 (25.9% and 39.3% respectively, p=0.033);
  - Disease activity (DAS28) at 6 months, mid-treatment (p=0.0005), 1 year, mid-treatment (p=0.001) and at 2 years, end of treatment (p=0.005);
  - Number of patients with disease remission (DAS28 <2.6) at 2 years, end of treatment (55.5% and 32.8% respectively, p=0.0005);
  - Functional disability (Swedish HAQ) at 6 months, mid-treatment (p=0.0005), 1 year, mid-treatment (p=0.002) and at 2 years, end of treatment (p=0.003);
  - Signals of Functional impairment (SOFI index) at 6 months, mid-treatment (p=0.0005), 1 year, mid-treatment (p=0.011) and at 2 years, end of treatment (p=0.018);
  - CRP level at 6 months, mid-treatment (p=0.004);
- The CS prednisolone + DMARD was better than DMARD alone for:
  - Number of patients with erosions (59% and 80% respectively) at 2 years (end of treatment).

- There was NS difference between the CS prednisolone + DMARD and placebo + DMARD for:
  - Radiographic damage – JSN score (SHS, median change from baseline) at 1 year (mid-treatment) and at 2 years (end of treatment);
  - CRP level at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Number of patients with disease remission (DAS28 <2.6) at 1 year (mid-treatment).

- The CS prednisolone + DMARD was similar to DMARD alone for:
  - Total number of withdrawals (N=3, 2.5% and N=5, 3.8% respectively);
  - Number of AEs leading to withdrawals (N=26 and N=24 respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Wassenberg, R. Rau, P. Steinfeld, and H. Zeidler. Very low-	RCT: 1+ Multicentre trial: 20 centres in Germany, Austria and Switzerland.	Total N=192 randomised (N=94 CS prednisolone, N=98 placebo).	**Inclusion criteria:** Adults 18-70 years, with RA (ACR criteria) between 6 months and 2 yrs duration; at least 3 of 4 activity indices (6 tender joints, 3 swollen joints, early morning stiffness for	Oral Prednisolone 5 mg daily + DMARD (MTX or parenteral gold) Gold sodium	Placebo + DMARD (MTX or parenteral gold)	6 months, 1 year and 2 years (end of treatment)	Radiological damage assessed by Ratingen score (38 joint, scale 0-5 according to amount of surface	Merck KGaA, Germany.

dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: A multicenter, double-blind, placebo-controlled trial. *Arthritis & Rheumatism* 52 (11):3371-3380, 2005. ID 2164	• Randomised (computer-generated randomisation list) • Double blind • Not true ITT analysis • High number of drop-outs	**Drop-outs:** CS: N=45 (48%) Placebo: N=44 (45%)	>60 mins and ESR >28mm/h). **Exclusion criteria:** Glucocorticoid-dependent disease such as asthma; previous oral glucocorticoid treatment (>3 months) abd previous treatment with or contraindications for, MTX or IM gold. **Baseline characteristics:** Prednisolone group: mean age 53.4 years (SD 12.6); Female 75%; Duration of RA = Early RA (<2 years mean 8.6 months, <2 years inclusion criteria); Ratingen score (joint surface destruction) 3.3 (SD 5.6). Placebo group: mean age 50.3 years (SD 13.0); Female 65%; Duration of RA = Early RA (<2 years mean 9.3 months, <2 years inclusion criteria); Ratingen score (joint surface destruction) 2.1 (SD 2.9). The groups were similar for all baseline characteristics. NSAIDs, osteoporosis prophylaxis with calcium and Vitamin D and oestrogen replacement therapy were permitted. Treatment with fluorine, bisphosphonates and calcitonin was not allowed.	thiomalate injections were started at 10 mg, then 20 mg followed by 50 mg once a week up to a total dose of 2000 mg. Thereafter, the maintenance dose was 50 mg every other week. MTX was started at 7.5 mg/week for 3 weeks followed by 10-15 mg/week (IM, IV or orally). If the 1st treatment (gold or MTX) was stopped due to lack of efficacy (not before 6 months of therapy) or due to toxicity, the other drug had to be initiated within 6 weeks. If complete remission was achieved for >6 month, investigators had the option to reduce the dosage.			joint destruction – range of scores 0-190) and by SHS (Sharp/van der Heijde score – 44 joints of hands and feet graded for erosions, range 0-280, 42 joints for JSN, range 0-448). Both scores added to yield total score range 0-448; Pain and overall condition (VAS); Swelling and tenderness (Thompson index =, 38 joints); Functional disability (FFbH score – Funktions-Frageboen Hannover Score; Depressed mood (Hautzinger and Bailer questionnaire); Clinical remission (ACR criteria); ESR; AEs.	

Effect size

ORAL CS (PREDNISOLONE) + DMARD (MTX or GOLD) vs ORAL PLACEBO + DMARD (MTX or GOLD)

- The CS prednisolone + DMARD was significantly better than placebo + DMARD for:
  - Radiological damage – surface joint destruction (Ratingen score, change from baseline) at 1 year, mid-treatment (mean difference 2.59, 95% CI 1.06 to 4.12; p=0.001) and at 2 years, end of treatment (mean difference 3.14, 95% CI 0.94 to 5.34; p=0.006);
  - Radiological damage – erosions (SHS score, change from baseline) at 1 year, mid-treatment (mean difference 4.66, 95% CI 1.79 to 7.54; p=0.002) and at 2 years, end of treatment (mean difference 4.91, 95% CI 1.23 to 8.58; p=0.01);
  - Radiological damage (combined SHS score, change from baseline) at 1 year, mid-treatment (mean difference 6.66, 95% CI 2.06 to 11.27; p=0.005) and at 2 years, end of treatment (mean difference 7.20, 95% CI 0.93 to 13.47; p=0.022).

- There was NS difference between the CS prednisolone + DMARD and placebo + DMARD for:
  - Radiological damage – JSN (SHS score, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Joints with erosions (%, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Swelling and tenderness (Thompson index , change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Pain (VAS, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Morning stiffness (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Functional disability (FFbH score, change rom baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Depressed mood (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - Patient's global condition (VAS, change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment);
  - ESR (change from baseline) at 1 year (mid-treatment) and 2 years (end of treatment).

- The CS prednisolone + DMARD and placebo + DMARD were similar for:
  - Total number of AEs (71% and 74% respectively) during 2 years (end of treatment);
  - Total number of SAEs (29% and 33% respectively) during 2 years (end of treatment);
  - Total number of withdrawals (48% and 44% respectively) during 2 years (end of treatment);
  - Withdrawals due to AEs (11% and 13% respectively) during 2 years (end of treatment).

- The CS prednisolone + DMARD was worse than placebo + DMARD for:
  - Withdrawals due to drug failure (6% and 13% respectively) during 2 years (end of treatment).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. H. Choy, G. H. Kingsley, B. Khoshaba, N. Pipitone, D. L. Scott, and	RCT: 1++ Single centre trial in UK. • Randomised	Total N=91 randomised (N=48 CS depomedrone (+ DMARD),	**Inclusion criteria:** Adults ≥18 years with RA (ACR criteria); disease duration between 2-10 years; erosions on plain x-ray examination of the hands, wrists	IM Depomedrone 120 mg once/month + current DMARD treatment	Placebo (IM saline) + current DMARD treatment	6 months, 1 year, 18 months and at 2 years	Disease activity (numbers of swollen and tender joints	Grant from the Arthritis Research Council,

Intramuscular Methylprednisolone Study Group. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Annals of the Rheumatic Diseases* 64 (9):1288-1293, 2005. ID 47	(method not mentioned) • Double blind • Allocation concealment • ITT analysis • Power study (progression of erosions) • Fairly high number of dropouts	N=43 Placebo (+ DMARD). **Drop-outs:** CS: 14 (29%) Placebo: N=17 (39%)	and feet; continuous stable DMARD treatment for atleast 3 months (with IM gold, penicillamine, mTX, azathioprine or ciclosporin; continuing active disease with >6 swollen joints and ESR >30 mm/1st hour. **Exclusion criteria:** End stage joint destruction (Larsen score >100); previous or current oral steroid treatment; contraindications to parenteral steroids; serious comorbidity; patients not taking DMARDs; taking experimental drugs; taking DMARDs that have no effect on x-ray progression (eg. Antimalarial drugs); taking DMARDs which may interact poorly with IM depot steroids (SSZ). **Baseline characteristics:** Depomedrone + usual DMARD group: mean age 59 years (SD 10); Female 75%; Duration of RA = Established RA (>2 years, mean 13 years, 2-10 years inclusion criteria); Pain (VAS) 45.8 (SEM 3.6). Placebo + usual DMARD group: mean age 56 years (SD 13); Female 81%; Duration of RA = Established RA (>2 years, mean 16 years, 2-10 years inclusion criteria); Pain (VAS) 46.2 (SEM 3.9). There were NS differences	All patients in both groups continued their current treatment of DMARDs at the same dose, NSAIDs and analgesics. One allowable DMARD (gold, penicillamine, mTX, azathioprine or ciclosporin) could be changed for another at the discretion of the supervising clinician. IA methylprednisiolone was restricted to 6 injections of ≤40 mg (given to N=6 and N=7 patinets in the CS and placebo groups respectively).		(end of treatment)	out of total 28); Articular pain (VAS); Patient's and physician's global assessments (VAS); HAQ scores; Disease activity (DAS28 score); Radiological damage in the hands and feet (modified Larsen method); ESR; CRP level; AEs.	UK.

			between the groups for any of the baseline characteristics.					

Effect size

IM CS (DEPOMEDRONE) + DMARD vs PLACEBO + DMARD

- The CS depomedrone + DMARD was significantly better than placebo + DMARD for:
  - DAS score, change from baseline (0.65 and 0.08 espectively, p=0.038) at 6 months, mid-treatment;
  - Swollen joints, change from baseline (p<0.03) at 6 months, mid-treatment;
  - HAQ score, change from baseline (p<0.02) at 6 months, mid-treatment;
  - Pain (VAS), change from baseline (p<0.01) at 6 months, mid-treatment;
  - Radiological damage (Larsen score, % change from baseline) at 2 years, end of treatment (12% and -5% respectively, p=0.028).

- The CS depomedrone + DMARD was better than placebo + DMARD for:
  - Total number of withdrawals (N=14, 29% and N=17, 39% respectively);
  - Number of withdrawals due to lack of efficacy (N=5, 10% and N=8, 19% respectively).

- There was NS difference between the CS depomedrone + DMARD and placebo + DMARD for:
  - DAS score, change from baseline at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Swollen joints, change from baseline at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Tender joints, change from baseline at 6 months and 1 year (mid-treatment) and at 2 years (end of treatment);
  - HAQ score, change from baseline at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Pain (VAS), change from baseline at 1 year (mid-treatment) and at 2 years (end of treatment);
  - Patient's global assessment (change from baseline) at 6 months and 1 year (mid-treatment) and at 2 years (end of treatment);
  - Physician's global assessment (change from baseline) at 6 months and 1 year (mid-treatment) and at 2 years (end of treatment);
  - Radiological damage (Larsen score, change from baseline) at 1 year (mid-treatment) and at 2 years (end of treatment);
  - ESR (change from baseline) at 6 months and 1 year (mid-treatment) and at 2 years (end of treatment).

- The CS depomedrone + DMARD was similar to placebo + DMARD for:
  - Number of withdrawals due to AEs (N=9, 19% and N=9, 21% respectively);
  - Total number of SAEs (N=4 and N=2 respectively).

- The CS depomedrone + DMARD was worse than placebo + DMARD for:
  - Total number of AEs (N=55 and N=42 respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Van Vliet-Daskalopoulou E., T. Jentjens, and R. T. C. Scheffer. Intra-articular rimexolone in the rheumatoid knee: A placebo-controlled, double-blind, multicentre trial of three doses. *British Journal of Rheumatology* 26 (6):450-453, 1987. ID 890	RCT: 1+ Multicentre trial: in The Netherlands • Randomised (method not mentioned) • Double blind • No ITT analysis • High % of drop-outs	Total N=137 randomised (Data given for N=140 patients: N=32 CS 10 mg; N=33 CS 20 mg; N=31 CS 40 mg; N=34 placebo). **Drop-outs:** CS 10 mg: 34% CS 20 mg: 28% CS 40 mg: 29% Placebo: 56%	**Inclusion criteria:** Adults with classical or definite RA involving at least 1 knee joint requiring local treatment. **Exclusion criteria:** Previous corrective orthopaedic surgery or received an IA CS injection of the study joint within the preceding 2 months. Concurrent systemic antirheumatic treatment was stable on entry Into the trial **Baseline characteristics:** Rimexolone 10 mg group: mean age 54.6 years; Female 78%; Duration of RA = Established RA (>2 years; mean 148 months). Rimexolone 20 mg group: mean age 56.1 years; Female 76%; Duration of RA = Established RA (>2 years; mean 111 months). Rimexolone 40 mg group: mean age 57.1 years; Female 71%; Duration of RA = Established RA (>2 years; mean 105 months). Placebo group: mean age 58.7 years; Female 68%; Duration of RA = Established RA (>2 years; mean 99 months). The groups were similar for all of the baseline characteristics except for RA disease duration, which was higher in the 10 mg	IA Rimexolone 10 mg IA Rimexolone 20 mg IA Rimexolone 40 mg	IA Placebo (vehicle)	7, 28, 56 and 84 days (approximately 3 months post-treatment)	Pain during previous 24 hrs (score 0 = absent to 4 = unbearable pain); Tenderness (Modified Ritchie Index, score 0 to 3); Duration of morning stiffness (mins, 0 = absent to 4 = <120 mins); Swelling (joint circumference, cm); Range of movement on passive flexion (degrees); Walking ability (0 = normal to 3 = severely impaired); Severity of disease score (summation of scores for pain, tenderness and duration of morning stiffness in the treated knee, divided by 3); Patients and investigators opinions of overall treatment	Not mentioned.

			group.				effects; AEs.	

Effect size

IA CS (RIMEXOLONE 10 mg) vs PLACEBO

- The CS rimexolone 10 mg was significantly better than placebo for:
    - Severity of disease score (pain, tenderness and duration of morning stiffness) at 7 days post-treatment ($p<0.05$).

- There was NS difference between the CS rimexolone 10 mg and placebo for:
    - Severity of disease score (pain, tenderness and duration of morning stiffness) at 28, 56 and 84 days post-treatment;
    - Swelling at 7, 28, 56 and 84 days post-treatment;
    - Range of movement at 7, 28, 56 and 84 days post-treatment;
    - Walking ability at 7, 28, 56 and 84 days post-treatment;
    - Patient's and investigator's opinions of overall treatment effect over the 84 days post-treatment.

- The CS rimexolone 10 mg was similar to placebo for:
    - Number of AEs.

IA CS (RIMEXOLONE 20 mg) vs PLACEBO

- The CS rimexolone 20 mg was significantly better than placebo for:
    - Severity of disease score (pain, tenderness and duration of morning stiffness) at 7 and 28 days post-treatment ($p<0.05$ and $p<0.01$ respectively);
    - Swelling at 7 days post-treatment (p value not given);
    - Walking ability at 7 and 28 days post-treatment ($p=0.03$);
    - Patient's and Investigator's opinions of overall treatment effect over the 84 days post-treatment ($p=0.02$).

- There was NS difference between the CS rimexolone 20 mg and placebo for:
    - Severity of disease score (pain, tenderness and duration of morning stiffness) at 56 and 84 days post-treatment;
    - Swelling at 28, 56 and 84 days post-treatment;
    - Range of movement at 7, 28, 56 and 84 days post-treatment;
    - Walking ability at 56 and 84 days post-treatment.

- The CS rimexolone 20 mg was similar to placebo for:
    - Number of AEs.

IA CS (RIMEXOLONE 40 mg) vs PLACEBO

- The CS rimexolone 40 mg was significantly better than placebo for:
    - Severity of disease score (pain, tenderness and duration of morning stiffness) at 7, 28 and 56 days post-treatment (all $p<0.01$);
    - Range of movement at 7, 28, 56 and 84 days post-treatment ($p=0.01$);

- Walking ability at 7, 28 and 56 days post-treatment (p=0.02);
- Patient's and Investigator's opinions of overall treatment effect over the 84 days post-treatment (p<0.01).

- There was NS difference between the CS rimexolone 40 mg and placebo for:
  - Severity of disease score at 84 days post-treatment;
  - Swelling at 7, 28, 56 and 84 days post-treatment;
  - Walking ability at 84 days post-treatment.

- The CS rimexolone 40 mg was similar to placebo for:
  - Number of AEs.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. M. Corkill, B. W. Kirkham, I. C. Chikanza, T. Gibson, and G. S. Panayi. Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. *British Journal of Rheumatology* 29 (4):274-279, 1990. ID 275	RCT: 1+ Single centre trial, UK. • Randomised (blocks of 4 and stratified by RA duration and age) • Single blind • ITT analysis • High number of drop-outs	Total N=59 randomised (N=35 CS; N=24 placebo). **Drop-outs:** CS N=13 (37%) Placebo: N=11 (45%)	**Inclusion criteria:** Adults aged 17-79 years old with classic or definite RA requiring DMARD treatment and had either persistent synovitis despite NSAID therapy for 3 months or progressive erosions on X-rays plus an ESR >40 mm/hr. **Exclusion criteria:** Previous treatment with gold; proteinuria, glucocorticoid treatment within the previous 2 months, insulin-requiring or unstable diabetes mellitus or hospital in-patient care within the 2 months prior to entry. **Baseline characteristics:** MPA group: mean age 54 years; Female 71%; Duration of RA = Established RA (>2 years; mean 5.5 years); Pain (VAS) 57.	IM depot methylprednisolone, MPA (120 mg) + DMARD (gold) In both groups IM injections of either CS or placebo were given at weeks 0, 4 and 8. Gold was given as 10 mg IM test dose at week 0 followed by 50 mg weekly until a total dose of 1.0 g was reached after which gold was continued at 50 mg monthly.	IM placebo (saline) + DMARD (gold)	8 weeks (end of treatment) with follow-up at 12 weeks and 24 weeks (4 and 16 weeks post-treatment)	Radiographic progression (Larsen score and modified Sharp score – using only erosion scores); Pain (VAS); Grip strength; HAQ; number of tender and swollen joints; Inex of disease activity (ESR, Hb, Pain, joint count, HAQ and grip strength were given a grade at each time point and the mean at each	Arthritis Foundation of New Zealand and the Rose Hellaby Trust.

			Placebo group: mean age 55 years; Female 54%; Duration of RA = Established RA (>2 years; mean 6 years); Pain (VAS) 47. The groups were similar for all of the baseline characteristics except for number of patients in each group which resulted from the use of 2 randomisation protocols, however authors state that this did not alter the power of the study.				assessment was then derived using modified method of Mallya and Mace to give the index score); ESR; AEs.	

Effect size

IM CS (METHYLPREDNISOLONE) + DMARD (GOLD) vs PLACEBO + DMARD (GOLD)

- The CS methylprednisolone + DMARD was significantly better than placebo + DMARD for:
  - Pain (VAS, change from baseline) at 4 weeks, mid-treatment ($p<0.01$), 8 weeks, end of treatment ($p<0.05$) and at 12 weeks, 4 weeks post-treatment ($p<0.05$);
  - HAQ score (change from baseline) at 4 weeks, mid-treatment ($p<0.05$) and at 12 weeks, 4 weeks post-treatment ($p<0.05$);
  - Joint count (number of tender and swollen joints, change from baseline) at 12 weeks, 4 weeks post-treatment ($p<0.05$);
  - ESR (change from baseline)at 4 weeks, mid-treatment ($p<0.05$);
  - Index of Disease Activity (change from baseline) at 4 weeks, mid-treatment ($p<0.01$), 8 weeks, end of treatment ($p<0.05$) and at 12 weeks, 4 weeks post-treatment ($p<0.01$).

- There was NS difference between the CS methylprednisolone + DMARD and placebo + DMARD for:
  - Pain (VAS, change from baseline) at 24 weeks (16 weeks post-treatment);
  - HAQ score (change from baseline) at 8 weeks (end of treatment) and at 24 weeks (16 weeks post-treatment);
  - Joint count (number of tender and swollen joints, change from baseline) at 4 weeks (mid-treatment), 8 weeks (end of treatment) and at 24 weeks (16 weeks post-treatment);
  - Grip strength (change from baseline) at 4 weeks (mid-treatment), 8 weeks (end of treatment), 12 weeks (4 weeks post-treatment) and at 24 weeks (16 weeks post-treatment);
  - ESR (change from baseline) at 8 weeks (end of treatment), 12 weeks (4 weeks post-treatment) and at 24 weeks (16 weeks post-treatment);
  - Index of Disease Activity at 24 weeks (16 weeks post-treatment);
  - Radiological Progression – erosion (Larsen score, change from baseline) over 24 weeks study – 16 weeks post-treatment;
  - Total number of withdrawals (over 24 weeks study – 16 weeks post-treatment);
  - Number of withdrawals due to lack of effect (over 24 weeks study – 16 weeks post-treatment);
  - Number of withdrawals due to AEs (over 24 weeks study – 16 weeks post-treatment);
  - Number of patients with AEs (over 24 weeks study – 16 weeks post-treatment);
  - Total number of transient AEs (over 24 weeks study – 16 weeks post-treatment).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Hansen, J. Podenphant, A. Florescu, M. Stoltenberg, A. Borch, E. Kluger, S. F. Sorensen,	RCT: 1+ Multicentre trial: 5 centres Denmark • Randomised (blocks of	Total N=102 randomised (N=51 CS prednisolone + DMARD; N=51 DMARD).	**Inclusion criteria:** Adults with active RA (ACR criteria - more than 3 swollen joints and 2 of the following: morning stiffness over 30 mins, ESR > 35mm 1st h and CRP > 150 nmol/l). **Exclusion criteria:** Metabolic	Oral Prednisolone + DMARD All patients in both groups were either currently being treated with DMARDs or were going to start taking	DMARD All patients in both groups were either currently	1 year (end of treatment)	Number of tender joints and swollen joints; Larsen Index (joint damage scale 0 = no damage to 5 = maximum	Grants from The Danish Rheumatism Association and The Velux Foundation of 1981,

and T. M. Hansen. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis. Clinical benefits and skeletal side effects. *Annals of the Rheumatic Diseases* 58 (11):713-718, 1999. ID 170	10, method not mentioned) • Allocation concealment • No mention of blinding • ITT analysis	**Drop-outs:** CS + DMARD: N=9 (18%) DMARD: N=17 (33%)	bone disease, liver disease, diabetes mellitus, malignant disease, other connective tissue disease, Steinbroker class IV, received systemic CS within the preceding 6 months. **Baseline characteristics:** Prednisolone + DMARD group: median age 65 years; Female 76%; Duration of RA = Established RA (>2 years; median 8.5 years); Larsen score (31.5). DMARD: mean age 60 years; Female 76%; Duration of RA = Established RA (>2 years; median 2.8 years). There were NS differences between the groups for any of the baseline characteristics except for RA disease duration, which was significantly lower in the DMARD group ($p<0.05$).	DMARDs at the same time as the study. Prednisolone was given as 30 mg once/day for 1 week, 20 mg once/day for 2nd week then 15 mg once/day at day 15. Thereafter patients were asked to choose a dose between 2.5 mg and 15 mg which would be sufficient to control their disease activity. They were allowed to change the daily dose by 1.25 mg at a time. Mean dose of prednisolone used was 6 mg (over 1 year): 4.5 mg at 6 months and 3.0 mg at 1 year. NSAIDs and simple analgesics were permitted.	being treated with DMARDs or were going to start taking DMARDs at the same time as the study.		damage); Patient and clinician's global evaluation (11 point scale 0 = best to 10 = worst possible); grip strength; HAQ score; Acute phase reactants (ESR, CRP); 20% and 50% clinical improvement scores (20% improvement in tender and swollen joints and at least 2 of the following variables: physician's global evaluation, HAQ score and CRP).	Denmark.

Effect size

ORAL CS (PREDNISOLONE) + DMARD TREATMENT vs DMARD TREATMENT

- The CS prednisolone + DMARD treatment) was significantly better than DMARD treatment alone for:
  - Joint damage (rate of progression, delta Larsen score) change from baseline (3.5 vs 1.8, p<0.03) at 1 year (end of treatment);
  - Number of patients with >20% clinical improvement (57% and 29% respectively, p<0.02) at 3 months (mid-treatment);
  - Number of patients with >50% clinical improvement (33% and 0% respectively, p<0.001) at 3 months (mid-treatment).

- There was NS difference between the CS prednisolone + DMARD treatment and DMARD treatment alone for:
  - Number of patients with joint damage progression, change from baseline at 1 year (end of treatment);
  - Number of patients with >20% clinical improvement at 6 months (mid-treatment) and at 1 year (end of treatment);
  - Number of patients with >50% clinical improvement at 6 months (mid-treatment) and at 1 year (end of treatment).

- The CS + DMARD treatment) was similar to DMARD treatment alone for:
  - CRP, mean % of the start (45% and 42% respectively – data approximate as taken from graphs presented in the paper) at 1year (end of treatment)

- The CS + DMARD treatment) was better than DMARD treatment alone for:
  - HAQ score, mean % of the start (50% and 85% respectively – data approximate as taken from graphs presented in the paper) at 1year (end of treatment)
  - Grip strength mean % of the start (172% and 110% respectively – data approximate as taken from graphs presented in the paper) at 1year (end of treatment)
  - Total number of withdrawals (N=9, 18% and N=17, 33% respectively) over 1 year (end of treatment).

- The CS + DMARD treatment) was worse than DMARD treatment alone for:
  - Swollen joints, mean % of the start (55% and 35% respectively – data approximate as taken from graphs presented in the paper) at 1year (end of treatment)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. M. Hansen, P. Kryger, H. Elling, D. Haar, M. Kreutzfeldt, Nielsen MW Ingeman, A. T. Olsson, C. Pedersen, A. Rahbek, and N. Tvede. Double blind placebo controlled trial of	RCT: 1+ Multicentre trial: 4 centres in Denmark. • Randomised (blocks of 10 to each centre) • Allocation	Total N=97 randomised (N=50 CS+DMARD, N=47 Placebo + DMARD). **Drop-outs:** N=29 (30%) Completers	**Inclusion criteria:** Adults with active RA (ARA criteria) of at least 4 weeks duration; at least 3 of the following criteria: 4 activity indices (6 or more tender joints, 3 or more swollen joints, morning stiffness for ≥45 mins and ESR >28mm/1st hour). **Exclusion criteria:**	IV methylprednisolone + DMARD CS given as 15 mg/kg body weight once every 4 weeks (total of 6 times over 20 weeks for at least 30 mins infusion) In both groups	IV Placebo (saline) + DMARD	20 weeks (end of treatment) and 1 year follow-up (7 months post-treatment)	Number of tender and swollen joints; Observer's evaluation of change in the patient's condition; patient's assessment of condition	Upjohn Denmark.

pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. *British Medical Journal* 301 (6746):268-270, 1990. ID 273	concealment • Double blind • No ITT analysis • High number of drop-outs	(those staying on same DMARD treatment throughout)CS: N=31 (62%) Placebo: N=26 (55%)	Functional class IV (ARA criteria); received IA or oral glucocorticosteroids within 6 weeks before the start of the study. **Baseline characteristics:** age 23-84 Methylprednisolone group: Female 66%; Self-assessed condidtion (VAS) 55. Placebo group: Female 66%; Self-assessed condidtion (VAS) 55. The groups were similar for all baseline characteristics except for duration of morning stiffness which was much higher in the placebo group. Therapeutic doses of NSAIDs, and analgesics were continued during the study. Patients given glucocorticoids in addition to the study treatment (either IA or oral) and patients who had syneovectomy or arthroplasty during the trial were regarded as dropouts.	DMARD given as: 7 days after starting CS or placebo, patients were started on penicillamine (PEN) or azathioprine (AZA). Given AZA only if had AEs to PEN or had not responded during previous treatment with PEN. All others given PEN. Those that failed to improve on PEN after 6 months or had unacceptable AEs had treatment changed to AZA. Those taking AZA and showed no clinical improvement after 6 months or unacceptable AEs were withdrawn from the trial and treated at the discretion of the doctor in charge. Initial dose of PEN was 150 mg daily increasing every 3 weeks by 150 mg to minimum of 450 mg and maximum of 900 mg daily. AZA was given 2.5 mg/kg body weight daily up to maximum 150 mg daily dose.			(VAS); Duration of morning stiffness; presence of erosions at least 1mm deep; change in number of erosions; ESR; CRP; AEs.	

Effect size

IV CS (METHYLPREDNISOLONE) + DMARD (PENICILLAMINE OR AZATHIOPRINE) vs IV PLACEBO + DMARD (PENICILLAMINE OR AZATHIOPRINE)

- There was NS difference between the CS methylprednisolone + DMARD and placebo + DMARD for:
  - Duration of morning stiffness (mins) at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Patient's assessment of disease activity (VAS) at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Observer's assessment of disease activity (VAS) at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Number of swollen joints at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Number of tender joints at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Number of erosions on radiography at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - Progression of erosions at 1 year follow-up (approximately 7 months post-treatment);
  - ESR (mm/1st hour) at 20 weeks and 1 year follow-up (approximately 7 months post-treatment);
  - CRP level (mg/l) at 20 weeks and 1 year follow-up (approximately 7 months post-treatment).

- The CS methylprednisolone + DMARD was significantly worse than placebo + DMARD for:
  - Total number of AEs ($p<0.05$) during 1 year (approximately 7 months follow-up).

7.3 BIOLOGICS (DRUG3 and ANAKIN)

7.3.1 DRUG 3

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Y. H. Lee, J. H. Woo, Y. H. Rho, S. J. Choi, J. D. Ji, and G. G. Song. Meta-analysis of the combination of	MA: 1++ RCT's of MA: 1+ and 1++ SR and MA included: N=3 trials with suitable data Trials were similar in terms of: • Population (all established	Total N=1040	**Inclusion criteria:** RCTs; compared anti-TNF + MTX vs MTX alone; patients suffering with active RA despite DMARD treatment, including	Anti-TNF + MTX	MTX	50 to 55 weeks	ACR20/50/70; HAQ; tender and swollen joints; AEs; withdrawals due to lack of efficacy.	None given

TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. *Rheumatology International* 28 (6):553-559, 2008. ID 3538	RA) • Study design (all RCTs) • Blinding (all double blind) • Comparison group (MTX) • Study quality – all included RCTs were reasonable to good quality (all randomised, double blind and some had ITT analysis). • Study duration – length of intervention (50-55 weeks) Trials differed with respect to: • Intervention (1 RCT Infliximab + MTX, 1 RCT Etanercept + MTX, 1 RCT Adalimumab + MTX) • Intervention – dose given and regimen • Study size (range N=174 to N=459) Tests for heterogeneity and quality assessment performed.		MTX; double-blind, randomised; completed 50-55 weeks of trial; doses of anti-TNFs were the recommended doses: etanercept 25 mg twice/day, infliximab 3 mg/kg iv q 8 weeks and adalimumab 40 mg sc q 2 weeks. Search was up to February 2006. **Exclusion criteria:** None given					

Effect size

Anti-TNF + MTX vs MTX

- Anti-TNF + MTX was significantly better than MTX alone for:
  - ACR 70 (3 RCTs, N=1040; RR 3.43, 95% CI 1.74 to 6.75, p=0.0004)
  - Withdrawal due to lack of efficacy (3 RCTs, N=1040; RR 3.43, 95% cI 1.74 to 6.75, p=0.0004)

- There was NS difference between Anti-TNF + MTX and MTX alone for:
  - Withdrawal due to AEs (3 RCTs, N=1040)

- There was significant heterogeneity with Anti-TNF + MTX vs MTX alone for:
  - ACR20 and ACR50 (both: 3 RCTs, N=1040)

Indirect comparisons – Infliximab vs adalimumab vs etanercept

- There was NS difference between infliximab and adalimumab for ACR20, ACR50, ACR70, withdrawals due to AEs and withdrawals due to lack of efficacy.
- Adalimumab was significantly better than etanercept for ACR20 (RR 0.46, 95% CI 0.34 to 0.61, p<0.0001), ACR50 (RR 0.37, 95% CI 0.22 to 0.60, p<0.0001), ACR70 (RR 0.44, 95% CI 0.21 to 0.93, p=0.003) was worse for withdrawals due to AEs (RR 0.38, 95% CI 0.17 to 0.86, p=0.02) but there was NS difference for withdrawals due to lack of efficacy
- Infliximab was significantly better than etanercept for ACR20 (RR 0.38, 95% CI 0.17 to 0.86, p=0.02), but there was NS difference for ACR50, ACR70, withdrawals due to AEs and withdrawals due to lack of efficacy

Authors' conclusions:
MA showed that the combination of MTX + anti-TNFs was more effective than MTX monotherapy and also showed that they were comparable for side-effects.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
F. Navarro-Sarabia, Ariza R. Ariza, Cruz B. Hernandez, and I. Villanueva. Adalimumab for treating rheumatoid arthritis.	MA: 1++ RCT's of MA: 1++ SR and MA included: N=6 trials with suitable data Trials were similar in terms of: • Population (all established RA) • Study design (all RCTs)	Total N=2381.	**Inclusion criteria:** RCTs or CCTs; adalimumab monotherapy or in combination with DMARDs vs placebo or other DMARDs; Patients with RA (ACR criteria) and active	Adalimumab + MTX/DMARD or Adalimumab alone	Placebo + MTX/DMARD c Placebo alone	Treatment ranged from 12 to 52 weeks	ACR20/50/70; EULAR response; HAQ; tender and swollen joints; Pain (VAS or categorical); Patients' and physicians' global assessment of	None given

COCHRANE DATABASE SYST REV (3):CD005113, 2005. ID 294	• Blinding (all double blind) • Intervention (Adalimumab + MTX/DMARD or Adalimumab alone) • Comparison group (Placebo + MTX/DMARD or Placebo alone) • Study quality – all included RCTs were good quality (all randomised, double blind and ITT analysis). Trials differed with respect to: • Intervention – dose given and regimen • Study size (range N=54 to N=636) • Study duration – length of intervention (12 weeks to 52 weeks) Tests for heterogeneity and quality assessment performed.		disease; patients who have failed previous DMARD therapy or DMARD-naïve patients were also included. Search was up to August 2004. **Exclusion criteria:** None given				disease activity; ESR; CRP radiographic progression (Sharp, modified Sharp or Larsen scores); AEs; SAEs; withdrawals due to AEs.	

Effect size

NOTE: RESULTS ARE REPORTED ONLY FOR WHEN MORE THAN ONE TRIAL WAS POOLED IN THE MA (all other results were reported for each trial separately and this has already been included in the evidence)

Adalimumab sc + MTX (or DMARDs) vs Placebo sc + MTX (or DMARDs)

- Adalimumab sc 4omg eow + MTX (or DMARDs) were significantly better than placebo sc + MTX (or DMARDs) for:
  - ACR50 (3 RCTs: RR 3.7, 95% CI 2.2 to 6.3, p<0.00001)
  - ACR70 (3 RCTs: RR 5.1, 95% CI 3.1 to 8.4, p<0.00001)
  - HAQ (2 RCTs: RR –0.3, 95% CI –0.4 to –0.2, p<0.00001)
  - Tender joints (2 RCTs: RR –6.7, 95% CI –9.0 to –4.3, p<0.00001)
  - Patient pain assessment (2 RCTs: RR –15.8, 95% CI –20.3 to -11.3, p<0.00001)

- There was NS difference between Adalimumab sc + MTX (or DMARDs) and placebo sc + MTX (or DMARDs) for:
  - Withdrawals (2 RCTs, N=1163)
  - AEs (all doses of adalimumab); (3 RCTs, N=1186)
  - SAEs (all doses of adalimumab); (3 RCTs, N=567)
  - Withdrawals due to AEs (all doses of adalimumab); (4 RCTs, N=1457)

- There was significant heterogeneity with Adalimumab sc + MTX (or DMARDs) and placebo sc + MTX (or DMARDs) for:
  - Adalimumab at 40mg eow - ACR20 at week 24 (3 RCTs, N-=1067)

Adalimumab sc vs Placebo

- Adalimumab sc was significantly better than placebo for:
  - Adalimumab at 20mg ew – ACR20 at week 2 (2 RCTs: RR 6.1, 95% CI 3.2 to 11.5 p<0.00001)
  - Adalimumab at 40mg ew – ACR20 at week 2 (2 RCTs, N=353, RR 6.7, 95% CI 2.3 to 19.1, p=0.0004)
  - Adalimumab at 40mg eow – ACR20 at week 24/46 (2 RCTs, N=228, RR 1.9, 95% CI 1.2 to 3.1, p=0.009)
  - Adalimumab at 20mg ew – ACR50 at week 2 (2 RCTs, N=363, RR 8.8, 95% CI 1.1 to 69.8, p=0.04)
  - Adalimumab at 40mg ew – ACR50 at week 2 (2 RCTs, N=353, RR 15.1, 95% CI 2.0 to 114.0, p=0.009)
  - Adalimumab all doses – withdrawals (2 RCTs, N=828, p<0.00001)

- There was NS difference between Adalimumab sc and placebo for:
  - SAEs (all doses of adalimumab); (3 RCTs, N=933)
  - Withdrawals due to AEs (all doses of adalimumab); (3 RCTs, N=933)

- There was significant heterogeneity with Adalimumab sc and placebo for:
  - Adalimumab all doses - AEs (2 RCTs, N=576)

Authors' conclusions:
On the basis of the 6 studies in the SR/MA, adalimumab in combination with MTX is efficacious and safe in the treatment of RA. Adalimumab 40 mg sc eow and 20 mg ew slows the radiographic progression at 52 weeks. Adalimumab in combination with DMARDs other than MTX is also efficacious and safe, even though data from only 1 study are available and the number of patients in each group is low. Adalimumab in monotherapy is efficacious and safe in the treatment of RA but the effect is lower than with combined therapy.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
Heijde D. Van Der, G. Burmester, Gomes J. Melo, C. Codreanu, E. M. Mola, R. Pedersen, B. Freundlich, D. J. Chang, and Study Etanercept. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Annals of the Rheumatic Diseases* 67	Extension of original RCT: 1++ • Centralised telephone randomisation • Double blind • ITT analysis • Power study (ACR-N AUC) • Fairly high number of dropouts in etanercept group • Multicentre (European, Australian, Israel)	Total N= 686 randomised at baseline TEMPO trial; N=227 entered the extension trial (MTX added N=76, ETN added N=55, Combination N=96) **Drop-outs within the 1 year extension trial:** MTX added: N=8 (11%) ETN added: N=3 (5%) Combination: N=3 (3%)	**Inclusion criteria:** patients who completed the 3 year TEMPO trial **Exclusion criteria:** none mentioned **Baseline characteristics:** MTX added: mean age 54 years; Female 84%; Duration of RA mean 9 years (Established RA); HAQ score mean 0.8. ETN added: mean age 57 years; Female 76%; Duration of RA mean 11 years (Established RA); HAQ score mean 0.7. Original combination: mean age 55 years; Female 75%; Duration of RA mean 10 years (Established RA); HAQ score mean 0.6. The 3 groups were similar for all baseline characteristics.	Originally patients were assigned to 3 groups: ETN, MTX or ETN + MTX. EXTENSION: Group 1: Patients on 3 years MTX added ETN 25mg (twice/week) Group 2: Patients on 3 years ETN added MTX (dose escalation 7.5 mg/week up to 20 mg/week by week 8) Group 3: MTX + ETN for 3 years – remained on this	4 years (1 year extension to the 3 year trial)	DAS remission (<1.6); DAS low disease activity (<2.4); EULAR moderate or good response; AEs.	Wyeth Research

(2):182-188, 2008. REF ID: 3507							

Effect size

ETANERCEPT added vs. METHOTREXATE added

- MTX with ETN added was better than ETN with MTX added for:
  - DAS remission (<1.6) at end of 1 year extension (OR 1.29, 95% CI 0.5 to 3.22)
  - DAS low disease activity (<2.4) at end of 1 year extension (OR 2.40, 95% CI 0.89 to 6.47)

ETANERCEPT + METHOTREXATE vs. METHOTREXATE added

- ETN + MTX was better than ETN with MTX added for:
  - DAS remission (<1.6) at end of 1 year extension (OR 1.26, 95% CI 0.51 to 3.09)
  - DAS low disease activity (<2.4) at end of 1 year extension (OR 0.65, 95% CI 0.25 to 1.70)

ETANERCEPT + METHOTREXATE vs. ETANERCEPT added

- ETN + MTX was better than MTX with ETN added for:
  - DAS remission (<1.6) at end of 1 year extension (OR 0.97, 95% CI 0.41 to 2.31)
  - DAS low disease activity (<2.4) at end of 1 year extension (OR 1.57, 95% CI 0.57 to 3.43)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Heijde D. Van Der, L. Klareskog, R. Landewe, G. A. Bruyn, A. Cantagrel, P. Durez, Beaumont G. Herrero, Y. Molad, C. Codreanu, G. Valentini, R. Zahora, R. Pedersen, D. MacPeek, J.	RCT: 1++ • Centralised telephone randomisation • Double blind • Multicentre (European, Australian,	Total N= 682 **Drop-outs:** Total 522/682 (76%) Etanercept only 30% Methotrexate only 24%	as for ID 2986	as for ID 2986	as for ID 2986	3 years	DAS28 <2.5 and <3.3 (Low disease activity) DAS<1.6 and DAS28<2.6 (DAS remission) ACR20, 50 and 70; HAQ; Radiographic progression (Total Sharp score – TSS,	Wyeth Research

Wajdula, and S. Fatenejad. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 56 (12):3928-3939, 2007. REF ID: 3543	Israel) • ITT analysis • Power study (ACR-N AUC) • Fairly high number of dropouts in etanercept group	Combination 16%					Erosion, JSN); TSS ≤0.5 (radiographic remission); AEs	

Effect size

ETANERCEPT vs. METHOTREXATE

- Etanercept was significantly better than MTX for:
  - total number of withdrawals at 3 years ($p<0.05$)
  - Radiographic progression (TSS change from baseline) at 3 years (1.6 vs 5.95, $p<0.05$)
  - Radiographic progression (erosion score change from baseline) at 3 years (0.39 vs 3.25, $p<0.05$)
  - number of patients achieving remission (TSS change ≤0.5 units) at 3 years (61% vs 51%, $p<0.05$)

- There was NS difference between etanercept and methotrexate for:
  - Radiographic progression (JSN change from baseline) at 3 years
  - SIMILAR FOR - proportion of patients with ≥1 treatment-emergent AEs or infections
  - Incidence of SAEs

ETANERCEPT + METHOTREXATE vs. METHOTREXATE

- Etanercept + MTX was significantly better than MTX for:
  - total number of withdrawals and withdrawals due to lack of efficacy at 3 years ($p<0.001$)
  - number of patients with low disease activity (DAS <2.4) at 3 years (65% vs 39%, $p<0.01$)
  - number of patients with low disease activity (DAS <3.2) at 3 years (56% vs 29%, $p<0.01$)
  - number of patients achieving remission (DAS <1.6) at 3 years (41% vs 18%, $p<0.01$)

- number of patients achieving remission (DAS28 <3.2) at 3 years (40% vs 19%, p<0.01)
- Number of patients achieving ACR 20 response at 3 years (85% vs 70%, p<0.01)
- Number of patients achieving ACR 50 response at 3 years (67% vs 44%, p<0.01)
- Number of patients achieving ACR 70 response at 3 years (47% vs 21%, p<0.01)
- HAQ improvement at 3 years (55% vs 33%, p<0.01)
- Number of patients with no disability (HAQ score 0) at 3 years (48% vs 33%, p<0.01)
- Radiographic progression (TSS change from baseline) at 3 years (-0.14 vs 5.95, p<0.05)
- Radiographic progression (erosion score change from baseline) at 3 years (-0.67 vs 3.25, p<0.05)
- Radiographic progression (JSN change from baseline) at 3 years (-0.67 vs 2.7, p<0.01)
- number of patients achieving remission (TSS change ≤0.5 units) at 3 years(76% vs 51%, p<0.05)

- There was NS difference between etanercept + MTX and MTX for:
  - SIMILAR FOR - proportion of patients with ≥1 treatment-emergent AEs or infections
  - Incidence of SAEs

ETANERCEPT + METHOTREXATE vs. ETANERCEPT

- Etanercept + MTX was significantly better than etanercept for:
  - total number of withdrawals and number of withdrawals due to lack of efficacy (p<0.001) at 3 years
  - number of patients with low disease activity (DAS <2.4) at 3 years (65% vs 44%, p<0.01)
  - number of patients with low disease activity (DAS <3.2) at 3 years (56% vs 33%, p<0.01)
  - number of patients achieving remission (DAS <1.6) at 3 years (41% vs 22%, p<0.01)
  - number of patients achieving remission (DAS28 <3.2) at 3 years (40% vs 21%, p<0.01)
  - Number of patients achieving ACR 20 response at 3 years (85% vs 71%, p<0.01)
  - Number of patients achieving ACR 50 response at 3 years (67% vs 46%, p<0.01)
  - Number of patients achieving ACR 70 response at 3 years (47% vs 26%, p<0.01)
  - HAQ improvement at 3 years (55% vs 37%, p<0.01)
  - Number of patients with no disability (HAQ score 0) at 3 years (48% vs 35%, p<0.01)
  - Radiographic progression (TSS change from baseline) at 3 years (-0.14 vs 1.6, p<0.05)
  - Radiographic progression (erosion score change from baseline) at 3 years (-0.67 vs 0.39, p<0.05)
  - Radiographic progression (JSN change from baseline) at 3 years (-0.67 vs 1.22, p<0.01)
  - number of patients achieving remission (TSS change ≤0.5 units) at 3 years (76% vs 61%, p<0.05)

- There was NS difference between etanercept + MTX and etanercept for:
  - SIMILAR FOR - proportion of patients with ≥1 treatment-emergent AEs or infections
  - Incidence of SAEs

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of

								funding
M. E. Weinblatt, E. C. Keystone, D. E. Furst, L. W. Moreland, M. H. Weisman, C. A. Birbara, L. A. Teoh, S. A. Fischkoff, and E. K. Chartash. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial.[see comment][erratum appears in Arthritis Rheum. 2003 Mar;48(3):855]. *Arthritis & Rheumatism* 48 (1):35-45, 2003. ID 2945	RCT: 1++ Multicentre trial: 35 sites in USA and Canada • Randomised (method not mentioned) • Double blind • ITT analysis • Power study (ACR 20) • Fairly high number of dropouts	Total N=271 randomised (N=69 20 mg adalimumab (+ DMARD); N=67 40 mg adalimumab (+DMARD); N=73 80 mg adalimumab (+DMARD); N=62 Placebo (+ DMARD). **Drop-outs:** N=110 non-completers (41%)	**Inclusion criteria:** Adults ≥18 years with RA (ACR criteria); active disease (at least 9 tender joints and 6 swollen joints); must have been treated with MTX for a minimum of 6 months and taking stable weekly dose for at least 4 weeks before entering the study; must have failed treatment with at least 1 DMARD besides MTX but no more than 4 DMARDs. **Exclusion criteria:** Standard exclusion criteria used in other trials of biologics in RA patients; anti-CD4 therapy or TNFα antagonists; history of active listeriosis or mycobacterial infection; major episode of infection requiring hospitalisation or treatment with antibiotics. **Baseline characteristics:** 20 mg Adalimumab + MTX group: mean age 53.5 years (SD 12.4); Female 75%; Duration of RA = Established RA (>2 years, mean 13 years); Pain (VAS) 55.1 (SD 20.6). 40 mg Adalimumab + MTX group: mean age 57.2 years (SD 11.4); Female 75%; Duration of RA = Established RA (>2 years, mean 12 years); Pain (VAS) 53.0 (SD 22.0). 80 mg Adalimumab + MTX group: mean age 55.5 years (SD	Subcutaneous injection of Adalimumab (20 mg, 40 mg or 80 mg) every other week as 2 injections + MTX* *All patients in both groups were receiving concomitant MTX therapy. In both groups all DMARDs except MTX were discontinued 4 weeks before the study. Concomitant RA therapies were permitted during the study including salicylates, NSAIDs and corticosteroids. High potency opioid analgesics were prohibited but other analgesics were allowed.	Placebo + MTX*	24 weeks (end of treatment)	ACR20, ACR50, ACR70; Improvements in ACR core set of disease activity measures (numbers of swollen and tender joints, patient and physican's global assessments of disease activity, HAQ disability index, CRP); SF-36; FACIT (Functional Assessment of Chronic Illness Therapy) fatigue scale; AEs.	Grant from Abbott Laboratories and Knoll Pharmaceuticals.

			11.7); Female 75%; Duration of RA = Established RA (>2 years, mean 13 years); Pain (VAS) 55.0 (SD 23.7). Placebo + MTX group: mean age 56.0 years (SD 10.8); Female 82%; Duration of RA = Established RA (>2 years, mean 11 years); Pain (VAS) 57.2 (SD 21.0). There were NS differences between the groups for any of the baseline characteristics.					

Effect size

BIOLOGIC (ADALIMUMAB 20 mg) + DMARD (concomitant MTX) vs PLACEBO + DMARD (concomitant MTX)

- The biologic adalimumab 20 mg + MTX was significantly better than placebo + MTX for:
  - ACR20 (% of patients improved) at 24 weeks, end of treatment (MD 24%, p<0.001);
  - ACR50 (% of patients improved) at 24 weeks, end of treatment (MD 17%, p=0.003);
  - Tender and swollen joint counts (change from baseline) at 24 weeks, end of treatment (MD 9.1 and 3.8, p<0.001 and p=0.002);
  - Patient's assessment of pain, VAS (change from baseline) at 24 weeks, end of treatment (MD 16.2, p<0.001);
  - Patient's and physician's global assessment of disease activity (change from baseline) at 24 weeks, end of treatment (MD 19.5 and 24.5, p<0.001);
  - Physician's global assessment of disease activity (change from baseline) at 24 weeks, end of treatment (p<0.001);
  - Disability index, HAQ (change from baseline) at 24 weeks, end of treatment (MD 0.27, p=0.004);
  - CRP levels (change from baseline) at 24 weeks, end of treatment (MD -1.5, p<0.001);

- The biologic adalimumab 20 mg + MTX was better than placebo + MTX for:
  - SF-36 score, improvement from baseline (in 7 of 8 domains and 4 of 8 domains respectively - values not given).

- There was NS difference between the biologic adalimumab 20 mg + MTX and placebo + MTX for:
  - ACR70 (% of patients improved) at 24 weeks, end of treatment;
  - Fatigue, FACIT (change from baseline) at 24 weeks, end of treatment.

- The biologic adalimumab 20 mg + MTX was similar to placebo + MTX for:
  - Withdrawals due to AEs (6% and 3% respectively).

BIOLOGIC (ADALIMUMAB 40 mg) + DMARD (concomitant MTX) vs PLACEBO + DMARD (concomitant MTX)

- The biologic adalimumab 40 mg + MTX was significantly better than placebo + MTX for:
  - ACR20 (% of patients improved) at 24 weeks, end of treatment (MD 36%, p<0.001);
  - ACR50 (% of patients improved) at 24 weeks, end of treatment (MD 32%, p<0.001);
  - ACR70 (% of patients improved) at 24 weeks, end of treatment (MD 4%, p<0.001)
  - Tender and swollen joint counts (change from baseline) at 24 weeks, end of treatment (MD 9.1 and 7.5, both p<0.001);
  - Patient's assessment of pain, VAS (change from baseline) at 24 weeks, end of treatment (MD 16.5, p<0.001);
  - Patient's and physician's global assessment of disease activity (change from baseline) at 24 weeks, end of treatment (MD 17.7 and 41.4, both p<0.001);
  - Disability index, HAQ (change from baseline) at 24 weeks, end of treatment (MD 0.35, p<0.001);
  - CRP levels (change from baseline) at 24 weeks, end of treatment (MD -1.7, p<0.001);
  - Fatigue, FACIT (change from baseline) at 24 weeks, end of treatment (MD 5.5, p=0.001);

- The biologic adalimumab 40 mg + MTX was better than placebo + MTX for:
  - SF-36 score, improvement from baseline (in 8 of 8 domains and 4 of 8 domains respectively – values not given) at 24 weeks, end of treatment.

- The biologic adalimumab 40 mg + MTX was similar to placebo + MTX for:
    - Withdrawals due to AEs (0% and 3% respectively).

BIOLOGIC (ADALIMUMAB 80 mg) + DMARD (concomitant MTX) vs PLACEBO + DMARD (concomitant MTX)

- The biologic adalimumab 80 mg + MTX was significantly better than placebo + MTX for:
    - ACR20 (% of patients improved) at 24 weeks, end of treatment (MD 11%, p<0.001);
    - ACR50 (% of patients improved) at 24 weeks, end of treatment (p<0.001);
    - ACR70 (% of patients improved) at 24 weeks, end of treatment (MD 11%, p=0.02)
    - Tender and swollen joint counts (change from baseline) at 24 weeks, end of treatment (MD 11.5 and 7.9, p<0.001);
    - Patient's assessment of pain, VAS (change from baseline) at 24 weeks, end of treatment (MD 19, p<0.001);
    - Patient's and physician's global assessment of disease activity (change from baseline) at 24 weeks, end of treatment (MD 14.6 and 31.2, both p<0.001);
    - Disability index, HAQ (change from baseline) at 24 weeks, end of treatment (MD 0.32, p=0.001);
    - CRP levels (change from baseline) at 24 weeks, end of treatment (MD -1.4, p<0.001);
    - Fatigue, FACIT (change from baseline) at 24 weeks, end of treatment (MD 6.5, p<0.001);

- The biologic adalimumab 80 mg + MTX was better than placebo + MTX for:
    - SF-36 score, improvement from baseline (in 8 of 8 domains and 4 of 8 domains respectively - values not given);

- The biologic adalimumab 80 mg + MTX was similar to placebo + MTX for:
    - Withdrawals due to AEs (1.4% and 3% respectively).

Adverse events

- Adalimumab and placebo were similar for the number of treatment-emergent AE's (2.16/patient year and 2.33 per patient year respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Klareskog, Heijde D. Van Der, J. P. de Jager, A. Gough, J. Kalden, M. Malaise, Mola E. Martin, K. Pavelka, J.	RCT: 1++ • Centralised telephone randomisation • Double blind • ITT	Total N= 682 **Drop-outs:** Etanercept only 30% Methotrexate only 24% Combination	**Inclusion criteria:** age ≥18 years, disease duration of 6 months to 20 years, active adult-onset RA (ACR functional class I-III) defined as ≥10 swollen and ≥12 painful joints and at least one of the following: ESR ≥28 mm/h, plasma CRP ≥20 mg/L or morning stiffness for ≥ 45min. Participants should also have had a less than satisfactory response at least 1 DMARD other than methotrexate. Individuals previously treated with methotrexate could be include provided they had not used it within 6 months of enrolment and had not had clinically important toxic effects or lack of	Etanercept 25 mg subcutaneously twice weekly + oral placebo Methotrexate 7.5 mg escalated to 20 mg orally once	Etanercept 25 mg subcutaneously twice weekly + methotrexate orally once a week All patients received 5 mg	52 weeks (end of treatment)	Primary efficacy endpoint: numeric index of ACR response (ACR-N) area under the curve (AUC) [at 24 weeks]	Wyeth Research

<table>
<tr>
<td>Sany, L. Settas, J. Wajdula, R. Pedersen, S. Fatenejad, M. Sanda, and TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.[see comment]. Lancet 363 (9410):675-681, 2004. ID 2951</td>
<td>analysis
• Power study (ACR-N AUC)
• Fairly high number of dropouts in etanercept group</td>
<td>16%</td>
<td>response.

Exclusion criteria: previous treatment with etanercept or other TNF antagonists, previous treatment with immunosuppressive drugs within 6 months of screening, use of any investigational drug or biological agent within 3 months of screening, any other DMARD or corticosteroid injection with 4 weeks of baseline visit, presence of relevant co-morbidity including active infections.

Baseline characteristics:
Demographic and baseline disease characteristics did not differ between the treatment groups.

<table>
<tr><td></td><td>Methotrexate</td><td>Etanercept</td><td>Combination</td></tr>
<tr><td>Mean age (years, SD)</td><td>53.0 (12.8)</td><td>53.2 (13.8)</td><td>52.5 (12.4)</td></tr>
<tr><td>Disease duration (mean, SD)</td><td>6.8 (5.5)</td><td>6.3 (5.1)</td><td>6.8 (5.4)</td></tr>
<tr><td>Sex (% women)</td><td>79</td><td>77</td><td>74</td></tr>
<tr><td>Previous methotrexate use (%)</td><td>42</td><td>42</td><td>44</td></tr>
<tr><td>RF + (%)</td><td>71</td><td>75</td><td>76</td></tr>
</table>
</td>
<td>a week + placebo subcutaneous injections

All patients received 5 mg folic acid twice a week</td>
<td>folic acid twice a week</td>
<td></td>
<td>ACR20

ACR50

ACR70

Disease activity score

Disability (assessed with the health assessment questionnaire)

Primary radiographic endpoint: modified total Sharp score (at 52 weeks)</td>
<td></td>
</tr>
</table>

Effect size

ETANERCEPT vs. METHOTREXATE

- ACR
  - There was no reported difference in the proportion of patients achieving ACR20, ACR50 or ACR70 between the groups.
  - The etanercept group had a ACR (AUC) than the methotrexate group: Mean difference 2.5 (0.8, 4.2); p=0.0034.
- DAS and remission
  - There was no difference in DAS between the groups, and no significant difference in the proportion of patients achieving remission.
- HAQ
  - There was no significant difference in mean HAQ scores between the groups.
- Radiology results
  - There was a greater mean change in the etanercept group than the methotrexate group in the modified Total Sharp Score which was just statistically significant [0.52 (-0.10, 1.15) vs. 2.80 (1.08, 4.51); p=0.0469], and in the erosion score [-0.30 (-0.65, 0.04) vs. 1.68 (0.61, 2.74); p=0.0077]. Similarly for the joint space narrowing score however there was no p value given [0.32 (0.00, 0.63) vs. 1.12 (0.34, 1.90); p not given].
- Adverse events
  - There was no significant difference between the groups in the incidence of adverse events or in withdrawals due to adverse events.

ETANERCEPT + METHOTREXATE vs. METHOTREXATE

- ACR
  - Significantly more patients in the combination therapy group achieved ACR20 (85% vs. 75%, p=0.0091), ACR50 (69% vs. 43%, p<0.0001) and ACR70 (43% vs. 19%, p<0.0001). The mean ACR-N AUC was significantly higher in the combination therapy group, mean difference 6.1 (4.5, 7.8); p<0.0001).
- DAS and remission
  - Mean DAS were significantly lower in the combination therapy group than the methotrexate group (p<0.0001). A significantly higher proportion of patients in the combination therapy group achieved remission (35% vs. 13%; p<0.0001).
- HAQ
  - Mean HAQ scores were significantly lower in the combination therapy group than the methotrexate group (p<0.001).
- Radiology results
  - There was a significantly greater mean change in the combination therapy group in the modified Total Sharp Score [-0.54 (-1.00, -0.07) vs. 2.80 (1.08, 4.51); p<0.0001], in joint space narrowing [-0.23 (-0.45, -0.02) vs. 1.12 (0.34, 1.90); p<0.001], and in the erosion score [-0.30 (-0.65, 0.04) vs. 1.68 (0.61, 2.74); p<0.001].
- Adverse events
  - There was no significant difference between the groups in the incidence of adverse events or in withdrawals due to adverse events.

ETANERCEPT + METHOTREXATE vs. ETANERCEPT

- ACR
  - Significantly more patients in the combination therapy group achieved ACR20 (85% vs. 76%, p=0.0151), ACR50 (69% vs. 48%, p<0.0001) and ACR70 (43% vs. 24%, p<0.0001). The mean ACR-N AUC was significantly higher in the combination therapy group, p<0.0001).
- DAS and remission
  - Mean DAS were significantly lower in the combination therapy group than the etanercept group (p<0.0001). A significantly higher proportion of patients in the combination therapy group achieved remission (35% vs. 16%; p<0.0001).

- HAQ
  - Mean HAQ scores were significantly lower in the combination therapy group than the etanercept group (p<0.001).
- Radiology results
  - There was a significantly greater mean change in the combination therapy group in the modified Total Sharp Score [-0.54 (-1.00, -0.07) vs. 0.52 (-0.10, 1.15); p=0.0006] and in joint space narrowing [-0.23 (-0.45, -0.02) vs. 0.32 (0.00, 0.63); p=0.0007]. There was also a greater mean change in the erosion score [-0.30 (-0.65, 0.04) vs. 0.21 (-0.20, 0.61); p not given].
- Adverse events
  - There was no significant difference between the groups in the incidence of adverse events or in withdrawals due to adverse events.

Summary: combination treatment alone was more efficacious than methotrexate or etanercept alone on all measures.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van der Heijde D, Klareskog L, Singh A, Tornero J, Melo GJ, Codreanu C, Pedersen R, Freundlich B, and Fatenejad S. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Annals of the Rheumatic Diseases: 65: 328 – 334, 2006 REF ID: 2986	RCT: 1++ • Centralised telephone randomisation • Double blind • Multicentre (European, Australian, Israel) • ITT analysis • Power study (ACR-N AUC) • Fairly high number of dropouts in etanercept group	Total N= 682 **Drop-outs:** Total 522/682 (76%) Etanercept only 30% Methotrexate only 24% Combination 16%	**Inclusion criteria:** age ≥18 years, disease duration of 6 months to 20 years, active adult-onset RA (ACR functional class I-III) defined as ≥10 swollen and ≥12 painful joints and at least one of the following: ESR ≥28 mm/h, plasma CRP ≥20 mg/L or morning stiffness for ≥ 45min. Participants should also have had a less than satisfactory response at least 1 DMARD other than methotrexate. Individuals previously treated with methotrexate could be include provided they had not used it within 6 months of enrolment and had not had clinically important toxic effects or lack of response. **Exclusion criteria:** previous treatment with etanercept or other TNF antagonists, previous treatment with immunosuppressive drugs within 6 months of screening, use of any investigational drug or	Etanercept 25 mg subcutaneously twice weekly + oral placebo Methotrexate 7.5 mg escalated to 20 mg orally once a week (if patients still had any painful or swollen joints)+ placebo subcutaneous injections All patients received 5 mg folic acid twice a week	Etanercept 25 mg subcutaneously twice weekly + methotrexate 7.5 mg escalated to 20 mg orally once a week All patients received 5 mg folic acid twice a week	52 weeks	Primary efficacy endpoint: Health Assessment Questionnaire (HAQ) disability index EuroQoL health status visual analogue scale (EQ5D VAS) Patient global assessment of overall RA activity (PGAD) 0-10 Patient General Health Assessment (GHVAS) 0-10 VAS Patient satisfaction (measured on a 5	Wyeth Research

			biological agent within 3 months of screening, any other DMARD or corticosteroid injection with 4 weeks of baseline visit, presence of relevant co-morbidity including active infections. **Baseline characteristics:** Demographic and baseline disease characteristics did not differ between the treatment groups. Methotrexate alone: mean age 53.0 years (SD 12.8); Female 79%; Duration of RA mean 6.8 years (SD 5.5), HAQ score mean 1.7 (SD 0.7), satisfied with previous medication 3.1%. Etanercept alone: mean age 53.2 years (SD 13.8); Female 77%; Duration of RA mean 6.3 years (SD 5.1), HAQ score mean 1.7 (SD 0.7), satisfied with previous medication 0.9%. Combination: mean age 52.5 years (SD 12.4); Female 74%; Duration of RA mean 6.8 years (SD 5.4), HAQ score mean 1.8 (SD 0.6), satisfied with previous medication 3.0%.				point scale)	

Effect size

ETANERCEPT vs. METHOTREXATE

- HAQ
  - There was no significant difference between etanercept and methotrexate for any HAQ subscale or for HAQ overall.
  - HAQ improvement: a significantly greater proportion of patients on etanercept alone than on methotrexate alone achieved a major improvement of >0.8 (45% vs. 36%; $p<0.05$).

- There were no significant differences between etanercept and methotrexate for either EQ5D VAS, PGAD or GHVAS.
- Patient satisfaction
  - A higher proportion of patients in the etanercept therapy group were satisfied with their treatment than those on methotrexate (85.5% vs. 71.9%, p=0.0005)

ETANERCEPT + METHOTREXATE vs. METHOTREXATE

- HAQ
  - Subjects receiving combination therapy achieved significantly greater improvement in functional status than those receiving methotrexate alone from 2 weeks onwards (p<0.01 at 52 weeks).
  - Subjects receiving combination therapy also achieved significantly greater improvements in all HAQ subscales except grip than the methotrexate alone group (p<0.05).
  - HAQ improvement: a significantly greater proportion of patients on combination therapy than on methotrexate alone achieved a clinically meaningful HAQ improvement of ≥0.22 (86% vs. 77%; p<0.05); as well as a major improvement of >0.8 (58% vs. 36%; p<0.05).
  - Combination therapy provided significantly faster onset of sustained HAQ scores of ≤0.5 than methotrexate alone, p=0.005.
- EQ5D VAS
  - Combination therapy patients had significantly higher EQ5D VAS scores than those on methotrexate alone, p<0.01
- PGAD
  - Combination therapy patients had significantly greater improvement in PGAD scores than those on methotrexate alone from 2 weeks onwards, p<0.05
- GHVAS
  - Combination therapy patients had significantly lower GHVAS scores than those on methotrexate alone, p<0.01
- Patient satisfaction
  - A higher proportion of patients in the combination therapy group were satisfied with their treatment than those on methotrexate alone (87.8% vs. 71.9, p<0.0001)

ETANERCEPT + METHOTREXATE vs. ETANERCEPT

- HAQ
  - Subjects receiving combination therapy achieved significantly greater improvement in functional status than those receiving etanercept alone from 4 weeks onwards (p<0.01 at 52 weeks).
  - Subjects receiving combination therapy also achieved significantly greater improvements in the eating, hygiene, reaching and walking HAQ subscales than the etanercept alone group (p<0.05).
  - HAQ improvement: a significantly greater proportion of patients on combination therapy than on etanercept alone achieved a clinically meaningful HAQ improvement of ≥0.22 (86% vs. 77%; p<0.05); as well as a major improvement of >0.8 (58% vs. 45%; p<0.05).
  - Combination therapy provided significantly faster onset of sustained HAQ scores of ≤0.5 than etanercept alone, p=0.002.
- EQ5D VAS
  - Combination therapy patients had significantly higher EQ5D VAS scores than those on etanercept alone, p<0.05
- PGAD
  - Combination therapy patients had significantly greater improvement in PGAD scores than those on etanercept alone from 12 weeks onwards, p<0.01
- GHVAS
  - Combination therapy patients had significantly lower GHVAS scores than those on etanercept alone, p<0.01
- Patient satisfaction

o There was no significant difference in patient satisfaction between the combination therapy group and those on etanercept alone (87.8% vs. 85.5%, p=0.4716)								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Van der Heijde D, Klareskog L, Rodriguez VV, Codreanu C, Bolosiu H, Melo GJ, Tornero MJ, Wajdula J, Pedersen R, Fatenejad S, and TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial.[see comment]. Arthritis & Rheumatism: 54: 1063 – 1074, 2006	RCT: 1++ • Centralised telephone randomisation • Double blind • ITT analysis • Power study (ACR-N AUC) • Fairly high number of dropouts in etanercept group • Multicentre (European, Australian, Israel)	Total N= 682, N=503 entered second year **Drop-outs:** Total 262/682 (38%) Year 2: 83/502 (16%) Etanercept only Total 86/223 (39%) Year 2: 26/163 (16%) Methotrexate only Total 109/ 228 (48%) Year 2: 33/152 (22%) Combination Total 67/231 (29%) Year 2:	**Inclusion criteria:** age ≥18 years, disease duration of 6 months to 20 years, active adult-onset RA (ACR functional class I-III) defined as ≥10 swollen and ≥12 painful joints and at least one of the following: ESR ≥28 mm/h, plasma CRP ≥20 mg/L or morning stiffness for ≥ 45min. Participants should also have had a less than satisfactory response at least 1 DMARD other than methotrexate. Individuals previously treated with methotrexate could be include provided they had not used it within 6 months of enrolment and had not had clinically important toxic effects or lack of response. **Exclusion criteria:** previous treatment with etanercept or other TNF antagonists, previous treatment with immunosuppressive drugs within 6 months of screening, use of any investigational drug or biological agent within 3 months of screening, any other DMARD or corticosteroid injection with 4 weeks of baseline visit, presence of relevant co-morbidity including active infections. **Baseline characteristics:** Demographic and baseline disease characteristics did not differ between the	Etanercept 25 mg subcutaneously twice weekly + oral placebo N= 163 in year 2 Methotrexate 7.5 mg escalated to 20 mg orally once a week (if patients still had any painful or swollen joints)+ placebo subcutaneous injections N=152 in year 2 All patients received 5 mg folic acid twice a week	Etanercept 25 mg subcutaneously twice weekly + methotrexate 7.5 mg escalated to 20 mg orally once a week N=188 in year 2 All patients received 5 mg folic acid twice a week	2 years	Primary efficacy endpoint: numeric index of ACR response (ACR-N) area under the curve (AUC) ACR20 ACR50 ACR70 HAQ Disease activity score: DAS and DAS28 Radiographic endpoints: modified total Sharp score (TSS) Erosions Joint space narrowing (JSN) Adverse events	Wyeth Research

REF ID: 151 (?2985)		24/188 (13%)	treatment groups, and in year 2 were similar to the study populations at baseline. Methotrexate alone: mean age 53.0 years (SD 12.8); Female 79%; Duration of RA mean 6.8 years (SD 5.5), HAQ score mean 1.7 (SD 0.7), mean methotrexate dose in year 2 was 16.5 mg (17.2 mg in year 1). Etanercept alone: mean age 53.2 years (SD 13.8); Female 77%; Duration of RA mean 6.3 years (SD 5.1), HAQ score mean 1.7 (SD 0.7). Combination: mean age 52.5 years (SD 12.4); Female 74%; Duration of RA mean 6.8 years (SD 5.4), HAQ score mean 1.8 (SD 0.6), mean methotrexate dose in year 2 was 16.4 mg (16.9 mg in year 1).					

Effect size

ETANERCEPT vs. METHOTREXATE

- ACR
  - There was no significant difference between the etanercept and methotrexate groups in ACR20, ACR50 and ACR70.
  - There was no significant difference between the groups in the individual components of the ACR criteria (number of swollen joints, pain VAS, physicians global assessment, patients global assessment, HAQ and CRP) except for the number of painful joints which was significantly higher in the etanercept than in the methotrexate group ($p<0.05$).
- DAS and remission
  - The proportion of patients achieving remission (DAS<1.6) was also significantly higher in the etanercept group than the methotrexate group (23% vs 16%, $p=0.05$).
- Radiology results
  - There was a significantly greater mean change in the etanercept group than the methotrexate group in TSS [1.10 (0.13, 2.07) vs. 3.34 (1.18, 5.50); MD 2.24, $p<0.05$] and erosion score [0.36(-0.25, 0.97) vs. 2.12 (0.66, 3.57); MD 1.76, $p<0.05$].
  - More patients on etanercept had no erosions than those on methotrexate (75% vs. 66%, $p<0.05$).

ETANERCEPT + METHOTREXATE vs. METHOTREXATE

- ACR
  - Significantly more patients in the combination therapy group than in the methotrexate alone group achieved an ACR20 response (86% vs. 71%, $p<0.01$); an ACR50 response (71% vs. 42%, $p<0.01$); and an ACR70 response (49% vs. 21%, $p<0.01$).
  - For all the individual components of the ACR criteria (number of swollen joints, number of painful joints, pain VAS, physicians global assessment, patients global assessment, HAQ and CRP), there was significantly greater improvement in the combination therapy group than in the methotrexate alone group ($p<0.01$ for all).
- DAS and remission
  - Mean DAS was significantly lower in the combination therapy group than the methotrexate group (2.2 vs. 3.0, $p<0.01$); proportion of patients achieving remission (DAS<1.6) was also significantly higher in the combination therapy group ($p<0.01$).
- HAQ
  - There was significantly greater improvement in HAQ scores in the combination therapy group than the methotrexate group ($p<0.05$)
  - More patients in the combination therapy group than those receiving methotrexate alone achieved a minimal clinically important improvement in HAQ score of ≥0.22 (87% vs. 74%, $p<0.01$); as well as a major improvement of >0.8 (62% vs. 35%; $p<0.05$).
- Radiology results
  - There was a significantly greater mean change in the combination therapy group than the methotrexate group in TSS [-0.56(-1.05, -0.06) vs. 3.34 (1.18, 5.50); $p<0.05$], erosion score [-0.76(-1.13, -0.38) vs. 2.12 (0.66, 3.57); $p<0.05$], and JSN score [0.20(-0.03, 0.44) vs. 1.23 (0.39, 2.06); $p<0.05$].
  - 78% of patients on combination therapy had no radiographic progression compared with 60% of those on methotrexate ($p<0.05$); 86% had no progression of erosions compared with 66% on methotrexate ($p<0.05$).

ETANERCEPT + METHOTREXATE vs. ETANERCEPT

- ACR
  - Significantly more patients in the combination therapy group than in the etanercept alone group achieved an ACR20 response (86% vs. 75%, $p<0.01$); an ACR50 response (71% vs. 54%, $p<0.01$); and an ACR70 response (49% vs. 27%, $p<0.01$).

- For all the individual components of the ACR criteria (number of swollen joints, number of painful joints, pain VAS, physicians global assessment, patients global assessment, HAQ and CRP), there was significantly greater improvement in the combination therapy group than in the etanercept alone group (p<0.05 for all).

- DAS and remission
  - Mean DAS was significantly lower in the combination therapy group than the etanercept group (2.2 vs. 2.9, p<0.01); proportion of patients achieving remission (DAS<1.6) was also significantly higher in the combination therapy group (p<0.01).
- HAQ
  - There was significantly greater improvement in HAQ scores in the combination therapy group than the etanercept group (p<0.05).
  - More patients in the combination therapy group than those receiving etanercept alone achieved a minimal clinically important improvement in HAQ score of ≥0.22 (87% vs. 76%, p<0.05); as well as a major improvement of >0.8 (62% vs. 42%; p<0.05)
- Radiology results
  - There was a significantly greater mean change in the combination therapy group than the etanercept group in TSS [-0.56(-1.05, -0.06) vs. 1.10 (0.13, 2.07); p<0.05], erosion score [-0.76(-1.13, -0.38) vs. 0.36 (-0.25, 0.97); p<0.05], but not for the JSN score [0.20(-0.03, 0.44) vs. 0.74 (0.25, 1.23), no p given].
  - 78% of patients on combination therapy had no radiographic progression compared with 68% of those on etanercept (p<0.05), 86% had no progression of erosions compared with 75% on etanercept (p<0.05).

Adverse events

There was no significant difference in the proportion of patients reporting 1/> adverse events across treatment groups.
No significant differences were seen between the groups in the incidence of serious adverse events, either infectious or non-infectious.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. C. Keystone, A. F. Kavanaugh, J. T. Sharp, H. Tannenbaum, Y. Hua, L. S. Teoh, S. A. Fischkoff, and E. K. Chartash. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis	RCT: 1+ Multicentre trial: 89 sites in USA and Canada • Randomised (method not mentioned) • Double blind • Not true ITT analysis • Power study (ACR 20) • Fairly high number of dropouts in 2 groups	Total N=619 randomised (N=212 20 mg adalimumab (+ MTX); N=207 40 mg adalimumab (+MTX); N=200 Placebo (+ MTX). **Drop-outs:** N=26 (13%) adalimumab	**Inclusion criteria:** Adults ≥18 years with RA (ACR criteria); and had ≥9 tender joints and ≥6 swollen joints; CRP >1 mg/dl and either rheumatoid factor positivity or at least 1 joint erosion on radiographs of the hands and feet; must have been treated with MTX for a minimum of 3 months at stable dose of 12.5-25 mg/week (or >10 mg/week on patients intolerant to MTX) for at least 4 weeks before entering the study. **Exclusion criteria:** Prior use of anti-CD4 therapy or TNFα antagonists; history of active inflammatory arthritide other than RA; history of active listeriosis or mycobacterial infection; malignancy within 5 years; major	Subcutaneous injection of Adalimumab (20 mg or 40 mg) every other week (with placebo injections on alternate weeks) + MTX* *All patients in the 3 groups were receiving concomitant MTX therapy. In all groups all	Placebo + MTX* Injections of placebo once/ week.	52 weeks (end of treatment)	ACR20, ACR50, ACR70; Improvements in ACR core set of disease activity measures (numbers of swollen and tender joints, patient and physican's global assessments of disease activity, patient's	Grant from Abbott Laboratories, USA.

factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis & Rheumatism* 50 (5):1400-1411, 2004. ID 2947		40mg + MTX N= 44 (21% adalimumab 20 mg + MTX N=60 (30%) placebo + MTX	episode of infection requiring hospitalisation or treatment with antibiotics; uncontrolled medical condition. **Baseline characteristics:** 20 mg Adalimumab + MTX group: mean age 57.3 years (SD 10.5); Female 76%; Duration of RA = Established RA (>2 years, mean 11 years); Pain (VAS) 55.2 (SD 23.0). 40 mg Adalimumab + MTX group: mean age 56.1 years (SD 13.5); Female 76%; Duration of RA = Established RA (>2 years, mean 11 years); Pain (VAS) 55.9 (SD 20.4). Placebo + MTX group: mean age 56.1 years (SD 12.0); Female 73%; Duration of RA = Established RA (>2 years, mean 11 years); Pain (VAS) 56.3 (SD 22.9). The 3 groups were similar for all baseline characteristics.	DMARDs except MTX were discontinued at least 28 days before the study. Concomitant RA therapies were permitted and kept constant during the study. Patients not achieving ACR20 at week 16 or thereafter were allowed to receive rescue treatment with a traditional DMARD at the discretion of their treating physician.			assessment of pain; HAQ disability index, CRP);Physical function (disability index of HAQ); Quality of Life (SF-36); Erosion score, Joint space narrowing score and total score (Sharp method); AEs.	

Effect size

BIOLOGIC (ADALIMUMAB 20 mg) + DMARD (concomitant MTX) vs PLACEBO + DMARD (concomitant MTX)

- The biologic adalimumab 20 mg + MTX was significantly better than placebo + MTX for:
    - Radiographic progression – total Sharp score (change from baseline) at 52 weeks, end of treatment (MD 1.9, p≤0.001);
    - Radiographic progression – joint erosion score (change from baseline) at 52 weeks, end of treatment (MD 1.2, p≤0.001);
    - ACR20 (% of patients improved) at 52 weeks, end of treatment (MD 30.7%, p≤0.001);
    - ACR50 (% of patients improved) at 52 weeks, end of treatment (MD 28.2%, p≤0.001);
    - ACR70 (% of patients improved) at 52 weeks, end of treatment (MD 28.2%, p≤0.001);
    - Tender joint count (change from baseline) at 52 weeks, end of treatment (MD 7.2, p≤0.001);
    - Swollen joint count (change from baseline) at 52 weeks, end of treatment (MD 6.1, p≤0.001);
    - Patient's assessment of pain, VAS (change from baseline) at 52 weeks, end of treatment (MD 16.2, p≤0.001);
    - Patient's and physician's global assessment of disease activity (change from baseline) at 52 weeks, end of treatment (MD 13.2 and 16.7, both p≤0.001);
    - Disability index, HAQ (change from baseline) at 52 weeks, end of treatment (p ≤0.001);
    - CRP levels (change from baseline) at 52 weeks, end of treatment (MD 0.6, p≤0.001);
    - SF-36 all domains (change from baseline) at 52 weeks, end of treatment (values not given, p≤0.001).

- The biologic adalimumab 20 mg + MTX was better than placebo + MTX for:
    - Total number of withdrawals (21% and 30% respectively);
    - Withdrawals due to lack of efficacy (8% and 12% respectively);
    - Withdrawals due to AEs (3% and 7% respectively).

- There was NS difference between the biologic adalimumab 20 mg + MTX and placebo + MTX for:
    - Radiographic progression – JSN score (change from baseline) at 52 weeks, end of treatment.

BIOLOGIC (ADALIMUMAB 40 mg) + DMARD (concomitant MTX) vs PLACEBO + DMARD (concomitant MTX)

- The biologic adalimumab 40 mg + MTX was significantly better than placebo + MTX for:
    - Radiographic progression – total Sharp score (change from baseline) at 52 weeks, end of treatment (MD 2.6, p≤0.001);
    - Radiographic progression – joint erosion score (change from baseline) at 52 weeks, end of treatment (MD 1.6, p≤0.001);
    - Radiographic progression – JSN score (change from baseline) at 52 weeks, end of treatment (MD 0.9, p≤0.001);
    - ACR20 (% of patients improved) at 52 weeks, end of treatment (MD 34.9%, p≤0.001);
    - ACR50 (% of patients improved) at 52 weeks, end of treatment (MD 32%, p≤0.001);
    - ACR70 (% of patients improved) at 52 weeks, end of treatment (MD 19.7%, p≤0.001);
    - Tender and swollen joint counts (change from baseline) at 52 weeks, end of treatment (MD 7 and 6.3, both p≤0.001);
    - Patient's assessment of pain, VAS (change from baseline) at 52 weeks, end of treatment (MD 18.2, p ≤0.001);
    - Patient's and physician's global assessment of disease activity (change from baseline) at 52 weeks, end of treatment (MD 16.6, p≤0.001);
    - Disability index, HAQ (change from baseline) at 52 weeks, end of treatment (MD 0.34, p≤0.001);
    - CRP levels (change from baseline) at 52 weeks, end of treatment (MD 0.6, p≤0.001);

- SF-36 all domains except emotional role (change from baseline) at 52 weeks, end of treatment (values not given, p≤0.001).

- The biologic adalimumab 40 mg + MTX was better than placebo + MTX for:
  - Total number of withdrawals (23% and 30% respectively);
  - Withdrawals due to AEs (3% and 7% respectively).

- There was NS difference between the biologic adalimumab 40 mg + MTX and placebo + MTX for:
  - SF-36 domain emotional role (change from baseline) at 52 weeks, end of treatment.

- The biologic adalimumab 40 mg + MTX was similar to placebo + MTX for:
  - Withdrawals due to lack of efficacy (13% and 12% respectively).

Adverse events

- Adalimumab and placebo were similar for the number of patients reporting at least 1 AE (93.3% and 90.5% respectively);
- Adalimumab and placebo were similar for the rate of AEs (1.07 and 1.12 patients/patient year respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D.E. Furst, M.H. Schiff, R.M Fleischmann, V. Strand, C.A Birbara, D. Compagnone, S.A. Fischkoff, E.K. Chartash. Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, and	RCT: 1++ Multisite study (US and Canada) • Randomisation method not mentioned • Double blind • Placebo controlled • ITT analysis • Power study (adverse events) • Low dropouts	Total N= 636 **Drop-outs:** 58/636 (9%) Adalimumab 28/318 (8.8%) Placebo 30/318 (9.4%)	**Inclusion criteria:** ≥18 years, active RA defined by ≥6 swollen joints and ≥9 tender joints, met the 1987 revised ACR criteria for RA for at least 3 months. **Exclusion criteria:** criteria used in trials of other biologic DMARD in RA, additional criteria were: patients treated with anti-CD4 therapy or biologic DMARD, and/or a history of an active inflammatory arthride other than RA, active listeriosis or mycobacterial infection, major episode of infection within 30 days prior to screening or oral antibiotics within 14 days prior to screening, any uncontrolled medical condition.	Adalimumab 40 mg subcutaneously every alternate week Patients in both groups continued to receive their baseline doses of standard anti-rheumatic therapy which could include traditional DMARD, low dose	Placebo	24 weeks	Primary endpoint: types and frequencies of adverse events Secondary endpoints: ACR20, ACR50, ACR70 (from baseline to week 24)	Abbott laboratories (USA)

concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) *Journal of Rheumatology* 30: 2563-71, 2003 ID 2946			**Baseline characteristics:** Age (yrs): Adalimumab 55.0 (12.8), Placebo 55.8 (12.4) Sex (% women): Adalimumab 79.6, Placebo 79.2 Disease duration (yrs): Adalimumab 9.3 (8.8), Placebo 11.5 (9.7) Pain (VAS 0-100mm): Adalimumab 55.1 (22.5), Placebo 55.6 (22.5) Traditional DMARD use: Adalimumab 57/318, Placebo 48/318 0 DMARD: Adalimumab 184/318, Placebo 172/318 1 DMARD: Adalimumab 66/318, Placebo 84/318 2 DMARD	corticosteroids, NSAID and/or analgesics.				

Effect size

BIOLOGIC (ADALIMUMAB) vs PLACEBO
Patients receiving adalimumab plus standard anti-rheumatic therapy achieved statistically superior ACR20 (52.8% vs. 34.9%), ACR50 (28.9% vs. 11.3%), ACR70 (14.8% vs. 3.5%); p≤0.001).
Patients receiving adalimumab 40mg with 1 or 2 traditional DMARDS achieved significantly greater ACR20 responses than did placebo (p ≤0.001).
Patients receiving adalimumab 40mg with 0, 1 or 2 traditional DMARDS achieved significantly greater ACR50 and ACR70 response rates than did placebo (p≤0.05).

Adverse events
There was no significant difference between the groups in the incidence of adverse events, serious adverse events, severe or life threatening adverse events or adverse events leading to withdrawal.
The only more frequently reported adverse events that occurred in significantly greater proportions of adalimumab treated patients were injection site reactions (p≤0.01), rash at site other than injection site (p≤0.05), and back pain (p≤0.01).
Adverse event profile did not appear to vary according to the number of concomitant traditional DMARD used.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Combe B, Codreanu C,	RCT 1++	N=254	**Inclusion criteria:** patients were ≥ 18 years of age,	Etanercept 25 mg	sulphasalazine 2/2.5/3g once	24 weeks	Primary efficacy endpoint: ACR20	Wyeth research,

Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Wajdula J, Fatenejad S, and Etanercept European Investigators Network (Etanercept Study. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Annals of the Rheumatic Diseases: 65: 1357 – 1362, 2006 REF ID: 100.	• Randomised (method not mentioned) • Double blind • Multicentre • ITT analysis • Allocation concealment not mentioned	Drop outs N=33/254 (13%)	disease duration ≤ 20 years, active adult-onset RA (functional class I-III)[defined as ≥ 6 swollen joints, ≥ 10 painful joints, and at least one of the following: ESR ≥ 28 mm/hr, CRP ≥20 mg/l or morning stiffness ≥ 45 min]. Patients must have received stable doses of sulphasalazine (2-3g/day) for ≥ 4 months before screening without signs of toxicity. **Exclusion criteria:** receipt of etanercept or other TNF antagonists, receipt of a DMARD other than sulphasalazine with 3 months before baseline, use of any immunosuppressive biological agents or cyclophosphamide within 6 months of screening, parenteral corticosteroids within 4 weeks of screening, presence of relevant co morbidity including active infections, cancer, congestive heart failure, uncontrolled hypertension, severe pulmonary disease, leucopenia, renal disease, thrombocytopaenia, connective tissue disorders other than RA, pregnancy or breastfeeding. **Baseline characteristics:** there were no major differences in baseline	subcutaneously twice weekly + placebo N=103 Etanercept 25 mg subcutaneously twice weekly + sulphasalazine 2/2.5/3g once daily N=101	daily + placebo N=50		Secondary efficacy endpoint: ACR50 ACR70 Disease Activity Score (DAS) Number of painful joints Number of swollen joints Morning stiffness (min) Physician and patient global assessments Pain VAS HAQ General health VAS EuroQoL VAS ESR CRP	USA

			characteristics other than the number of patients with a history of corticosteroid use. Etanercept group: mean age 51.3 years (SD 13.5); Female 78.6%; Duration of RA = Established RA (>2 years, mean 7.1 years); Pain (VAS) 62.6 (SD 21.7); proportion using corticosteroids 59.2%. Sulphasalazine group: mean age 53.3 years (SD 12.8); Female 82%; Duration of RA = Established RA (>2 years, mean 5.6 years); Pain (VAS) 58.8 (SD 20.0); proportion using corticosteroids 40%. Etanercept + sulphasalazine group: mean age 50.6 years (SD 12.3); Female 80.2%; Duration of RA = Established RA (>2 years, mean 6.5 years); Pain (VAS) 58.5 (SD 20.7); proportion using corticosteroids 44.6%.					

Effect size

ETANERCEPT vs. SULPHASALAZINE vs. ETANERCEPT + SULPHASALAZINE

- The proportion of patients achieving ACR20, ACR50 and ACR70 was significantly higher in the groups receiving etanercept than those receiving sulphasalazine alone.

	ETANERCEPT	ETANERCEPT + SULPHASALAZINE	SULPHASALAZINE
ACR20 (%)	73.8	74.0	28.0 p<0.05 vs. etanercept; p<0.05 vs. combination At week 24, p<0.01 vs. any etanercept group
ACR50 (%)	46.6	52.0	14.0

		At week 2 and week 4, p<0.05 vs. etanercept	p<0.05 vs. etanercept; p<0.05 vs. combination At week 24, p<0.01 vs. any etanercept group
ACR70 (%)	21.4	25.0	2 p<0.05 vs. etanercept; p<0.05 vs. combination At week 24, p<0.01 vs. any etanercept group

For all other efficacy variables, etanercept alone or in combination resulted in significantly greater improvement than the improvement with the continuation of sulphasalazine alone. At all visits the improvements in the groups receiving etanercept were not different from each other:

- DAS: there was significantly greater improvement in the groups receiving etanercept alone (48.2%) and in combination (49.7%), than the group receiving sulphasalazine alone (19.6%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Painful joints: there was significantly greater improvement in the groups receiving etanercept alone (65.4%) and in combination (62.0%), than the group receiving sulphasalazine alone (22.7%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Swollen joints: there was significantly greater improvement in the groups receiving etanercept alone (68.7%) and in combination (70.1%), than the group receiving sulphasalazine alone (38.5%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Morning stiffness (min): there was significantly greater improvement in the groups receiving etanercept alone (62.8%) and in combination (68.5%), than the group receiving sulphasalazine alone (-21.1%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Physician global assessments: there was significantly greater improvement in the groups receiving etanercept alone (59.9%) and in combination (62.0%), than the group receiving sulphasalazine alone (16.0%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Patient global assessments: there was significantly greater improvement in the groups receiving etanercept alone (50.5%) and in combination (53.5%), than the group receiving sulphasalazine alone (13.6%); p<0.01 for etanercept or combination vs. sulphasalazine.
- Pain VAS: there was significantly greater improvement in the groups receiving etanercept alone (55.6%) and in combination (53.9%), than the group receiving sulphasalazine alone (13.6%); p<0.01 for etanercept or combination vs. sulphasalazine.
- HAQ: there was significantly greater improvement in the groups receiving etanercept alone (35.3%) and in combination (40.2%), than the group receiving sulphasalazine alone (9.2%); p<0.01 for etanercept or combination vs. sulphasalazine.
- EuroQoL VAS: there was significantly greater improvement in the groups receiving etanercept alone (64.6%) and in combination (67.6%), than the group receiving sulphasalazine alone (20.1%); p<0.01 for etanercept or combination vs. sulphasalazine.
- ESR: there was significantly greater improvement in the groups receiving etanercept alone (37.6%) and in combination (43.0%), than the group receiving sulphasalazine alone (0.2%); p<0.01 for etanercept or combination vs. sulphasalazine.
- CRP: there was significantly greater improvement in the groups receiving etanercept alone (69.9%) and in combination (66.7%), than the group receiving sulphasalazine

alone (32.9%); p<0.01 for etanercept or combination vs. sulphasalazine.

Adverse events

- There was no significant difference in the proportion of patients in each group that withdrew because of adverse events.
- Infections: there were significantly more infections in the group receiving etanercept alone (45.6%) than the group receiving the combination (30.7%; p<0.05 vs. etanercept alone) or sulphasalazine alone (26.0%; p<0.05 vs. etanercept alone).
- There was a significant decrease in mean white blood cell counts in those receiving combination treatment than those receiving either monotherapy (p<0.001).
- There were significantly more injection site reaction in the group receiving etanercept alone (33%) than the group receiving the combination (16%; p<0.05 vs. etanercept alone) or sulphasalazine alone (1%; p<0.05 vs. etanercept alone or combination).
- Headache, nausea and asthenia occurred most often in the combination treatment group (p<0.05 vs. etanercept alone)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU, and START Study Group. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various co morbidities: a large, randomized, placebo-controlled trial. Arthritis & Rheumatism:	RCT 1++ • Randomised (adaptive allocation, stratified according to site and steroid use) • Double blind • Multicentre • Allocation concealment not mentioned • ITT analysis • Power study Sites were in North America, Europe, Australia, New Zealand and Argentina.	N=1084 Drop outs at week 22: Group 1: 23/363 (6.3%) Group 2: 26/360 (7.2%) Group 3: 32/361 (8.9%)	**Inclusion criteria:** eligible patients had RA according to ACR criteria, had active disease [defined as the presence of 6 swollen and 6 tender joints] despite receiving methotrexate, may or may not been treated with other concomitant DMARDs, all patients must have been receiving methotrexate for at least 3 months and on a stable dose for 4 weeks prior to randomisation. **Exclusion criteria:** opportunistic infections, serious infections during the 2 months prior to screening, known HIV infection, active TB or history of active TB with inadequate documentation of treatment, latent TB (positive PPD) and an inability to receive prophylaxis with isoniazid, lymphoproliferative disease or	**Group 2** (N=360) Weeks 0-22 Infliximab 3 mg/kg at weeks 0, 2, 6, 8 Weeks 23-46 Infliximab 3 mg/kg with a dose increase of 1.5 mg/kg if their tender joint count (TJC) and swollen joint count (SJC) was greater than the threshold of response	**Group 1** (N=363) Weeks 0-22 Placebo Weeks 23-46 This group crossed over to receive Infliximab 3 mg/kg at weeks 22, 26, 30, 38, 46 Patients in all groups continued to receive stable doses of methotrexate up to 25	22 weeks to initial comparisons	Primary outcome: proportion of patients reporting a serious infection within the first 22 weeks Other outcomes: Adverse events TJC and SJC DAS28	Centocor research and development, Johnson and Johnson

54: 1075 – 1086, 2006 REF ID: 2989			malignancy, or congestive heart failure. Patients also excluded if they had been treated with an investigational drug within 3 months or 5 half lives, cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents, >5 mg/kg of cyclosporine or with any approved or investigational biologic agent including infliximab at any time prior to the study, except vaccines. **Baseline characteristics:** Methotrexate + placebo: median age 52.0 years (IQR 44-61); Female 83.2%; Duration of RA median 8.4 years (IQR 4-15), pain VAS median 5.9 (IQR 5-7), HAQ median 1.5 (IQR 1-2), proportion of patients on methotrexate only 70.0%, 25.3% on methotrexate + 1 other DMARD, 4.4% on methotrexate + 2 other DMARDs Methotrexate + infliximab 3 mg/kg: median age 53.0 years (IQR 45-61); Female 80.0%; Duration of RA median 7.8 years (IQR 3-15), pain VAS median 6.1 (IQR 5-8), HAQ median 1.5 (IQR 1-2), proportion of patients on methotrexate only 70.8%, 24.4% on methotrexate + 1 other DMARD, 4.7% on methotrexate + 2 other DMARDs Methotrexate + infliximab 10	**Group 3** (N=361) Weeks 0-22 Infliximab 10 mg/kg at weeks 0, 2, 6, 8 Weeks 23-46 Infliximab 10 mg/kg every 8 weeks	mg/week and other study approved anti-rheumatic drugs throughout the study.			

			mg/kg: median age 52.0 years (IQR 43-60); Female 77.8%; Duration of RA median 6.3 years (IQR 3-14), pain VAS median 5.9 (IQR 4-7), HAQ median 1.5 (IQR 1-2), proportion of patients on methotrexate only 69.8%, 24.9% on methotrexate + 1 other DMARD, 5.3% on methotrexate + 2 other DMARDs The differences in baseline characteristics were not statistically different.					

Effect size

PLACEBO + METHOTREXATE vs. INFLIXIMAB 3 mg/kg + METHOTREXATE vs. INFLIXIMAB 10 mg/kg + METHOTREXATE
Results at 22 weeks:

- Occurrence of a serious infection at 22 weeks (stratified by steroid use):
  - Combined group receiving infliximab + methotrexate vs placebo + methotrexate: relative risk 2.0 (95% CI 0.8-5.0, p=0.116)
    - North American participants relative risk 3.5 (95% CI 0.4-28.8, p=0.212)
    - European participants relative risk 3.4 (95% CI 0.7-15.1, p=0.095)
    - Australia/New Zealand relative risk 1.7 (95% CI 0.2-15.9, p=0.641)
    - Argentina relative risk 0.3 (95% CI 0.02-2.9, p=0.236)
  - Infliximab 3 mg/kg + methotrexate vs placebo + methotrexate: relative risk 1.0 (95% CI 0.3-3.1, p=0.995)
  - Infliximab 10 mg/kg + methotrexate vs placebo + methotrexate: relative risk 3.1 (95% CI 1.2-7.9, p=0.013)
- ACR response criteria
  - For ACR20, ACR50 and ACR70 there was significantly better response in the infliximab 3 mg/kg (p<0.0001 vs. placebo: ACR20 (MD 31.5%), ACR50 (MD 22.4%), ACR70 (MD 32%), the infliximab 10 mg/kg (ACR20 (MD 35.5%), ACR50 (MD 25.7%), ACR70 (MD 11.4%), p<0.0001 vs. placebo) groups and the combined infliximab group (p<0.001 vs. placebo) than the placebo group.
- DAS28
  - Mean DAS28 score at 22 weeks was significantly lower in the infliximab 3 mg/kg (MD 0.9%), 10 mg/kg (MD 1.1%) and the combined group than the placebo group (p<0.001 vs. placebo for all).
  - A significantly higher proportion of patients achieved remission in the infliximab groups than the placebo group (both: MD 17%, p<0.001 vs. placebo for all).
- Adverse events
  - Adverse events reported in 66.2% of placebo group, 69.7% of infliximab 3 mg/kg group and 72.3% of infliximab 10 mg/kg group (no significant difference).

Dose escalation phase:

- Adverse events
  - Types of adverse and serious adverse events that occurred in the 2nd phase of the study did not differ significantly from those reported in the first 22 weeks
  - Overall rates of serious infections were similar between the treatment groups.
  - There were similar rates of infections, serious infections and other adverse events among those who had a dose escalation and those who did not have a dose escalation (i.e. they continued at infliximab dose 3 mg/kg).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Strand V, Balbir GA, Pavelka K, Emery P, Li N, Yin M, Lehane PB, and Agarwal S. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology: 45: 1505 – 1513, 2006 REF ID: 2982	RCT 1++ • Randomised (method not mentioned) • Double blind • ITT analysis • Allocation concealment not mentioned	N= 161 Drop outs: At 24 weeks: Total 10/161 (6.2%) RIT 2/40 (5%) RIT+CTX 4/41 (9.8%) RIT+MTX 1/40 (2.5%) MTX 3/40 (7.5%) At 104 weeks: Total 125/161 (77.6%) RIT 36/40	**Inclusion criteria:** Adult RF seropositive patients with RA diagnosed according to 1987 ARA criteria, who failed 1-5 DMARDs and had active disease despite ongoing treatment with methotrexate (≥10 mg/week) for ≥16 weeks, with a SJC ≥8, TJC ≥8 and at least 2 of the following: elevated CRP ≥1.5g/dl or ESR ≥30 mm/hr, or morning stiffness ≥45 min. **Exclusion criteria:** Not reported **Baseline characteristics:** RTX alone: mean age 53.5 years (SD 10.2); Female 72.5%; Duration of RA mean 9.3 years (SD 5.5), HAQ-DI mean 2.0 (SD 0.6), DAS28 mean 6.8 (SD 1.0) RTX + CTX: mean age 52.9 years (SD 9.9); Female 82.9%; Duration of RA mean 9.8 years (SD 6.1), HAQ DI mean 1.8 (SD 0.7), DAS28 mean 6.9 (SD 0.8)	Rituximab (RIT) alone 1000 mg iv infusion (day 1 & 15) N=40 Rituximab + cyclophosphamide (CTX) (750 mg iv on days 3 & 17) N=41 Rituximab + methotrexate (MTX) (≥10 mg/week) N=40 All patients received methylprednisolone 100 mg iv before infusions (rituximab or placebo) and oral prednisolone for 2 weeks after the first infusion	Methotrexate (≥10 mg/week) + placebo rituximab N=40	2 years	Primary endpoint: ACR50 at week 24 Secondary endpoints: EULAR responses (based on improvements in DAS derived from TJC, SJC, patient assessment of disease activity and ESR or CRP).	? Genentech

		(90%) RIT+CTX 32/41 (88.1%) RIT+MTX 22/40 (55%) MTX 34/40 (85%)	RTX + MTX: mean age 53.5 years (SD 11.9); Female 75%; Duration of RA mean 11.5 years (SD 7.3), HAQ DI mean 1.8 (SD 0.6), DAS28 mean 6.8 (SD 0.9) MTX alone: mean age 53.7 years (SD 11.2); Female 80%; Duration of RA mean 11.0 years (SD 7.1), HAQ DI mean 2.0 (SD 0.5), DAS28 mean 6.9 (SD 0.7)	No further rituximab treatment was given unless initial clinical benefit lapsed and a repeat treatment was indicated.				

Effect size

PLACEBO + MTX vs. RTX alone

- The RTX alone group had greater improvements than the placebo and MTX group for:
  - ACR20 65% vs. 38% at week 24, p<0.01
  - % patients with HAQ-DI reductions ≥ 0.25 at week 24: 68% vs. 45%, p not given. These changes persisted at week 48.

PLACEBO + MTX vs. RTX + CTX

- The RTX + CTX group had greater improvements than the placebo and MTX group for:
  - ACR20 76% vs. 38% at week 24, p<0.01; 46% vs. 20% at week 48, p<0.05
  - ACR50 41% vs. 13% at week 24, p<0.01; 24% vs. 5% at week 48, p<0.05
  - EULAR response 24% vs. 16%, p not given.
  - % patients with HAQ-DI reductions ≥ 0.25 at week 24: 59% vs. 45%, p not given. These changes persisted at week 48.

PLACEBO + MTX vs. RTX + MTX

- The RTX + MTX group had greater improvements than the placebo and MTX group for:
  - ACR20 73% vs. 38% at week 24, p<0.01; 68% vs. 20% at week 48, p<0.01
  - ACR50 43% vs. 13% at week 24, p<0.01; 35% vs. 5% at week 48, p<0.01
  - ACR70 23% vs. 5% at week 24, p<0.05; 15% vs. 0% at week 48, p<0.05
  - EULAR response 39% vs. 16%, p not given
  - % patients with HAQ-DI reductions ≥ 0.25 at week 24: 63% vs. 45%, p not given. These changes persisted at week 48.

Adverse events

There were no differences in the occurrence of adverse events that led to withdrawal, serious adverse events or infections in the rituximab groups compared with the placebo + methotrexate group.

Reference	Study type Evidence level	Number of	Patient characteristics	Intervention	Comparison	Length of	Outcome measures	Source of

		patients				follow-up		funding
Emery P, Kosinski M, Li T, Martin M, Williams GR, Becker JC, Blaisdell B, Ware JE, Jr., Birbara C, and Russell AS. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. Journal of Rheumatology: 33: 681 – 689, 2006 REF ID: 2978	RCT 1+ • Randomised • Double-blind • Multicentre • No ITT analysis	N= 339 **Drop-outs:** Total 104/339 (30.7%) ABA2 + MTX 31/105 (29.5%) ABA10 + MTX 25/115 (20.7%) MTX + placebo 48/119 (40.3%)	**Inclusion criteria:** ARA criteria for RA while meeting functional class I, II or III according to the revised ACR criteria; >10 swollen, >12 tender joints and CRP >1mg/dl; been treated with MTX for ≥6 months and on a stable dose for 28 days prior to enrolment; be washed out of all DMARD other than MTX for >28 days. **Exclusion criteria:** not mentioned **Baseline characteristics:** <u>ABA2 + MTX</u>: mean age 54.4 years (range 23-80); Female 62.9%; Duration of RA mean 9.7 years (SD 8.1), RF+ 85.7%, MTX dose mean 15.8 (SD 4.8) <u>ABA10 + MTX</u>: mean age 55.8 years (range 17-83); Female 74.8%; Duration of RA mean 9.7 years (SD 9.8), RF+ 86.1%, MTX dose mean 15.0 (SD 4.4) <u>MTX + placebo</u>: mean age 54.7 years (range 23-80); Female 66.4%; Duration of RA mean 8.9 years (SD 8.3), RF+ 75.6%, MTX dose mean 15.8 (SD 4.1)	Abatacept 2 mg/kg (ABA2) + methotrexate (MTX) N=105 Abatacept 10 mg/kg (ABA10) + methotrexate N=115	Methotrexate + placebo N=119	1 year	SF-36 SF-6D (a health utility index derived from 11 items of SF-36)	Bristol-Myers Squibb

Effect size

ABA2 + MTX vs. PLACEBO + MTX

- The ABA2 group had greater improvements than the placebo group in the following:
  - 3 of the 8 components of SF-36, including physical functioning ($p<0.05$) and bodily pain ($p<0.05$). Mean change, range 2.6 to 3.0; all $p<0.05$
  - The SF-36 physical ($p<0.05$) component summary scores.
  - A greater proportion of patients than would be expected, improved across the SF-36 scales in the ABA2 group than in the placebo group, reaching statistical significance on 2 of 11 comparisons.

ABA10 + MTX vs. PLACEBO + MTX

- The ABA10 group had greater improvements than the placebo group in the following:
  - All components of SF-36, although the largest differences were observed in the bodily pain, vitality and physical functioning components, mean change, range 2.5 to 5.8, $p<0.0001$ for all.
  - The SF-36 physical ($p<0.0001$) and mental ($p<0.05$) component summary scores.
  - SF-6D mean score change ($p<0.001$).
  - A greater proportion of patients than would be expected, improved across the SF-36 scales in the ABA10 group than in the placebo group, reaching statistical significance on 10 of 11 comparisons.

ABA2 + MTX vs. ABA10 + MTX

- The ABA10 group showed greater improvement than the ABA2 group in the following:
  - 5 of the 8 SF-36 component scores; physical functioning ($p<0.05$), role physical ($p<0.05$), bodily pain ($p<0.05$), vitality ($p<0.001$) and social functioning ($p<0.05$)
  - The SF-36 physical ($p<0.05$) component summary scores.
  - SF-6D mean score change ($p<0.001$).
  - A greater proportion of patients than would be expected, improved across the SF-36 scales in the ABA10 group than in the ABA2 group, reaching statistical significance on 7 of 11 comparisons.

The magnitude of the mean score improvement on each SF-36 scale, summary measure and the SF-36 increased incrementally with increasing levels of ACR improvement.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Westhovens R, Cole JC, Li T, Martin M, MacLean R, Lin P, Blaisdell B,	RCT 1++ • Multicentre study • Double	N=391 Drop outs: Abatacept/DMARD	**Inclusion criteria:** patients were ≥18 years old, had RA for ≥1 year, met the ACR criteria for RA, treated with anti-TNF-α therapy of infliximab, etanercept or both at the approved dose for at least 3 months	Abatacept + DMARD N+258	Placebo + DMARD N=133	6 months	Health Related Quality of Life (HRQoL) measured	

<table>
<tr>
<td>Wallenstein GV, Aranda R, and Sherrer Y. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology: 45: 1238 – 1246, 2006
REF ID: 97.</td>
<td>blind
• Placebo controlled
• ITT analysis</td>
<td>13.6%

Placebo/DMARD 25.6%</td>
<td>with inadequate treatment efficacy. At randomisation patients were required to have ≥10 swollen and ≥12 tender joints and CRP levels ≥1 mg/dl.

Exclusion criteria: RA patients not treated with oral DMARDs or anakinra for at least 3 months prior to the study, not receiving a stable dose for at least 28 days or both, pregnant or nursing women. Use of mycophenolate, mofetil, cyclosporine, other calcineurin inhibitors and D-penicillamine was not permitted, nor were changes in the dose of background DMARD except for toxicity.

Baseline characteristics:
<table>
<tr><td></td><td>Abatacept/DMARD</td><td>Placebo/ DMARD</td></tr>
<tr><td>Mean age (SD)</td><td>53.4 (12.4)</td><td>52.7 (11.3)</td></tr>
<tr><td>Female (%)</td><td>77.1</td><td>79.9</td></tr>
<tr><td>Mean RA duration (SD)</td><td>12.2 (8.5)</td><td>11.4 (8.9)</td></tr>
<tr><td>RF +ve (%)</td><td>73.3</td><td>72.9</td></tr>
</table>
No significant differences were found between the groups on age, gender, race, disease duration, QoL outcomes, swollen and tender joint counts, and disease activity and pain scores.</td>
<td>Patients received a fixed dose of abatacept approximating 10mg/kg (either 500, 750 or 1000 mg depending on weight)

Oral corticosteroid use was allowed</td>
<td>Oral corticosteroid use was allowed</td>
<td></td>
<td>using SF-36 and including both scales and composite measures.

HAQ and HAQ-DI

VAS fatigue scale (0-100mm)

DAS28 (0-10)</td>
<td></td>
</tr>
</table>

Effect size

ABATACEPT + DMARD VS. PLACEBO + DMARD

On all SF-36 subscales and composite scores, HAQ-DI (MD 0.4) and fatigue VAS (MD 69.7), the abatacept + DMARD group fared significant better than the placebo + DMARD group.

The abatacept group had significantly more patients in the favourable change group i.e. patients who were 'doing better' than the placebo group in all SF-36 measures except role functioning (p=0.1901) and the mental component score (p=0.0723).

The abatacept group also had a significantly larger rate of change for all QoL outcomes (HAQ, fatigue, SF-36 - values not given) except for the SF-36 measure role emotional.

QoL improvement was significantly more related to lower baseline DAS28 values among the abatacept patients compared with placebo.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, Freundlich B, MacPeek D, and Add Enbrel or Replace Methotrexate Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Annals of the Rheumatic Diseases: 65:	RCT 1+ • Randomised • Parallel group • Open-labelled • ITT analysis • Powered study • Multi-country study	N= 314 **Drop-outs:** 30/314 (9.6%) ETN 17/160 (10.6%) ETN + MTX 13/155 (8.4%)	**Inclusion criteria:** ≥18 years, have active RA, be in ACR functional class I-III, receiving MTX ≥12.5 mg/week for a minimum of 3 months at a stable dose for at least 6 weeks at the time of enrolment. Patients must have been at least 16 years old at onset of RA, must not have used any DMARDs other than MTX within 12 weeks of screening and had inadequate control of RA symptoms on MTX treatment as defined by the presence of DAS28 ≥3.2 or a combination of ≥ 5 swollen joints, ≥ 5 painful joints and an ESR ≥10 mm/hr. **Exclusion criteria:** patients requiring concurrent use of prednisone > 10mg/day or its equivalent, presence of known relevant concurrent medical diseases, use of bolus corticosteroids within 6 weeks or intra-articular corticosteroid injections within 4 weeks of the screening visit,	Etanercept (ETN) 25 mg subcutaneously twice weekly + previous stable baseline dose of methotrexate (MTX) ≥ 12 mg/week orally or by injection N=155	Etanercept (ETN) 25 mg subcutaneously twice weekly N=160 MTX decreased and discontinued over a 4 week period.	16 weeks	Primary endpoint: proportion of patients achieving DAS28 improvement of >1.2 units Secondary endpoints: proportion of patients achieving DAS28 improvement of >1.2 units (excluding GH VAS) Time to achieve an improvement in DAS28 Flare of disease at week 4 Clinical remission EULAR response Proportion of patients achieving improvements in	Wyeth research

1478 – 1483, 2006 REF ID: 2987			and previous treatment with ETN or any other biologic treatment. **Baseline characteristics:** ETN: mean age 53 years, female 79.2%, disease duration mean 10.0 years, RF + 70.9%, HAQ mean 1.6, use of NSAIDs 74.2, use of steroids 51.6% ETN + MTX: mean age 54 years, female 76.8%, disease duration mean 9.8 years, RF + 69.5%, HAQ mean 1.7, use of NSAIDs 81.3%, use of steroids 56.8%				ACR20, ACR50 and ACR70.	

Effect size

ETN 25mg vs. ETN 25 mg + MTX

There was no significant difference between the groups with respect to the following:

- Proportion of patients with an improvement in DAS28 of >1.2 units: 72.8% vs. 75.2% respectively; p=0.658
- Proportion of patients with an improvement in DAS28 (excluding GH VAS) of >1.2 units: 64.7% vs. 72.8%; p=0.126
- The median time to achieve DAS28 improvement >1.2 units was approximately 32 days for both groups.
- Flares were not observed in any patient in the ETN group and in 1 (0.9%)patient in the ETN + MTX group.
- Proportion of patients who experienced a clinical remission was similar between the groups: 14.6% vs. 17.3%, p=0.52
- Proportion of patients who experienced a 'good' or 'moderate' EULAR response was similar between the groups: 80.0% vs. 82.4%.
- There was no significant difference in the proportion of patients achieving ACR20 (p=0.46), ACR50 (p=0.75) or ACR70 (p=0.82).
- There were no significant differences reported in the incidence of adverse events between the groups.

There was a significant difference in the final mean ESR between the groups: ETN 26.4 mm/hr vs. ETN + MTX 20.8 mm/hr; (MD -6.1, 95% CI -9.6 to -2.7, p=0.001).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Klareskog L, Gaubitz M, Rodriguez VV, Malaise M, Dougados M,	Case series 3 • Open label • Extension	N= 549 (N=41 from one trial and N=508	**Inclusion criteria:** to be included in the double-blinded trials patients had to have failed at least one DMARD, have functional class I-III of the ARA criteria for RA, met the 1987 ACR	Etanercept 25 mg subcutaneously twice weekly	Nil Treatment with a DMARD or cytotoxic agent	3 years	Primary endpoints were safety parameters: Adverse events Serious adverse	Wyeth Research

Wajdula J, and Etanercept S. A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs. Annals of the Rheumatic Diseases: 65: 1578 – 1584, 2006 REF ID: 94.	study • Multi country • Powered to detect adverse events • Patients recruited from 2 double-blind trials of etanercept vs. placebo	from the other) **Drop-outs:** At year 1 15% At year 2 25% At year 3 34%	criteria for RA, onset of RA after age 16 years and disease duration ≤15 years.[13] **Exclusion criteria:** relevant concurrent medical disease including cancer, uncompensated congestive heart failure, active infection and noticeable laboratory abnormalities, use of any investigational drug ≤ 3 months before screening for the double blind studies, use of immunosuppressive agents, or previous administration of an anti-TNF agent other than etanercept. **Baseline characteristics:** Age mean 53 years, female 79%, mean number of prior DMARDs 3.3, RF+ 86.4%, mean RA duration 7.4 years	Treatment with a DMARD or cytotoxic agent was prohibited. Corticosteroids (≤10 mg/day prednisolone or equivalent) were permitted)	was prohibited. Corticosteroids (≤10 mg/day prednisolone or equivalent) were permitted)		events Secondary endpoints were efficacy parameters: Painful joints Swollen joints (Baseline values for these were estimated at start of double-blind trials)	
Effect size Efficacy outcomes: • ACR20 remained relatively stable throughout the trial and was 77.8% at month 36. • ACR50 increased from 39.5% at month 3 to 50.6% at month 36; NS. • ACR70 increased from 18.6% at month 3 to 27.0% at month 36; NS. • DAS decreased from 5.1 at baseline to 3.0 at month 3 and continued to decrease marginally thereafter; NS. • Painful joints reduced by 63% at month 3 and 71% at month 36. • Swollen joint reduced by 65% at month 3 and 72% at month 36. • CRP decreased from 43.4 mg/l at baseline to 12.1 g/l at month 36 (-19.5 mm/h). • ESR decreased from 44.3 mm/hr at baseline to 24.8 mm/hr at month 36; (-31.3 mg/l) • HAQ score (median) decreased from 1.8 at baseline to 1.1 at month 36; (39% improvement). • Physician global assessment of 6.6 at baseline decreased to 2.9 at month 3 with a small additional improvement by month 36. • Patient global assessment of 6.7 at baseline decreased to 3.4 at month 3 with a small additional improvement by month 36. • Patient pain scores improved by 49.21% from baseline by month 36								

[13] Active RA was defined by the presence of ≥ 6 swollen joints, ≥ 12 tender joints, and one of the following: ESR ≥ 28mm/hr, CRP >20 mg/l, or morning stiffness ≥ 45 min.

Safety and tolerability outcomes:

- The 2 most common reasons for discontinuation from etanercept were adverse events (13%) and unsatisfactory response (11%).
- There were no predominant adverse events leading to discontinuation. No persistent clinically relevant laboratory abnormalities were found.
- Rates of serious infection remained unchanged over the extended course of the study.
- Rates of malignancies per patient-year remained stable throughout the study and were not higher than expected.

7.3.9 ANAKINRA (ANAKIN)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. B. Cohen, J. M. Woolley, W. Chan, and Study Group. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. *Journal of Rheumatology* 30 (2):225-231, 2003. ID 98	RCT: 1++ Multicentre trial (36 centres in USA, Canada and Australia). • Randomised (method not mentioned) • Double blind • ITT analysis	Total N=419: N= 105 had 12 weeks treatment - randomised to placebo (N=27), anakinra 0.1 mg/kg (N=28), 0.4 mg/kg (N=23), 2.0 mg/kg (N=27); N=317 had 24 weeks treatment - randomised to placebo (N=47); anakinra 0.04	**Inclusion criteria:** >6 months and <12 years symptoms of RA (ACR criteria); at least 6 swollen joints and at least 2 of the following: 9 tender/painful joints, morning stiffness lasting at least 45 mins, serum CRP level at least 1.5 mg/dl. Patients had received methotrexate (MTX) for at least 6 consecutive months, with the dosage stable for at least 4 weeks before study entry. **Exclusion criteria:** Received IA or systemic CS injection within 4 weeks of study enrollment; received penicillamine, oral or parenteral gold, azathioprine or cyclosporine within 12 weeks before study start, received hydroxychloroquine or sulfasalazine within 8 weeks before study start. **1.7 Baseline characteristics:** Placebo group (N=74): mean age 53 years;	Anakinra – doses of either 0.04, 0.1, 0.4 1.0 and 2.0 mg/kg (once daily) Patients continued to receive their current treatment of MTX (15-25 mg) throughout the study.	Placebo (once daily)	Assessments made every 4 weeks for a total period of 12 weeks (N=419 patients) or 24 weeks (N= 317 patients)	HAQ (20 items on functioning and 4 items on aids and devices – scores from 0 without difficulty to 3 unable to do). HAQ-DI (weighted sum of the scale sores. Lower scores = better functional status. MCID = decrease of	Amgen Inc., USA.

		mg/kg (N=63); 0.1 mg/kg (N=46); 0.4 mg/kg (N=54); 1.0 mg/kg (N=59) and 2.0 mg/kg (N=45). **Drop-outs:** Not mentioned	Female 85%; Duration of RA 7.8 years; HAQ-DI score 1.4. Anakinra 0.04 mg/kg group (N=63): mean age 53 years; Female 78%; Duration of RA 6.3 years; HAQ-DI 1.4. Anakinra 0.1 mg/kg group (N=74): mean age 53 years; Female 80%; Duration of RA 8.8 years; HAQ-DI 1.5. Anakinra 0.4 mg/kg group (N=77): mean age 53 years; Female 77%; Duration of RA 7.0 years; HAQ-DI 1.5. Anakinra 1.0 mg/kg group (N=59): mean age 49 years; Female 85%; Duration of RA 6.5 years; HAQ-DI 1.3. Anakinra 2.0 mg/kg group (N=72): mean age 54 years; Female 63%; Duration of RA 8.0 years; HAQ-DI 1.3. The groups were similar for all baseline characteristics. All had moderate to severe RA (based on HAQ-DI scores).				0.19 to 0.22 or 33% change.	

Effect size

ANAKINRA 0.04 mg/kg vs PLACEBO

- There was NS difference between Anakinra 0.04 mg/kg and placebo for:
  - HAQ-DI (change from baseline) at 12 weeks and 24 weeks (end of study)
  - Percentage of patients reporting no impairment of function (HAQ-DI = 0) at week 24, end of study (11.1% and 5.4% respectively)

ANAKINRA 0.1 mg/kg vs PLACEBO

- There was NS difference between Anakinra 0.1 mg/kg and placebo for:
  - HAQ-DI (change from baseline) at 12 weeks and 24 weeks (end of study)
  - Percentage of patients reporting no impairment of function (HAQ-DI = 0) at week 24, end of study (9.5% and 5.4% respectively)

ANAKINRA 0.4 mg/kg vs PLACEBO

- There was NS difference between Anakinra 0.4 mg/kg and placebo for:
  - HAQ-DI (change from baseline) at 12 weeks and 24 weeks (end of study)
  - Percentage of patients reporting no impairment of function (HAQ-DI = 0) at week 24, end of study (6.5% and 5.4% respectively)

ANAKINRA 1.0 mg/kg vs PLACEBO

- Anakinra 1.0 mg/kg was significantly better than placebo for:
  - HAQ-DI (change from baseline) at 12 weeks (-0.35, $p<0.05$) and 24 weeks, end of study (-0.37, $p<0.05$)
  - Percentage of patients reporting no impairment of function (HAQ-DI = 0) at week 24, end of study (18.6% and 5.4% respectively, $p<0.05$; OR 4.76, 95% CI 1.1 to 20.0)

ANAKINRA 2.0 mg/kg vs PLACEBO

- Anakinra 2.0 mg/kg was significantly better than placebo for:
  - HAQ-DI (change from baseline) at 12 weeks (-0.39, $p<0.01$) and 24 weeks, end of study (-0.51, $p<0.01$)

- There was NS difference between Anakinra 2.0 mg/kg and placebo for:
  - Percentage of patients reporting no impairment of function (HAQ-DI = 0) at week 24, end of study (12.5% and 5.4% respectively)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. C. Genovese, S. Cohen, L. Moreland, D. Lium, S. Robbins, R.	RCT: 1+ USA • Randomised 1:1:1 ratio	Total N=244 randomised (N=242 received medication).	**Inclusion criteria:** Adults ≥18 years, > 6 month history of RA (ACR criteria); at least 6 swollen joints and 9 tender/painful joints and at least 2 of the following: morning stiffness lasting at least 45 mins, serum CRP level at	Etanercept 25mg BIW (twice a week) Both drugs	Etanercept 25mg QW (once a week) + anakinra 100 mg QD (4	24 weeks (end of treatment) and follow-up at 4 weeks post-treatment or time of early	ACR core set of disease activity measures (ACR 20, 50 and 70 - ie. ACR 20%, 50% and 70%	Amgen Inc., USA.

Newmark, P. Bekker, and Study Group. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis & Rheumatism* 50 (5):1412-1419, 2004. ID 71	(method not mentioned) • Double blind • Not true ITT analysis	N=80 etanercept, N=81 etancercept (once/week) + anakinra, etanercept (twice/week) + anakinra **Drop-outs:** N=5 (7%) etanercept 25mg BIW, N=18 (12%) etanercept 25mg QW + anakinra 100 mg QD, N=15 (20%) etanercept 25mg BIW + anakinra 100 mg QD	least 1.5 mg/dl, ESR at least 28 mm/hour. Patients had received methotrexate (MTX) for at least 16 weeks, with the doseage stable at 10-25 mg/week for at least 8 weeks. **Exclusion criteria:** Received any DMARD other than MTX within the past 4 weeks, had ever been treated with anakinra or any protein-based TNFα inhibitor, had received any IA or systemic corticosteroid injections within the past 4 weeks, recent history o significant infection or other important concurrent illness. **Baseline characteristics:** Etanercept group: mean age 54.4 years (SD 13.6); Female 83%; Weight, kg 75 kg (SD 18); Duration of RA 9.7 years (SD 9.4); HAQ score 1.5 (SD 0.6). Etanercept once/week + anakinra group: mean age 53.8 years (SD 11.8); Female 72%; Weight, kg 82 kg (SD 21); Duration of RA 9.5 years (SD 10.3); HAQ score 1.5 (SD 0.6). Etanercept twice/week + anakinra group: mean age 55.7 years (SD 13.0); Female 78%; Weight, kg 80 kg (SD 23); Duration of RA 10.6 years (SD 9.8); HAQ score 1.6 (SD 0.6). The groups were similar for all baseline characteristics.	administered subcutaneously. Patients continued to receive stable doses of MTX and other medications (e.g. corticosteroids) throughout the study.	times a day) Etanercept 25mg BIW (twice a week) + anakinra 100 mg QD (4 times a day)	discontinuation.	response); modified Disease Activity Score (DAS); European League Against Rheumatism (EULAR) response (a measure of change in disease activity and current disease activity; % of patients good, moderate or non-responders); duration of morning stiffness; SF-36 (QoL); AEs; withdrawals. ACR50 responder = ≥50% reduction in number of tender and swollen joints and 3 of the following 5 measures: patient's global assessment of disease activity (VAS), Patients assessment of pain (VAS), disability score (HAQ) and	

							acute-phase reactants (CRP or ESR).	

Effect size*

ETANERCEPT vs ETANERCEPT (ONCE A WEEK) + ANAKINRA

- Etanercept was significantly better than etanercept (once a week) + anakinra for:
    - ACR20 (68% and 51% respectively; OR 1.98, 95% CI 1.05 to 3.78; p=0.037) at 24 weeks (end of treatment)
    - Number of withdrawals due to AEs (0% and 8.6% respectively, p value not given) at 24 weeks (end of treatment)

- Etanercept was better than etanercept (once a week) + anakinra for:
    - EULAR response (79% and 66% patients respectively) at week 24 (end of treatment)
    - Number of withdrawals (7% and 12% respectively) at 24 weeks (end of treatment)
    - Number of SAEs (2.5% and 4.9% respectively) at 24 weeks (end of treatment)
    - Number of infections and number of serious infections over 24 weeks (end of treatment)

- There was NS difference between Etanercept and etanercept (once a week) + anakinra for:
    - ACR50 (41% and 39% respectively) at 24 weeks (end of treatment)
    - ACR 70 (21% and 24% respectively) at 24 weeks (end of treatment)

- Etanercept was similar to etanercept (once a week) + anakinra for:
    - DAS score, % reduction (39% and 40% respectively) at 24 weeks (end of treatment)

ETANERCEPT vs ETANERCEPT (TWICE A WEEK) + ANAKINRA

- Etanercept was significantly better than etanercept (twice a week) + anakinra for:
    - Number of withdrawals due to AEs (0% and 7.4% respectively, p value not given) at 24 weeks (end of treatment)

- Etanercept was better than etanercept (twice a week) + anakinra for:
    - EULAR response (79% and 73% patients respectively) at week 24 (end of treatment)
    - Number of withdrawals (7% and 20% respectively) at 24 weeks (end of treatment)
    - Number of SAEs (2.5% and 14.8% respectively) at 24 weeks (end of treatment)
    - Number of infections and number of serious infections over 24 weeks (end of treatment)

- There was NS difference between Etanercept and etanercept (twice a week) + anakinra for:
    - ACR20 (68% and 62% respectively) at 24 weeks (end of treatment)
    - ACR50 (41% and 31% respectively) at 24 weeks (end of treatment)
    - ACR 70 (21% and 14% respectively) at 24 weeks (end of treatment)

- Etanercept was similar to etanercept (twice a week) + anakinra for:

o DAS score, % reduction (39% and 41% respectively) at 24 weeks (end of treatment)								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
G. Nuki, B. Bresnihan, M. B. Bear, D. McCabe. Long-term safety and maintenance of clinical improvement following treatment with Anakinra (Recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis. Arthritis & Rheumatism; 46 (11): 2838-2846, 2002 ID 107	Extension of RCT (before and after study): 3 Placebo group from original randomisation was randomised into anakinra 30/75/150 mg/day groups • Randomised (method not mentioned) • Double blind in extension phase • Not true ITT analysis (only those with triplicate radiographs were analysed) • Multicentre trial (11 European countries)	N=472 in original study N=309 (89.6%) enrolled into the extension phase; N=76 from the placebo group and N=233 from anakinra groups **Drop-outs:** 91/309 (29.4%) at 52 weeks of extension phase Anakinra to anakinra group 70/233	**Inclusion criteria:** all patients met the ACR criteria for classification of RA, disease duration ≥12 months and< 8.5 years. **Exclusion criteria:** previous receipt of other biological agents Other study inclusion and exclusion criteria were not listed in this paper. 1.8 **Baseline characteristics (of patients entering the extension phase):** Placebo to anakinra group (N=76): mean age 53.1 ± 11.3 years; Female 69.7%; Duration of RA 3.7 ± 2.5 years; presence of erosive disease 73.7%. Anakinra to anakinra group (N=233): mean age 52.7 ± 13.6 years; Female 76.8%;	Anakinra 30 mg/day by subcutaneous injection Anakinra 75 mg/day by subcutaneous injection Anakinra 150 mg/day by subcutaneous injection Above patients remained in their treatment groups for 48 weeks	Patients treated with placebo in first 24 weeks then randomised to anakinra 30/75/150 mg/day during the extension phase.	Original study 24 weeks This study extension phase a further 52 weeks	Primary efficacy endpoint: American College of Rheumatology (ACR) composite score. ACR20 as assessed at week 48 (week 24 of extension phase) Sustained ACR20 responders: at least 1 respnse at week 36 or 48 ACR50 (as assessed at week 48) ACR70 (as assessed at week 48) Secondary clinical efficacy endpoints: Total Modified Sharp Score (TMSS) [derived from radiographic evaluation of the hands only] Change form baseline in: Number of swollen joints Number of tender joints Patients assessment of disease activity (0-4 scale) Physicians assessment of disease activity (0-4 scale) Health Assessment Questionnaire score (HAQ score) Level of CRP ESR	Amgen Inc

		(30%) Placebo to anakinra group 21/76 (28%)	Duration of RA 4.1 ± 2.4 years; presence of erosive disease 74.2%.					

Effect size

<u>Efficacy over 48 weeks</u>

PLACEBO to ANAKINRA
ACR20
At week 48 there was a significantly higher proportion of patients who achieved an ACR20 response in the placebo to anakinra group (p=0.007) compared with the response at week 24. For the individual doses of Anakinra there were no significant differences between weeks 24 and 48.
At week 48 there was a significantly higher proportion of patients who achieved a sustained ACR20 response in the placebo to anakinra group (p<0.001) compared with the response at week 24. For the individual doses of Anakinra there were significant differences between weeks 24 and 48 for Anakinra 75mg (p=0.016) and Anakinra 150mg (p=0.022).

ACR50 and ACR70
ACR50 increased from 12% at week 24 to 20% at week 48 (p not given).
ACR70 was unchanged at 1% at weeks 24 and 48.

ACR component measures
Improvements in all ACR components were statistically significant for the combined cohort of patients that switched from placebo to anakinra (weeks 24 to 48): number of swollen joints (-4.1 ± 1.1, p<0.001), number of tender joints (-5.6 ± 1.3, p<0.001), patient global assessment (-0.3 ± 0.1, p<0.05), investigator assessment (-0.3 ± 0.1, p<0.05), pain assessment (-0.09 ± 0.03, p<0.005), HAQ (-0.26 ± 0.05, p<0.001), CRP (-1.0 ± 0.3, p<0.005), and ESR(-11.9 ± 2.2, p<0.001).
Improvements were also statistically significant for some of the parameters in the individual dose groups:
Anakinra 30mg: HAQ (-0.33 ± 0.1, p<0.005), CRP (-1.2 ± 0.5, p<0.05), and ESR(-11.9 ± 3.4, p<0.005)
Anakinra 75mg: number of swollen joints (-5.0 ± 1.1, p<0.05), number of tender joints (-6.1 ± 1.9, p<0.005), patient global assessment (-0.3 ± 0.1, p<0.05), and ESR(-15.0 ± 3.4, p<0.001)
Anakinra 150mg: number of swollen joints (4.4 ± 1.2, p<0.005), number of tender joints (-5.5 ± 1.8, p<0.05), and HAQ (-0.35 ± 0.1, p<0.005).

ANAKINRA to ANAKINRA
ACR20
There was no significant difference in the proportion of patients who achieved an ACR20 response in the anakinra to anakinra group between weeks 24 and 48. For the individual doses of anakinra there were no significant differences between weeks 24 and 48.
There was no significant difference in the proportion of patients who achieved a sustained ACR20 response in the anakinra to anakinra group between weeks 24 and 48.

ACR50 and ACR70
ACR50 decreased from 21% at week 24 to 18% at week 48 (p not given).
ACR70 was unchanged at 3% at weeks 24 and 48.

ACR component measures
For the combined cohort there was a small but statistically significant deterioration in the HAQ (+0.06 ± 0.03, p<0.05), and no difference in the other component measures.
In the group on anakinra 150 mg, there was deterioration of the patients global assessment (+0.2 ± 0.1, p<0.05), assessment of pain (+0.07 ± 0.03, p<0.05), and the HAQ (+0.1 ± 0.05, p<0.05).

Long term safety and tolerability/ adverse events (evaluated over 72 weeks)
Rates of withdrawal during the extension phase were similar to those during the placebo-controlled phase; 29% overall in extension phase vs 25% in anakinra group (p not given).
Rates of withdrawal due to adverse vents were 18% in placebo/anakinra group vs. 14% in the anakinra/anakinra group vs. 17% in the anakinra group in the placebo controlled phase (p not given).

The most common adverse events were injection site reactions (ISR), the frequency and severity increased with increasing dose of anakinra. Frequency of ISR up to week 24 was: 0.82/patient year of exposure in placebo group, 1.01/patient year of exposure in anakinra 30 mg group, 2.43/patient year of exposure in anakinra 75 mg group, 3.73/patient year of exposure in anakinra 150 mg group, and 2.00/patient year of exposure in anakinra group overall.

Adverse events leading to withdrawal:
The most common adverse events leading to withdrawal were arthritis flare (placebo/anakinra group 5.2% vs. anakinra/anakinra group 6.0%, p not given).
1.3% of patients in each group withdrew due to infection, with an incidence of 1.40/patient year of exposure in placebo group, 0.91/patient year of exposure in anakinra 30 mg group, 1.0/patient year of exposure in anakinra 75 mg group, 1.1/patient year of exposure in anakinra 150 mg group (no p values given for comparisons).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
B. Bresnihan, R. Newmark, S. Robbins, H. K. Genant. Effects of anakinra monotherapy on joint damage in patients with rheumatoid	RCT: 1+ Placebo group from original randomisation was randomised into anakinra 30/75/150 mg/day groups	N=472 in original study N=309 (89.6%) enrolled into the extension phase; N=76 from the placebo group and	**Inclusion criteria:** aged between 18-75 years, active RA (defined as ≥10 swollen joints and at least 3 of the following: ≥10 tender or painful joints, disease activity graded as severe or very severe by the physician and a CRP > 1.5 mg/dl), had symptoms for > 6 months and < 8 years. **Exclusion criteria:** previous receipt of other biological agents Other study inclusion and exclusion criteria were	Anakinra 30 mg/day by subcutaneous injection Anakinra 75 mg/day by subcutaneous injection Anakinra 150	Patients treated with placebo in first 24 weeks then randomised to anakinra 30/75/150 mg/day for 24 weeks	Original study 24 weeks This study extension phase a further 24 weeks	Primary efficacy endpoint: American College of Rheumatology (ACR) composite score. Secondary	Amgen Inc

arthritis. Extension of a 24-week randomized, placebo-controlled trial. *Journal of Rheumatology* 31 (6):1103-11, 2004. ID 67	• Randomised (method not mentioned) • Double blind in extension phase • Not true ITT analysis (only those with triplicate radiographs were analysed)	N=233 from anakinra groups **Drop-outs:** 91/309 (29.4%) Anakinra 30 total drop out 19/101 (18.8%) Anakinra 75 total drop out 33/103 (32%) Anakinra 150 total drop out 29/95 (30.5%)	not listed in this paper. 1.9 **Baseline characteristics:** Placebo group (N=121): mean age 52.2 years; Female 70.2%; Duration of RA 3.7 years; HAQ 1.3, presence of erosive disease 74.4%. Anakinra group (N=351): mean age 53.4 years; Female 76.6%; Duration of RA 4.1 years; HAQ 1.6, presence of erosive disease 73.2%.	mg/day by subcutaneous injection Above patients remained in their treatment groups for 48 weeks			clinical efficacy endpoints: Total Modified Sharp Score (TMSS) [derived from radiographic evaluation of the hands only]	

Effect size

ANAKINRA vs PLACEBO

	Anakinra 30	Anakinra 75	Anakinra 150	Placebo
ACR 20 response at 24 weeks (%)	39 (NS vs placebo)	34 (NS vs placebo)	43 (p=0.014 vs placebo)	27
ACR 20 response at 48 weeks (%)	44	53	49	-
ACR 20 response at 48 weeks among placebo group randomised to receive anakinra in extension phase (%)	50 (N=30)	44 (N=24)	71 (N=22)	-

Radiographic evaluation of joint damage after 48 weeks (changes from baseline)

	All Anakinra	Anakinra 30	Anakinra 75	Anakinra 150	Placebo[1]
TMSS mean change	2.12 (p=0.015 vs placebo)	2.43 (NS vs placebo)	1.91 (p=0.025 vs placebo)	1.90 (p=0.025 vs placebo)	3.81
Erosion score mean change	1.15 (p=0.006 vs placebo)	0.88 (p=0.004 vs placebo)	1.18 (p=0.035 vs placebo)	1.21 (p=0.038 vs placebo)	2.03
Joint space narrowing mean change	0.89 (NS vs placebo)	1.19 (NS vs placebo)	0.66 (p=0.048 vs placebo)	0.79 (NS vs placebo)	1.53

[1]Patients in the placebo group received anakinra between weeks 24 and 48.

Changes in radiographic progression in 2 consecutive 24 week treatment periods

- Among both groups (placebo subjects randomised to anakinra in second 24 weeks and those treated with anakinra for 48 weeks) significantly less joint damage, as measured by the Modified Sharp Score, occurred in the second 24 week period than in the first 24 week period (p<0.001 for both groups)
- In the placebo group there was a significant reduction in TMSS, modified Sharp erosion score and modified Sharp joint narrowing score for all anakinra doses in the extension (2nd 24 weeks) period. (p<0.001)
- In patients treated with anakinra for 48 weeks, the TMSS and modified Sharp erosion score were significantly lower in the extension period (2nd 24 weeks) for the higher anakinra doses (75 and 150 mg/day), with no significant difference for the 30 mg/day dose and for the modified Sharp joint narrowing score at any dose.

Sensitivity analyses:
Comparison of patients who entered the extension phase with those who dropped out at 24 weeks showed that in the placebo group, those who dropped out had greater structural damage than those who continued into the extension phase. In the anakinra group, those who continued had greater joint damage than the dropouts.

7.4 SYMPTOM CONTROL

7.4.1 ANALGESICS

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Glowinski J, Boccard E. Placebo-controlled study of the analgesic efficacy of a paracetamol 500 mg/Codeine 30 mg combination together with low-dose vs high-dose diclofenac in rheumatoid arthritis. *Clinical Drug Investigation.* 1999; 18(3):189-197. Ref ID: 429	RCT 1+ multicentre France • Double blind • Randomised: no details • Treatment allocation: no details • ITT analysis	N=60 N=58 global efficacy	**Inclusion criteria:** Adults with RA according to the ACR criteria and who had been stabilised for at least 2 months by their treatment and 1) aged 18 to 75 yrs; 2) presented permanent residual pain 3) judged the pain over the last 24 hrs to be greater than or equal to moderate pain 4) interrupted previous analgesic and NSAID treatment during the study **Exclusion criteria included:** use of oxicam in 48 hrs prior to study **Baseline characteristics:** mean age 57 yrs, mean disease duration 9 yrs, 83% female **The groups were well matched at basline** Concurrent medication: See inclusion criteria plus rescue medication after day 1 of treatment	Paracetamol 500 mg + codeine 30 mg three times daily Plus a placebo diclofenac tablets in the morning and diclofenac 50 mg in the evening	Placebo + diclofenac 50 mg in the morning and evening	7 days	Residual pain (5-point scale and VAS); diary; patient assessment of efficacy (5-point scale and VAS) and physician efficacy assessment (5-point scale); Ritchie Index; adverse events	Laboratoiries UPSA

			Withdrawals: No reported due to inefficacy N=3 withdrawals due to adverse events the paracetamol-codeine group N=1 in the diclofenac group					

Effect size

Paracetamol plus codeine plus diclofenac 50 mg vs diclofenac 100 mg

- There were no statistical differences for:
  - Pain (VAS)
  - Global judgement of efficacy (patient) (NS)
  - Number of nocturnal awakenings on the disability scores (NS)
  - Duration of morning stiffness (NS)
  - Ritchie Index (NS)
  - Desire to resume treatment (NS)

Adverse events N=17:

- N=8 in the paracetamol-codeine group
- N=9 in the diclofenac group
- N=3 withdrawals due to adverse events the paracetamol-codeine group
- N=1 in the diclofenac group
- There were no statistical differences between the treatments on the global assessment of tolerability (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Herrero-Beaumont G, Bjorneboe O, Richarz U. Transdermal fentanyl for the treatment of pain caused	Case-series (prospective): 3 multicentre in 29 centres in 9 countries • ITT analysis	Total N=292 screened N=104 recruited	**Inclusion criteria:** Adults with RA according to ARA criteria requiring supplementary analgesic treatment because of moderate or sever pain which was not adequately controlled with existing medication. Patients were aged over 18 yrs.	Transdermal Fentanyl (TDF) One week run-in period. Nonopioid analgesic treatment was optimised or increased to the maximum tolerated dose,	Baseline values	28 days	Pain control (5-point scale); pain assessment questionnaire (Wisconsin Brief Pain Inventory WBPI 10-point scale); pain	Janssen-Craig

by rheumatoid arthritis. *Rheumatology International.* 2004; 24(6):325-332 ID 3076	and per-protocol analysis		**Exclusion criteria:** Patient with: acute flares; on regular treatment with strong opioid in the 4 weeks before the study, including those taking weaker analgesics or weak opioids exceeding the maximum recommended doses; or patients who had undergone surgery/arthroscopy, intra/periarticular injections, or arthrocentesis within 3 months, 6 weeks, and 4 weeks of study start respectively **Baseline characteristics:** Mean 63 yrs and 85% female **Concurrent medication:** If taking DMARDs or corticosteroids, patients must have been on stable dosage for at least 3 months before screening and on stable dose for the duration of the trial N=72 (75%) DMARDs N=61 (59%) NSAIDs N=33 (32%) COX-2 inhibitors All 104 patients had analgesic treatment in the month before screening: 80% nonopioids and 75% weak opioids 53% patients had used a combination of a nonopioid and weak opioid; 22% a nonopoioid only and 20% a weak opioid	while weak opioids were kept stable. All patients with insufficiently controlled pain at the end of this period were started on TDF TDF of 28 days duration 25µ/h replaced every 72 hrs. Weak opioid were discontinued Titration: If required the dose of TDF was titrated upwards in steps of 25µ/h every 72 hrs (days 3, 6 and 9) until adequate pain control was achieved. After 28 days or when necessary e.g., if side effects occurred or if treatment was not effective a similar downward titration regimen was used. No short acting opioids were added during down-titration. Metoclopramide (10 mg tid) was given concurrently to all patients during the first week of treatment Supplementary analgesia could be provided using 500-mg tablets of			intensity (diary); nausea and vomiting (diary) (reported elsewhere); treatment assessment questionnaire; quality of life (Short Form – 36 SF-36); functionality (Health Assessment Questionnaire HAQ)	

			only Concomitant medication with possible analgesic effect during treatment: 83% paracetamol, 66% weak opioids, 59% NSAIDs, 54% steroids, 32% COX-2s, 4% analgesics and 1% strong opioids N=2 rescue medication up to week 2 (protocol violators)_ 76% used rescue medication, all using nonopioids Discontinuations: N=20 (19%) patients discontinued during the treatment phase, all because of adverse events 9% dropped out in the first week of TDF treatment N=42 patients started the tapering off phase with one third dropping out prematurely	paracetamol at up to 4g/day				

1.10 Effect size

Transdermal fentanyl (TDF) vs baseline
Pain (primary outcome)

- The mean daily dose over the trial period was 32.8µ/h (range 25µ/h to 125µ/h). The mean duration of treatment was 22.8 days (range 1 to 37)
- The addition of TDF further increased pain control with an associated increase in mean pain score from 2.1 to 3.2, and were statistically better at all time points ($p<0.001$)
- The change in pain control between baseline and endpoint was significantly related to baseline values ($p<0.001$), with greater pain relief for those with poorer pain control at baseline

WBPI:

- TDF was associated with a significant ($p<0.001$) in pain on each item of the WBPI at every time point ($p<0.001$)
- From patients' diaries, the mean pain score for the degree of pain was significantly decreased at each time point and from severe to moderate from the run-in to endpoint ($p<0.001$)

Treatment assessment:

- 66% patient rate the treatment positively with respect to pain control
- Scores were significantly better than before treatment for all time points ($p<0.001$)

Quality of life:

- There were statistically significant improvement in all domains on the SF-36 from baseline to endpoint, for example physical health (summary) ($p<0.001$) and mental health (summary) ($p<0.05$)

HAQ:

- The mean change scored significantly improved for eating and activities ($p<0.001$ for both) and for arising ($p<0.05$)
- Overall, there was a significant improvement in the mean HAQ disability index score ($p<0.001$)

Adverse events:

- 5% reported adverse events in the run-in period, 65% in the treatment period and 29% in the optional tapering-off period
- The study medication was permanently stopped in 27%, particularly due to nausea and fatigue
- There were thought to be no serious adverse events related to the study medication

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Berliner MN, Giesecke T, Bornhovd KD.	Prospective case series 3	Total N=226	**Inclusion criteria:** Adults with RA according to ACR criteria and if 1) the decision had been	Transdermal fentanyl (TF)	Baseline	30 days (initial study)	Functional capacity (Steinbroker method); Number	Janssen-Cilag GmbH

Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. *Clinical Journal of Pain.* 2007; 23(6):530-534 ID 3057	Multicentre trial: Germany • Open trial	**Drop-outs:** None reported for the initial study N=58 available for long-term (12 month follow-up)	made to add transdermal fentanyl (TF) to the treatment regimen, 2) they had unsatisfactory treatment with NSAIDs leading to a level of pain intensity of 6 (scale 0 to 10), and 3) they had not been treated previously with TF **Exclusion criteria included:** See above **Baseline characteristics:** 76% female, mean age 66 yrs, 173/226 outpatients, mean pain duration 65 months, pain at the knee 73%, hands 69% and shoulder 61% region. Steinbrocker stage index I 4%, II 27%, III 58%, IV 11%, **Patients available for follow-up (N=58)** 81% female and mean age 66 yrs Steinbrocker stage index I 3%, II 25%, III 67%, IV 5%, **Concurrent medication** Top three: Glucocorticoids 61%, NSAIDs 67% and Methotrexate 31% **Concurrent therapy** Exercise therapy 85%, occupational therapy 23%, cryotherapy 37%	Treatment initiated as the smallest dose 25 µg/h and increased if necessary every 72 hrs by steps of 25 µg/h		12 months (long-term)	of swollen and tender joints; average pain 24 hrs and long-term tolerable pain (numerical rating scale NRS 0 to 10); sleep, pain-related impairment of daily activities and treatment satisfaction (5-point verbal rating scale VRS); well-being (The Marburg Questionnaire)	Germany

Effect size

TRANSDERMAL FENTANYL (TF) vs baseline

Pain:

- There was a significant improvement from baseline associated with TF on:
  - Mean pain intensity ($p<0.001$)

Quality of sleep:

- There was a significant improvement from baseline associated with TF on:
  - Mean quality of night time sleep improvement ($p<0.05$)
  - Disturbance of sleep due to pain ($p<0.05$)
  - 84% patients reported improvement in either quality of night time sleep or in disturbance of sleep due to pain ($p<0.05$)

Impairments of activities:

- There was a significant improvement from baseline associated with TF on:
  - Activities of daily living (ADL) ($p<0.05$)
  - Social acitivites ($p<0.05$)
  - 85% and 83% of patients on TF improved by at least one category on the 5-point VAS for ADL and social activities ($p<0.05$)

Treatment satisfaction:

- There was a significant improvement from baseline associated with TF on:
  - Satisfaction with pain treatment ($p<0.05$)
  - 85% of patients on TF reported an improvement of at least one unit on the 5-pint VRS for treatment satisfaction ($p<0.05$)

Marburg questionnaire on general well-being:

- TF was associated with a improvement of approximately 1.5 units on each item

Long-term results (N=58):

- The mean pain intensity of this sub-group remained stable from the end of the initial study (30 days) to 12 month follow-up
- Improvements in ADL and social activities did not deteriorate from end of study to 12 month follow-up
- Consistently, treatment satisfaction remained high throughout the follow-up
- The mean dose of TF in this sub-group increased from 28.8 µg/h at day 30 to 49.1 µg/h at 12 months

Tolerability:

- 75 adverse events were recorded in 39/226 (17%) patients mostly related to the study medication
- 85% of symptoms disappeared by the end of the study
- 40% required symptomatic medication
- 9% of symptoms persisted
- N=23 patients (10%) adverse events alone or in combination with other reasons led to a discontinuation of treatment

o Blood pressure and heart rate did not show any clinically relevant changes during the study								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Seideman P, Melander A. Equianalgesic effects of paracetamol and indomethacin in rheumatoid arthritis. *British Journal of Rheumatology.* 1988; 27(2):117-122 ID 3064	RCT: 1+ Single centre trial: Sweden • Randomised: No details • Allocation concealment: No details • Double blind • Pre-treatment wash-out period but not between treatments • No ITT analysis	Total N=20 randomised (N=17 completers) DMARD). **Drop-outs:** N=3 (15%) Excluded during first treatment period	**Inclusion criteria:** Adults with classic or definite RA (ARA criteria) **Exclusion criteria:** Gastrointestinal, hepatic or renal disease or previous intolerance to indomethacin **Baseline characteristics:** age 33 to 68 (mean 47 yrs); disease duration mean 10 yrs (SD 8) Stabilised maintenance doses of gold (N=1), penicillamine (N=3), or chloroquine (N=5) were given. These DMARDs had been given for at least 6 months and did not change throughout the study. There were no differences between the treatments/groups treated in the first two weeks and the second two weeks	Indomethacin 50mg daily (Two doses of 25mg) + Paracetamol 1g four times daily) All patients: 3-day pre-treatment washout 7-day tolerability to 150mg indomethacin. All other NSAIDs were withheld Escape analgesia: Dextropropoxyphene 50mg	Indomethacin 150 mg daily (Four doses of 50mg, 25mg, 25mg and 50mg) Escape analgesia: Dextropropoxyphene 50mg	Four weeks	Pain: VAS, pain at rest, night and day pain, joint pain, morning stiffness; Grip strength; No. of painful joints (Ritchie); Joint circumference Side effects; Side effects, ESR, leucocyte count, haemoglobin, platelets, serum creatinine, liver enzymes, serum orosomucoid, haptoglobin, CRP, time-concentration profiles of indomethacin Responders vs non-responders classified according to grading of clinical findings of Mallya and	Swedish Medical Research Council

							Mace (night and day pain, morning stiffness, patient's overall assessment, grip strength and Ritchie artciular index). 2.2 classified as responders and 2.3 and 4 as non-responders	

Effect size

Drug levels:

- There were NS differences between responders vs non-responders on the 150mg indomethacin dose for:
  - Mean indomethacin levels (NS)
  - Recorded peak levels in elimination half-lives (NS)

Efficacy:

- There was NS difference between the Indomethacin 150mg vs Indomethacin 50mg + paracetamol 4g for:
  - The number of dextroproproxyphene tables (NS)
  - Mean joint circumference (NS)
  - Mean articular index (NS)
  - Mean morning pain (VAS) score (NS)
  - Pain at night (NS)
  - Joint movement (NS)
  - Assessment of therapeutic efficacy (NS)
  - Mean duration of morning stiffness (NS)
  - Night pain (NS)

Side-effects:

- Indomethacin 50mg + paracetamol 4g:
  - N=3 headache, tiredness and vertigo and N=1 anorexia, dyspepsia and vomiting

Indomethacin 150mg:

- N=6 headache, tiredness and vertigo and N=5 anorexia, dyspepsia and vomiting

Blood chemistry:

- There were no significant differences in the laboratory data for indomethacin 150mg vs. indomethacin 50mg + paracetamol 4g

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. *British Journal of*	RCT crossover 1+ single centre Sweden • Double blind • No drop outs	N=20 N=3 excluded and replaced No drop-	**Inclusion criteria:** Adults with RA according to the ARA criteria **Exclusion criteria:** None stated	Naproxen 500, 1000 and 1500 mg/day Narpoxen 500 and 1000 mg/day _ 4g paracetamol 'Flare-period' 3 to 7 day duration where	See intervention	Two weeks (end of treatment)	Number of painful joints to digital pressure or passive movement (Ritchie); duration of morning stiffness; pain at rest and movement	Swedish Society of Medicine and Medical Research Council

Rheumatology. 1993; 32(12):1077-1082. Ref ID: 103	• N=3 replaced in initial flare up phase	outs reported	**Baseline characteristics:** mean age 52 yrs and mean disease duration 4 yrs Concurrent medication N=12: N=4 penicillamine, N=4 aurothiomalate and N=4 chloroquine All patients had been on a fixed dose of these DMARDs for at least 6 months and the medication remained stable throughout the study Discontinuation: None reported	no NSAIDs were taken. Patients showing no flared up after 7 days were excluded and replaced (N=3) Two treatment period			(VAS); Global assessment of disease activity (5-point scale); Activities of Daily Living (ADL); side effects and adverse events	

Effect size

Naproxen (500, 1000 and 1500 mg/day):

- There was a significant relationship between naproxen dose ($p<0.001$ for all) and:
  - Joint index
  - Morning stiffness
  - Pain during movement and rest

- There was a significant relationship between naproxen concentration and:
  - Clinical global effect ($p<0.01$)
  - Joint index ($p<0.002$)
  - Morning stiffness ($p<0.001$)
  - Pain during movement and rest ($p<0.001$)

Naproxen (500, 1000 and 1500 mg/day) vs Naproxen 500 and 1000 mg/day + 4g paracetamol

- Naproxen 500 mg/day plus paracetamol 4 g/day showed a significant improvement on:
  - Global effect ($p<0.001$)
  - Joint index ($p<0.001$)
  - Joint pain ($p<0.001$)
  - Morning stiffness ($p<0.05$)
- Naproxen 1000 mg/day plus paracetamol 4 g/day showed a significant improvement on:
  - All variables ($p<0.05$-0.01) except for ADL

Side effects:

- Side effects were significantly related to naproxen dose ($p<0.01$) and concentration ($p<0.05$)
- No major side effects were reported and no patients discontinued treatment due to side effects
- Significantly fewer side effects were observed with naproxen 500 mg + 4 g paracetamol than 1000 mg naproxen ($p<0.02$)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Frank RG, Kashani JH, Parker JC et al. Antidepressant analgesia in rheumatoid arthritis.[see	RCT cross-over: 1+ Single centre USA • Randomised • Allocation concealmen	Total N=256 considered N=73 randomised **Drop-outs:** N=26	**Inclusion criteria:** Adults with definite or classic RA and self-reported pain rating of 2 or greater (0 to 5 scale) **Exclusion criteria included:** ARA functional class IV	Amitriptyline Trazodone HCL Drug dosages were based on patient weight. For the first 3 days of	Placebo	32 weeks Treatment was 7 weeks for each arm of the cross-	Depression and mood: Diagnostic interview schedule (DIS) VAS mood and pain scale	Janssen Korea Inc

comment]. *Journal of Rheumatology*. 1988; 15(11):1632-1638 ID 3063	t: ordered sequences • Double blind • 36% non-completers (study duration 8 months) • No ITT analysis	N=3 due to adverse reactions to interventions There were no statistical differences between the completers and non-completers except that the former were older	**Baseline characteristics:** Anatomic stage – Stage I 49%, II 22%, III 27%, IV 2% ARA functional Class II – Stage I 2%, II 89%, III 9% Mean age 58 yrs, mean education 11 yrs **Concurrent medication:** NSAIDs 92%, Acetaminophen 11%, Oral prednisone 23%, remittive/slow acting drugs 73%, diuretic drugs 2%, beta blockers 7%	each drug: Amitriptyline 1.0 mg/kg/day Trazodone 1.5 mg/kg/day Thereafter Amitriptyline 1.5 mg/kg/day Trazadone 3.0 mg/kg/day Patients over 60 yrs received ½ this dose For both medications 1/3 dose was taken in the morning and 2/3 in the evening Dosage tapering: 7th week. 8th week neither antidepressant or placebo were given (washout)		over trial	Pain: McGill Pain Questionnaire (MPQ); pain intensity ratings Disease activity measures: ESR; joint pain, t	

Effect size

AMATRIPTYLINE vs TRAZADONE vs PLACEBO

Pain

- Overall, for one-way MANOVA there was a significant effect for:
  - Number of words chosen (MPQ) ($p \leq 0.0001$)
  - Present pain intensity ($p \leq 0.05$)
  - Pain Rating Index (MPQ) ($p \leq 0.0001$)
  - Worst pain ($p \leq 0.0001$)
  - Pain duration ($p \leq 0.01$)

- Overall, for one-way MANOVA there were no significant differences for:
  - VAS
  - Average pain
  - Least pain
  - Current physical incapacitation

- When comparing end-of-treatment to baseline there were significant differences for:
  - Amitriptyline and trazadone for number of words chosen (MPQ), Pain Rating Index (MPQ), worst pain and pain duration ($p<0.05$ for all)
  - Amitriptyline on present pain intensity ($p<0.05$), average pain ($p<0.05$)

- There were significant differences compared to placebo for:
  - Amitriptyline compared to placebo on present pain intensity and worst pain

- There were no statistical differences when comparing amitriptyline or trazadone with baseline or placebo for:
  - VAS, least pain or current physical incapacitation

Mood

- Overall, for one-way MANOVA there was a significant effect for:
  - Life dissatisfaction ($p \leq 0.01$)
  - "Down" mood ($p \leq 0.01$)
  - Negative effect ($p \leq 0.05$)
  - Chronic fatigue ($p \leq 0.001$)
  - Self-blame ($p \leq 0.05$)

- Overall, for one-way MANOVA there were no significant differences for:
  - Self-esteem
  - Problem with "nerves"

- Hopelessness
- Social isolation
- Sleep onset insomnia
- Loss of appetite

- When comparing end-of-treatment to baseline there were significant differences for (all $p<0.05$):
  - Placebo on life dissatisfaction and "down" mood and chronic fatigue
  - Amitriptyline on life dissatisfaction, self-esteem, "down" mood, social isolation, negative effect, chronic fatigue, self-blame
  - Trazadone on life dissatisfaction, "down" mood, chronic fatigue, self-blame

Disease course

- Overall, for one-way MANOVA there was a significant effect for:
  - Total number of painful tender joints ($p \leq 0.05$)
  - Total number of swollen joints ($p \leq 0.05$)

- Overall, for one-way MANOVA there were no statistical differences for:
  - Morning stiffness
  - Walking time
  - Grip strength
  - Severity rating summary of painful tender joints
  - ESR

- When comparing end-of-treatment to baseline and placebo there were significant differences for:
  - Amitriptyline on total number of painful tender joint and severity rating summary of painful tender joints ($p<0.05$)

Depression by drug
The MANOVA showed a significant main effect for depression ($p<0.003$) and drug type ($p<0.003$)
There was no statistical interaction between depression and drug type (NS)
Patients classified as depressed indicated significantly ($p<0.05$) higher levels of pain on all pain measures except for physical incapacity and the VAS

Age by drug interaction
There were no statistical interactions between age/dose and intervention

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
E. M. Grace, N. Bellamy, Y.	RCT: 1+ Single centre	Total N=36 (N=18	**Inclusion criteria:** Patients with definite or classic RA	Amitriptyline	Placebo	12 weeks	Pain (5-point scale); Ritchie	Arthritis Society of

Kassam, and W. W. Buchanan. Controlled, double-blind, randomized trial of amitriptyline in relieving articular pain and tenderness in patients with rheumatoid arthritis. *Current Medical Research & Opinion* 9 (6):426-429, 1985. ID 3066	Canada • Randomised (method not mentioned) • Double blind • ITT analysis (not mentioned)	each group) **Drop-outs:** N=4 in each group (22%)	(ARA criteria) attending urban rheumatic disease clinic; persistent pain despite adequate NSAID analgesic therapy; some had received chrysotherapy and penicillamine in the past, but not at the time of the study. None were receiving oral CS therapy and none recently received IA CS therapy. **Baseline characteristics:** Amitriptyline: mean age 58 yrs, female 83%; functional class II 61%; functional class III 39%. Placebo: mean age 59 yrs, female 78%; functional class II 67%; functional class III 33%. The 2 groups were similar or NS difference for all baseline characteristics **Concurrent medication:** Patients were instructed to continue with their NSAID analgesic medication	25 mg/day for 1 week then increased to 50 mg/day for week 2 then 75 mg/day thereafter. Patients reduced the doses if experienced any side-effects.	Identical tablets taken with identical instructions.		Articular Index (RAI for joint tenderness).	Canada.

Effect size

AMITRIPTYLINE vs PLACEBO

- There was NS difference between amitrytiline and placebo for:
  - Pain at 12 weeks
  - Joint tenderness at 12 weeks
  - Total number of withdrawals (both N=4)

- Amitrytiline and placebo were similar for:
  - Withdrawals due to AEs (N=2 and N=3 respectively)
  - Withdrawals due to lack of efficacy (N=2 and N=1 respectively)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Emery P, Gibson T. A double-blind study of the simple analgesic nefopam in rheumatoid arthritis. *British Journal of Rheumatology*. 1986; 25(1):72-76 ID 133	RCT 1+ Single centre trial: UK. • Randomised • Allocation concealment not specified • Double blind • High number of drop-outs • No ITT analysis	Total N=27 randomised N=22 analysed **Drop-outs:** N=5 withdrawn at 5 days of Nefopam treatment due to nausea	**Inclusion criteria:** Adults with RA **Exclusion criteria:** None stated **Baseline characteristics:** mean 59 yrs; 25:2 female: male; mean disease duration 4 to 30 yrs Concurrent medication All patients were receiving maximal doses of one or more NSAIDs, but had persistent pain N=14 were being treated with second-line drugs (sodium aurothiomalate, D-penicillamine, chloroquine, prednisolone) for at least 4 months. Discontinuation	Nefopam 60 mg three time daily Four weeks treatment One week washout Four weeks on the alternative treatment (Nefopam or placebo)	Placebo	4 weeks (end of treatment)	Pain (VAS); morning stiffness (VAS); Grip strength; Joint tenderness; Proximal interphalangeal circumference; Haemoglobin; ESR	None reported

			N=4 patients taking pure analgesics and these were discontinued one week before the trial					

Effect size

NEFOPAM vs PLACEBO

- At baseline, there were no significant differences between the two treatment groups for either treatment period (NS)

- At two and four weeks treatment there was a significant difference in favour of nefopam for:
  - Pain ($p<0.01$)
  - Morning stiffness ($p<0.01$)
  - Grip strength ($p<0.05$)
  - Joint tenderness ($p<0.01$)

- At two and four weeks treatment there were no significant differences between nefopam and placebo for:
  - Proximal interphalangeal circumference (NS)
  - Haemoglobin (NS)
  - ESR (NS)

- Improvements associated with nefopam for these variables were consistent across the treatment periods

Adverse-effects

- N=9 (35%) patients experienced an adverse event, all whilst on nefopam
  - N=5 nausea (patients withdrawn in first 10 days of nefopam treatment)
  - N=4 sweating
  - N=1 each of insomnia, pruritis and malaise
  - There were no changes in laboratory results thought to be associated with nefopam

7.4.8 NSAIDS

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-	Outcome measures	Source of funding

						up		
F. Porzio. Meta-analysis of two double-blind comparative studies with the sustained-release form of etodolac in rheumatoid arthritis. *Rheumatology International* 13 (2 suppl):1-30, 1993. ID 1649	MA: 1- RCT's of MA: not known MA included: N=2 trials (N=202) Trials were similar in terms of: • Study design (All RCTs) • Intervention (etodolac SR) • Study duration (4 weeks) Trials differed with respect to: • Study size • Comparison group (1 RCT diclofenac, 1 RCT piroxicam) Tests for heterogeneity was performed and studies were found to have SIGNIFICANT heterogeneity (due to treatment and centre used), thus pooled results cannot be used.	Total N=202	Inclusion criteria: 2 RCTs; diagnosis of RA ; adults >18 years;	Etodolac SR (600 mg)	Diclofenac SR 100 mg Piroxicam 20 mg	4 weeks	Patient's and investigator's overall assessment; Number of painful and swollen joints; Pain intensity; AEs.	Grant from the NIH.

Effect size

Author's conclusions:
The MA showed that etodolac SR is effective in the treatment of RA and has a very good safety profile and the drug is comparable to that of marketed NSAIDs. Etodolac appeared to be safe for the GI tract and well tolerated in elderly patients.

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of**	**Outcome measures**	**Source of**

						follow-up		**funding**
W. Shi, Y. M. Wang, L. S. Li, M. Yan, D. Li, N. N. Chen, and B. Y. Chen. Safety and efficacy of oral nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis : a six-month randomised study. *Clin.Drug Investig.* 24 (2):89-101, 2004. REF ID: 1561	RCT 1- Multicentre trial: China • Randomised (computer generated numbers, ratio 3:3:3:1, stratified randomised list at each centre • No mention of blinding • Not ITT analysis	N= 461 **Drop-outs:** Diclofenac 12% Nabumetone 12% Meloxicam 12% Celecoxib 9%	**Inclusion criteria:** 20-69 years of age; RA (ACR criteria); required NSAID therapy of 6 months or longer. **Exclusion criteria:** Allergy or contraindication to NSAIDs; those receiving gastroprotective agents; GI problems or severe disease. **Baseline characteristics:** There were NS differences between the groups for any of the baseline characteristics. Population was Early RA (duration <2 years).	Meloxicam 15 mg Celecoxib 200 mg	Diclofenac 75-100 mg Nabumetone 100 mg	6 months	Efficacy analysis; ACR20; ACR50; AEs	Grant from the State Food and Drug Administration of China.
Effect size Authors' conclusions: Among the investigated NSAIDs, celecoxib did not prove to be superior to diclofenac, nabumetone or meloxicam for efficacy; however it did show good patient compliance and safety profiles.								

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
E. Collantes, S. P. Curtis, K. W. Lee, N. Casas, T. McCarthy, A. Melian, P. L. Zhao, D. B. Rodgers, C. L. McCormick, M. Lee, C. R. Lines, and B. J. Gertz. A multinational	RCT 1+ Multicentre trial: 67 centres worldwide • Randomised (2:2:1, method not mentioned • Double blind	N=891 randomised (N=357 placebo, N=353 etoricoxib, N=181 naproxen)	**Inclusion criteria:** ≥18 years, RA (ARA criteria); established diagnosis of RA for at least 6 months prior to entering the study; history of clinical response to NSAID therapy; taking NSAID therapy on a regular basis (at least 25 of the past 30 days). **Exclusion criteria:** CV disease;	etoricoxib 90 mg (once/day) naproxen 1000 mg (500 mg twice/day) All patients in all groups underwent an	Placebo	12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of disease activity and response to therapy;	Not mentioned but pharma company conflict of interests

randomized, controlled, clinical trial of etoricoxib inthetreatment of rheumatoid arthritis [ISRCTN25142273]. *BMC Family Practice* 3 (pp 1-10):-10, 2002. REF ID: 1937	• Not true ITT analysis	**Drop-outs:** placebo 22% etoricoxib 17% naproxen 17%	stroke; warfarin, ticlopidine, clopidogrel and aspirin use; potentially confounding secondary medical diagnoses; allergy to paracetamol, aspirin or NSAIDs. **Baseline characteristics:** Placebo: mean age 52 years, female 82%, disease duration mean 9 years (Established RA), Disease activity (VAS) 65. Etoricoxib: mean age 53 years, female 81%, disease duration mean 8 years (Established RA), Disease activity (VAS) 66. Naproxen: mean age 52 years, female 82%, disease duration mean 8 years (Established RA), Disease activity (VAS) 65. The groups were similar for all baseline characteristics.	initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare criteria were satisfied. Patients were allowed to take low dose aspirin; Patients on stable doses of DMARDs and low doses of CS were allowed to continue.			morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs	

Effect size*

Etoricoxib vs placebo

- Etoricoxib was significantly better than placebo for:
  - Tender and swollen joint count at 12 weeks ($p<0.001$ and <0.05 respectively)
  - Patient's and investigator's global assessment of disease activity at 12 weeks ($p<0.001$)
  - Pain (VAS) at 12 weeks ($p<0.001$)
  - HAQ score at 12 weeks ($p<0.001$)
  - Withdrawals due to lack of efficacy at 12 weeks ($p<0.001$)
  - CRP level at 12 weeks ($p<0.05$)
  - ACR20 completers ($p<0.001$)

- There was no significant difference between etoricoxib and placebo for:
  - Number of patients with SAEs
  - Withdrawals due to AEs

- Etoricoxib was similar to placebo for:
    - Total number of withdrawals
    - GI nuisance symptoms

- Etoricoxib was significantly worse or worse than placebo for:
    - Number of patients with drug-related AEs ($p<0.05$)
    - Hypertension AEs

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
    - Tender and swollen joint count at 12 weeks ($p<0.001$ and <0.05 respectively)
    - Patient's and investigator's global assessment of disease activity at 12 weeks ($p<0.001$)
    - Pain (VAS) at 12 weeks ($p<0.001$)
    - HAQ score at 12 weeks ($p<0.001$)
    - Withdrawals due to lack of efficacy at 12 weeks ($p<0.001$)
    - ACR20 completers ($p<0.001$)

- There was no significant difference between naproxen and placebo for:
    - CRP level at 12 weeks
    - Number of patients with drug-related AEs
    - Number of patients with SAEs
    - Withdrawals due to AEs

- Naproxen was similar to placebo for:
    - Total number of withdrawals
    - GI nuisance symptoms

- Naproxen was worse than placebo for:
    - Hypertension AEs

Etoricoxib vs naproxen

- There was NS difference between Etoricoxib and naproxen for:
    - Tender and swollen joint count at 12 weeks ($p<0.001$ and <0.05 respectively)
    - Patient's and investigator's global assessment of disease activity at 12 weeks ($p<0.001$)
    - Pain (VAS) at 12 weeks ($p<0.001$)

- HAQ score at 12 weeks (p<0.001)
- Withdrawals due to lack of efficacy at 12 weeks (p<0.001)
- CRP level at 12 weeks (p<0.05)
- ACR20 completers (p<0.001)

- Etoricoxib was similar to naproxen for:
  - Number of patients with drug-related AEs
  - Number of patients with SAEs
  - Total number of withdrawals
  - Withdrawals due to AEs
  - GI nuisance symptoms
  - Hypertension AEs

*all statistical outcomes are based on 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. K. Matsumoto, A. Melian, D. R. Mandel, H. H. McIlwain, D. Borenstein, P. L. Zhao, C. R. Lines, B. J. Gertz, S. Curtis, and Etoricoxib Rheumatoid Arthritis Study Group. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis.[see comment]. *Journal of Rheumatology*	RCT 1+ Multicentre trial: 88 centres USA • Randomised (stratified by low dose CS use; method not mentioned) • Double blind • Not true ITT analysis • Power study (etoricoxib vs placebo) • High number of dropouts, especially in placebo	N=816 randomised (N=323 placebo, N=323 etoricoxib, N=170 naproxen) **Drop-outs:** placebo 62% etoricoxib 29% naproxen 45%	**Inclusion criteria:** ≥18 years, RA (ARA criteria); established diagnosis of RA for at least 6 months prior to entering the study; history of clinical response to NSAID therapy; taking NSAID therapy on a regular basis (at least 25 of the past 30 days). **Exclusion criteria:** CV disease; stroke; warfarin, ticlopidine, clopidogrel and aspirin use; potentially confounding secondary medical diagnoses; allergy to paracetamol, aspirin or NSAIDs. **Baseline characteristics:** Placebo: mean age 56 years, female 81%, disease duration mean 9 years (Established RA),	etoricoxib 90 mg (once/day) naproxen 1000 mg (500 mg twice/day) All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare criteria were satisfied.	Placebo	12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of disease activity and response to therapy; morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs	Merck Research Laboratories

29 (8):1623-1630, 2002. REF ID: 3082	group)		Disease activity (VAS) 66. Etoricoxib: mean age 55 years, female 73%, disease duration mean 9 years (Established RA), Disease activity (VAS) 65. Naproxen: mean age 56 years, female 77%, disease duration mean 10 years (Established RA), Disease activity (VAS) 63. The groups were similar for all baseline characteristics.	Patients were allowed to take low dose aspirin Patients on stable doses of DMARDs and low doses of CS were allowed to continue;				

Effect size*

Etoricoxib vs placebo

- Etoricoxib was significantly better than placebo for:
  - Tender and swollen joint count (at 12 weeks) p<0.01
  - Patient's and investigator's global assessment of disease activity (at 12 weeks) p<0.01
  - Pain, VAS (at 12 weeks) p<0.01
  - Modified HAQ score (at 12 weeks) p<0.01
  - Withdrawals due to lack of efficacy (at 12 weeks) p<0.01
  - CRP level (at 12 weeks) p<0.01
  - ACR20 completers p<0.01

- Etoricoxib was better than placebo for:
  - Total number of withdrawals (29% and 62% respectively)

- There was no significant difference between etoricoxib 25 mg and placebo for:
  - Number of patients with drug-related AEs
  - SAEs
  - Withdrawals due to AEs

- Etoricoxib was similar to placebo for:
  - Dyspepsia AEs

- Etoricoxib was worse than placebo for:

- Hypertension AEs

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - Tender and swollen joint count (at 12 weeks) p<0.01
  - Patient's and investigator's global assessment of disease activity (at 12 weeks) p<0.01
  - ACR20 completers (at 12 weeks) p<0.01
  - Pain, VAS (at 12 weeks) p<0.01
  - Modified HAQ score (at 12 weeks) p<0.01
  - CRP level (at 12 weeks) p<0.01

- Naproxen was better than placebo for:
  - Total number of withdrawals (45% and 62% respectively)

- There was no significant difference between naproxen and placebo for:
  - Number of patients with drug-related AEs#
  - Withdrawals due to AEs
  - SAEs

- Naproxen was worse than placebo for:
  - Dyspepsia AEs
  - Hypertension AEs

Etoricoxib vs naproxen

- Etoricoxib was significantly better than naproxen for:
  - Tender and swollen joint count (at 12 weeks) p<0.01 and p<0.05 respectively
  - Patient's and investigator's global assessment of disease activity (at 12 weeks) p<0.01
  - ACR20 completers (at 12 weeks) p<0.01
  - Pain, VAS (at 12 weeks) p<0.01
  - Modified HAQ score (at 12 weeks) p<0.01
  - Withdrawals due to lack of efficacy (at 12 weeks) p<0.01

- Etoricoxib was better than naproxen for:
  - Total number of withdrawals (29% and 45% respectively)

- There was NS difference between Etoricoxib and naproxen for:
  - CRP level (at 12 weeks)

- Etoricoxib was similar to naproxen for:
    - Dyspepsia AEs
    - Hypertension AEs

*all statistical outcomes are based on 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Matsumoto, A. Melian, A. Shah, and S. P. Curtis. Etoricoxib versus naproxen in patients with rheumatoid arthritis: a prospective, randomized, comparator-controlled 121-week trial. *Current Medical Research & Opinion* 23 (9):2259-2268, 2007. REF ID: 3497	EXTENSION OF RCT: 1+ Multicentre trial: 88 centres USA • Randomised (computer-generated random code) • No mention of blinding • Not true ITT analysis	N=717 randomised into extension part 1	As for ID 3082	Patients originally on Etoricoxib 90 mg (once/day) were randomised to the same treatment or 120 mg Patients originally on Naproxen 1000 mg (500 mg twice/day) continued on this treatment Patients were allowed to take rescue low dose aspirin	Patients originally on Placebo were randomised to naproxen or etoricoxib 90 mg	Extension 1 = 52 weeks Extension 2 = 121 weeks	Tender and swollen joint count; patient's and investigator's global assessment of disease activity and response to therapy; morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs For long-term results (121 weeks) only patients who were assigned in the extension study to the same therapy	Merck Research Laboratories

							as they were on in the 12 week study, were compared	

Effect size*

Etoricoxib 90 mg vs Naproxen (patients who remained on this treatment from the initial 12 week study)

- Etoricoxib 90 mg was comparable to Naproxen at 121 weeks for:
  - Swollen and tender joint count, patients' and investigators' global assessment
  - Number of AEs

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. Geusens, R. Alten, J. Rovensky, V. S. Sloan, G. Krammer, G. Kralidis, and P. Richardson. Efficacy, safety and tolerability of lumiracoxib in patients with rheumatoid arthritis. *International Journal of Clinical Practice* 58 (11):1033-1041, 2004. REF ID: 38	RCT 1+ Multicentre trial: 83 centres in 16 countries • Randomised (method not mentioned) • Double blind, double dummy • Not true ITT analysis (but LOCF) • Slightly underpowered • High number of dropouts	N=1023 randomised (N=280 lumiracoxib 200 mg, N=281 lumiracoxib 400 mg, N=279 naproxen, N=284 placebo) **Drop-outs:** Lumiracoxib 200 mg - 31% Lumiracoxib 400 mg - 36% Naproxen - 31%	**Inclusion criteria:** ≥18 years, RA (ACR criteria); functional class I, II or III; symptoms ≥3 months and receiving regular NSAID therapy. **Exclusion criteria:** receiving ≥3 DMARDxs, systemic CS, gastroprotective medication; any NSAID other than low-dose aspirin (≥325 mg/day) for CV prophylaxis; history of GI ulceration or bleeding; hypersensitivity to NSAIDs or significant medical problems. **Baseline characteristics:** Lumiracoxib 200 mg: mean age 54 years, female 78%, disease duration mean 9 years (Established RA), Pain (VAS) 67.	lumiracoxib 200 mg (once/day) lumiracoxib 400 mg (once/day) naproxen 1000 mg (500 mg twice/day) All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare	Placebo	26 weeks	Tender and swollen joint count; patient's and investigator's global assessment of disease activity and response to therapy; morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs, SAEs	Novartis Pharma AG, Switzerland.

		Placebo - 44%	Lumiracoxib 400 mg: mean age 53 years, female 80%, disease duration mean 9 years (Established RA), Pain (VAS) 68. Naproxen: mean age 54 years, female 79%, disease duration mean 11 years (Established RA), Pain (VAS) 68. Placebo: mean age 53 years, female 79%, disease duration mean 9 years (Established RA), Pain (VAS) 68.	criteria were satisfied. Rescue paracetamol was allowed during the trial				

Effect size*

LUMIRACOXIB ARMS NOT INCLUDED AS THI DRUG NOW WITHDRAWN

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - Swollen joint count at 26 weeks ($p<0.05$)
  - Tender joint count at 13 and 26 weeks ($p<0.05$)
  - Patient's and investigator's global assessment of disease activity at 13 and 26 weeks ($p<0.01$ and $p<0.05$ respectively)
  - Pain, VAS at 13 and 26 weeks ($p<0.01$)
  - Modified HAQ score at 13 and 26 weeks ($p<0.05$)

- There was no significant difference between naproxen and placebo for:
  - Swollen joint count at 13 weeks
  - CRP level at 13 and 26 weeks
  - Use of rescue medication at 26 weeks

- Naproxen was better than placebo for:
  - Total number of withdrawals
  - Withdrawals due to lack of efficacy

- Naproxen was worse than placebo for:
  - % of patients with AEs
  - Discontinuation due to AEs/SAEs
  - GI AES and hypertension
  - Pre-specified GI disorders

*all statistical outcomes are based on 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
W. Bensen, A. Weaver, L. Espinoza, W. W. Zhao, W. Riley, B. Paperiello, and D. P. Recker. Efficacy and safety of valdecoxib in treating the signs and symptoms of rheumatoid arthritis: a randomized, controlled comparison with placebo and naproxen. *Rheumatology* 41 (9):1008-1016, 2002. ID 95	RCT 1+ Multicentre (sites not mentioned) o Randomised (method not mentioned) o Double blind o Not true ITT analysis o High number of drop-outs	N=1,090 randomised N=222 placebo, N=209 valdecoxib 10mg N=212 valdecoxib 20mg N=221 valdecoxib 40mg N=226 Naproxen 500mg **Drop-outs:** placebo 130	**Inclusion criteria:** Patients with adult onset RA, for at least 6 months . Stable RA on conventional NSAID therapy for at least 1 months and a Functional Capacity Classification between I and II at the screening assessment. Patients with RA in a flare state at the baseline assessment within 2-7 days following discontinuation of conventional NSAID, were included in the study. **Exclusion criteria:**. Patients were excluded if they had any other form of inflammatory arthritis that interfered with the evaluation of study medication in the treatment of RA. GI problems; serious disease; warfarin or other a-coagulants within 30 days; oral CS within 4 weeks; IA/IM CS within 8 weeks; a-neoplastic agents within 12 weeks; a-inflammatory analgesics within 48 hrs (12 hrs for paracetamol) before start of study treatment Patients were allowed to continue their DMARD therapy but those who	naproxen 500 mg twice/day valdecoxib 10mg valdecoxib 20mg valdecoxib 40mg Placebo The study period was preceded by a screening visit, a 2-7 day washout period and baseline visit.		12 weeks	Number of patients responding to treatment according to the ACR-20 Patient's Global Assessment of Disease Activity Physicians Global Assessment of Disease Activity Patient's Assessment of Arthritis Pain-VAS Tender Painful Joint Score Safety Assessment	Pfizer Inc. Pharmacia Corp.

		Valdecoxib (77, 80, 90) 247 Naproxen 89	changed their dosing or starting new therapy were exclude. **Baseline characteristics:** Placebo: mean age 55.7, female 77% Disease duration (yr) 10.3 Naproxen: mean age 55.4, female 81%. Disease duration (yr) 9.9 There were NS differences between the groups for any of the baseline characteristics apart from mHAQ functional disability, which was higher in the valdecoxib 20mg group and lower in the valdecoxib 10mg group (p=0.03) Treatment groups were similar with respect to the % of patients taking methotrexate and / or other DMARDs				

Effect size*

NOTE: VALDECOXIB IS NOT LICENSED IN THE UK AND THUS ONLY THE NAPROXEN VS PLACEBO ARM IS REPORTED IN THE RESULTS HERE

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
    - ACR20 responders at 12 weeks ($p \leq 0.01$)
    - Score for Patient's and Physician's Global Assessment of Disease Activity ($p \leq 0.05$)
    - Reduction in the number of tender/painful joints ($p \leq 0.01$)
    - Tender /Painful Joint Score ($p \leq 0.01$)
    - Pain (VAS) at 12 weeks ($p<0.001$)
    - Duration of Morning stiffness at 12 weeks ($p<0.001$)
    - Withdrawals due to lack of efficacy ($p<0.001$

- Naproxen was worse than placebo for:

- Overall incidence of AEs ($p \leq 0.05$)
- Incidence of Hypertension (naproxen 2.7%, placebo 0%)

- There was no significant difference between naproxen and placebo for:
  - Increases in BUN and Serum Creatinine

*all results are 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
P. P. Geusens, K. Truitt, P. Sfikakis, P. L. Zhao, L. DeTora, S. Shingo, C. S. Lau, A. Kalla, and G. Tate. A placebo and active comparator-controlled trial of rofecoxib for the treatment of rheumatoid arthritis. *Scand.J Rheumatol.* 31 (4):230-238, 2002. REF ID: 117	RCT 1++ Multicentre trial: 87 centres worldwide • Randomised (method not mentioned) • Double blind • ITT analysis	N=1023 randomised (N=289 placebo, N=306 rofecoxib 25 mg, N=286 rofecoxib 50 mg, N=142 naproxen 1000 mg) **Drop-outs:** Total: 84%	**Inclusion criteria:** ≥18 years, RA (ACR criteria); history of therapeutic benefit from NSAIDs, COX-2s and have required therapeutic doses on a regular basis prior to study entry. Stable therapy with most DMARDs (for previous 6 months) was permitted. **Exclusion criteria:** TNF-sequestrant use; warfarin, ticlopidine, clopidogrel and aspirin use; potentially confounding secondary medical diagnoses; allergy to paracetamol, aspirin or NSAIDs. **Baseline characteristics:** Placebo: mean age 54 years, female 85%, disease duration mean 9 years (Establised RA), Disease activity (0-4 Likert) 2.6. Rofecoxib 25 mg: mean age 53 years, female 80%, disease duration mean 8 years (Establised RA), Disease activity (0-4 Likert)	rofecoxib 25 mg (once/day) rofecoxib 50 mg (once/day) naproxen 1000 mg (500 mg twice/day) All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare criteria were satisfied. Rescue paracetamol	Placebo Patients could continue oral CS use (low dose) but only if had been stable over the past 30 days. Concomitant therapy with non-study NSAIDs or COX-2s was prohibited. Use of gastroprotective agents was not permitted at entry but allowed as necessary to treat symptoms that arose during the trial.	12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of disease activity and response to therapy; morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs	Not mentioned

			2.5. Rofecoxib 50 mg: mean age 54 years, female 84%, disease duration mean 9 years (Establised RA), Disease activity (0-4 Likert) 2.5. Naproxen: mean age 54 years, female 82%, disease duration mean 9 years (Establised RA), Disease activity (0-4 Likert) 2.6. The groups were similar for all baseline characteristics.	was allowed during the trial for pain				

Effect size*

ROFECOXIB WITHDRAWN thus arms not reported

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - Tender joint count at 12 weeks ($p<0.05$)
  - Patient's and Investigator's Global assessment of disease activity at 12 weeks ($p<0.05$)
  - ACR20 responder index at 12 weeks ($p<0.05$)
  - Pain (VAS) at 12 weeks ($p<0.05$)
  - Patient's and Investigator's Global assessment of response to therapy at 12 weeks ($p<0.05$)
  - Morning stiffness at 12 weeks ($p<0.05$)
  - Withdrawals due to lack of efficacy at 12 weeks ($p<0.05$)
  - Use of rescue therapy at 12 weeks ($p<0.05$)

- There was no significant difference between naproxen and placebo for:
  - Swollen joint count (at 12 weeks)
  - CRP level (at 12 weeks)
  - Number of patients with 1 or more clinical AEs
  - Number of patients with drug-related AEs
  - Withdrawals due to AEs
  - Number of patients with hypertension AEs
  - Number of patients with GI AEs

*effect sizes are changes from baseline to 12 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. Gibofsky, J. Rodrigues, J. Fiechtner, M. Berger, and S. Pan. Efficacy and tolerability of valdecoxib in treating the signs and symptoms of severe rheumatoid arthritis: a 12-week, multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapeutics* 29 (6):1071-1085, 2007. REF ID: 3077	RCT 1+ Multicentre trial: 61 centres in USA and Canada o Randomised (computer generated, stratified by centre, block sizes of 10) o Double blind o Not true ITT analysis o Power study o High number of drop-outs	N=508 randomised (N=171 placebo, N=170 valdecoxib, N=167 naproxen) **Drop-outs:** placebo 47% naproxen 28%	**Inclusion criteria:** ≥18 years, RA (ARA criteria); established diagnosis of RA for at least 6 months prior to entering the study; stable RA with therapy including an NSAID (for at least 4 weeks) plus at least 1 DMARD or a-TNF for at least 12 weeks; functional class II or III. **Exclusion criteria:** other forms of inflammatory arthritis or secondary non-inflammatory arthritis; GI problems; serious disease; warfarin or other a-coagulants within 30 days; oral CS within 4 weeks; IA/IM CS within 8 weeks; a-neoplastic agents within 12 weeks; a-inflammatory analgesics within 48 hrs (12 hrs for paracetamol) before start of study treatment . **Baseline characteristics:** Placebo: mean age 56 years, female 84%, disease duration mean 12 years (Established RA). Naproxen: mean age 57 years, female 71%, disease duration mean 10 years (Established RA).	naproxen 1000 mg (500 mg twice/day) Placebo All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare criteria were satisfied. Patients already receiving DMARDs had to remain on stable doses during the trial. Patients taking aspirin (<325 mg/day) for at least 30 days for cardioprophylaxis we allowed to continue their regimen during the study. Paracetamol up to 2 g/day was permitted as a rescue medication.		12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of arthritis; morning stiffness; patient's global assessment of pain (VAS); HAQ; ACR20 response; ACR-N; SF-36; PTSS (Patient Treatment Satisfaction Scale); CRP level; AEs	Pfizer Inc.

			There were NS differences between the groups for any of the baseline characteristics except the naproxen group had significantly more men.				

Effect size*

NOTE: VALDECOXIB IS NOT LICENSED IN THE UK AND THUS ONLY THE NAPROXEN VS PLACEBO ARM IS REPORTED IN THE RESULTS HERE

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - Tender and painful joint count at 12 weeks ($p \leq 0.001$)
  - Tender and painful joint score at 12 weeks ($p \leq 0.001$)
  - Swollen joint count at 12 weeks ($p \leq 0.001$)
  - Swollen joint score at 12 weeks ($p \leq 0.001$)
  - Patient's and Physician's global assessment of disease activity at 12 weeks ($p \leq 0.001$)
  - ACR20 responders at 12 weeks ($p \leq 0.001$)
  - ACR-N at 12 weeks ($p \leq 0.001$)
  - PTSS at 12 weeks ($p \leq 0.001$)
  - Pain (VAS) at 12 weeks ($p \leq 0.001$)
  - HAQ score at 12 weeks ($p \leq 0.001$)
  - Morning stiffness at 12 weeks ($p \leq 0.001$)
  - SF-36 Physical (all domains except general health)
  - SF-36 Mental (all domains except role-emotional)

- Naproxen was better than placebo for:
  - Withdrawals due to lack of efficacy (13% and 35% respectively)

- Naproxen was similar to placebo for:
  - Total number of patients with AEs (55% and 53% respectively)
  - Hypertension AEs
  - Number of SAEs

- There was no significant difference between naproxen and placebo for:
  - CRP level at 12 weeks

- Naproxen was worse or significantly worse than placebo for:

- Withdrawals due to AEs (10% and 5% respectively)
- Dyspepsia AEs (p=0.034)

*all results are 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
H. Krug, L. K. Broadwell, M. Berry, R. DeLapp, R. H. Palmer, and M. Mahowald. Tolerability and efficacy of nabumetone and naproxen in the treatment of rheumatoid arthritis. *Clinical Therapeutics* 22 (1):40-52, 2000. REF ID: 199	RCT 1+ Multicentre trial: 31 centres in USA o Randomised (method not mentioned) o Double blind o Not true ITT analysis o Power study (physician's global assessment) o High number of drop-outs	N=346 randomised (N=173 placebo, N=173 naproxen) **Drop-outs:** nabumetone 35% naproxen 28%	**Inclusion criteria:** ≥18 years, RA (ARA criteria); active disease; received NSAID therapy for at least 3 months prior to entering the study; functional class I, II or III. **Exclusion criteria:** Hypersensitivity to aspirin or other NSAID; significant GI, CV, renal or hepatic disease; functional class IV; those requiring physiotherapy, systemic CS or stable use of DMARDs for <3 months. **Baseline characteristics:** Placebo: mean age 54 years, female 73%, disease duration mean 11 years (Established RA), Pain (VAS) 69. Naproxen: mean age 55 years, female 72%, disease duration mean 10 years (Established RA), Pain (VAS) 67. There were NS differences between the groups for any of the	naproxen 1000 mg (500 mg twice/day) Nabumetone 2000 mg (1000 mg twice/day) All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified disease activity and flare criteria were satisfied. Patients were allowed to take paracetamol as rescue medication during the first 2 weeks of the trial IA CS were not allowed within 2 weeks of screening, prophylactic use of antacids or a-ulcer medication was prohibited but could be prescribed for those who developed GI signs and symptoms during the study.		12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of arthritis; pain (VAS); AIMS2; RADAR (Rapid Assessment of Disease Activity in Rheumatology); CRP level; AEs	Smith-Kline Beecham Pharmaceuticals Inc., USA.

			baseline characteristics.				

Effect size*

Naproxen vs nabumetone

- Naproxen was significantly better than nabumetone for:

- Naproxen was similar to nabumetone for:
  - Number of patients with ≥1 AE
  - Withdrawals due to lack of efficacy

- There was no significant difference between naproxen and nabumetone for:
  - Change in number of tender, swollen and painful joints at 12 weeks
  - Patient's and investigator's global assessment at 12 weeks
  - Pain (VAS) at 12 weeks
  - AIMS2 dimensions at 12 weeks
  - RADAR dimensions at 12 weeks
  - Use of rescue paracetamol
  - Clinical change in number of joints involved (≥50% reduction)
  - Clinical change in number of tender, swollen and painful joints (≥50% reduction)
  - Serious GI AEs (N=0 in both groups)
  - Withdrawals due to treatment-related AEs
  - Total withdrawals

*all results are 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. S. Simon, A. L. Weaver, D. Y. Graham, A. J. Kivitz, P. E. Lipsky, R. C. Hubbard, P. C. Isakson, K. M. Verburg, S. S. Yu, W. W. Zhao, and G. S. Geis. Anti-inflammatory and	RCT 1+ Multicentre trial: 79 centres in USA and Canada o Randomised (computer generated, stratified by centre, block	N=1149 randomised (N=231 placebo, N=154 celecoxib 100 mg, N=235 celecoxib 200 mg,	**Inclusion criteria:** ≥18 years, RA (ARA criteria); established diagnosis of RA for at least 3 months prior to entering the study; functional calss I, II or III. **Exclusion criteria:** GI problems but not PUD. **Baseline characteristics:**	naproxen 1000 mg (500 mg twice/day) Placebo All patients in all groups underwent an initial washout period for NSAIDs and were then randomised if prespecified		12 weeks	Tender and swollen joint count; patient's and investigator's global assessment of arthritis; morning stiffness;	Not mentioned but pharma company conflict of interests

upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial.[see comment]. *JAMA* 282 (20):1921-1928, 1999. REF ID: 3087	sizes of 10) o Double blind o Not true ITT analysis o Power study o High number of drop-outs	N=218 celecoxib 400 mg, N=225 naproxen) **Drop-outs:** placebo 57% naproxen 39%	Placebo: mean age 54 years, female 73%, disease duration mean 11 years (Established RA), Pain (VAS) 69. Naproxen: mean age 55 years, female 72%, disease duration mean 10 years (Established RA), Pain (VAS) 67. There were NS differences between the groups for any of the baseline characteristics.	disease activity and flare criteria were satisfied. Patients were allowed to take aspirin (<325 mg/day) and paracetamol up to 2 g/day for no longer than 3 consecutive days except within 48 hrs of assessment when no analgesic was allowed. NSAIDs, injectible CS, anti-ulcer drugs and anti-coagulants were prohibited. Oral glucocorticoids or DMARDs were allowed. Patients already receiving glucocorticoids, DMARDs or MTX had to remain on stable doses during the trial		patient's global assessment of pain (VAS); HAQ; ACR20 response; CRP level; AEs	

Effect size*

NOTE: This is the same trial as Zhao et al., ID 3085 THE CELECOXIB ARMS WERE INCLUDED IN THE TA AND THUS ONLY THE NAPROXEN VS PLACEBO ARM IS REPORTED IN THE RESULTS HERE

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - Swollen joint count at 12 weeks ($p<0.05$)
  - ACR20 responders at 12 weeks ($p<0.05$)
  - Pain (VAS) at 12 weeks ($p<0.05$)
  - HAQ score at 12 weeks ($p<0.05$)
  - Morning stiffness at 12 weeks ($p<0.05$)
  - Withdrawals due to lack of efficacy ($p<0.05$)

- Naproxen was better than placebo for:
  - Total number of withdrawals (39% and 57% respectively)

- There was no significant difference between naproxen and placebo for:

- Tender and painful joints at 12 weeks
- Patient's and investigator's global assessment of arthritis at 12 weeks
- CRP level at 12 weeks
- Withdrawals due to AEs
- Hypertension AEs

- Naproxen was worse than placebo for:
  - Total GI AEs
  - Withdrawals due to GI AEs
  - Total number of AEs

*all results are 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
G. W. Williams, A. J. Kivitz, M. T. Brown, and K. M. Verburg. A comparison of valdecoxib and naproxen in the treatment of rheumatoid arthritis symptoms. *Clinical Therapeutics* 28 (2):204-221, 2006. ID 3078	RCT 1+ Multicentre: 225 sites in North America and South America o Randomised (method not mentioned) o Double blind o Not true ITT analysis o High number of drop-outs	N=1,093 randomised N=220 placebo, N=226 valdecoxib 10mg N=219 valdecoxib 20mg N=209 valdecoxib 40mg N=219 Naproxen 500mg	**Inclusion criteria:** Patients with adult onset RA, for at least 6 months . Stable RA on conventional NSAID therapy for at least 1 months and a Functional Capacity Classification between I and II at the screening assessment. Patients with RA in a flare state at the baseline assessment within 2-7 days following discontinuation of conventional NSAID, were included in the study. **Exclusion criteria:**. Patients were excluded if they had any other form of inflammatory arthritis that interfered with the evaluation of study medication in the treatment of RA. GI problems; serious disease; warfarin or other a-coagulants within	naproxen 500 mg twice/day valdecoxib 10mg valdecoxib 20mg valdecoxib 40mg Placebo		12 weeks	**Primary outcomes** Number of patients responding to treatment according to the ACR-20 Patient's Global Assessment of Disease Activity Physicians Global Assessment of Disease Activity **Secondary outcomes**	Pfizer Inc. Pharmacia Corp.

		Drop-outs: Total: 442 40.4% placebo 125 (11.4%) Valdecoxib (89, 82, 72) 243 Naproxen 74 (6.7%)	30 days; oral CS within 4 weeks; IA/IM CS within 8 weeks; a-neoplastic agents within 12 weeks; a-inflammatory analgesics within 48 hrs (12 hrs for paracetamol) before start of study treatment Patients were also excluded if they met any of the following criteria: Diagnosed or treated for oesophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before the first dose of study medication; active GI disease, a chronic or acute renal or hepatic disorder, or significant coagulation defect. **Baseline characteristics:** Placebo: mean age 58.1 female 72.7% Disease duration (yr) 11.5 Naproxen: mean age 54.5, female 74.9%. Disease duration (yr) 10.4 There were NS differences between the groups for any of the baseline characteristics apart from Age. Mean age was higher in the placebo group (58.1) and lower in the naproxen 500mg BID group (54.5)			Patient's Assessment of Arthritis Pain-VAS Tender Painful Joint Score Safety Assessment	
Effect size* **NOTE: VALDECOXIB IS NOT LICENSED IN THE UK AND THUS ONLY THE NAPROXEN VS PLACEBO ARM IS REPORTED IN THE RESULTS HERE** **Naproxen vs placebo** • Naproxen was significantly better than placebo for: o ACR20 responders at 12 weeks ($p \leq 0.001$) o Tender /Painful Joint Score ($p \leq 0.01$)							

- Reduction in the number of tender/painful joints (p= 0.03)
- Score for Physician's Global Assessment of Disease Activity (p≤ 0.001)

- Naproxen was worse than placebo for:
  - Overall incidence of AEs (Placebo 45.5% Naproxen 62.6%)
  - GI AEs (Placebo 20%, Naproxen 32.9%) (p≤0.05)

*all results are 'changes from baseline'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Z. Zhao, J. I. Fiechtner, E. A. Tindall, S. D. Dedhiya, W. W. Zhao, J. T. Osterhaus, and S. S. Yu. Evaluation of health-related quality of life of rheumatoid arthritis patients treated with celecoxib. *Arthritis Care & Research* 13 (2):112-121, 2000. REF ID: 3085	RCT 1+ Multicentre trial: 79 centres in USA and Canada As for Simon et al ID 3085	As for Simon et al ID 3085	As for Simon et al ID 3085	As for Simon et al ID 3085		As for Simon et al ID 3085	SF-36 domains (Physical and mental components)	G. D. Searle & Co.

Effect size*

NOTE: This is the same trial as Simon et al., ID 3087 THE CELECOXIB ARMS WERE INCLUDED IN THE TA AND THUS ONLY THE NAPROXEN VS PLACEBO ARM IS REPORTED IN THE RESULTS HERE

Naproxen vs placebo

- Naproxen was significantly better than placebo for:
  - SF-36 Physical (all domains) at 12 weeks (all: p<0.01)

o SF-36 Mental (all domains) at 12 weeks (all: p<0.05) *all results are 'changes from baseline'

8. MONITORING RHEUMATOID ARTHRITIS (MONIT, REVIEW)

8.1 MONITORING DISEASE (MONIT)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding

J. S. Dixon, S. Hayes, P. D. L. Constable, and H. A. Bird. What are the 'best' measurements for monitoring patients during short-term second-line therapy? *British Journal of Rheumatology* 27 (1):37-43, 1988. ID: 532	Case-series (prospective): 3 Single centre, UK	Total N=71 **Drop-outs:** Not mentioned	**Inclusion criteria:** classical or definite RA and moderate disease severity of sufficient activity to require ARD therapy **Exclusion criteria:** Not mentioned **Baseline characteristics mean range:** Female 67 to 80%; mean age 46 to 54 years; disease duration, mean 5 to 12 years (established RA). The 5 groups were similar for all baseline characteristics.	Not applicable All patients were treated for at least 24 weeks with one of 5 ARDs: D-pen (N=15); Sodium aurothiomalate (N=14); SSZ (N=15); clobuzarit (N=12) and Sulphapyridine (N=15). In addition all patients received NSAIDs.	24 weeks (end of treatment) with assessments at 2, 4, 8, 12, 16, 20 and 24 weeks	RAI; Pain (1-5 scale); early morning stiffness; Grip strength; Joint size; summated change score (patient's global assessment of well-being – VAS – successive scores were summated); NSAID dose; ESR; CRP; PV (plasma viscosity).	Roche Products Limited.

Effect size

VARIABLES SHOWING THE FASTEST CHANGE (TIME OF EARLIEST SIGNIFICANT IMPROVEMENT AND THE CHANGE ARISING AT THEIS TIME FOR CLINICAL AND LAB VARIABLES):

- RAI, summated change score and ESR had equal fastest responses at 4 weeks, while change of NSAID dose, morning stiffness, plasma viscosity and IgM had the next fastest responses at 8 weeks.
- When the earliest significant improvement was seen early in the treatment period, the improvement in mean data tended to be less.
- The median time across the variables within each treatment suggests a tendency for clinical response to occur earlier than lab response with the notable exception of clobuzarit where there was a more rapid lab change.

VARIABLES SHOWING MOST CHANGE:

- The most change was seen for summated change score, RAI, joint size and change in NSAID dose. For lab measures the most change was seen in ESR.
- When clinical and lab results were combined, the top 3 positions were lab measurements (R+ESR, PV and IgM) followed by Summated change score and RAI.

PERIODS OF MOST CHANGE

- The peiod of most change was consistent for all treatments, and the results revealed earlier change in clinical measures.
- Period of greatest change started after 2.3 weeks for clinical variables and after 3.2 weeks for lab variables. The period of greatest change was seen within 18 weeks and before the end of the treatment period (24 weeks)

VARIABLES MOST CLOSELY REFLECTING CHANGE IN OTHERS (data not shown):

- Most of the correlations were small, indicating a very weak or negligible relationships between most variables. The few high correlations were between variables known to be related (eg. ESR and PV).

Authors' conclusions: The results consistently showed that RAI and summated change score were the 'best' clinical measures, while ESR and plasma viscosity were the 'best' laboratory measures. Tradtional measures such as grip strength and joint size fared badly and cannot be recommended. Clinical variables improved slightly more rapidly than lab measures, by=ut the lab measures showed the greater change. Detailed measurement of function is important in assessing RA activity. Functional impairment in RA is a dynamic process influenced by changes in clinical disease activity with treatment.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding

J. S. Dixon, H. A. Bird, N. G. Sitton, M. E. Pickup, and V. Wright. C-reactive protein in the serial assessment of disease activity in rheumatoid arthritis. *Scandinavian Journal of Rheumatology* 13 (1):39-44, 1984. ID: 3417	Case-series (prospective): 3 Single centre, UK	Total N=105 **Drop-outs:** None	**Inclusion criteria:** classical or definite RA (ARA criteria); at least moderate disease activity; had not previously received anti-rheumatoid drug in the previous 6 months. **Exclusion criteria:** not mentioned. **Baseline characteristics of all 5 groups:** Female 60% to 87%; mean age 48 to 61 years; disease duration, mean 5 to 12 years (established RA).	All patients were treated with DMARDs (15 patients in each group) received: D-pen; alclofenac; hydroxychloroquine; sodium aurothiomalate; SSZ; azathioprine; aspirin.	24 weeks (assessments at weeks 2, 4, 8, 12, 16, 20 and 24)	CRP; ESR; haptoglobin and fibrinogen; Articular index; pain (1-5 scale).	Roche Products Limited.

Effect size

Articular index vs CRP

- Compared to ESR, CRP (mean over time) had the highest correlation with Articular index for all study drugs
- The more effective drugs exhibited more significant correlations as a consequence of the strong directional trends in the data.
- Best significant correlation with all drug groups: CRP and Articular index (range 64% to 95% correlations) compared to ESR and Articular Index (range 53% to 85% correlation)

Authors' conclusions: The estimation of CRP was found to be more useful than haptoglobin, fibrinogen and ESR as an index of disease activity.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding

A. A. Kalla, P. R. Smith, G. M. Brown, O. L. Meyers, and D. Chalton. Responsiveness of Keitel functional index compared with laboratory measures of disease activity in rheumatoid arthritis. *British Journal of Rheumatology* 34 (2):141-149, 1995. ID: 407	Case-series (prospective): 3 Single centre, South Africa	Total N=115 **Drop-outs:** Yes – number not mentioned; analysis confined to all those who had no missing data in the course of the study (N=115 patients – all completed 18 months follow-up and had no missing data)	**Inclusion criteria:** RA (ACR criteria); patients receiving SAARD therapy (due to 6 or more swollen joints not responsive to NSAID therapy and 2 or more of the following: early morning stiffness >45 mins; ESR >28 mm/hr; 9 or more tender joints) **Exclusion criteria:** ACR functional class III or IV. **Baseline characteristics:** Female 82%; mean age 49 years; disease duration, mean 7 years (established RA).	Not applicable N=28 patients were concurrently receiving corticosteroids. All patients received NSAIDs and simple analgesics throughout the study, as needed. All patients were referred to an OT and PT for advice about joint protection and use of devices as well as maintaining joint movement.	18 months (4 follow-up assessments 6 months apart)	Kietel Functional Index (KFI); Hand function Index (HFI); CRP; ESR; RAI; Fatigue; early morning stiffness; swollen joint count. Lansbury Systemic Index (LSI) Efficiency was measured by the standardised response mean: mean change in outcome divided by the SD of the change.	Grant from the MRC South Africa and the University of Cape Town Research Fund, South Africa.

Effect size

CORRELATIONS BETWEEN RAI, KFI AND HFI WITH CLINICAL AND LABORATORY VARIABLES (AT ONSET AND END OF STUDY):

- Early morning stiffness explained 5% of the variation in RAI at onset and 12% at the end of the study. The KFI and HFI showed poor correlation with early morning stiffness throughout the study.
- Fatigue (time to onset) correlated significantly with RAI throughout the study (P<0.0001) but only with KFI and HFI after therapy (p<0.03).
- Swollen joint count showed greater correlations with the 3 variables of interest after therapy than before treatment; at end of study almost 25% of the variation in HFI was explained by variation in swollen joint count.
- There was a clear relationship between joint swelling, tenderness and reduced function.
- ESR correlated best with KFI at onset of therapy (p=0.003), but at the end of therapy the correlation was greatest with the HFI (p=0.0001).
- CRP showed significant correlations with all 3 variables only after therapy. There was almost no correlation at the onset of therapy.
- LSI showed significant correlations with all 3 variables throughout the study and this was considerably increased at the end of the study.

STANDARDISED RESPONSE MEANS:

- Clinical measures such as the RAI and swollen joint count showed marked sensitivity to change with treatment.
- ESR proved to be a better measure of efficiency than CRP in this study.
- Time to onset of fatigue and duration of early morning stiffness were equally responsive to SAARD therapy.
- KFI and HFI were similar in their measure of efficiency and both were better than CRP.
- LSI was the best overall measure of efficiency, emphasising the importance of pooled indices in the measurement of the disease process in RA.

CORRELATION MATRIX (LIKELIHOOD OF ASSOCIATED CHANGE IN THE DIFFERENT VARIABLES IN RTELATION TO EACH OTHER):

- The change in KFI with therapy correlated significantly with change in RAI (r=0.4, p=0.001), EMS (r=0.27, p=0.004), swollen joint count (r=0.3, p=0.0005); CRP (r=0.21, p=0.03) and LSI (r=0.35, p=0.002) but not with change in time to onset of fatigue or ESR.
- Change in HFI correlated significantly with the same variables, but less of the variance was explained than with the KFI. This suggests a strong likelihood of improvement in function if there is an improvement in function if there is an improvement of other markers of disease activity with treatment.
- Correlation between change in HFI and: change in RAI (r=0.02, p=0.02), morning stiffness (r=0.11, NS), swollen joint count (r=0.29, p=0.002), CRP (r=0.17, NS) and LSI (r=0.18, NS)
- The change in ESR correlated significantly with the change in CRP (p=0.0001) but these 2 variables were clearly not mutually exclusive.

Authors' conclusions: Detailed measurement of function is important in assessing RA activity. Functional impairment in RA is a dynamic process influenced by changes in clinical disease activity with treatment.

Reference	Study type Evidence level	Number of patients	1.11 Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding

J. S. Smolen, F. C. Breedveld, M. H. Schiff, J. R. Kalden, P. Emery, G. Eberl, P. L. van Riel, and P. Tugwell. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 42 (2):244-257, 2003. ID 3401	Pooled analysis of 3 RCTs: 1+ Multinational RCTs trials • ITT analysis but no other details of trial methodology are mentioned	Total N=1839 **Drop-outs:** Not mentioned	**Inclusion criteria:** Patients enrolled in 3 Phase III clinical trials (RCTs): Adults with RA (ACR criteria); functional class I, II or III. The 3 RCTs were: 1. Leflunomide vs placebo vs SSZ (6 months treatment). 2. Leflunomide vs placebo vs MTX (12 months treatment) 3. Leflunomie vs MTX (12 months treatment) **Exclusion criteria:** not given **Baseline characteristics:** Trial 1: N=358; mean age 59 years; Female 73%; Duration of RA = Established RA (mean 7 years); SDAI mean 50. Trial 2: N=999; mean age 58 years; Female 71%; Duration of RA = Established RA (mean 4 years); SDAI mean 51. Trial 3: N= 482; mean age 55 years; Female 72%; Duration of RA = Established RA (mean 7 years); SDAI mean 43.	Pooled analysis of data from 3 RCTs	12 months (end of treatment); assessments performed at baseline, 6 and 12 months	SDAI (linear sum of: tender and swollen 28-joint count, patient and physician's global assessment of disease activity and CRP); Sharp total score; DAS28; HAQ; ACR response	Not mentioned

Effect size

NOTE: data are from 3 Phase III trials

SDAI vs HAQ

- In all 3 RCTs there was a significant correlation between change in SDAI and change in HAQ score at all time-points (up to 12 months); p<0.0001 for all RCTs
- When SDAI was modified - physician's global assessment was replaced by pain (as fro DAREA) – change in SDAI and change in HAQ were almost identical, p<0.0001
- When SDAI was further modified – excluded CRP – the change in SDAI was again significantly correlated to change in HAQ
- Thus there was a linear relationship between the SDAI and HAQ/MHAQ as well as between changes in the SDAI and HAQ/MHAQ in all 3 studes at all time points, confirming the validity and usefulness of the SDAI. Moreover, exchange of the physician's global assessment of disease activity as a component of the SDAI by patinet's pain assessment (the component of the DAREA replaced in the SDAI by physician's global assessment) did not change the correlations.

SDAI vs DAS28

- There was a significant linear association for the correlation between SDAI and DAS28 in all studies at all time-points (baseline and 6 months, range: r=0.91 to 0.93, all p<0.0001)) and for change in SDAI and change in HAQ (range: r=0.53 to 0.66, all p<0.0001).

SDAI vs ACR response

- There was a greater change in the SDAI for the ACR20 to 90% response criteria

All data together reveal that an absolute SDAI value of 5-20 relates to mild disease activity, while an SDAI of 21-40 corresponds to moderate disease activity and an SDAI of >40 is associated with severe disease activity.

SDAI vs radiographic changes

- Major improvement in SDAI at 12 months of treatment corresponded to mean increase of total sharp score of 1.1.
- Moderate improvement in SDAI at 12 months of treatment corresponded to mean increase of total sharp score of 1.9.
- No improvement in SDAI at 12 months of treatment corresponded to mean increase of total sharp score of 3.2.
- The corresponding values for DAS gave similar Sharp scores as for the SDAI.
- When the Larsen score was used, there were smaller changes among patients with major SDAI improvement than among those with no improvement, confirming the results obtained using the Sharp score.

Authors' conclusions: The SDAI is a valid and sensitive assessment of disease activity and treatment response is comparable with the DAS28 and ACR response criteria; it is easy to calculate and thus a viable tool for day-to-day clinical assessment of RA treatment.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding
D. M. van der Heijde, M. A. van't Hof, P. L. van Riel, M. A. Van Leeuwen, M. H. van Rijswijk, and L. B. van de Putte. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 51 (2):177-181, 1992. ID: 3416	Case-series (prospective): 3 2 centres, The Netherlands	Total N=233 **Drop-outs:** Not mentioned	**Inclusion criteria:** classical or definite RA (ARA criteria); disease duration <1 year; not previously treated with SAARDs. **Exclusion criteria:** not mentioned. **Baseline characteristics (mean of patients in the 2 centres):** Female 66%; mean age 51 years; disease duration, mean 7 years (established RA).	Not applicable	Mean 30 months – range 8 to 58 months (assessments every 4 weeks)	1. Mallya Index of disease activity (morning stiffness; Pain, VAS; grip strength; articular index; haemoglobin; ESR. Each variable divided into 4 classes and the mean of the 6 variables gives the full score – range 1 to 4) 2. Riel Index (modified Mallya index – morning stiffness; number of tender joints; haemoglobin; ESR. Calculated same way as Mallya index). 3. Disease activity score (Ritchie Index; number of swollen joints; ESR and general health). Also measured were the individual variables and additionally HAQ, swollen joints; Sharp total score (radiographic damage).	Grants from the Program for Stimulation of Health Research and the Netherlands League against Rheumatism.

Effect size

VALIDITY

- The median and mean correlations of disease activity measures with clinical status (physical disability measured by rheumatologists) were highest for Disease activity score (0.70 and 0.44) followed by Ritchie index (0.68 and 0.42) and the Mallya index (0.60 and 0.43).
- Ability to discriminate between high and low disease activity (based on use of DMARDs) was highest for Disease activity score (SD 1.66), followed by Riel index (SD 1.46) and the Mallya Index (SD 1.37)
- Correlation between increase in joint damage (erosions, JSN and total score) over 2 years was highest for: CRP (r=0.40, 0.52 and 0.50), swollen joints (r=0.54, 0.39 and 0.48), ESR (r=0.19, 0.36 and 0.29), disease activity score (0.31, 0.26 and 0.30), Mallya index (0.25, 0.30 and 0.31), Riel Index (0.22, 0.21 and 0.24) and Grip strength (-0.32, -0.39 and -0.38).

Authors' conclusions: The Disease Activity score and the Mallya index showed the best validity. The best single variable was the number of swollen joints. The validity of most single variables was poor and these were not suitable as single endpoint measures in clinical trials.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention Comparison	Length of follow-up	Outcome measures	Source of funding

M. A. Van Leeuwen, M. Van Rijswijk, D. Van der Heijde, G. Te Meerman, P. Van Riel, P. M. Houtman, L. Van de Putte, and P. C. Limburg. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: A prospective study during the first three years of the disease. *British Journal of Rheumatology* 32 (6):9-13, 1993. ID: 1835	Case-series (prospective): 3 Single centre, The Netherlands	Total N=110 **Drop-outs:** None	**Inclusion criteria:** classical or definite RA (ARA criteria); disease duration <1 year **Exclusion criteria:** not mentioned. **Baseline characteristics:** Female 63%; mean age 51 years; disease duration, mean 26 weeks (early RA).	Not applicable N=98 (89%) of patients were treated with DMARDs and low-dose oral CS were given as an adjuvant treatment to 10 patients.	At least 3 years (assessments every month for CRP and every 6 months for radiographs)	CRP (cumulative values – AUC); ESR; radiographic progression (erosions, JSN, total score; Sharp-van der Heijde method).	Grant from Het Nationaal Reumafonds, The Netherlands

Effect size

- Time integrated CRP was significantly correlated with radiological progression over 6 months, 1 year, 2 years and 3 years (P<0.001; values not given).
- However, a wide variation was observed due to inter-individual differences. The greatest variation was found in the lower range of CRP values, where inter-individual variation could not be accounted for by RF+, HLA type, age or gender.

Authors' conclusions: The prognostic use of serial measurements of APPs (CRP) for the assessment of radiological progression is limited due to inter-individual variation. Knowledge of the factors underlying these differences will increase the applicability of CRP in the production of joint damage for individual patients.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
J. Fransen, H. B. Moens, I. Speyer, and P. L. van Riel. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial.[see comment]. *Annals of the Rheumatic Diseases* 64 (9):1294-1298, 2005. ID 3394	RCT (cluster): 1++ Multicentre: 24 centres in The Netherlands • Randomised by cluster/trial centre (random number generator) • Partial allocation concealment • Single blind for joint counts; • ITT analysis • Sample size calculation (DAS28)	Total N=205 randomised (N=205 systematic monitoring + treatment adjustment; N=179 usual care). **Drop-outs:** Monitoring: N=16 (8%) Usual care: N=20 (11%)	**Inclusion criteria:** Adults (aged at least 18 years) with RA (ACR criteria); medical need for NSIAD treatment. **Exclusion criteria:** history of allergy to NSAIDs; serious diseases; suspicion of or have peptic ulcer of GI bleeding; malignancy; substance abuse or mental disorders. **Baseline characteristics:** systematic monitoring + treatment adjustment group: mean age 58 years; Female 67%; Duration of RA = Established RA (mean 6 years). usual care group: mean age 58 years; Female 74%; Duration of RA = Established RA (mean 7 years). There were NS differences	Systematic monitoring + treatment adjustment Monitoring of disease activity was carried out at weeks 0, 4, 12 and 24 by assessment of DAS28. The aim was to reach DAS28 ≤3.2 (low disease activity) by changing DMARD treatment if the score was above 3.2. In both groups all patients were on DMARD treatment and started treatment with 200 mg/day celecoxib.	Usual care No systematic monitoring of disease activity was done and no guideline to adapt treatment strategy was applied.	24 weeks (monitoring assessments made at 0, 4, 12 and 24 weeks)	DAS28; (28 tender and swollen joint count; ESR and general health); patient assessed pain and global disease activity; HAQ.	Pfizer

			between the two groups for all of the baseline characteristics except for RF+ which was higher in the systematic monitoring group.					

Effect size

Systematic monitoring + treatment adjustment vs Usual care (no systematic monitoring or treatment adjustment)

- Systematic monitoring + treatment adjustment was significantly better than Usual care (no systematic monitoring or treatment adjustment) for:
  - Mean difference in proportion of patients with low disease activity (DAS28 <3.2) at 24 weeks (MD 15, 95% CI 3 to 27, p=0.028)
  - DMARD changes (significantly higher) over 24 weeks, (MD 9%, 95% CI 2% to 16%, p=0.013;
  - Patient global assessment of disease activity over 24 weeks (data not given)

- There was NS difference between the Intensive strategy and the conventional strategy for:
  - Mean dose of non-oral steroids, prednisone and MTX dose over 24 weeks
  - AEs over 24 weeks
  - Pain (VAS) at 24 weeks
  - Disability at 24 weeks

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Grigor, H. Capell, A. Stirling, A. D. McMahon, P. Lock, R. Vallance, W. Kincaid, and D. Porter. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A	RCT: 1++ Multicentre: 2 centres in the UK • Randomised (randomisation software) • Allocation concealment • Single blind (assessors) • ITT analysis • Power study	Total N=111 randomised (N=55 each group). **Drop-outs:** Intensive: N=2 (4%) Routine: N=5 (9%)	**Inclusion criteria:** Adults (aged 18 to 75 years) with RA; duration <5 years; active disease (Disease activity score >2.4). **Exclusion criteria:** previously received combination DMARD treatment or had concurrent liver, renal or haematological disease. **Baseline characteristics:** Intensive group: mean age 51 years; Female 71%; Duration of RA = Early RA (19 months); Pain (VAS) mean 62.	Intensive strategy Patients were seen every month by the same rheumatologist and their disease activity score was calculated. Any swollen joint was injected with IA CS unless had been injected within the previous 3 months – up to total dose of 120 mg triamcinolone acetonide per visit,	Routine care Patients were also reviewed every 3 months with no formal composite measure of disease activity used in clinical decision-making. DMARD monotherapy was given to patients with active synovitis and failure of	18 months (end of treatment); assessments every 3 months	Fall in disease activity score (RAI, ESR, swollen joints and patients' assessment of disease activity); Good response (EULAR disease activity score <2.4); remission	Scottish Executive

single-blind randomised controlled trial. *Lancet* 364 (9430):263-269, 2004. ID 2168	(responders)		Routine group: mean age 54 years; Female 69%; Duration of RA = Early RA (20 months); Pain (VAS) mean 59. There was no clinically significant difference between the two groups for any of the baseline characteristics.	After month 3, at every assessment, patients with disease activity score of >2.4 received an escalation of their DMARD treatment.	treatment resulted in change in monotherapy or addition of a second or third drug at the discretion of the rheumatologists. IA CS was given as for those in the intensive group.		(EULAR); ACR20, 50 and 70;Pain (VAS); HAQ; patient's and physician's assessment of disease activity; ESR; radiographic progression (Sharp-van der Heijde score); SF-12 (QoL).	

Effect size

Intensive strategy (treatment adjustment based on disease activity measures of response) vs Routine strategy (rheumatologist's criteria for treatment adjustment)

- The Intensive strategy was significantly better than the routine strategy for:
  - EULAR good response at 18 months (p<0.0001)
  - EULAR remission at 18 months (p<0.0001)
  - ACR20, ACR50 and ACR70 at 18 months (p<0.0001)
  - Disease activity score at 18 months (p<0.0001)
  - Joint swelling at 18 months (p=0.0028)
  - Joint tenderness at 18 months (p=0.0003)
  - Patient's and assessor's global assessment of disease activity at 18 months (both: p<0.0001)
  - Pain (VAS) at 18 months (p<0.0001)
  - ESR at 18 months (p=0.0007)
  - HAQ at 18 months (p=0.0025)
  - SF-12 physical domain at 18 months (p=0.021)
  - Erosion score at 18 months (p=0.002)
  - Total sharp score at 18 months (p=0.02)

- The Intensive strategy was better than the conventional strategy for:
  - Number of AEs (N=46 vs N=85) over 18 months
  - Higher prescription of IM and IA CS over 18 months
  - Higher prescription of combination DMARDs over 18 months
  - Higher doses of MTX over 18 months

- There was NS difference between the Intensive strategy and the routine strategy for:
  - CRP at 18 months
  - SF-12 mental domain at 18 months
  - JSN at 18 months
  - Doses of SSZ over 18 months

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Verstappen SM, Jacobs JW van der Veen MJ Heurkens AH Schenk.	RCT: 1+ Multicentre: 6 centres in The Netherlands	Total N=299 randomised (N=151 intensive strategy; N=148	**Inclusion criteria:** Adults (aged >16 years) with RA (ACR criteria); duration <1 year; active disease (DAS28 >2.0).	Intensive strategy (started on oral MTX 7.5 mg/week) Dose was adjusted based on a) computer-	Conventional strategy (started on oal MTX 7.5 mg/week)	2 years (end of treatment); assessments every 3 months	Remission for at least 3 months (no swollen joints and at least 2 of the	Not mentioned

Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Annals of the Rheumatic Diseases* 66 (11):1443-1449, 2007. ID 1171	• Randomised (blocks of 9, method not mentioned) • Single blind for radiographs; • Unblinded for other measures • ITT analysis • Higher drop-outs in the intensive group	Conventional strategy). **Drop-outs:** Intensive: N=59 (39%) Conventional: N=35 (24%)	**Exclusion criteria:** previous use of glucocorticoids or any DMARDs, use of cytotoxic or immunosuppressive dri=ugs within 3 months before study start; alcohol abuse and psychological problems; medical conditions that could interfere with MTX usage. **Baseline characteristics:** Intensive group: mean age 54 years; Female 69%; Duration of RA = Early RA (<1 year inclusion); Pain (VAS) mean 51. Control diet group: mean age 53 years; Female 66%; Duration of RA = Early RA (<1 year inclusion); Pain (VAS) mean 47. The two groups were similar for all of the baseline characteristics.	decision programme which calculated whether or not predefined criteria of response to treatment were met. Response criteria were: 20% improvement of swollen joints and 2 of the 3 criteria (ESR, tender joints and VAS general well-being). Patients were assessed once every 4 weeks and the maximum dose of 30 mg/week could be reached after 18 weeks. In both groups the dose was increased at each visit by 5 mg/week to a maximum of 30 mg/week. In both groups Oral glucocorticoids were not allowed during the trial; use of NSAIDs was permitted.	Patients visited the outpatient clinic once every 3 months; dose adjustments were made based on the opinion of the individual rheumatologist (reduced number of swollen joints, or tender joints, ESR and VAS general well-being) The maximum dose of 30 mg/week could be reached at a minimum of 52 weeks.		following: ≤3 tender joints, ≤20 mm/hr first ESR; ≤20mm VAS general well-being); AUC for all variables disease activity; ACR50; Physician's global assessment; AEs.	

Effect size

Intensive strategy (dose adjustment based on disease measures of response) vs Conventional strategy (rheumatologist's criteria for dose adjustment)

- The Intensive strategy was significantly better than the conventional strategy for:
  - Number of patients reaching remission for 3 months over year 1 and year 2 (Year 1: 35% vs 14%, p<0.001; Year 2: 50% vs 37%, p=0.029)
  - Mean time until first period of remission, (10.4 vs 14.3 months);
  - Duration of all periods of remission, (11.6 vs 9.1 months, p=0.025);
  - Median AUC for morning stiffness (11.6 vs 9.1 months, p=0.025);
  - Median AUC for ESR (MD 3.9, p=0.007);
  - Median AUC for tender(MD 1.09) and swollen joint (MD 2.0) counts (both: p<0.001);
  - Median AUC for VAS general well-being (MD 12.2, p<0.001);
  - Median AUC for VAS pain (MD 7.0, p=0.001);
  - Modified ACR50 at 1 year (58% vs 43%, p=0.018)
  - Use of NSAIDs after 6 months and 2 years (6 months: 79% vs 93%, p=0.002; 2 years: 46% vs 71%, p<0.001)

- The Intensive strategy was better than the conventional strategy for:
  - Number of patients with AEs and number of AEs (87% vs 94%) over 2 years

- There was NS difference between the Intensive strategy and the conventional strategy for:
  - Median AUC for Functional disability;
  - Modified ACR50 at 2 years;
  - Radiographic progression over 2 years;
  - Number of IA CS given over 2 years

8.2 Content and frequency of review (REVIEW)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. Hewlett, K. Mitchell, J. Haynes, T. Paine, E. Korendowych,	RCT: 1+ Single centre trial: UK	Total N=209 randomised N=105	**Inclusion criteria:** consecutive patients with established RA attending rheumatology clinic **Exclusion criteria:** no exclusion	N=93 Shared Care Group (SCG) Procedure: SCG had care	N=89 Control group	24 months	Pain (VAS); disability (HAQ), helplessness (Arthritis Helpless Index),	NHS Research and Development National Programme

<table>
<tr>
<td>and J. R. Kirwan. Patient-initiated hospital follow-up for rheumatoid arthritis. Rheumatology 39 (9):990-997, 2000.

ID: 3377</td>
<td>Randomised (method not stated)
Unclear Allocation concealment
Single blind (assessor)
Not true ITT analysis (per protocol)
similar dropouts in each arm
powered, ;target was N=186; they randomised N=209.</td>
<td>shared care group randomised

N=104 control group randomised

Drop-outs: N Shared Care group: N=12/105 (11%) Control: N=15/104 (14%)</td>
<td>criteria

Baseline characteristics: NS between groups, except for higher grip strength in SCG vs control (p<0.05)
<table>
<tr><td></td><td>control</td><td>SCG</td></tr>
<tr><td>N</td><td>89</td><td>93</td></tr>
<tr><td>male/female</td><td>27/62</td><td>31/62</td></tr>
<tr><td>Duration of disease, median, years</td><td>12</td><td>11</td></tr>
<tr><td>Duration morning stiffness (min), median</td><td>58</td><td>65</td></tr>
<tr><td>HAQ, mean</td><td>1.4</td><td>1.4</td></tr>
<tr><td>Age, mean</td><td>59</td><td>57</td></tr>
</table></td>
<td>provided by a GP, but with no scheduled hospital review. SCG group patients or GPs could request review by any rheumatology team member through a nurse-run telephone helpline. A maximum wait of 10 working days for review. Control patients had a traditional medical review ordered routinely every 3-4 months or according to standard practice. In emergency, all patients were seen immediately. CRP, Hb, hand X-rays, grip strength, knee and elbow range of motion, articular index assessed at baseline and at 24 months. Clinical and psychological status assessed at 3 month intervals with questionnaires. A safety net, using 3-monthly questionnaires, was used to monitor all patients. Safety net</td>
<td>3-4 month regular review (traditional hospital care)</td>
<td></td>
<td>anxiety and depression (Hospital Anxiety and Depression), self-efficacy, medication changes, DAS, RA complications</td>
<td>Grant</td>
</tr>
</table>

				Failure defined as increase of ≥ 20% in pain, disease activity, or disability.				

Effect size

The majority of 3 month questionnaires were returned : 88.8% SCG and 88.9% control

Rapid access (shared care with GP, SCG) vs 3-4 month regular review (traditional hospital care; control)

- SCG had significantly lower pain scores (VAS) than control ($p<0.05$) at 24 months
- SCG had significantly less change in pain than control over 24 months ($P<0.01$)
- SCG groups had significantly higher self-efficacy score than control at 6, 15, 18, and 21 months ($p<0.05$)

There was NS difference between the two groups over 24 months for:

- Patient's opinion of disease activity
- Disability (HAQ)
- Anxiety and depression
- Frequency of safety-net failures
- Medication changes
- Radiograph Larsen scores

RA complications reported in 4 SCG and 10 control patients

Note: lead rheumatologist could not be blinded to group assignment

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
J. R. Kirwan, K. Mitchell, S. Hewlett, M. Hehir, J. Pollock, D. Memel, and B. Bennet. Clinical and psychological outcome from a randomized controlled trial of patient-initiated direct-access hospital follow-up	RCT: 1+ Single centre trial: UK • Randomised (method not stated) • Unclear Allocation concealment • Single blind (assessor) • Not true ITT analysis (per	Total N=209 randomised N=105 shared care group randomised N=104 control group randomised **Drop-outs at 4**	**Inclusion criteria:** As for ID 3377	As for ID 3377	As for ID 3377	4 years	As for ID 3377	NHS Research and Development Grant

for rheumatoid arthritis extended to 4 years. *Rheumatology (Oxford)* 42 (3):422-426, 2003. ID: 10	protocol) • similar dropouts in each arm • powered, ;target was N=186; they randomised N=209.	**years:** Direct access group: 30% 3-4 month regular review (traditional hospital care): 42%						

Effect size

The majority of 3 month questionnaires were returned : 88.8% SCG and 88.9% control

Rapid access (shared care with GP) vs 3-4 month regular review (traditional hospital care)

- Rapid access (SCG) was significantly better than control (regular review) at 4 years (change from baseline) for: ROM (right elbow), $p<0.05$ and for patient satisfaction and confidence (both: $p<0.01$).

There was NS difference between the two groups at 4 years (change from baseline) for:

- Pain (VAS)
- ROM (left elbow and both knees)
- Patient's opinion of disease activity
- Disability (HAQ)
- Anxiety and depression
- Morning stiffness

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. G. Mowat, P. J. Nichols, E. M. Hollings, R. J. Haworth, and L. C. Aitken. A comparison of follow-up regimes in rheumatoid	RCT: 1+ Single centre trial: UK • Randomised (method not mentioned) • Single blind (assessor)	Total N=132 randomised (Numbers in each of 3 groups not mentioned) **Drop-outs:** 1 year: N=13 (10%)	**Inclusion criteria:** definite arthritis, treated in rheumatology clinic for at least 14 days. **Exclusion criteria:** if treatment with special drugs or new operative procedures required close supervision by the rheumatology unit.	Group 1: GP follow-up: patient returned for further assessment and advice only on request Group 2: Routine hospital out-patient	Group 3: OT follow-up A senior OT visited patient at home at 3-monthly intervals.	2 years	Articular Index; ESR; Functional capacity (37-item evaluation)	Not mentioned

arthritis. *Annals Rheumatic Diseases* 39 (1):12-17, 1980. ID: 3422	• No mention of ITT analysis • High dropouts (but 2 year study)	2 years: N=60 (45%)	**Baseline characteristics:** There were NS differences between the groups for baseline characteristics Disease duration not mentioned	follow-up: patient attended as often as considered necessary – usually at 3 monthly intervals				

Effect size

GP follow-up (on request) vs routine hospital follow-up (3-monthly) vs OT follow-up (3-monthly)

- There were NS differences between the groups for:
  - Articular Index at 1 year
  - ESR at 1 year and 2 years
  - Functional capacity at 1 year and 2 years

- OT follow-up (3-monthly) was significantly better than GP follow-up (on request) and routine hospital follow-up (3-monthly) for:
  - Articular Index at 2 years ($p<0.05$)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
D. Symmons, K. Tricker, M. Harrison, C. Roberts, M. Davis, P. Dawes, A. Hassell, S. Knight, D. Mulherin, D. L. Scott, and British Rheumatoid	RCT: 1+ 5 centre trial: UK • Randomised with computerised minimisation program on age, gender, centre,	Total N=466 randomised N=233 symptom control shared care group (SCSC) randomised N=233 aggressive treatment/hospital (ATH) group randomised	**Inclusion criteria:** people ≥ 18 years with ACR rheumatoid arthritis duration ≥ 5 years and < 20 years, current outpatient attendee ≥ 12 months; taking ≤ 7.5 mg/day prednisolone; no change in DMARD or steroid therapy for ≥ 6 months **Exclusion criteria:** HAQ ≥ 2.5; pregnancy; major organ involvement from RA; participation	N=201 symptom control shared care group (SCSC) Procedure: SCSC group managed in primary care and the goal was to control joint pain, stiffness from patient's perspective.	N=203 aggressive treatment/hospital (ATH) group	36 months	Primary outcome: HAQ Secondary outcomes: Patient global (VAS), physician global, tender joint	NHS

<table>
<tr>
<td>Outcome Study Group. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs--results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. Rheumatology 45 (5):558-565, 2006.
ID: 3376</td>
<td>disease duration
• Unclear Allocation concealment
• Single blind (assessor)
• Not true ITT analysis
• similar dropouts in each arm
• Slightly underpowered, target was N=480; they randomised N=466.
ANCOVA adjusted for baseline HAQ, age, gender, disease duration, centre</td>
<td>Drop-outs:
SCSC: N=32/233 (14%)
ATH: N=30/233 (13%)
1 patient allocated to SCSC was recorded as being allocated to ATH and managed accordingly. For ITT, this person was analysed in the SCSC group. Also, error in minimisation program produced more people in the ATM arm at Macclesfield (61%) and fewer in Stoke (47%)</td>
<td>in another trial. Major co-morbidity (life expectancy < 5 years due to other illness)

Baseline characteristics: NS between groups

<table>
<tr><td></td><td>SCSC</td><td>ATH</td></tr>
<tr><td>N</td><td>201</td><td>203</td></tr>
<tr><td>% female</td><td>68.2</td><td>67.8</td></tr>
<tr><td>Duration of disease, mean, years</td><td>12.6</td><td>12.5</td></tr>
<tr><td>HAQ, mean</td><td>1.25</td><td>1.31</td></tr>
<tr><td>Age, mean</td><td>60.4</td><td>60.8</td></tr>
</table>
</td>
<td>NSAIDS, 1 intra-articular injection/month, DMARDS, prednisolone, physiotherapy permitted. Patients advised to visit GP if new symptoms or deterioration occurred. Nurse visited every 4 months and conducted an interview. Problems identified dealt with nurse or referral to GP/hospital. ATH group managed predominantly in hospital and aim was to control joint pain, stiffness and to suppress clinical and lab evidence of inflammation (minimise inflamed joints and to keep CRP < 2x ULN). Patients attended rheumatology clinic at least once every 4 months. ESR and CRP measured every 4 months. Any SCSC drugs allowed + ciclosporin, parenteral steroids, prednisolone,</td>
<td></td>
<td></td>
<td>count, swollen joint count, pain (VAS), ESR, DAS-28, Larsen score, eroded joint count, OSRA disease activity score, OSRA damage score</td>
<td></td>
</tr>
</table>

				cyclophosphamide permitted. All patients had HAQ every 4 months, annual OMERACT, OSRA, DAS-28, assessment of extra articular features. X-rays of hands and feet done at baseline and end of study				

Effect size

Overall, 94% attended first year follow-up, 88% attended first and second year follow-up, 85% attended first, second, and third year follow-up.

SCSC vs ATH at 36 months

The adjusted mean difference for the OSRA disease activity score was -0.40 (95% CI -0.71 to -0.10) in favour of ATH arm (p=0.01).

There was NS difference between the two groups over 36 months for:

- HAQ
- Patient global assessment
- Physicians global assessment
- tender joint count
- swollen joint count
- pain (VAS)
- ESR
- DAS-28
- Larsen score
- eroded joint count
- OSRA damage score

8.3 Timing and referral for surgery (REFER2)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
A. K. Alderman, P. A. Ubel, H. M. Kim, D. A. Fox, and K. C. Chung. Surgical management of the rheumatoid hand: consensus and controversy among rheumatologists and hand surgeons. *Journal of Rheumatology* 30 (7):1464-1472, 2003. ID 3446	Cross-sectional survey of experts' opinions: 4 Single centre trial: USA	N=1000 physicians (N=500 surgeons, N=500 rheumatologists)	**Inclusion criteria:** rheumatologists and hand surgeons who were active physician members of the ACR and American Society for Surgery of the Hand. **Exclusion criteria:** None given **Baseline characteristics of all physicians (mean):** mean age 53 years; Female 10%	Cross-sectional survey was distributed to random sample of 500 members of the ACR and 500 of the American Society for Surgery of the Hand.	2 waves of questionnaires sent – immediate follow-up.	Physician survey – survey focused on the indications and timing of different types of surgical procedures for rheumatoid hand disease Outcomes measured on 1-5 Likert Scale (1= always, 5= never)	Grant from the Robert Wood Foundation and an Outcomes Studies Grant rfom the American Society for Surgery of the Hand.

Effect size*

Physicians attitudes towards the indications for surgical interventions for RA had deformities

- MCP joint arthroplasty
  - Most hand surgeons and rheumatologists thought that impaired hand function was the most important indication (55% and 65% respectively), the second most important was MCP joint pain (40% and 21% respectively)
  - Most hand surgeons and rheumatologists thought that Stage 3 MCP joint disease was the most appropriate time to perform MCP joint arthroplasty.

- Small joint synovectomy
  - Most hand surgeons (50%) thought that progressive joint synovotis was the most important indication, while most rheumatologists (40%) thought that it was never indicated

- Resection of the distal ulna
  - Most hand surgeons and rheumatologists (approximately 80% and 57%) thought that impending tendon rupture was the most important indication (63% and 74% respectively), the second most important was wrist pain (26% and 13% respectively).

- Extensor tenosynovectomy
  - Most hand surgeons and rheumatologists agreed that 3-6 months is the most appropriate time to intervene if the synovitis is resistant to medical therapy. However, 26% of rheumatologists vs 2% of surgeons believed tat the procedure is appropriate after 12 months or more and 8% and 2% thought that extensor synovectomy is never appropriate.

* for most indications there was a ot of disagreement on the indications for RA hand surgery between hand surgeons and rheumatologists.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
A. K. Alderman, A. S. Arora, L. Kuhn, Y. Wei, and K. C. Chung. An analysis of women's and men's surgical priorities and willingness to have rheumatoid hand surgery.	Cross-sectional survey of patients' and physicians' opinions: 4 Single centre trial: USA • Powered study • Men were oversampled to ensure	Total N=126 patients N=1000 physicians (N=500 surgeons, N=500 rheumatologists)	**Inclusion criteria:** RA patients at the rheumatology clinic. **Exclusion criteria:** None given **Baseline characteristics of all patients (mean):** mean age 53 years; Female 66%; Duration of RA = Established RA	Cross-sectional survey was distributed to random sample of 500 members of the ACR and 500 of the American Society for Surgery. It was also distributed to consecutive RA patients at the rheumatology clinic.	2 waves of questionnaires sent – immediate follow-up.	1. Physician survey – focused in the indications and timing of different types of surgical procedures for rheumatoid hand disease 2. Patient survey - In-depth personal interviews including components of the Michigan Hand Outcomes	Not mentioned

Journal of Hand Surgery - American Volume 31 (9):1447-1453, 2006. ID 3451	even gender distribution and adequately represented the national prevalence of the disease.		(mean years); had hand surgery already mean 23%.			Questionnaire. Focused on patients' hand priorities and willingness for surgical interventions.	

Effect size

Physicians

- 73% of Physicians (Rheumatologists and hand surgeons) perceived women as valuing hand aesthetics significantly more than men ($p<0.001$).
- 77% thought that there was NS difference between men and women for value of hand function.
- 52% believed there was no difference between men and women in their willingness to have hand surgery
- 43% perceived women as being more willing to have a surgical intervention than men ($p<0.001$).

Patients

- Most women and men ranked either hand function or hand pain as the primary hand concern; few patients ranked hand appearance as the primary concern.
- There were NS differences between men and women in willingness to have surgery for appearance, function or pain
- Pain was the reason most people would be willing to have surgery
- Women were more concerned than men about the potential inconveniences of surgery, pain, risk of anaesthesia and surgical complications.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
K. C. Chung, S. V. Kotsis, H. M. Kim, F. D. Burke, and E. F. Wilgis. Reasons why rheumatoid arthritis patients seek surgical treatment for	Cross-sectional survey: 3 3 centres (UK and USA) • Study sample from a larger	Total N=62 enrolled, N=1 excluded from the analysis as	**Inclusion criteria:** Age 18 to 80 years; RA; had 50 degrees or more of aggregate deformity in the more severe hand (aggregated deformity calculated by summing the average MCP joint deviation of the index, middle, ring and little fingers with the average MCP joint extensor	All patients were considered by their hand surgeons to be appropriate candidates for MCP joint arthroplasty. Enrollment of thse	Immediate	MHQ (questionnaire) – regression used to assess which baseline characteristics predict patients' choice of MCP joint arthroplasty.	National Institute of Arthritis and musculoskeletal and Skin Diseases, USA

hand deformities. *Journal of Hand Surgery - American Volume* 31 (2):289-294, 2006. ID 78	NIH study	did not complete the questionnaire before surgery.	lag of the same 4 fingers). **Exclusion criteria:** initiation of disease-modifying anti-rheumatic disease medication within the past 3 months; swan neck or boutonniere deformity requiring surgical correction; concomitant extensor tendon rupture; medical comorbidities precluding surgery. **Baseline characteristics:** Surgical patients: mean age 59 years; 88% female. Non-Surgical patients: mean age 63 years; 71% female.	study was independent of the patient's decision whether or not to proceed with surgery. Enrolled patients then placed themselves into either the surgical group (electing to have MCP joint replacement) or the nonsurgical group (no surgery); or undecided group.			

Effect size

<u>Predictors of surgery from baseline characteristics</u>

- Bivariate analysis found that:
  - Age and gender were associated with choosing MCP joint arthroplasty surgery
  - After correcting for age and gender, patients with lower functioning, more pain and lower aesthetic scores were more likely to coose MCP joint arthroplasty.
  - Function was the most important predictor for choosing surgery, followed by pain
- Multivariate analysis found that:
  - Patient age categories of 51-60, 61-70 and 71 years or more had nearly the same relationship on choosing surgery and were thus combined in the final model.
  - Patients older than 50 years had OR 0.03 (ie. 3% likelihood of choosing surgery relative to those 50 years or younger.
  - Male patients were only 11% as likely to choose surgery compared to female patients (after controlling for age, function and pain)
  - The OR for function domain was 0.58 (p=0.02) ie. A 42% decrease in the odds of choosing surgery with every 10-point increase in the function domain score.
  - Greater pain showed a tendency toward an increased likelihood of choosing surgery (however, was NS)
  - Aesthetics domain was also NS.

- **Overall:**
  - **Function is the most important predictor for patients choosing MCP joint arthroplasty procedure, followed by pain. Aesthetic consideration was not statistically significant.**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of

							funding
J. D. Hamilton, M. M. Gordon, I. B. McInnes, R. A. Johnston, R. Madhok, and H. A. Capell. Improved medical and surgical management of cervical spine disease in patients with rheumatoid arthritis over 10 years. *Ann Rheum Dis* 59 (6):434-438, 2000. ID 3536	Case-series (retrospective): 3 Patient records taken from 5 consultants rheumatology clinics (UK)	Total N=111 patients were referred for MRI (N=27 required surgery and N=84 had conservative therapy)	**Inclusion criteria:** RA (ACR criteria); attended the rheumatology clinics; had undergone MRI or cervical spine surgery or both. **Exclusion criteria:** None mentioned. **Baseline characteristics:** Surgery group - Age at symptom onset mean 58 years; Female 85%; disease duration median 16 years (established RA). Conservative therapy group - Age at symptom onset mean 60 years; Female 75%; disease duration median 16 years (established RA).	Patients who underwent conservative therapy vs those who underwent surgery Indications for surgery were: uncontrolled cervical spine pain, neurological impairment attributable to cervical spine instability and progressive radiological appearances. Indications for MRI were: cervical spine pain not controlled with conservative management; neurological symptoms or signs suggestive of cervical myelopathy, atlantoaxial subluxation on plain x-ray.	Previous 10 years	To compare clinical outcome and symptomology of rheumatoid cervical myelopathy between patients managed conservatively and surgically.	Not mentioned

Effect size

- Patients who underwent surgery were significantly more likely to report the following symptoms and examination findings: paraesthesia ($p<0.05$), weakness ($p<0.005$) or unsteadiness ($p<0.005$) and to exhibit extensor plantar reflexes ($p<0.005$), gait disturbances ($p<0.005$) and reduced power ($p<0.005$); Ranawat grades II (NS) or III ($p<0.005$).
- Patients who underwent surgery were significantly less likely to report the following symptoms and examination findings: Normal examination findings ($p<0.005$).
- Patients who underwent surgery were significantly more likely to have the following MRI findings: performed in neutral ($p<0.005$), Cord compression ($p<0.005$), impingement on cord ($p<0.05$),
- Patients who underwent surgery were significantly less likely to have the following MRI findings: Cervical spondylosis ($p<0.05$), Abnormal but no compression or impingement ($p<0.005$)

Author's conclusions:
Patients presenting with rheumatoid cervical myelopathy are now referred for surgery at an earlier stage of disease. Clinical findings correlate poorly with MRI findings, therefore clinical history should remain the key to determining the need for MRI.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
E. Loza, L. Abasolo, D. Clemente, and R. Lopez-Gonzalez. Variability in the use of orthopedic surgery in patients with rheumatoid arthritis in Spain. *Journal of Rheumatology* 34 (7):1485-1490, 2007. ID 519	Cross-sectional study: 3 Multicentre, Spain (Probabalistic sample of Medical records from all regions of Spain. 1 record per 25,000 inhabitants was taken) • Sample size calculation • Medical records were randomly selected by stratified	Total N=1379 (out of total N=1550 patients records randomly selected for review)	**Inclusion criteria:** Age ≥16 years; RA diagnosis; patients who were followed at specialised healthcare units. **Exclusion criteria:** Hospitals without Rheumatology or internal medicine services. Fractures or infection-related surgeries were excluded. TJR as a consequence of fractures. **Baseline characteristics:** Mean age at disease onset: 51 years; female 73%; long term RA (≥10 years) 42%.	Patients were classified into 3 groups based on the number of swollen joints and acute phase reactants. 1. Non-active disease 2. Relapsing active disease 3. Persistent active disease	Immediate	1. Any orthopaedic surgery (AOS) defined as the presence of at least one RA-related orthopaedic surgery including primary and secondary total jiont arthroplasty at any location, reconstructive surgery, resections, joint fusions and synovectomy. 2. Total joint replacement (TJR) defined as total replacement of a joint at any location from the beginning of the RA.	Partially funded by grant from Novartis Pharmaceutics, Barcelona, Spain.

	sampling from regions and hospitals.					Revision surgery was considered as a new RA-related surgery if first replacement was considered RA-related.	

Effect size

Rate of orthopaedic surgery

- 26% of patients underwent orthopaedic surgery during the disease course and 14% had a TJR.
- Median time to first procedure was 13 years from the onset of RA symptoms and the rate of AOS was 6 procedures/100 person-years from the beginning of RA, while rate of TJR was 3.2 interventions/100 person-years.

Variables associated with surgery

- AOS:
  - Probabilty of undergoing AOS was higher in female patients, younger patients, those with long-term disease, a poor functional ability, persistent active disease despite treatment, RF+ and presence of extraarticular complications and significant comorbidity.
  - Multivariate regression model: female gender, long-term disease (≥10 years), ACR functional grade III/IV and the presence of extraarticular complications remained associated with a higher risk for having undergone AOS.
- TJR:
  - Probabilty of undergoing TJR was higher in female patients, those with long-term disease, functional class III/IV, persistent active disease despite treatment, presence of extraarticular complications and/or significant comorbidity.
  - Multivariate regression model: long-term disease (≥10 years), ACR functional grade III/IV and the presence of extraarticular complications remained associated with a higher risk for having undergone TJR.

Author's conclusions:
Clinical variables reflecting disease activity and severity are predictors of orthopaedic surgery.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
L. A. Mandl, F. D. Burke, E. F. Shaw Wilgis, S. Lyman, J. N. Katz, and K. C.	Cross-sectional survey: 3 3 centres (UK and	Total N=56 patients given questionnaire	**Inclusion criteria:** Age 18 to 80 years; RA; had 50 degrees or more of aggregate deformity in the more severe hand	All patients were considered by their hand surgeons to be	Immediate	Questionnaire considering their expectations and hopes from MCP joint	National Institute of Arthritis and musculoskeletal

Chung. Could preoperative preferences and expectations influence surgical decision making? Rheumatoid arthritis patients contemplating metacarpophalangeal joint arthroplasty. *Plastic & Reconstructive Surgery* 121 (1):175-180, 2008. ID 3452	USA) • Study sample from a larger NIH study	The N=8 patients with previous MCP arthroplasty were excluded from subsequent analyses.	(aggregated deformity calculated by summing the average MCP joint deviation of the index, middle, ring and little fingers with the average MCP joint extensor lag of the same 4 fingers). **Exclusion criteria:** initiation of disease-modifying anti-rheumatic disease medication within the past 3 months; swan neck or boutonniere deformity requiring surgical correction; concomitant extensor tendon rupture; medical comorbidities precluding surgery. 41% of patients decided to have surgery; 48% did not. The severity of MCP joint deformity was similar in both surgical and non-surgical groups. 11% were undecided.	appropriate candidates for MCP joint arthroplasty. Enrollment of thse study was independent of the patient's decisionwhether or not to proceed with surgery. Enrolled patients then placed themselves into either the surgical group (electing to have MCP joint replacement) or the nonsurgical group (no surgery); or undecided group.		arthroplasty. Open-ended questions: hopes of outcome of surgery (regardless of whether they decided to have surgery or not). Individual responses were categorised according to common themes and placed in 1 of 11 categories for analyses. Structured questions: covered relevant patient-centred domains such as pain, appearance, ability to work and hand function.	and Skin Diseases, USA

Effect size

Patients' responses

- Hopes of what surgery will do (NS difference between patients who went on to have surgery and those who did not):
    - 44% stated that improving appearance was very important;
    - 44% stated that improving function was very important;
    - 27% stated that reducing pain was very important;
    - 15% stated that improving strength was very important;

- Open-ended questions (NS difference between patients who went on to have surgery and those who did not):
    - 75% of patients said ability to perform everyday activities was very important
    - 73% of patients said improvement of hand weakness was very important
    - 71% of patients said ability to do one's normal work
    - 50% of patients said reduction in hand pain was very important
    - 35% of patients said improvement of hand appearance was very important

- What bothered patients most about how RA had affected their hands:
    - 41% of patients: hand function
    - 21% of patients: pain
    - 18% of patients: hand appearance
    - 16% of patients: hand weakness
    - Patients who chose to have surgery were significantly more likely to be bothered by inability to work or do things with their hands (p=0.02) and those who did choose to have surgery were significantly more bothered by hand weakness (p=0.01) and appearance (p=0.046). There was NS difference between the groups for pain.

- Post-operative expectations:
    - Patients who chose to have surgery were significantly less likely to expect difficulty with post-operative rehabilitation (p=0.03);
    - NS difference between the groups in their belief in the chance of any serious complications postoperatively
    - 37% of all patients thought there was a >5% chance of serious complications, and 5% thought there was <10% chance.

- Expectations for status 1 year into the future:
    - Patients who chose to have surgery were much more likely than patients who elected non-operative management to expect the ability to do more with their hands in 1 year, to do more of their work, have les pain and improved hand appearance.
    - 36% of patients had discussed the possibility of surgery with their primary care doctor (NS difference between the groups)

- Most important person to influence decision to have surgery:
    - NS difference between the groups however more patients who chose to have surgery relied on expert opinion compared with non-experts (self, spouse, previous MCP patients).
    - Patients who chose not to have surgery were more likely to value their own opinion as moist important.

- Surgical patients hopes for what MCP arthroplasty would do for them had no correlations with expectations of improvement in pain, appearance, improved function or ability to work. Ie. No matter how strongly they hoped for certain outcomes, these hopes did not correlate with what they actually expected would happen.
- Among the non-surgical group, there were extremely high, significant correlations between the importance of improving strength as a goal of surgery and the expectations of worse pain, worse hand appearance (all $p<0.05$) and decreased ability to do work in 1 year's time ($p<0.01$). ie. The more important it was to these patients (those who chose not to have surgery) regarding their hope for improved hand strength, the more likely that these patients expected in 1 year's time to have poor hand appearance, pain and function in 1 year's time.

Author's conclusions:
Patients who are eligible for MCP arthroplasty but decline surgery appear to have different baseline expectations and preferences than those who choose surgery. Patients who choose surgery may use information differently in their decision process. Understanding and addressing patients' expectations and preferences preoperatively could help identify those patients who would most likely benefit from surgery.

9. OTHER ASPECTS OF TREATMENT

9.1 Diet (DIET)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Skoldstam, L. Hagfors, and G. Johansson. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 62	RCT: 1+ Single centre trial: Sweden • Randomised (blocks of 10, method not mentioned) • No mention of blinding (but not possible for	Total N=56 randomised (N=29 MD; N=27 Control). **Drop-outs:** Control: N=2 (7%) MD: N=3 (10%)	**Inclusion criteria:** Adults with RA (ACR criteria); duration at least 2 years; active disease (DAS28 >2.0); disease characterised as stable and under adequate control at the latest consultation before the trial. **Exclusion criteria:** DMARD treatment unchanged for ≥3 months, CS for ≥4 weeks and NSAIDs for ≥10 days before beginning of trial. Daily dose of oral CS not >12.5 mg of	Mediterranean diet (MD) The Cretan Mediterranean diet (Olive oil and rapeseed oil, small amount of dairy produce). Because Swedish people eat more dairy produce the MD was adjusted – all MD patients were to reduce their consumption of dairy	Control diet (usual diet) Patients were served ordinary hospital food during the ORP stay (3 weeks). For rest of the study (9 weeks) they were asked to return to	3 months (end of treatment)	Swollen and tender joints; DAS28; patient's global assessment of disease activity; SF-36; Pain (VAS); morning stiffness; grip ability test (GAT); SOFI (signals of functional impairment); HAQ score;	Grants from Umea university, Sweden; Swedish Foundation for Health Care Sciences and Alllergy Research; Health Research Council; Swedish

(3):208-214, 2003. ID 56	the patients to be blinded) • Not mention ITT analysis		prednisolone; no other condition that demanded active medical attention; vegetarians or those already living on a Mediterranean-like diet. **Baseline characteristics:** MD group: mean age 58 years; Female 81%; Duration of RA = Established RA (mean 17 years); DAS28 score mean 4.4; BMI mean 28.4. Control diet group: mean age 59 years; Female 80%; Duration of RA = Established RA (mean 10 years); DAS28 score mean 4.3; BMI mean 25.6. There were NS differences between the groups for any of the baseline characteristics except for BMI and disease duration which were significantly higher in the MD group ($p<0.05$).	products or choose low fat options. To compensate for the polyphenols in wine, the MD group were encouraged to drink green or black tea. Patients for the first 3 weeks attended the ORP (outpatient based rehabilitation programme at a rheumatology unit of a hospital) and received meals there and lessons in cooking the MD. For the remaining 9 weeks they prepared MD meals at home. Patients' daily doses of concomitant DMARDs and CS remained constant throughout the study, NSAIDs could be adjusted; dietary supplements that the patient had taken before the study had to remain unchanged throughout the trial.	their usual diets at home.		Acute phase reactants (ESR, CRP)	Rheumatism Association and other non-pharma sources.

Effect size

Mediterranean diet vs Control (usual) diet

- The Mediterranean diet was significantly better than the control (usual) diet for:
  - DAS28 (change from baseline) at 12 weeks (end of treatment), p=0.047;
  - HAQ score (change from baseline) at 12 weeks (end of treatment), p=0.012;
  - Swollen joint count (change from baseline) at 12 weeks (end of treatment), p=0.001;
  - Pain, VAS (change from baseline) at 12 weeks (end of treatment), p=0.006 ;
  - CRP level (change from baseline) at 12 weeks (end of treatment), p=0.006;
  - Weight loss (change from baseline) at 12 weeks (end of treatment) – 3kg vs 0 kg; p<0.001;

- The Mediterranean diet was significantly better than the control (usual) diet for:
  - SF-36, all dimensions (change from baseline) at 12 weeks (end of treatment);
  - Withdrawals (N=3 and N=2 respectively)

- There was NS difference between the Mediterranean diet and the control (usual) diet:
  - Tender joint count (change from baseline) at 12 weeks (end of treatment);
  - ESR (change from baseline) at 12 weeks (end of treatment);
  - Patients' global assessment of disease activity (change from baseline) at 12 weeks (end of treatment);
  - Morning stiffness (change from baseline) at 12 weeks (end of treatment);
  - SOFI score (change from baseline) at 12 weeks (end of treatment);
  - GAT score (change from baseline) at 12 weeks (end of treatment);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. S. Panush, R. L. Carter, P. Katz, B. Kowsari, S. Longley, and S. Finnie. Diet therapy for rheumatoid arthritis. *Arthritis & Rheumatism* 26 (4):462-471, 1983.	RCT: 1+ Single centre trial: USA • Randomised (assigned by sequence of study enrollment) • Double blind • Not mention	Total N=33 randomised **Drop-outs:** Control: N=7 (21%)	**Inclusion criteria:** Adults with RA (onset after 16 years of age); stage I-III, class I-III RA (ARA criteria); on stable medication regimens; active disease. **Exclusion criteria:** other medical problems or special nutritional needs or habits. **Baseline characteristics:** Experimental group: mean age	Experimental diet – to maintain or reduce weight Little meat (except fish and occasional fowl); no fruit, no herbs or spices, no dairy products, no alcohol, no additives and no preservatives.	Placebo diet - to maintain or reduce weight Excluded selected items form major food groups so as to resemble the experimental	10 weeks (end of treatment)	Swollen, painful and tender joints; patient's and physician's global assessment; Pain (VAS); morning stiffness; grip strength; 50-foot walk time; HAQ score; RF, ESR	Grants from Umea university, Sweden; Swedish Foundation for Health Care Sciences and Alllergy Research; Health Research

ID 3191	ITT analysis • Sample size calculation / power calculation • Fairly high drop-outs		54 years; Female 45%; Duration of RA = Established RA (mean 15 years). Placebo group: mean age 56 years; Female 27%; Duration of RA = Established RA (mean 11 years). There were NS differences between the groups for any of the baseline characteristics.	Patients in both groups were advised to supplement their diets with daily iron-containing vitamins since the diets were deficient in certain minerals and vitamins. Patients were permitted to continue pre-study therapy for their arthritis (or other) conditions. No changes in antirheumatic drugs were allowed during the course of the study.	diet, but included those foods that were excluded in the experimental diet			Council; Swedish Rheumatism Association and other non-pharma sources.

Effect size

Experimental diet vs Placebo diet

- There was NS difference between the experimental diet and the placebo diet for:
  - Morning stiffness (change from baseline) at 10 weeks (end of treatment);
  - Grip strength (change from baseline) at 10 weeks (end of treatment);
  - Walk time (change from baseline) at 10 weeks (end of treatment);
  - Tender and swollen joints (change from baseline) at 10 weeks (end of treatment);
  - Patient's and physician's global assessment (change from baseline) at 10 weeks (end of treatment);
  - ESR (change from baseline) at 10 weeks (end of treatment);
  - RF (change from baseline) at 10 weeks (end of treatment);

Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
G. V. O. Hansen, L. Nielsen, E.	RCT: 1+ Single centre trial: Denmark	Total N=109 randomised (numbers in	**Inclusion criteria:** Active RA (ARA criteria).	Experimental diet The Experimental diet:	Control (usual) diet	6 months (end of treatment)	Swollen and tender joints; Radiographs	Not mentioned

Kluger, M. Thysen, H. Emmertsen, K. Stengaard-Pedersen, E. L. Hansen, B. Unger, and P. W. Andersen. Nutritional status of Danish rheumatoid arthritis patients and effects of a diet adjusted in energy intake, fish-meal, and antioxidants. *Scandinavian Journal of Rheumatology* 25 (5):325-330, 1996. ID 330	• Randomised (method not mentioned) • Single blind (assessors, but not possible for the patients to be blinded) • Not mention ITT analysis	each group not mentioned). **Drop-outs:** Control: N=10 Experimental D: N=18	**Exclusion criteria:** Underweight; severe concomitant disorders. **Baseline characteristics:** Experimental Diet group: mean age 59 years; Female 76%; Duration of RA = Established RA (mean 7 years). Control group: mean age 50 years; Female 72%; Duration of RA = Established RA (mean 48 months). There were NS differences between the groups for any of the baseline characteristics.	The 'Graastener diet' was composed of an energy intake adjusted so as to obtain near-standard BMI. Fat contributed only 20-30% of the total energy consumption and ratio of sat: unsat fat was 1:1. Protein intake: increased to 1.5 g/kg/day; fish oil intake: increased to 800 g fresh fish/week. If necessary capsules containing omega-3 fish oils were supplemented to a total of 1.2g n=3 oils/day. To increase the intake of scavengers supplements of vitamins C, A E and selenium were taken as well as antioxidants (gluthathion-rich such as niuts and beans) All patients were taking NSAIDs. Patients' were told to continue pre-study therapy for their arthritis. No changes in antirheumatic drugs were allowed during the course of the study.			(Larsen score); patient's and physician's global assessment of disease; Pain intensity (VAS); morning stiffness; HAQ score; ESR; CRP; BMI; AEs.	

Effect size

Experimental diet vs Control diet

- The Experimental diet was significantly better than the control (usual) diet for:
  - Swollen joint count at 6 months (end of treatment), p=0.01;
  - Morning stiffness at 6 months (end of treatment), p=0.02;
  - Pain at 6 months (end of treatment), p=0.01;

- The Experimental diet was worse than the control (usual) diet for:
  - Withdrawals (N=18 and N=10 respectively)

- There was NS difference between the Experimental diet and the control (usual) diet in multivariate analysis (adjusted for BMI) for:
  - BMI at 6 months (end of treatment);
  - Weight at 6 months (end of treatment);
  - Tender joint count at 6 months (end of treatment);
  - Physician's global assessment of disease at 6 months (end of treatment);
  - HAQ score at 6 months (end of treatment);
  - Larsen Score at 6 months (end of treatment);

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. E. Holst-Jensen, M. Pfeiffer-Jensen, M. Monsrud, U. Tarp, A. Buus, I. Hessov, E. Thorling, and K. Stengaard-Pedersen. Treatment of rheumatoid arthritis with a peptide diet: a randomized, controlled trial.	RCT: 1+ Single centre trial: Denmark • Randomised (blocks of 6, method not mentioned) • Single blind (assessors, but not possible for the patients to be blinded)	Total N=30 randomised (N=15 Elemental Diet; N=15 Control). **Drop-outs:** Control: N=2 (7%) MD: N=3 (10%)	**Inclusion criteria:** Adults aged 18-75 years with RA (ACR criteria); duration at least 6 months; active disease. If on DMARD, NSAID or CS treatment they had to be maintained at same regimen and dose before the study. **Exclusion criteria:** Signs and symptoms of other severe disease, pacemaker, prosthetic joints, electrolyte derangement, oedema.	Elemental diet The Elemental diet (food in its simplest formulation: protein as aminoacids or oligopeptides, carbohydrate as glucose or small saccharides and fat as medium-chain triglycerides). This diet is considered hypoallergenic. Patients were given 4 weeks intervention. All	Control diet (usual diet) Patients were requested not to change their food habits in the study period.	4 weeks (end of treatment) and follow-up at 3 months (2 months post-treatment)	Swollen and tender joints; Progression of RA (EULAR); RAI (tenderness); ACR20; patient's general assessment of health; Pain intensity (VAS); morning stiffness; HAQ score; ESR; CRP; RF; AEs.	Danish Rheumatism Association and Ferrosan Ltd, Denmark.

Scandinavian Journal of Rheumatology 27 (5):329-336, 1998. ID 3210	• Not mention ITT analysis		**Baseline characteristics:** Elemental Diet group: mean age 46 years; Female 93%; Duration of RA = Established RA (mean 9 years); HAQ score mean 1.0; BMI mean 23. Control group: mean age 56 years; Female 67%; Duration of RA = Established RA (mean 13 years); HAQ score mean 1.2; BMI mean 25. There were NS differences between the groups for any of the baseline characteristics.	victuals were withdrawn and replaced with a commercial liquid diet (Top Up Standard, Ferrosan Ltd, Denmark) and water and plain soda water was allowed. Daily dosage was calculated from a recommended energy intake of 30 kcal/kg body weight/day. Dietary oils were not permitted. After 4 weeks of diet, normal food was reintroduced at once. Patients' were told to keep their daily doses of concomitant DMARDs, NSAIDs and CS constant throughout the study.				

Effect size

Elemental diet vs Control (usual) diet

- The Elemental diet was significantly better than the control (usual) diet for:
  - Swollen joint count at 4 weeks (end of treatment), p=0.006;
  - ESR at 4 weeks (end of treatment), p=0.018;
  - General Assessment of Health (average during last week) at 4 weeks (end of treatment), p=0.037;
  - BMI at 4 weeks (end of treatment), p=0.005;

- The Elemental diet was similar to the control (usual) diet for:
  - Withdrawals (N=2 and N=1 respectively)

- There was NS difference between the Elemental diet and the control (usual) diet:
  - CRP at 4 weeks (end of treatment) and at 12 weeks (2 months post-treatment)
  - BMI at 12 weeks (2 months post-treatment);
  - Swollen joint count at 12 weeks (2 months post-treatment);
  - ESR at 12 weeks (2 months post-treatment);
  - General Assessment of Health (average during last week) at 12 weeks (2 months post-treatment);
  - RAI at 4 weeks (end of treatment) and at 12 weeks (2 months post-treatment)
  - Swollen joint count at 4 weeks (end of treatment) and at 12 weeks (2 months post-treatment);
  - Pain at 4 weeks (end of treatment) and at 12 weeks (2 months post-treatment)
  - Morning stiffness at 4 weeks (end of treatment) and at 12 weeks (2 months post-treatment)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kavanagh R, Workman E, Nash P et al. The effects of elemental diet and subsequent food reintroduction on rheumatoid arthritis. *British Journal*	RCT: 1+ Single centre trial: Denmark • Randomised (method not mentioned) • Single blind (assessors, but not possible for	Total N=47 randomised N=24 experimental N=23 control **Drop-outs:** N=15 prior to the elimination/reintroduction N=39 prior to total follow-up period	**Inclusion criteria:** Definite RA (ARA criteria). **Exclusion criteria:** Patients on cortcosteroids and DMARDs **Medication:**	Experimental diet The Experimental diet: The 'Elemental 026' (EO28) diet alone was poorly tolerated in a pilot study,	Control (usual) diet + Two sachets of EO28 daily	Weekly during elimination/reintroduction period and monthly until 24 weeks	Weight, thermographic joint score, Ritchie articular index, grip strength, functional score, duration of morning stiffness, ESR	Arthritis and Rheumatism Council

of Rheumatology. 1995; 34(3):270-273. Ref ID: 3206 ID 3206	the patients to be blinded) • No mention ITT analysis		NSAIDs allowed **Baseline characteristics:** Experimental Diet group: mean age 43 yrs, male: female 6:18, duration of disease 4 yrs Control group: mean age 49 yrs, male: female 4:19, mean duration of disease 4 yrs There were NS differences between the groups for any of the baseline characteristics.	and consequently chicken, fish, rice, carrots, runner beans and bananas were added. These foods were thought unlikely to cause food intolerance. The diet was of 4 weeks duration (elimination phase) and was followed by a period of food reintroduction (reintroduction phase). Initially, foods unlikely to cause a food intolerance were reintroduced, followed by foods more often the cause of intolerance. Foods were introduced one at a time at intervals no shorter than 2			and CRP	

				days so as to allow up to 46 hrs for any effect to take place. If reintroduction of a food stuff was suspected by a patient of causing a worsening of joint pain or stiffness, it was eliminated from the diet NSAIDs were allowed				

Effect size

Experimental diet vs Control diet

- The Experimental diet was significantly better than the control (usual) diet for:
  - Average grip strength (end of elemental diet) (p=0.008);
  - Ritchie score (end of elemental diet) (p=0.006)
  - Weight loss (end of elemental diet) (p=0.001)

- There was NS difference between the Experimental diet and the control (usual) diet for:
  - CRP (end of elemental diet) (NS)

- There was a significant correlation in the diet group for:
  - Weight loss and grip strength (one week) (p=0.009) and at four weeks (p=0.027)
  - These correlations were not significant (NS) in the control group

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

P. Sarzi-Puttini, D. Comi, L. Boccassini, S. Muzzupappa, M. Turiel, B. Panni, and A. Salvaggio. Diet therapy for rheumatoid arthritis: A controlled double-blind study of two different dietary regimens. *Scandinavian Journal of Rheumatology* 29 (5):302-307, 2000. ID 3187	RCT: 1+ Single centre trial: Italy • Randomised (method not mentioned) • Double blind • Not mention ITT analysis • Sample size calculation	Total N=50 randomised (N=25 Experimental Diet; N=25 Control). **Drop-outs:** Control: N=4 (16%) MD: N=3 (12%)	**Inclusion criteria:** Adults aged 25-70 years with definite or classical RA (ACR criteria); Stenbroker functional class I-III; stable dosage of anti-rheumatic therapy for at least 12 weeks prior to study entry. duration at least 6 months; active disease; active disease. **Baseline characteristics:** Experimental Diet group: mean age 50 years; Female 76%; Duration of RA = Established RA (mean 50 months); HAQ score mean 1.9; BMI mean 29. Control group: mean age 50 years; Female 80%; Duration of RA = Established RA (mean 48 months); HAQ score mean 1.7; BMI mean 28. There were NS differences between the groups for any of the baseline characteristics.	Experimental diet The Experimental diet: contained common hypoallergenic foods such as rice, cornmeal, cornbread, hydrolysed milk, fresh pineapple and cooked apple. Diet was deprived of allergenic foods such as wheat, eggs, milk, strawberries and acidic fruit, tomato, chocolate, crustaceans, dried fruit (only lean cuts of red meat were allowed no more than 3 times/week as horse or lamb or white meat as rabbit or turkey. All canned or transformed foods and spices and aromatic plants were excluded from the diet. Ratio of unsaturated to saturated FA approx. 2:1 In both diets, olive oil was used. All patients were taking NSAIDs. Patients' were told to continue pre-study therapy for their arthritis. No changes in antirheumatic drugs were allowed during the course of the study.	Control diet Control diet: ratio of unsaturated to saturated FA approx. 1:1. Control diet included common allergenic foods but restricted intake of nourishment containing a lot of saturated FA. (FA = fatty acid).	24 weeks (end of treatment)	Swollen and tender joints; RAI (tenderness); Responders (Paulus Index) 20% and 50%; patient's global assessment of disease; Pain (VAS); morning stiffness; HAQ score; ESR; CRP; BMI; AEs.	Not mentioned

Effect size

Experimental diet vs Control diet

- The Experimental diet was significantly better than the control diet in multivariate analysis (adjusted for BMI) for:
  - Tender joint count at 24 weeks (end of treatment), p=0.014;
  - RAI at 24 weeks (end of treatment), p<0.05;
  - ESR at 24 weeks (end of treatment), p=0.025;

- The Experimental diet was similar to the control diet for:
  - Withdrawals (N=3 and N=4 respectively)

- There was NS difference between the Experimental diet and the control diet in multivariate analysis (adjusted for BMI) for:
  - BMI at 24 weeks (end of treatment);
  - Weight at 24 weeks (end of treatment);
  - Swollen joint count at 24 weeks (end of treatment);
  - Morning stiffness at 24 weeks (end of treatment);
  - Pain severity (VAS) at 24 weeks (end of treatment);
  - HAQ at 24 weeks (end of treatment)
  - CRP at 24 weeks (end of treatment)
  - Responders (Paulus Index – 20% and 50%) at 24 weeks (end of treatment)
  - Patient's global assessment of disease at 24 weeks (end of treatment)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
M. Van de Laar and J. K. van der Korst. Food intolerance in rheumatoid arthritis. I. A double blind, controlled trial of the clinical effects of elimination of	RCT: 1+ Single centre trial: the Netherlands • Randomised(method not mentioned) • Double blind • Powered tins with a 'double blind code' • Not mention ITT analysis	Total N=800 contacted N=232 available for intake investigation N=116 fulfilled entrance criteria and randomised N=94 entered the	**Inclusion criteria:** Adults aged with RA (ARA criteria) (fulfilling at leas t 6 of the criteria), including a positive rheumatoid factor test. Disease activity was sustained by at least 3 of the 4 criteria: ESR ≥28 mm/h; morning stiffness ≥ 45 mi; more than 5 tender joints; and more than 2 swollen joints	Allergen-free diet Both diets were artificial food, supplying all nutritional requirements. The diet was free from all potentially allergenic materials, additives and preservatives. There were five colour-coded flavourings which were	Allergen-restricted diet The diet contained milk allergens and azo colourings, but was free from other potential	Every 2 weeks for 12 weeks	Morning stiffness (NS); Number of swollen joints; Number of tender joints ; Ritchie index; Global assessment; Fatigue score;	Het Praeventiefonds

milk allergens and azo dyes. *Annals of the Rheumatic Diseases* 51 (3):298-302, 1992. ID 185		study N=78 completers (Hyopallergic N=49 and Allergen free N=45) **Drop-outs:** Only those patients who were still motivated to participate after a preliminary trial of the experimental diet entered the study N=16 randomised but unable to start N=6 randomised but no longer met inclusion criteria N=13 of 94 unable to comply with diet N=2 of 94 changed drug treatment N=1 of 94 fractured hip	**Exclusion criteria:** Patients in functional class 4 (Steinbrocker) **Baseline characteristics:** Hypoallergic group: mean age 59 yrs, 73% female, mean disease duration 11 yrs Allergen free: mean age 58 yrs, 67% female, mean disease duration 11 yrs There were NS differences between the groups for any of the baseline characteristics.	allergen free No other food were allowed apart from 3 apples a day, tea, allergen free chewing gum and sugar Baseline: Four weeks duration of patients' following their usual diet Diet: Four week duration Rechallenge: Four weeks of usual diet Patients' were told to keep their daily doses of medication constant throughout the study. DMARDs had to be used in constant doses for at least three months before the start of the study. Corticosteroids were allowed in doses not exceeding the equivalent of 10 mg/d prednisone	allergic materials, additives and preservatives Schedule as for intervention		Grip strength; Walking time; ESR; CRP; IgM; Body weight	

		N=78 completers						

Effect size

ALL PATIENTS

- All patients showed an improvement in the four week diet period for:
    - Morning stiffness ($p<0.05$);
    - Tender joints ($p<0.05$);
    - Swollen joints ($p<0.05$);
    - Global assessment ($p<0.05$);
    - Ritchie index ($p<0.05$);
    - Fatigue score ($p<0.05$)

- For all patients, there was no significant (NS) different in the four week diet period for:
    - Grip strength (NS)
    - Walking time (NS)
    - ESR (NS)
    - CRP (NS)
    - IgM RF (NS)

- For all patients, there was a significant deterioration during the rechallenge phase for:
    - Number of tender joints (p value not specified)
    - Global assessment (p value not specified)

- For all patients, there was a significant deterioration during the rechallenge phase for:
    - Number of tender joints (p value not specified)
    - Global assessment (p value not specified)

- For all patients, there were no significant differences (NS) during the rechallenge phase for:
    - Morning stiffness ($p<0.05$);
    - Swollen joints ($p<0.05$);
    - Ritchie index ($p<0.05$);
    - Fatigue score ($p<0.05$);
    - Grip strength (NS);
    - Walking time (NS);
    - ESR (NS);
    - CRP (NS);
    - IgM RF (NS)

ALLERGEN-FREE VS ALLERGEN RESTRICTED

- There was a significantly greater reduction in the patients on allergen-free diet compared to the allergen-restricted diet in the diet phase on:

- Weight reduction ($p<0.05$)

- There were no significant differences (NS) between those patients on the allergen-free diet and allergen-restricted diet in the diet phase on:
  - Number of tender joints (NS);
  - Global assessment (NS);
  - Morning stiffness (NS);
  - Swollen joints (NS);
  - Ritchie index (NS);
  - Fatigue score (NS);
  - Grip strength (NS);
  - Walking time (NS);
  - ESR (NS);
  - CRP (NS);
  - IgM RF (NS)

- There were no significant differences (NS) between those patients on the allergen-free diet and allergen-restricted diet in the rechallenge phase on:
  - Number of tender joints (NS);
  - Global assessment (NS);
  - Morning stiffness (NS);
  - Swollen joints (NS);
  - Ritchie index (NS);
  - Fatigue score (NS);
  - Grip strength (NS);
  - Walking time (NS);
  - Weight reduction (NS);
  - ESR (NS);
  - CRP (NS);
  - IgM RF (NS)

RESPONDERS vs NON-RESPONDERS

- N=9 patients were selected in whom artificial feeding was accompanied by at least a 20% improvement and rechallenging induced more than 20% deterioration. These comprised of N=3 patients from the allergen restricted diet and N=6 from the allergen free group
- For these responders (N=9) there was a significant improvement in the diet phase compared with the baseline on:
  - Number of tender joints ($p<0.05$);
  - Ritchie index ($p<0.05$);
  - Global assessment ($p<0.05$);
  - Fatigue score ($p<0.05$)

- For these responders (N=9) there were no significant differences in the diet phase compared with the baseline on:
    - Morning stiffness (NS);
    - Swollen joints (NS)
    - Grip strength (NS);
    - Walking time (NS);
    - ESR (NS);
    - CRP (NS);
    - IgM (NS);
    - Body weight (NS)

- For these responders (N=9) there was a significant deterioration in the rechallenge phase compared with the end of diet on:
    - Number of tender joints ($p<0.05$);
    - Ritchie index ($p<0.05$);
    - Global assessment ($p<0.05$);
    - Fatigue score ($p<0.05$)

- For these responders (N=9) there were no significant differences in the rechallenge phase compared with the diet phase on:
    - Morning stiffness (NS);
    - Swollen joints (NS)
    - Grip strength (NS);
    - Walking time (NS);
    - ESR (NS);
    - CRP (NS);
    - IgM (NS);
    - Body weight (NS)

- For the non-responders (N=69) there was a significant improvement in the diet phase compared with the baseline on:
    - The number of swollen joints ($p<0.05$)

- For the non-responders (N=9) there were no significant differences in the diet phase compared with the baseline on:
    - Morning stiffness (NS);
    - Number of tender joints (NS);
    - Ritchie index (NS);
    - Global assessment (NS);
    - Fatigue score (NS);
    - Grip strength (NS);
    - Walking time (NS);
    - ESR (NS);
    - CRP (NS);

- IgM (NS);
- Body weight (NS)

- For the non-responders (N=9) there were no significant differences in the rechallenge phase compared with the diet phase on:
  - Morning stiffness (NS);
  - The number of swollen joints (NS);
  - Number of tender joints (NS);
  - Ritchie index (NS);
  - Global assessment (NS);
  - Fatigue score (NS);
  - Grip strength (NS);
  - Walking time (NS);
  - ESR (NS);
  - CRP (NS);
  - IgM (NS);
  - Body weight (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. Little and T. Parsons. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (4):CD002948, 2000. ID 1023	MA: 1++ RCT's of MA: 1+ to 1++ SR and MA included: N=11 trials with suitable data Trials were similar in terms of: • Study design (All RCTs) • Blinding (all double blind) • Comparison group (all placebo) Trials differed with respect to: • Intervention [N=7 RCTs used GLA (sources: evening primrose oil, blackcurrant seed oil, borage seed oil); N=1 RCT used feverfew, N=1 RCT	Total N=248.	**Inclusion criteria:** RCTs; placebo-controlled; effects of herbal interventions on RA; persons diagnosed with RA. Any rout e of administration; Herbal interventions included any whole plant extract. Search was up to 2000. **Exclusion criteria:** Patients	Herbal therapy	Placebo	Treatment ranged from 4 weeks to 15 months	Pain (scale 0-5; VAS; AIMS2); Global evaluation; Morning stiffness; Joint tenderness and swelling; Grip strength; 15-metre walk time; Patients and Physicians global assessment	Partial funding by Laing Foundation, Southampton University Hospital, UK.

	used Trypterygium wilfordii hook F, N=1 RCT used topical capsaicin and N=1 RCT used Reumalex (contains willow bark)] • Study size (range N=20 to N=70) • Study quality – max score of 5 (N=10 studies reasonable to good quality; N=1 study poor quality) • Study duration – length of intervention (4 weeks to 15 months) Tests for heterogeneity and quality assessment performed.		with 'joint pain'; herbal therapy in conjunction with other treatments or combined with a non-herbal substance; homeopathy, aromatherapy or any preparation of synthetic origin or consisting only of plant derivatives.					

Effect size

NOTE: the trial looking at Reumalex was not included in the results here as it used a mixed RA and OA population

GLA vs placebo

- GLA was significantly better than placebo for:
  - Pain (VAS - % change from baseline) (3 RCTs, N=82; effect size WMD –32.8, 95% CI –56.3 to –9.4; p=0.006);
  - Pain (% change in pain scale 0-4) (3 RCTs, N=82; effect size WMD –25.9, 95% CI –46.7 to –5.0; p=0.02);
  - Patient's Global evaluation (3 RCTs, N=82; effect size WMD –20.9, 95% CI –39.4 to –2.3; p=0.03);
  - Morning stiffness (% change from baseline) (3 RCTs, N=82; effect size WMD –63.3, 95% CI –64.0 to –62.5; p<0.00001);
  - % change in joint tenderness score (scale 0-3) (3 RCTs, N=82; effect size WMD –43.0, 95% CI –63.8 to –22.2; p=0.00006);
  - % change in joint tenderness count (out of 68) (3 RCTs, N=82; effect size WMD –37.4, 95% CI –55.7 to –19.1; p=0.00006);

- There was NS difference between GLA and placebo for:
  - Pain (absolute score) at end of treatment (1 RCT, N=18);
  - Morning stiffness (absolute score) at end of treatment (1 RCT, N=18);
  - % change in joint swelling score (scale 0-3) (3 RCTs, N=82;
  - % change in joint swelling count (out of 66) (3 RCTs, N=82);
  - Reduction in NSAID consumption (2 RCTs, N=60)

- There was significant heterogeneity for:
  - GLA vs placebo – Physician's global evaluation

Trypterygium wilfordii Hook F vs placebo

- Trypterygium wilfordii Hook F was significantly better than placebo for:
  - Joint tenderness score (scale 0-3) (1 RCT, N=58; effect size WMD –14.0, 95% CI –19.0 to –9.0; p<0.00001);
  - Joint swelling count (out of 60) (1 RCT, N=58; effect size WMD –3.1, 95% CI –5.5 to –0.7; p=0.01);

- There was NS difference between Trypterygium wilfordii Hook F and placebo for:
  - Morning stiffness (1 RCT, N=58);
  - Grip strength (1 RCT, N=58);
  - 15 metre walk time (1 RCT, N=58);

Topical capsaicin vs placebo

- Topical capsaicin was significantly better than placebo for:

- Physician's global evaluation (1 RCT, N=29; effect size WMD 1.4, 95% CI 0.5 to 2.2; p=0.001);

- There was NS difference between Topical capsaicin and placebo for:
  - Pain (VAS, % change from baseline) (1 RCT, N=29)
  - Pain (categorical scale, change from baseline) (1 RCT, N=29);
  - Grip strength (1 RCT, N=40);

Author's conclusions:
There appears to be some potential benefit for the use of GLA in RA, although further studies are required to establish optimum dosage and duration of treatment.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. J. Goldberg and J. Katz. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain* 129 (1-2):210-223, 2007. ID 3218	MA: 1++ RCT's of MA: 1- to 1++ SR and MA included: N=17 trials with suitable data Trials were similar in terms of: • Study design (All RCTs) • Blinding (all double blind) • Comparison group (all inert substances – olive oil or non-olive oil) Trials differed with respect to: • Intervention – total omega-PUFA (not reported and range 1.7g to 9.6g) • Study size (range N=12 to N=90) • Study quality – max score of 5 (N=12 studies reasonable to good quality; N=5 studies poor quality) • Study duration – length of	Total N=823.	**Inclusion criteria:** RCTs; omega-3 PUFAs vs inert substance Search was up to 2006. **Exclusion criteria:** Studies manipulating analgesic consumption during the treatment period were excluded.	omega-3 PUFAs (polyunsaturated fatty acids)	Inert substanc (olive oil or no olive oil)	Treatment ranged from 1 month to 15 months	Pain (VAS); Global evaluation; Morning stiffness; Number of tender and painful joints; RAI	Authors supported by non-pharma grants

	intervention (1 month to 15 months) Tests for heterogeneity and quality assessment performed.							

Effect size

NOTE: N=1/17 trials was a non-RA population (dysmenorrhea) and N=1/17 trials was a population of RA caused by IBD.

<u>Omega-3 PUFAs vs placebo</u>

- Omega-3 PUFAs were significantly better than placebo for:
  - Patient's assessment of Pain (13 RCTs, N=501; effect size SMD –0.26, 95% CI –0.49 to –0.03; p=0.03);
  - Morning stiffness (8 RCTs, N=306; effect size SMD –0.43, 95% CI –0.72 to –0.15; p=0.003);
  - Number of painful/tender joints (10 RCTs, N=425; effect size SMD –0.29, 95% CI –0.48 to –0.10; p=0.003);
  - NSAID consumption (3 RCTs, N=156, effect size SMD –0.40, 95% CI –0.72 to –0.08; p=0.01);

- There was NS difference between Omega-3 PUFAs and placebo for:
  - Physician's assessment of Pain (3 RCTs, N=123)
  - RAI (4 RCTs, N=135);

Author's conclusions:
The results suggest that omega-3 PUFAs are an attractive adjunctive treatment for joint pain associated with RA, IBD and dysmenhorrhea.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
B. Galarraga, M. Ho, H. M. Youssef, A. Hill, H. McMahon, C. Hall, S. Ogston, G. Nuki, and J. J. Belch. Cod liver oil (n-3	RCT: 1++ Multicentre trial: 2 centres, UK • Randomised (manual generation, blocks of 10)	Total N=97 (N=49 fish oils; N=48 placebo) **Drop-outs:** fish oils	**Inclusion criteria:** Adults aged at least 18 years; RA (ARA criteria); stable RA disease activity; medication for at least 3 months prior to entering the study; regular NSAID therapy; Steinbroker functional class I, II or III. **Exclusion criteria:** Ongoing RA disease activity requiring change of therapy; prednisolone at a daily dose of >7.5	Fish oils (10 g/day) 10 capsules/day containing a blend of cod liver oil and fish oil (each 1g capsule	Placebo	9 months (with assessments at 4, 12, 24 and 36 weeks)	Tender and swollen joints; grip strength; early morning stiffness; Pain (VAS); DAS28-CRP; HAQ; CRP levels and RF; Reduction of	Willem Vas Dias abd Seven Seas Ltd, UK.

fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology* 47 (5):665-669, 2008. ID 3531	• Double blind • ITT analysis • Power study (NSAID requirement) • High number of drop-outs especially in the placebo group	N=17 (35%) placebo N=22 (46%)	mg/day; severe intercurrent illness or patients routinely taking supplements containing EPA or other EFA. **Baseline characteristics:** Fish oils group: Mean age 49 years; 69% female; mean disease duration 13 years (Established RA); HAQ mean 1.5; Pain (VAS) mean 38 Placebo group: Mean age 48 years; 73% female; mean disease duration 13 years (Established RA); HAQ mean 1.5; Pain (VAS) mean 31 The groups were similar for all baseline characteristics and all patients were on NSAIDs, 75% fish oil group vs 80% placebo group were on DMARDs	contains 150 mg EPA, 70 mg of DHA, 80ug of vitamin A, 0.5ug of vitamin D and 2.0 IU of vitamin E.			daily NSAID dose	

Effect size

FISH OILS vs PLACEBO

- Fish oils were significantly better than placebo for:
  - Reduction in daily NSAID requirement by >30% (39% vs 10% of patients respectively, p=0.002) at 36 weeks
  - Improvement in Pain (VAS), (-6.7 vs 1.9 respectively, p=0.03) at 36 weeks

- There was NS difference between Fish oils and placebo for:
  - HAQ, morning stiffness, DAS28-CRP, CRP, Grip strength at 36 weeks
  - Number or type of AEs
  - Number of withdrawals
  - Type of AEs leading to withdrawal

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
S. E. Edmonds and P. G.	RCT: 1++ Two centre trial UK	Total N=42 randomised	**Inclusion criteria:** Adults ≥18 years ≤ 80 yrs with RA (ARA	Vitamin E 1200 mg *d*-ũ-	Placebo	1, 4, 8, 12 and	Disease activity (numbers of	None reported

Winyard. Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial. *Annals of the Rheumatic Diseases* 56 (11):649-655, 1997. ID 3221	and Germany (unclear) • Randomised (method not mentioned) • Double blind • ITT analysis • Power study (VAS)	(N=20 intervention and N=22 placebo) **Drop-outs:** Intervention: None Placebo: N=3 (inclusion criteria violated)	criteria). Active inflammatory disease defined as a Ritchie articular index of at least six or early morning stiffness lasting at least one hour, or both. Medication Patients had to be on stable NSAID treatment and 'second' line medication. Intra-articular aspiration with corticosteroid injections were allowed. Patients continued taking their disease-modifying, NSAID and analgesic medication throughout the study **Exclusion criteria:** Any change in medication, either NSAIDs or second line agents, including corticosteroids, within eight weeks before entering the study. Those who had been taking vitamin E supplementation or who were vitamin E hypersensitive **Baseline characteristics:** Vitamin E: mean age 55 yrs, female:male 16:4, mean Ritchie articular index 16, mean morning stiffness 45 min, mean number of swollen joints 9, mean morning pain (VAS) 5 and mean evening pain (VAS) 5 Placebo: mean age 52 yrs,	tocopheryl acetate as 2 x 2 capsules daily 'Run in' period of three weeks to ensure the patient fulfilled exclusion/inclusion criteria	Run in period as for intervention	20 weeks	swollen and tender joints out of total 28); Articular pain (VAS); Patient's and physician's global assessments (VAS); HAQ scores; Disease activity (DAS28 score); Radiological damage in the hands and feet (modified Larsen method); ESR; CRP level; AEs.	

			female: male 15:7, mean Ritchie articular index 15, mean morning stiffness 30 min, mean number of swollen joints 10, mean morning pain (VAS) 4 and mean evening pain (VAS) 4 There were NS differences between the groups for any of the baseline characteristics. There were no significant differences in the distribution of concomitant drugs or combination of drugs					

Effect size

VITAMIN E vs PLACEBO

- There was no significant (NS) difference between the vitamin E and placebo groups on:
    - Ritchie articular index (NS);
    - Duration of early morning stiffness (NS);
    - Mean number of swollen joints (NS)

- At week 12, there was a significant reduction in pain in favour of vitamin E compared with placebo on:
    - Pain in the morning (p=0.006);
    - Pain in the evening (p=0.017);
    - Pain after chosen activity (p=0.04)

- The response rates (week 12 compared with week 1) showed a significantly greater reduction associated with vitamin E compared with placebo for:
    - Pain in the morning (p=0.031);
    - Pain after chosen activity (p=0.028)

- The response rates (week 12 compared with week 1) showed no significant difference associated with vitamin E compared with placebo for:
    - Pain in the evening (NS)

- There was no observable difference in pain scores associated with vitamin E until week 2 and the analgesic effect remained until the end of treatment

- Multivariate regression analysis showed confirmed that the changes in pain were correlated only with the study medication:
    - Pain in the morning (p=0.011);
    - Pain in the evening (p=0.034)

- At twelve weeks, patients on vitamin E compared with placebo:
    - Had a higher score on the global assessment of efficacy (p value not specified)
    - Had a higher investigators rating of global assessment of efficacy (p value not specified)

- At week 20 at the end of follow-up and after the treatment had been stopped there were no significant differences (NS) between the vitamin E and placebo groups on:
    - Ritchie articular index (NS);
    - Any measures of pain (NS);
    - Duration of early morning stiffness (NS);
    - Mean number of swollen joints (NS);
    - Global assessment of efficacy (NS)

Adverse events

- There were no differences between the vitamin E and the placebo groups on:
  - The number of adverse events;
  - No patient withdrew from the study because of adverse reactions
  - Reported symptoms were mild and non-specific and associations with trial drugs uncertain

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Peretz A, Siderova V, Neve J. Selenium supplementation in rheumatoid arthritis investigated in a double blind, placebo-controlled trial. *Scandinavian Journal of Rheumatology.* 2001; 30(4):-212. ID 3190	RCT multicentre 1+ Belgium • Blocked randomised • Concealment allocation not specified • Placebo-controlled • Double blind • Intention to treat analysis	Total N=55 (randomised) Selenium N=28 Placebo N=27 **Drop-outs** N=7 (no breakdown by group)	**Inclusion criteria:** Patients aged 18 to 80 yrs with classical or definite RA (ACR criteria). All had active disease defined as 6 or more swollen and tender joints, ESR > 25 mm/h or CRP > 1 mg/dl. Medication (inclusion and exclusion): Patients included had been treated with metothrexate at a weekly dose not exceeding 10 mg for at least two months and no longer than five years. NSAIDs and oral glucorticosteroids (not more than 10 mg/d) were allowed as complementary treatment but patients receiving	Selenium Selenium-enriched yeast capsules 2 x 100 µg/d 90 days	Placebo	30, 60 and 90 days follow-up	Pain: VAS< Ritchie Index, no. of painful and swollen joints Laboratory: CRP, ESR and rheumatoid factor. Trace elements in plasma (selenium, zinc and copper) Quality of life: EMIR questionnaire (adapted from AIMS2)	Supported by Labcatal laboratory

			larger doses of glucocortisteroids and/or DMARDs or immunosuppressive drugs were not included. A stable dose of corticosteroids and of DMARDs was mandatory. **Exclusion criteria:** See medication **Baseline:** Selenium: mean age 61 yrs, male:female 7:21 (no disease duration specified) Placebo: mean age 60 yrs, male: female 7:20 The groups were well matched at baseline except that the placebo group had a significantly higher plasma zinc level than the selenium group (p=0.02)					

Effect size

SELENIUM vs placebo

Adverse events

- There was NS difference between selenium and placebo for:
  - The proportion of adverse events

CLINICAL FACTORS

- There was NS difference between Selenium and placebo for:
  - Pain (VAS) (NS);
  - Ritchie index (NS);
  - Number of tender joints (NS);
  - Number of swollen joints (NS);
  - Morning stiffness (NS);
  - The time by treatment interaction (NS)

SELENIUM

- Selenium was associated with a significant improvement over time for:
  - Pain (VAS) ($p<0.03$);
  - Ritchie index ($p<0.001$);
  - Number of tender joints ($p<0.001$);
  - Number of swollen joints ($p<0.05$)

- There was NS difference over time associated with selenium for:
  - Morning stiffness (NS)

PLACEBO

- Placebo was associated with a significant improvement over time for:
  - Pain (VAS) ($p<0.01$);
  - Ritchie index ($p<0.01$);
  - Number of tender joints ($p<0.001$);
  - Number of swollen joints ($p<0.05$);
  - Morning stiffness ($p<0.01$)

LABORATORY VALUES

SELENIUM VS PLACEBO

- At 90 days, there was a significant difference associated with selenium compared with placebo for:
  - CRP decrease ($p<0.02$);
  - Selenium increase ($p<0.001$)

SELENIUM

- There was a significant decrease from day 60 to day 90 associated with selenium:
  - CRP ($p<0.0005$)

QUALITY OF LIFE
SELENIUM VS PLACEBO

- There was a significant improvement associated with selenium compared with placebo for:
  - Arm movements ($p<0.005$);
  - Health perception ($p<0.01$)

- There was a NS difference compared with placebo for:
  - Daily and social activities (NS);
  - Mood (NS);
  - For the five components model (physical activity, mood, symptoms, social life, work) (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hafstrom I, Ringertz B, Spangberg A et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens.[see comment]. *Rheumatology.* 2001; 40(10):1175-1179.	RCT: 1++ Single centre trial in Finland • Randomised (method not mentioned) • X-rays read blind • ITT analysis and valid compliant completer analysis (diet for 9 months or more)	Total N=66 * **Drop-outs:** Vegan: N=16 Non-vegan N=3 (completing less than 9 months)	**Inclusion criteria:** Adults with RA (ACR criteria) between 20 and 69 yrs. Disease duration between 2 and 10 yrs. No previous attempts at dietary manipulation. On stable doses of NSAIDs, oral glucocorticosteroids (≤ 7.5 mg prednisolone) and DMARDs **Exclusion criteria:** End stage joint destruction (Larsen score >100); previous or current oral steroid treatment; contraindications to parenteral steroids; serious comorbidity; patients not taking DMARDs; taking experimental drugs; taking DMARDs that have no effect on x-ray progression (eg.	Vegan diet free of gluten (N=38) Contained vegetables, roots vegetables, nuts and fruits. Buckwheat, millet, corn, rice and sunflower seeds. Unshelled sesame seeds in the form of sesame milk was a daily source of	Well-balanced non-vegan diet (N=28) 1mg/day vitamin B12 and 50 µg/day selenium Duration and advice as for intervention	3, 6 and 12 months	ACR20 response criteria Antibodies against food-related antigensL IgG and IgA antibody levels against gliadin and β-lactoglobulin Radiographic assessment: Hands and feet assessed at 6 and 12 months using the	Axel and Margaret Ax:son Johnsons Foundation, the Swedish Rheumatism Association and the Swedish Medical Research Council

ID 3216			Antimalarial drugs); taking DMARDs which may interact poorly with IM depot steroids (SSZ). **Baseline characteristics:** Vegan vs non-vegan: Mean age 50 yrs vs 51 yrs, mean disease duration 5 vs 6 yrs, rheumatoid factor positivity 79 vs 75%. The groups were well matched at baseline	calcium 1mg/day vitamin B12 and 50 µg/day selenium Duration: One year Advice was available from health professionals			modified Larsen score. Also assessed number of eroisions and number of eroded joints	

Effect size

VEGAN vs NON-VEGAN DIET

- A significantly higher proportion of patients on the vegan compared with the non-vegan diet:
    - Were categorised as responders on the ACR20 (9/22 (41%) vs 1/25 (4%) at twelve months

- Analysis of the separate disease activity outcome measures contained within the ACR response criteria revealed that vegan diet responders showed a significantly improvement on:
    - All variables except CRP
    - CRP at twelve months compared to baseline ($p<0.05$)

- Analysis of the separate disease activity outcome measures contained within the ACR response criteria revealed that non-vegan diet responders showed a significantly improvement on only:
    - Swollen joints
    - Physician global assessment of disease activity

- There was a significant reduction from baseline in the vegan compared with the non-vegan diet group for:
    - IgG anti-gladin and anti-β-lactoglobulin, but sub-group analysis showed that this was specific to the responder subpopulation

- There was no significant different at any time point for either the vegan or non-vegan groups for:
    - Total IgG and IgA (NS)

- There was no significant difference between the vegan and non-vegan groups on:
    - Radiographic progression (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kjeldsen KJ, Haugen M, Borchgrevink CF et al. Vegetarian diet for patients with rheumatoid arthritis--status: two years after introduction of	RCT 1++ Single centre trial in Norway • Randomised (blocked) • Single blind • Allocation concealmen	Total N=53 randomised (N=27 vegan + vegetarian diet, N=26 omnivorous diet) N=45	**Inclusion criteria:** Patients with classic or definite ///ra in functional class II or III. All patients had active disease, as defined by the prescence of three of the four: ≥ 3 swollen joints; ≥ 6 tender joints; morning stiffness ≥ 45	Vegetarian diet (Previously the Gluten-free vegan diet followed by lacto-vegetarian diet (vegan + vegetarian) group) N=27 Sent to health farm for four weeks.	Omnivorous diet (previously control group) N=26 Convalescent home for four weeks + omnivorous	Patients followed up for one year after the end of the original study (approximately two years since the intervention (see 3205))	Pain (VAS 0 to 10); Duration of morning stiffness; Functional ability (HAQ); Global Assessment (one item);	Norwegian Women's Public Health Association, the Anders Jahre's Fund for Promotion of Science,

the diet.[erratum appears in Clin Rheumatol 1994 Dec;13(4):649]. *Clinical Rheumatology.* 1994; 13(3):475-482. ID 3203	t not mentioned	(this trial) **Drop-outs:** ORIGINAL TRIAL: Vegan + vegetarian diet: N=4 (N=1 one month, N=1 4 months, N=3 7 months). N=5 treatment related Control: N=7 (N=1 at one month, N=3 at 4 months, N=1 at 7 months and N=2 at 10 months). N=2 treatment related CURRENT TRIAL: N=8 Vegetarian diet: Responders N=2; Non-responder N=3	min; ESR ≥ in the first hour **Medication** Patients using SAARDs or cytostatic drugs had to be on a stable dose for at least three months prior to inclusion. Corticosteroid dosase was not to exceed 7.5 mg/day prednisone equivalent and the dose must have been stable for four weeks prior to entry. The dosage of NSAIDs had to be stable for three weeks. No change in the dosage of SAARDs, cytostatic drugs, or corticosteroids was allowed during the study. If necessary, the dosage of NSAIDs and analgesics could be changed during the study. Patients were asked not to use omega-3 fatty acid supplements except for cod liver oil; the dose had to be stable six months prior to study entry and was kept stable throughout **Baseline characteristics:** Vegan + vegetarian Mean age 53 yrs,	Fasted for seven to ten days. Dietary intake included herbal teas, vegetable broth, garlic, decoction of potatoes and parsley, and juice extracts from carrots, beets, and celery. No fruit juices were allowed. The daily energy intake during the fast varied between 800 and 1260 kJ. After the fast the patients reintroduced a new food item every 2nd day. If they notice an increase in pain, stiffness, or joint swelling within 2-48 hrs this items was omitted from the diet for at least seven days. If symptoms were exacerbated during reintroduction of this food item, it was excluded from the diet for the rest of the study. During the first three to five months, the patients were asked avoid gluten, meat, fish, eggs, diary products, refined sugar, or citrus fruits. Also salt, strong spices, preservatives, alcoholic beverages, tea and coffee were avoided. After this period patients were allowed to reintroduce milk, other dairy products, and gluten containing foods.	diet for the study period Physiotherapy as for intervention		Joint count (Ritchie articular index, number of tender or painful joints on movement, the number of swollen joints); Grip strength Hand, wrist and forefoot radiographs at baseline and on study on completion Laboratory analyses (Haemoglobin, ESR, platelet count, white cell count, CRR and serum albumin)	Isberg's Legacy, Grethe Harbitz Legacy, Eckbo's Legacy, Nycomed Pharma AS, Oslo

		Omnivorous diet: N=3 all non-responders	male:female 3:24, mean disease duration 6 yrs Control: Mean age 56 yrs, male:female 5:21, mean disease duration 8 yrs There were NS differences between the groups for any of the baseline characteristics. At the start of the clinical trial there were no significant differences between the responders, non-responders and controls on the main baseline variables except for Ritchie articular index ($p<0.02$) and HAQ index ($p<0.04$). Both variables were lower in the responders than the non-responders and controls. Only 30% of the diet responders were RF positive	Continued this diet for approximately three months Physiotherapy three times a week whilst at health farm **Responders and non-responders**: All diet responders will still on the diet at the time of follow-up compared with only half of the non-responders ($p<0.02$) Most of the patients, however, did not follow the initial diet rigorously, but they had excluded certain food items which they felt had exacerbated the arthritis symptoms. It was not possible to identify food items specific to the responders only				

Effect size

RESPONDERS VS NON-RESPONDERS:

- These were classified according to:
    - The number of swollen joints, Stanford HAQ, pain score (VAS), number of tender joints, patients' global assessment and ESR. A 2-grade improvement on the scale for patients' global assessment was defined as a substantial improvement and for the other five variables a ≥ 20% improvement compared with baseline values was required. The patients who showed substantial improvement in ≥3 of these core variables at all of the last threeclinical examinations in the original clinical trials were classified as responders.
    - In the control group, only N=2 patients were classified as responders and the results of this group were therefore pooled (responders and non-responders)

RESPONDERS vs NON-RESPONDERS vs CONTROLS (main effects and post-hoc analyses (for the latter $p<0.05$ for all). For all variables there was a significantly greater improvement in the responders compared to both non-responders and controls:

- Overall, there were groups differences for:
    - Pain ($p<0.005$);
    - Duration of morning stiffness ($p<0.005$);
    - HAQ ($p<0.02$);
    - Global assessment ($p<0.007$);
    - The number of tender joints ($p<0.0003$) Ritchie articular index ($p<0.0001$);

RESPONDERS vs NON-RESPONDERS vs CONTROLS
There was a significant main effect for

- Number of swollen joints ($p<0.05$), but responders were only significantly different from the control group

There were no significant differences between the groups on:

- Grip strength (NS)
- ESR (NS)
- Medication change (NS)

- The Vegan + vegetarian group was not significantly (NS) different compared with the control group on:
    - Radiographic score, with both groups deteriorating slightly (NS)

NOTE:
Responders and non-responders: All diet responders will still on the diet at the time of follow-up compared with only half of the non-responders ($p<0.02$) Most of the patients, however, did not follow the initial diet rigorously, but they had excluded certain food items which they felt had exacerbated the arthritis symptoms. It was not possible to identify food items specific to the responders only

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Kjeldsen-Kragh J, Mellbye OJ, Haugen M et al. Changes in laboratory variables in rheumatoid arthritis patients during a trial of fasting and one-year vegetarian diet. *Scandinavian Journal of Rheumatology*. 1995; 24(2):85-93. ID 3204	RCT 1++ Single centre trial in Norway • Randomised (blocked) • Single blind • Allocation concealment not mentioned • ITT analysis (LOCF) • High number of drop-outs (but 13 month duration)	Total N=53 randomised (N=27 vegan + vegetarian diet, N=26 omnivorous diet) **Drop-outs: 19/54 (35%)** Vegan + vegetarian diet: N=10 (N=1 one month, N=3 4 months, N=5 7 months and N=1 10 months). N=5 treatment related Omnivorous diet: N=9 (N=1 at one month, N=4 at 4 months, N=1 at 7 months and N=3 at 10 months). N=2 treatment related	As for ID 3203	As for ID 3203	As for ID 3203	1, 4, 7, 10 and 13 months	IgA RF IgM RF (Latex)	Norwegian Women's Public Health Association, the Anders Jahre's Fund for Promotion of Science, Isberg's Legacy, Grethe Harbitz Legacy, Eckbo's Legacy, Nycomed Pharma AS, Oslo

Effect size

VEGETARIAN or OMNIVOROUS DIET:

- At one month, there was no significant (NS) differences when compared with baseline for either the patients on the vegetarian diet and those on the omnivorous diet on:
  - IgA RF (NS)

- At one month, there was no significant (NS) difference when compared with baseline for the patients on the omnivorous diet on:
  - IgM RF (NS)

- At one month, there was a significant decrease when compared with baseline for the patients on the vegetarian diet on:
  - IgM RF ($p<0.02$)

VEGETARIAN vs OMNIVOROUS DIET:

- Overall, there was no significant difference (NS) between patients on the vegetarian diet those on the omnivorous diet on:
  - IgA RF (NS)

- Overall, patients on the vegetarian diet had a significantly lower level than those patients on the omnivorous diet on:
  - IgM RF ($p<0.02$)

- Overall, there was no significant difference (NS) between patients on the vegetarian diet who were responders and those who were non-responders on:
  - IgM RF (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kjeldsen-Kragh J, Haugen M, Borchgrevink CF et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet.* 1991; 338(8772):899-	RCT 1++ Single centre trial in Norway • Randomised (blocked) • Single blind • Allocation concealment not mentioned	Total N=53 randomised (N=27 vegan + vegetarian diet, N=26 omnivorous diet) **Drop-outs: 19/54**	As for ID 3203	As for ID 3203	As for ID 3203	At four weeks and then every three months for a duration of 13 months	Pain (VAS 0 to 10); Duration of morning stiffness; Functional ability (HAQ); Global Assessment (one item); Joint count (Ritchie articular index,	Norwegian Women's Public Health Association, the Anders Jahre's Fund for Promotion of Science, Isberg's Legacy,

902. ID 3205	• ITT analysis (LOCF) • High number of drop-outs (but 13 month duration)	**(35%)** Vegan + vegetarian diet: N=10 (N=1 one month, N=3 4 months, N=5 7 months and N=1 10 months). N=5 treatment related Omnivorous diet: N=9 (N=1 at one month, N=4 at 4 months, N=1 at 7 months and N=3 at 10 months). N=2 treatment related					number of tender or painful joints on movement, the number of swollen joints); Grip strength Hand, wrist and forefoot radiographs at baseline and on study on completion Laboratory analyses (Haemoglobin, ESR, platelet count, white cell count, CRR and serum albumin)	Grethe Harbitz Legacy, Eckbo's Legacy, Nycomed Pharma AS, Oslo

Effect size

VEGAN + VEGETARIAN RESPONDERS vs OMNIVOROUS DIET:

- At one month and throughout the year, patients on the vegan + vegetarian diet showed significant improvement compared to baseline on:
  - The number of tender joints ($p<0.0002$);
  - Ritchie articular index ($p<0.0004$);
  - Number of swollen joints ($p<0.04$);
  - Pain ($p<0.001$);
  - Duration of morning stiffness ($p<0.002$);
  - ESR ($p<0.002$);
  - CRP ($p<0.005$);
  - Grip strength ($p<0.0005$);
  - HAQ score ($p<0.0001$)

- After four weeks in the convalescent home, patients in the control group showed a significant improvement on:
  - Pain score ($p<0.02$) only;
  - There were no other significant improvements, and at the end of the study the patients had deteriorated

- At 13 months, the vegan + vegetarian group showed a significant improvement compared with the control group on:
  - Pain ($p<0.02$);
  - Duration of morning stiffness ($p<0.0001$);
  - HAQ ($p<0.0001$);
  - Global assessment ($p<0.0001$);
  - Grip strength ($p<0.02$)
  - The number of tender joints ($p<0.0001$);
  - Ritchie articular index ($p<0.0004$);
  - The number of swollen joints ($p<0.02$)
  - Weight reduction ($p<0.02$)
  - ESR ($p<0.001$)
  - CRP ($p<0.0001$)

- The Vegan + vegetarian group :
  - Total number of AEs (N=55 and N=42 respectively).

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Skoldstam L, Brudin L, Hagfors L et al. Weight reduction is not a major reason for improvement in rheumatoid arthritis from lacto-vegetarian, vegan or Mediterranean diets. *Nutrition Journal.* 2005; 4(15) ID 3186	Pooled analysis: 1+ Three trials (two prospective, randomised and parallel studies and one prospective, crossover study)	Total N=95 (plus N=7 studied in a crossover design)	**Inclusion criteria:** Caucasian patients with a diagnosis of RA according to ACR criteria (1984). All but one had active disease. **Baseline characteristics:** The three populations showed equal distributions with respect to sex, age, disease duration, functional capacity and stage of RA disease Diet group (N=60): mean age 55 yrs, 18% male, mean weight 72 kg, mean disease duration 13 yrs Control (N=42): mean age 57 yrs, 17% male, mean weight 69 kg and mean disease duration 12 yrs At baseline, there were no significant differences in age, gender, body weight or disease duration were found between the two groups or in the disease measures ESR and pain scores	Lacto-vegetarian Strictly vegetarian Modified Cretan Mediterranean diet	Control	Studies: 1) Not stated 2) Control period 2 to 5 months followed by 4 months diet 3) No stated	Two measures identically assessed in all three studies: ESR (Westergren) Pain score (VAS 0 to 100 mm) Measures assessed differently across studies: Blood-plasma: One study measured this with the reaction in plasma concentration of orosomucoid and the other two studies with the corresponding reaction of CRP Physical function: Measured using a local constructed questionnaire, a non-validated version of the Stanford-health assessment questionnaire and the	None reported

							Swedish version of the HAQ. Tender Joint Count: Measured with the Ritchie joint index and the number of tender joints from palpation of 40, and 28, peripheral joints respectively. These three variables were dichotomised in the statistical analysis	

Effect size

DIET vs CONTROL

- The diets versus control resulted in (univariate analysis):
    - Significantly greater weight lose (average 3.5 vs 0.1 kg respectively; p< 0.001)
    - Significantly reduced pain score (-10 units vs +2) (p=0.011) and for the dichotomised pain score (p=0.007)

- Body weight reduction was univariately correlated with:
    - Acute-phase response (dichotomised score) (p=0.03)

- Body weight reduction was not significantly correlated with:
    - ESR (NS)

- In the logistic regression, diet was significantly correlated with:
    - Acute-phase response (dichotomised score) (p=0.007);
    - Pain (dichotomised score) (p=0.004);
    - Physical function (dichotomised score) (p=0.002);

- In the logistic regression, diet was not significantly correlated with:
    - ESR (dichotomised) (NS);
    - Tender joint count (dichotomised) (NS)

- In the multivariate analysis, diet was correlated
    - Acute-phase response (dichotomised score) (p=0.007);
    - Pain (dichotomised score) (p=0.005);
    - Physical function (dichotomised score) (p=0.002)
    -
- In the multivariate analysis, diet was not significantly (NS) correlated with
    - ESR (dichotomised) (NS);
    - Tender joint count (dichotomised) (NS);
    - Hence, bodyweight reduction was not significantly coupled with any outcome variable when diet was taken into account (NS)

Authors conclusion: Body weight reduction did not significantly contribute to the improvement in RA when eating lacto-vegetarian, vegan or Mediterranean diets

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Nenonen MT, Helve TA, Rauma AL et al. Uncooked, lactobacilli-rich, vegan food and rheumatoid arthritis. *British Journal of Rheumatology*. 1998; 37(3):274-281. ID 115	RCT: 1+ Single centre trial in Finland. • Randomised (method not mentioned) • Clinical evaluation blind (single blind) • Power study	Total N=43 randomised (N=2 patients excluded, one from each group, for the analysis on interfering variables) **Drop-outs:** N=3 could not eat all of the diet, two stopping after a few weeks and one stopped later (intervention group). N=2 control group N=8 after two months from the diet group. Controls stopping the follow-up after 2 months were selected to match the	**Inclusion criteria:** Adults ≥18 years with active (Steinbrocker's functional class II-III) and chronic RA (ARA criteria). All patients had active joint symptoms (more than three swollen or five tender joints) and elevated ESR >20mm/h, or CRP > 10 mg/l. **Baseline characteristics:** Diet group: Male: female 1:18, mean age 49 yrs, mean BMI 26, mean disease duration 13 yrs Control group: Male: female 1:19, mean age 56 yrs, mean BMI 24, mean disease duration 16 yrs There were NS differences between the groups for any of the baseline characteristics except that patients were significantly older in the control group (p=0.02)	**Uncooked, lactobacilli-rich, vegan** diet The diet was prepared by a kitchen and patients recorded any items they did not consume Caffeine-containing drinking, chocolate, alcohol and tobacco was prohibited in both groups **The intervention last for three months** All patients in both groups continued their current treatment with the least possible changes. **Medications** included gold, methotrexate, sulphapyridine, steroids and NSAIDs	Control Continuance of previous omnivorous diet	Three months (after study period)	Subjective experience and gastro-intestinal functions (VAS 0 to 10); Fasting blood, urine	Juho Vainio Foundation

		drop-outs.						

Effect size

VEGAN vs. NON-VEGAN DIET

- The vegan group showed a significant 'improvement' compared to the non-vegan group for:
    - Weight reduction (9% decrease vs 1% increase; p=0.0001) (not explained by medication);

Activity measures of RA

- There was NS difference between the vegan and non-vegan diet for:
    - CRP(NS);
    - ESR (NS);

Subjective effects

- During the intervention, the vegan group showed a significant improvement compared to the non-vegan group on:
    - Rheumatic pains (p<0.03);
    - Rheumatic joint swelling (p<0.03);
    - Morning stiffness (p<0.03);
    - General impression (p<0.03)

- During the intervention, there was no significant (NS) difference between the vegan and the non-vegan group on:
    - Ability to move (NS)

- At three month follow-up, the vegan group showed a significant improvement compared to the non-vegan group on:
    - Rheumatic pains (p<0.007);
    - Rheumatic joint swelling (p<0.004);
    - Morning stiffness (p<0.005)

- At three month follow-up, there were no significant (NS) differences between the vegan and the non-vegan group on:
    - Ability to move (NS);
    - General impression (NS)

Composite indices

- A stepwise regression model showed a significant association with:
    - Decrease disease activity (DAS) (p=0.02) during the intervention with increasing daily amount of what grass drink and fermented wheat drink, increased intake of dietary fibre, and decreased intake of iron during the intervention, and no need for gold, methotrexate or steroid medication at entry. However, in the intervention group as a whole the changes in DAS were not clinically significant (NS)

There was NS difference between the vegan and non-vegan diet for

- The composite index for changes in disease activity (NS);
- The mean amount of deterioration (NS)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
A. C. Elkan, B. Sjoberg, B. Kolsrud, B. Ringertz, I. Hafstrom, and J. Frostegard. Gluten-free vegan diet induces decreased LDL and oxidized LDL levels and raised atheroprotective natural antibodies against phosphorylcholine in patients with rheumatoid arthritis: A randomized study. *Arthritis Research and Therapy* 10 (2), 2008. ID 3530	RCT: 1- Single centre, Sweden • Randomised (method not mentioned) • No mention of blinding • No mention of ITT analysis	Total N=66 randomised (N=38 vegan diet; N=28 non-vegan). **Drop-outs:** N=8 (21%) vegan N=0 (0%) non-vegan	**Inclusion criteria:** Adults with active RA (ACR criteria) **Baseline characteristics:** All: mean age 50 years; Female 86%; Duration of RA = Established RA (mean duration 5 years).	Gluten-free vegan diet	Well-balanced non-vegan diet	1 year	DAS28; HAQ; CRP; Cholesterol levels	Grant from the Swedish Rheumatism Assocaiation and several Foundations

Effect size

The Vegan gluten-fre diet was better than non-vegan diet for change in DAS28 score, change in HAQ score but worse for change in CRP levels.

Authors' conclusion: A gluten-free vegan diet in RA induces changes that are potentially atheroprotective and anti-inflammatory, including decreased LDL and oxLDL levels and raised anti-PC IgM and IgA levels.

9.2 COMPLEMENTARTY THERAPIES (CAM)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
L. Casimiro, L. Barnsley, L. Brosseau, S. Milne, V. A. Robinson, P. Tugwell, and G. Wells. Acupuncture and electroacupuncture for the treatment of rheumatoid arthritis.[update of Cochrane Database Syst Rev. 2002;(3):CD003788; PMID: 12137715]. [Review] [24 refs]. *Cochrane Database of Systematic Reviews* (4):CD003788, 2005. ID 3424	MA: 1++ RCT's of MA: 1+ to 1++ SR and MA included: N=2 trials with suitable data Trials were similar in terms of: • Study design (RCTs) • Blinding (not mentioned) • Comparison group (placebo) Trials differed with respect to: • Intervention [N=1 RCT used acupuncture (needles manipulated); N=1 RCT used electroacupuncture] • Study size (range N=20 and N=64) • Study quality – max score of 5 (N=1 study good quality; n=1 study reasonable quality) • Study duration – length of intervention (N=1 RCT 5 weeks; N=1 RCT 3 months) Tests for heterogeneity	Total N=84.	**Inclusion criteria:** RCTs; Adult patients with classic or definite RA treated with acupuncture or electroacupuncture; any joint except the spine. Search was up to 2005. **Exclusion criteria:** Trials which used patients as their own control.	Acupuncture or electroacupuncture Using any combinations of parameters (eg. use of electric current, stimulation of various points or types of needles employed)	Placebo	Treatment ranged from 5 weeks to 3 months	Pain; tender and swollen joints; Patients and Physicians global assessment; functional status.	Partial funding by Laing Foundation, Southampton University Hospital, UK.

	and quality assessment performed.							

Effect size

Electroacupuncture vs placebo

- Electroacupuncture was significantly better than placebo for:
  - Pain (0-4 scale) at end of treatment-24 hours (1 RCT, N=20; effect size WMD –2.0, 95% CI –3.6 to –0.4; p=0.01) and at 4 month follow-up (1 RCT, N=20; effect size WMD –0.2, 95% CI –0.36 to –0.04; p=0.01)

Acupuncture vs placebo

- There was NS difference between Acupuncture and placebo for:
  - Pain (VAS) at end of treatment-5 weeks (1 RCT, N=55);
  - Swollen and tender joints at end of treatment-5 weeks (1 RCT, N=55);
  - Disease activity (DAS) at end of treatment-5 weeks (1 RCT, N=55);
  - Global Health Questionnaire end of treatment-5 weeks (1 RCT, N=55);
  - ESR (1 RCT)
  - CRP (1 RCT)
  - Analgesic uptake (1 RCT)
  - Patient's global assessment (1 RCT)

Author's conclusions:
The results of the electroacupuncture study show that electroacupuncture may be beneficial to reduce symptomatic knee pain in patients with RA 24hrs and 4 months post-treatment; however the trial was poor quality and small sample size so this may preclude its recommendation. Acupuncture trial had no effect on ESR, CRP, Pain, Patient's global assessment, number of tender and swollen joints, disease activity, General Health Questionnaire and reduction in analgesics. These conclusions are limited by methodological considerations such as the type of acupuncture (acu vs electracu), the site of the intervention, the low number of clinical trials and the small sample size of the included studies.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
T. Field, M. Diego, Reif M. Hernandez, and J. Shea.	RCT: 1+ Single centre trial: USA	Total N=22 randomised **Drop-outs:** None	**Inclusion criteria:** adults already diagnosed with wrist/hand arthritis. **Exclusion criteria:** none	Massage therapy Massage (15 mins) of the affected wrist/hand by a	Control group (standard treatment) Patients	4 weeks treatment (assessments every week)	Pain (VAS); Perceived grip strength (10-point scale); STAI (State	Grants from Johnsona nd Johnson

Hand arthritis pain is reduced by massage therapy. *Journal of Bodywork and Movement Therapies* 11 (1):21-24, 2007. ID 3439	• Randomised (method not mentioned • No mention of blinding • No mention of ITT analysis, however no dropouts • Power study	mentioned	given. **Baseline characteristics:** mean age 47 years; Female 93%; Duration of RA = not mentioned; Pain (VAS) mean 3.0. There were NS differences between the randomised groups for baseline characteristics.	therapist once/week for 4 weeks. Also patients were taught self-massage on the wrist/hand that was to be done daily at home prior to bedtime.	received the same assessments as the massage group but did not receive massage therapy during the study. They were taught the self-massage routine at the end of the study.		anxiety inventory); POMS (profile of mood states – 5 point Likert scale including helpless or gloomy feelings, depression and anxiety).	Paediatric Institute and Biotone, USA.

Effect size

Hand massage vs Control (standard treatment) – ANIOVA group interaction effects

- Hand massage was significantly better than control (standard treatment) at 4 weeks (end of treatment) for:
  - Pain (VAS, change from baseline) mean change -0.8 and –0.1 respectively, $p<0.01$;
  - Anxiety (STAI, change from baseline) mean change –4.5 and –0.6 respectively, $p<0.05$;
  - Depression (POMS, change from baseline) mean change –1.1 and –0.2 respectively, $p<0.01$;
  - Grip strength (change from baseline) mean change +0.8 and –0.2 respectively, $p<0.05$.

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention and Comparison	Length of follow-up	Outcome measures	Source of funding
E. Freye and L. Latasch. Analgesic therapy of rheumatoid arthritis - Part II: A study of combined allopathic and homeopathic therapy.	Case-series (prospective): 3 Germany	Total N=30	**Inclusion criteria:** Patients with classic symptoms of RA, rheumatic pain and inflammation; patients who sought more effective or alternative treatment due to persistent pain or excessive AEs of current medication and a resulting decline in QoL. **Exclusion criteria:** not	Plant-based homeopathic preparations + antioxidants (Vitamin C 1000 mg and Vitamin E 800 mg intramuscularly) 2 treatments/week for 5 weeks	5 weeks (2 treatments/week)	Patients were questioned about pain during movement (VAS), degree of restriction of movement (scale 1-3) and general level of well-being (VAS).	Not mentioned

Biomedical Therapy 18 (2):193-196, 2000. ID 3440			mentioned **Baseline characteristics:** Age mean 57 years; female 70%; disease duration mean 12 years (established RA).	Nerve block injections were administered concurrently to relieve acute pain and prevent sensitisation and the development of chronic pain syndrome.			

Effect size*

- At 5 weeks (end of study), patients treated with Plant-based homeopathic preparations + antioxidants had decreased Pain (VAS) change from baseline -1.5, increased level of well-being (VAS) change from baseline +8.0 and decreased restriction of movement, change from baseline -8.0.
- Reduction of drugs patients' had been previously taking was successful (all causing AEs were immediately eliminated – NSAIDs, MTX and/or paracetamol)

Author's conclusions:
Over the course of treatment with homeopathic therapy + vitamin supplements + allopathic therapy, gradual improvement in pain, movement and well-being was noted and standard allopathic therapy was reduced or eliminated.

*values are approximate and have been taken from graphs published in the paper

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
R. G. Gibson, S. L. Gibson, A. D. MacNeill, and W. W. Buchanan. Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic	RCT (cross-over): 1-Single centre trial: UK • Divided into groups (patients were assigned into the 2 groups so	Total N=46 Divided into 2 groups (N=23 in each) **Drop-outs:** N=2 placebo; N=1 homeopathy	**Inclusion criteria:** RA (ARA criteria). Patients were divided into 2 groups: those with good prescribing symptoms (R) and those with poor prescribing symptoms (U). Patients with good prescribing symptoms have 3 or more of the following: onset of symptoms following a sudden fright, breavement, physical injury or other profound emotional or physical trauma; complaint affected by climatic	Homeopathy	Placebo	3 months	Pain (VAS); Articular Index; Grip strength; Morning stiffness (limbering up time)	Not mentioned

trial. *British Journal of Clinical Pharmacology* 9 (5):453-459, 1980. ID 3432	that as far as possible there were equal numbers of U and R patients in each group) – method of assignment not mentioned • Double blind • Allocation concealment • No mention of ITT analysis • No washout period between cross-over treatments		conditions; complaint markedly affected by other factors such as movement, rest or time of day; outstanding factors affecting the patient not necessarily associated with the disease, such as marked craving or aversion for certain foods. **Exclusion criteria:** none given. **Baseline characteristics:** Homeopathy: mean age 54 years; Female 70%; Duration of RA = established RA (mean 7 years). Placebo: mean age 52 years; Female 65%; Duration of RA = established RA (mean 9 years). The 2 groups were similar for all baseline characteristics.					
Effect size **Authors' conclusions:** There was significant improvement in pain, articular index, stiffness and grip strength in those patients receiving homeopathic remedies whereas there was NS change in the patients who received placebo. However, there were NS differences between the 2 groups. No side-effects were observed with the homeopathic remedies..								
Reference	**Study type Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
R. G. Gibson, S. L. M. Gibson, A. D. MacNeill, and W. W.	RCT (cross-over): 1-Single centre trial: UK	Total N=46 Divided into 2 groups (N=23 in each)	**As for ID 3432**	Homeopathy	Placebo	3 months followed by 3 months cross-	Pain (VAS); Articular Index; Grip strength; Morning stiffness (limbering up	Not mentioned

Buchanan. The place for non-pharmaceutical therapy in chronic rheumatoid arthritis: A critical study of homoeopathy. *British Homoeopathic Journal* 69 (3):121-133, 1980. ID 3434	• Divided into groups (patients were assigned into the 2 groups so that as far as possible there were equal numbers of U and R patients in each group) – method of assignment not mentioned • Double blind • Allocation concealment • No mention of ITT analysis • No washout period between cross-over treatments	**Drop-outs:** N=2 placebo; N=1 homeopathy				over	time)	
Effect size **Authors' conclusions:** There was significant improvement in patients receiving homeopathic remedies whereas there was NS change in those who received placebo. No side-effects were observed with the homeopathic remedies.								