The RCN Rheumatology Forum welcomes the decision to undertake the appraisal of sequential treatment options following failure of the initial Tumour Necrosis Factor alpha treatment.

Introduction

In providing this statement in relation to the appraisal considering the next treatment options following failure of one TNF inhibitor we would like to highlight factors that we feel should be considered in the context of overall strategy for patients with a diagnosis of Rheumatoid Arthritis (RA).

These include:

1. The significant costs of biologic therapies warrant an emphasis on the management approaches outlined in the recent NICE guidelines for the management of RA (2009) which will ultimately change the long term outcomes for future generations diagnosed with RA.
2. Evidence supports public health messages that should improve outcomes including:
    a. Encouraging individuals who have joint pain to be assessed by competent practitioners who can ensure those with inflammatory joint disease are promptly diagnosed and treated
    b. Smoking cessation
    c. Improved and aggressive management of cardiovascular risk assessment in line with those seen for diabetes.
    d. Exercise to improve physical function and reduce cardiovascular risk factors and depression
    e. Recognition that supporting and maintaining social participation and work are important indicators that reduce the risk of other co-morbidities and improve outcomes.
    f. The BSRBR evidence has demonstrated that results over time show that outcomes have improved with the more recently treated patients whose disease remains of moderate duration (9 years) but slightly reduced to early evidence but importantly have failed less DMARDs (3) (Watson et al, 2009)

3. We recognise the significant cost to the healthcare economy yet feel that it is appropriate to consider the wider indirect costs that ultimately led to poorer health outcomes. Current NHS data capture fails to adequately the true costs of care.
4. The National Joint Registry should be reviewed and considered together with any Hospital Episode and Statistics data that may provide some insight into recent trends in patient care, costs and outcomes where possible.
5. It would be welcomed if (given important health economics and safety issues) that consideration is made to enabling patients to make some choices regarding treatment options based upon route (this clearly needs to be considered in the context of reasonable health economic factors and safety)

Although we recognise the expense such drugs cost and have to be borne by the health economy we feel it is imperative that the cost factors are adequately balanced against the true costs of the disease upon the individual, society and the economy (Hulsemann et al, 2005, Cole et al 2008, Joyce et al, 2009) . We also welcome any potential opportunities to develop a more collaborative framework with the pharmaceutical industry to enable patients to trial such therapies given a robust pre-treatment assessment and clear criteria of cessation of treatment when treatment is ineffective. This approach allows us to give patients access to treatments and provide clinicians with practical experience of these therapies (strengths and weaknesses) within routine clinical care.

We also welcome the recognition of the need for more of a treatment pathway approach to reviewing the place for other biologic (b-cell depleters, co-stimulatory blockers and therapies recently or about to be licensed). This approach is clearly presents a complex challenge but is a much needed approach to provide transparency for patients about the possible options and a degree of 'hope' whilst reducing the fear about 'what happens when this fails me' questions that faces nurses and doctors on a daily basis in clinic.

NICE has a significant task in reviewing the evidence for this appraisal. The RCN Rheumatology forum is faced with challenges in having sufficient resources and expertise to adequately analyse information regarding some of the factors in economic modelling etc. The time frame to prepare additional evidence and information about sources of information has been a challenge, particularly as the holiday period has added to the difficulty.

Although the evidence submitted today is by no means extensive we wish to highlight areas that we would stress should be scoped to provide a greater context of the impact of the disease and costs related Rheumatoid Arthritis care currently delivered within the NHS. Additional evidence that may inform interpretation of evidence includes;

- The National Audit Office Report on RA (2009)
- The Kings Fund Report on RA services (2009)
- Reports and reviews of services and outcomes from the Department of Health Musculoskeletal Strategy Group

It is proposed that NICE consider evidence in relation to the following areas:

1. Orthopaedic activity and costs related to management of RA
2. Hospital activity
3. Co-morbidities
4. Treating early
5. The use of outcome measures (functional)
6. The use of Disease Activity Assessments (DAS 28)
7. Treatment options

1. Orthopaedic issues:

In discussion with Mr. Peter Kay (Chair of the Department of Health Musculoskeletal Strategy Group) I understand that a company called Northgate manage the National Joint Registry and also manage the HES data and hope these sources may be used to provide greater insight into costs and hospital activity of RA patients. However, we recognise that although there is specific data on knee and hip surgery for RA patients the time frames since the start of the registry and demonstration of changes at this time point may be limited. However an orthopaedic representative might be helpful in outlining the clinical issues such as the need for a consultant to undertake patients who present for joint replacements who have a diagnosis of RA. The operations are technically more challenging and frequently also require a consultant anaesthetist

Over recent years international centres of excellence have focussed on early and aggressive disease management with a resulting trend towards milder disease and less joint damage (Emery et al, 2008, Pincus et al, 2006) the improved outcomes are also reflected for those treated with biologic therapies based upon the reduction in erosions and joint damage and in some cases possible improvement from the original joint damage (Smolen et al, 2008).

It is hoped that the work undertaken by the NICE Interventional procedural guidance 110 (2005) for joint replacement surgery of the hands in end stage arthritis will be able to provide some helpful evidence and cost analysis data.

Orthopaedic Evidence:

Information from the National Joint Registry and British Orthopaedic Association with regard to;

a. The data on cost, number and complex nature of surgery for RA patients
b. Any data that shows other orthopaedic surgery – commonly the hands, wrists, ankles.
c. The cost issues (e.g. usually require only consultant to operate, with a consultant anaesthetist to manage complex patients)
d. Evidence that demonstrates the difference in changes over the last five years in joint destruction of small joints (e.g. hands and feet x-rays) of those receiving biologic therapies and controls.

References:

Changes in surgical intervention patterns in rheumatoid arthritis over 10 years...
Kolling et al. Ann Rheum Dis.2009; 68: 1372-1373

Welsing PM, Fransen J, van Riel PL. Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. Arthritis Rheum 2005;52:2616–24

Sokka T, Kautiainen H, Hannonen P. Stable occurrence of knee and hip total joint replacement in Central Finland between 1986 and 2003: an indication of improved long-term outcomes of rheumatoid arthritis. Ann Rheum Dis 2007;66:341–4.[

Pincus T, Sokka T, Chung CP, Cawkwell G. Declines in number of tender and swollen joints in patients with rheumatoid arthritis seen in standard care in 1985 versus 2001: possible considerations for revision of inclusion criteria for clinical trials. Ann Rheum Dis 2006;65:878–83.

Smolen JS et al (2008) Radiographic changes in rheumatoid arthritis patients attaining different disease states with methotrexate Monotherapy and infliximab plus methotrexate; the impacts of remission and TNF blockade. Ann Rheum Dis. Accessed on line July 2008.

NICE (2005) Interventional procedures technology 110.

2. Hospital activity

Dixon (2008) that in the pre TNF inhibitor era people with RA had a nearly two fold increased risk of hospitalisation for infections compared to controls. The increased risk appears to be related to the disease (and steroids use) and not disease modifying drugs therapies (Avalos et al, 2008).

The appraisal committee will be aware of earlier evidence submitted during the first TNF inhibitor scope in relation to evidence of reduction in rheumatology inpatient beds, bed days and inpatient activity.

Although there may be other drivers to improving hospital activity statistics the fact remains that changes have been achieved to a great extent by improved treatment approaches. This improvement is also demonstrated in the greatly reduced need for rehabilitation facilities supported by multi-professional teams.

Table 1. Hospital Episodes and Statistics (HES) – MO5 Seropositive RA. Based upon 15 HRG of original admissions.

Year	All ages Consultant episodes	Admissions	Emergency	Waiting List	Day cases	Bed Days
2002/03	6410	6277	565	3563	3566	24120
2005/06	8432	8179	496	3106	5985	19778

The reductions seen in RA appear to be going against the trend in recent HES data showing a general increase in admission/readmission rates. There are significant limitations to the HES Data but it appears that the number of bed days has reduced in the last few years (see above) which is an area of greatest concern and cost for the NHS. Greater risk of inpatient admission is also related to those with one or more long term condition. As expected there is an increase in day case activity. A more detailed analysis of the coding/activity related to day case may outline rapid response and proactive management of flares of one specific joint as well as attendances for infusions or management of complex co-morbidity issues.

Hospital activity evidence:
Changes in activity in relation to use of hospital services for patients with RA.

a. To explore whether there is coding that will outline activity in relation to RA patients admitted through different medical specialities (particularly cardiology, respiratory, surgical, oncology)
b. Changes to inpatient (reduction in bed days) or outpatient activity in the last five years
c. Evidence with regard to changes in rehabilitation and other additional costly interventions (orthoptist etc)

References:

Dixon W (2008) NHS evidence. Musculoskeletal. What is the relation in 2008 between infection and rheumatoid arthritis (RA)? www.library.nhs.uk

Avalos I, Rho YH;Chung CP;Stein CM (2008) Atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. Clinical and Experimental Rheumatology. 26 (suppl 51) S5 S13

3. Co-morbidities

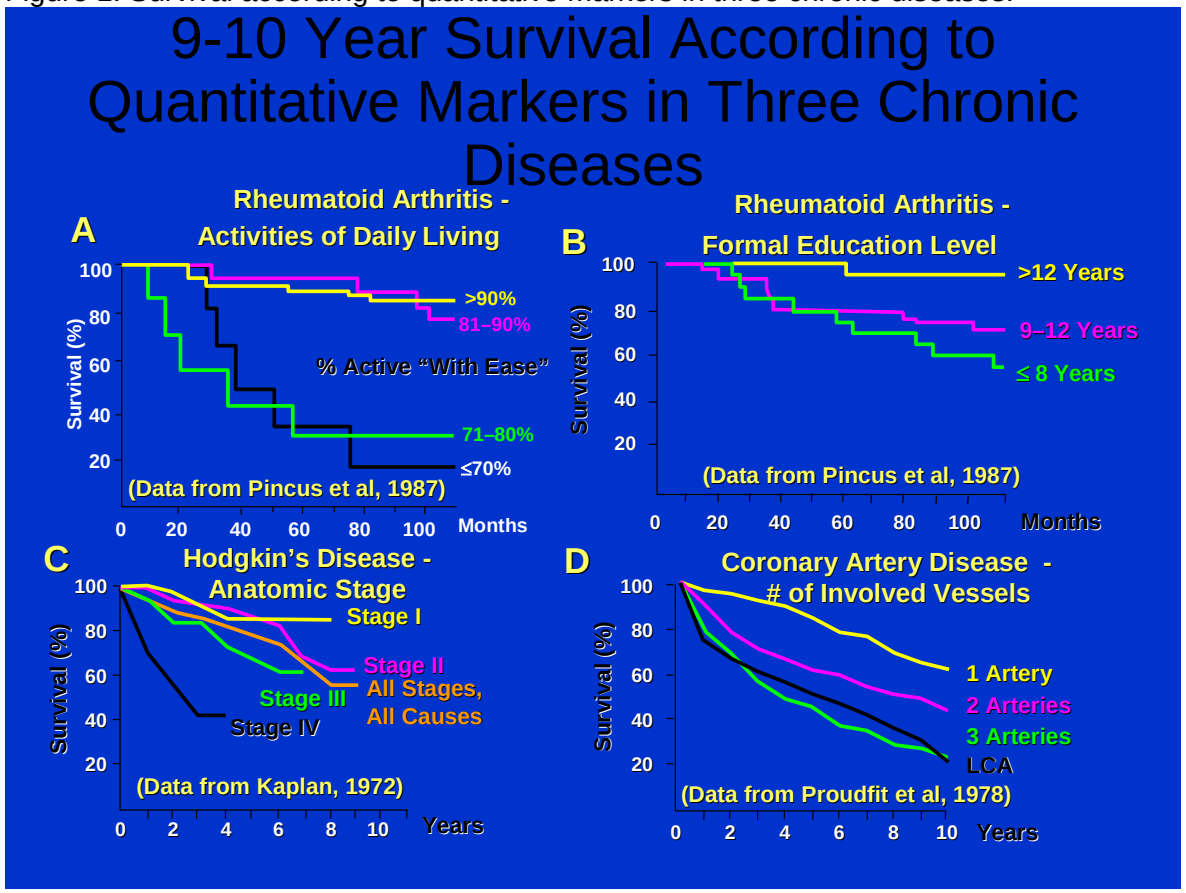
A growing body of evidence has identified that RA confers a twofold risk of cardiovascular disease compared to the general population although the mechanism of this additional risk remains and area of on-going research it appears to be related to the

underlying inflammatory process. (Gabriel, 2008, Sokka et al, 2008) The use of steroids, shown to be beneficial in disease control may contribute to this greater risk. Therefore there is an increasing need to reduce the effects of inflammatory disease as promptly as possible and where possible with limited steroid use particularly in long term use. The costs of RA with cardiovascular disease and depression has been identified in one study (n=10298) in the United States. A general population of RA patients (there we no measures of disease activity or rheumatoid factor) including those with relatively mild disease demonstrated that RA and Cardiovascular Disease (CVD) was present in 5.9% of the population studies and CVD and depression with RA in 0.5% (Joyce et al, 2009). TNF inhibitors are shown to reduce High Density Lipoprotein (HDL) (Popa, et al, 2008)

Co-morbidities evidence
Further evidence in relation to co-morbidities and costs particularly;

a. Cardiovascular disease – clarity about what is the degree of additional risk related to Cardiovascular disease with RA
b. Mortality and morbidity data and any possible changes that might be evident
c. Osteoporosis issues and costs (see NICE guidance re osteoporosis which specifically highlights RA as a risk factor).

Figure 1: Survival according to quantitative markers in three chronic diseases.



Reference: CV Hall and Dalbeath

References:

Joyce et al (2009) Hidden cost of rheumatoid arthritis; estimating cost of comorbid cardiovascular disease and depression among patients with RA.

Sokka, Abelson and Pincus (2008) Mortality in rheumatoid arthritis: 2008 update

Gabriel SE (2008) Why do people with RA still die prematurely? Ann Rheum Dis. 67.(Supp III) iii30-34

Popa C, et al (2009) Anti-inflammatory therapy with tumour necrosis factor alpha inhibitors improves high density lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. Ann Rheum Dis. 68. 868-872

Choy and Sattar (2009) Interpreting lipid levels in the context of high grade inflammatory states with a focus on rheumatoid arthritis; a challenge to conventional cardiovascular risk actions. Ann Rheum Disease; 68 460-469

Abstract from Eular 2008/2009

[FRI0074] PROSPECTIVE STUDY REVEALS RHEUMATOID ARTHRITIS TO BE AN IMPORTANT INDEPENDENT RISK FACTOR FOR INCIDENT CARDIOVASCULAR DISEASE

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Background: It has been established that patients with rheumatoid arthritis (RA) have an increased risk for cardiovascular disease (CVD), possibly comparable to type 2 diabetes. However, these observations have mostly been ascertained in cross-sectional studies, and longitudinal studies are limited in RA.
Objectives: Hence, we compared the incidence of CVD in Dutch RA patients with that in the general population.
Methods: In the 'CARRÉ' study, 3-year incident CVD was studied in a prospective cohort of 353, randomly selected outpatients with RA (diagnosed between 1989 and 2001, aged between 50 and 75 years). Information about CVD was not received from 25 (7.1%) RA patients, because they stopped or had moved from the area. This incidence was compared to the 3-year incidence of CVD in 1852 participants of a population-based cohort study, the 'Hoorn' study. In both studies fatal and non-fatal CVD was defined as ICD codes 798, 410.0-410.9, 8036, 8038, 359.6, and 360. Cox proportional hazards models compared the incidence of CV events in RA to that of the general population. CV-events that occurred during a mean follow-up period of almost 3 years were included.
Results: At least 1 CV-event was reported in 8.6% of the RA patients and in 4.3% of the general population, corresponding with an incidence of 3.14 per 100 patient/years (95%-CI: 1.98-4.30) for RA patients, and 1.51 per 100 person/years (95%-CI: 1.18-1.84) for the general population. Cox regression hazard analyses revealed an age- and gender-adjusted relative risk of 2.01 (95%-CI: 1.30-3.11, p = 0.002) in RA patients relative to the general population (Table 1, model II). Adjustment for CV risk factors, i.e. blood

pressure, anti-hypertensive agents use, total cholesterol, statin use, waist to hip ratio and smoking, slightly attenuated this risk to 1.97 (95%-CI: 1.18-3.29, p = 0.01)(Table 1, Model III).

Cox regression hazard ratios for CVD in RA compared to HS-group

	Odds ratio	95% Confidence Interval	p-value
Model I	2.08	1.35-3.20	p < 0.01
Model II	2.01	1.30-3.11	p < 0.01
Model III	1.97	1.18-3.29	p = 0.01

Model I: crude. II: corrected for age+gender. III: corrected for CV-risk factors.

Conclusion: The risk of incident CVD in RA is significantly elevated compared to the general population, even after adjustment for a higher prevalence of traditional CV risk factors. Therefore, RA itself should be considered an important, permanent, CV risk factor.

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[SAT0148] CARDIOVASCULAR RISK AMONG PATIENT WITH RA IN CORRONA: COMPARING THE EXPLANATORY VALUE OF TRADITIONAL CARDIOVASCULAR RISK FACTORS WITH RA FACTORS

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Background: Background: Controversy surrounds the correlates of cardiovascular outcomes in patients with RA. Several papers have suggested that traditional cardiovascular risk factors (CVRFs) do not adequately explain the increased risk among patients with RA compared with the general population. However, the relative value of these CVRFs compared with RA disease factors (RADFs) is unclear.
Objectives: We undertook this analysis among a very large cohort of patients with RA to assess the explanatory value of these different types of risk factors.

Methods: All data were drawn from the CORRONA registry that contains data on over 14,000 patients with rheumatoid arthritis (RA), as well as several other rheumatic conditions. Patients with at least two visits recorded within CORRONA who had no evidence of psoriatic arthritis were included in the present study. Information on CVRFs and RADFs was drawn from baseline questionnaires. Cardiovascular outcomes included myocardial infarction (MI), stroke and transient ischemic attack reported and then confirmed by the treating rheumatologist. CVRFs included a history of coronary artery disease or MI, diabetes, hypertension, family history of premature MI, body mass index, dyslipidemia (assessed as use of a lipid-lowering agent), race, and current tobacco use. RADFs included duration of RA, RF status, HAQ, clinical disease activity index (CDAI), subcutaneous nodules, Sjogrens, tender jint count, swollen joint count, and total joint replacements. These variables were assessed as predictors of cardiovascular outcomes in separate Cox regression models, with age and gender included in both. Finally, the discriminatory value of these variables was assessed by calculating the area under the receiver operating characteristic curve (C statistic) in logistic regression.
Results: Our study cohort consisted of 10,870 patients with RA followed for a median of 24 months. We observed 75 MIs or strokes during follow-up for a composite event rate of 3.27 per 1,000 patient-years. In multivariable Cox regression models, the CVRFs with increased relative risks included race (RR 1.26), BMI (RR 1.25), prior MI (RR 1.75), and tobacco use (RR 1.92). The RADFs with increased relative risks were subcutaneous nodules (RR 1.44), HAQ-DI (RR 1.20) and the CDAI (RR 1.06). The c-statistic in logistic models adjusting only for age and gender was 0.69. The c-statistics of the CVRF model (including age and gender) was 0.75. The c-statistic of the RADF model was also 0.75. When all of the above variables are place in the same model, the c-statistic was 0.80.
Conclusion: RA disease factors appear to have a similar explanatory value as do cardiovascular risk factors in explaining cardiovascular endpoints. Developing more robust clinical prediction rules for cardiovascular outcomes in RA may allow for targeting specific therapies.

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4. Treating early – the future. When to stop treatment

The changes in treatment approaches with rapid access to combination therapy will mean patients will come to biologic therapies with less functional changes and potentially less co-morbidities/use of steroids for their first TNF inhibitor. Outcomes appear to be greater when patients have received methotrexate promptly before levels of disability have substantially changed (Kristensen et al, 2008). Following failure of the first TNF inhibitor subsequent treatments may be required less often This will impact upon the long term costs and benefits with potentially lower HAQ scores (and possibly improved Quality of Life indices) when being treated with a further biologic.

Treating early evidence:

a. Exploring the potential benefits of biologic therapies following aggressive treatment approaches delivered to target
b. BSRBR data – consideration should be made based upon the time frame for evaluating benefit from the registry (e.g. 6 months review rather than 3 month reviews).

References:

Kristensen et al (2008) Predictors of response to anti-TNF therapy according to ACR and Eular criteria in patients with established RA; results from the South Swedish Arthritis Treatment Group Register. Rheumatology. 47, 495-499

Kievit W; Fransen et al (2009) Evaluating Guidelines of continuation of anti-TNF treatment after three months; clinical effectiveness and costs of observed care and different alternative strategies. Ann Rheum Dis. 68: 844-849

Hyrich et al (2007) Outcomes after switching from one anti-tumour necrosis factor agent to a second anti-tumour necrosis factor agent in patients with rheumatoid arthritis. Arthritis and rheumatism. Vol 56. No 1. p 13-20

Pocock JM, vasconcelos JC and AJK Ostor (2008) Assessment of anti-TNF a efficacy in rheumatoid arthritis; is 3 months sufficient? Rheumatology. Advance access published May 25.

Abstract presented at the Eular meeting 2008/2009

[SAT0147] MORE ACTIVE TREATMENT APPROACH HAS PROFOUND EFFECTS ON THE LONG TERM DISEASE COURSE AND HEALTH STATUS OF RA PATIENTS. RESULTS FROM THE MALMÖ (SWEDEN) POPULATION-BASED RA COHORT 1997-2005

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Background: Pharmacological treatment for rheumatoid arthritis (RA) has during the last decade moved towards earlier and more

active treatment with a treatment aim of remission.
Objectives: To study trends in health status and antirheumatic treatment in a population-based register of RA patients in Malmö in southern Sweden 1997-2005.
Methods: A continuously updated population-based RA register was established in Malmö city in southern Sweden in 1997. Questionnaires sent to patients in the register in 1997, 2002 and 2005 were used to collect information on demographics, medication, and health status with response rates of 65-70%. Cross-sectional comparisons were made in 1997, 2002 and 2005 for patients answering the HAQ.
Results: 724 patients answered the HAQ in 1997, 594 in 2002, and 1024 in 2005. The proportion receiving DMARDs (52% in 1997 vs. 88% in 2005), methotrexate (24% vs. 52%) and biologics (0% vs. 20%) increased continuously between 1997 and 2005 whereas the proportion receiving corticosteroids (23 vs. 24%) was stable. In parallel, health status improved as evaluated by mean HAQ (1.2 in 1997 vs. 0.9 in 2005). All SF-36 (Short Form 36) subscales improved 1997-2005. The largest improvements 1997 vs. 2005 were seen in mean SF-36 physical function subscale (mean 1997 46 vs. mean 2005 56), SF-36 bodily pain subscale (43 vs. 51), SF-36 role physical (40 vs. 48) and SF-36 role emotional subscale (57 vs. 64). Age, sex and disease duration were similar at all three cross-sectional evaluation points (1997-2002-2005).
Conclusion: In a population-based setting, health status 1997-2005 improved in parallel with more active pharmacological treatment with DMARDs, methotrexate and biologics. More active treatment approach has profound effects on the long term disease course and health status of the RA patients
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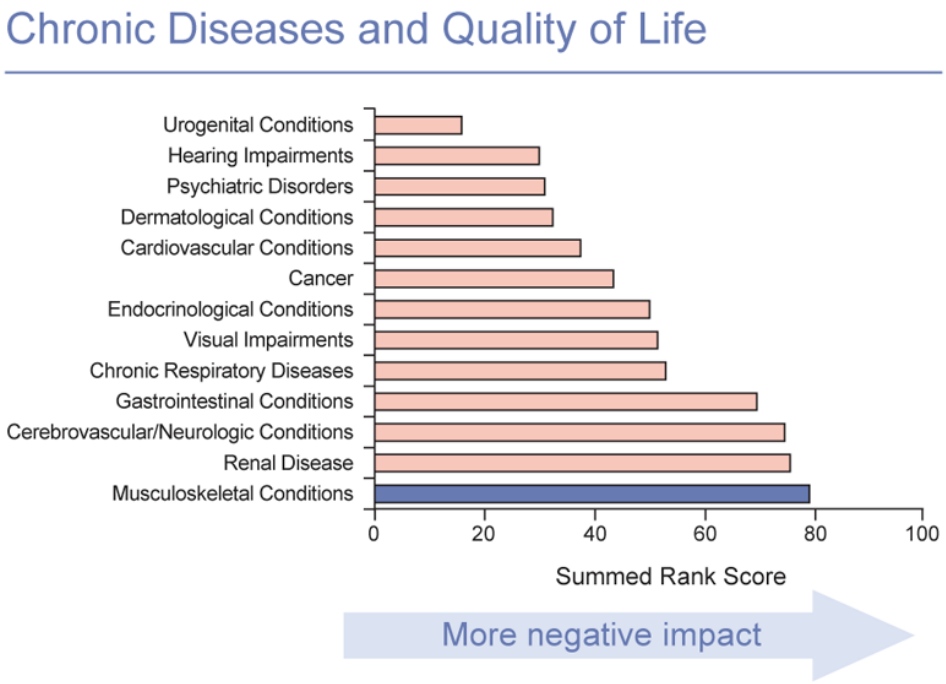
5. Evaluation using outcome measures. Functional and quality of life.

Sokka and Hakkinen (2008) review evidence of physical fitness and predictors of mortality in normal populations and patients with rheumatic and other diseases and highlight the added cardiovascular risks that poor physical function add to those with RA.

a. It is pivotal that the relationship between different levels of HAQ is correlated with Quality of Life (QoL) measures such as the Euroquol. What is the minimally clinically important difference in HAQ changes that has a positive impact on the individual's ability to lead an independent, productive and acceptable life? One study has shown that there is poor correlation between these measures indicating that patients' quality of life may have improved yet their long term joint damage remains unchanged (Scott et al, 2007).
b. What is the primary care cost for routine monitoring, attendance at clinics for pain relief and re –referral (the common route now for many who do not access to Follow Up appointments without being re-referred)
c. Musculoskeletal conditions as evaluated by the SF36 compared less favourable in QoL than other LTC.

d. Patients who have pain and active disease have an increased risk of developing depression.

Table – evidence from www.medicines.ox.ac.uk /bandolier



Reference: A. Moore, Peer Review Press, 2008 source: Bandolier. www.medicine.ox.ac.uk/bandolier

References:

Scott DL et al (2007) Limited correlation between the HAQ and EuroQol in RA; questionable validity of deriving quality adjusted life years from HAQ. Ann Rheumatic Diseases 66; 1534-37

Sokka and Hakkinen (2008) Poor physical fitness and performance as predictors of mortality in normal populations and patients with rheumatic diseases. Clinical and experimental rheumatology. 26. (suppl 51) S14-20

Abstracts from Eular 2008/2009

FRI0141] CERTOLIZUMAB PEGOL (CZP) INDUCES RAPID AND SUSTAINED CLINICALLY MEANINGFUL IMPROVEMENTS IN PHYSICAL FUNCTION AND HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA): THE RAPID 1 AND 2 RANDOMISED CLINICAL TRIALS (RCTS)

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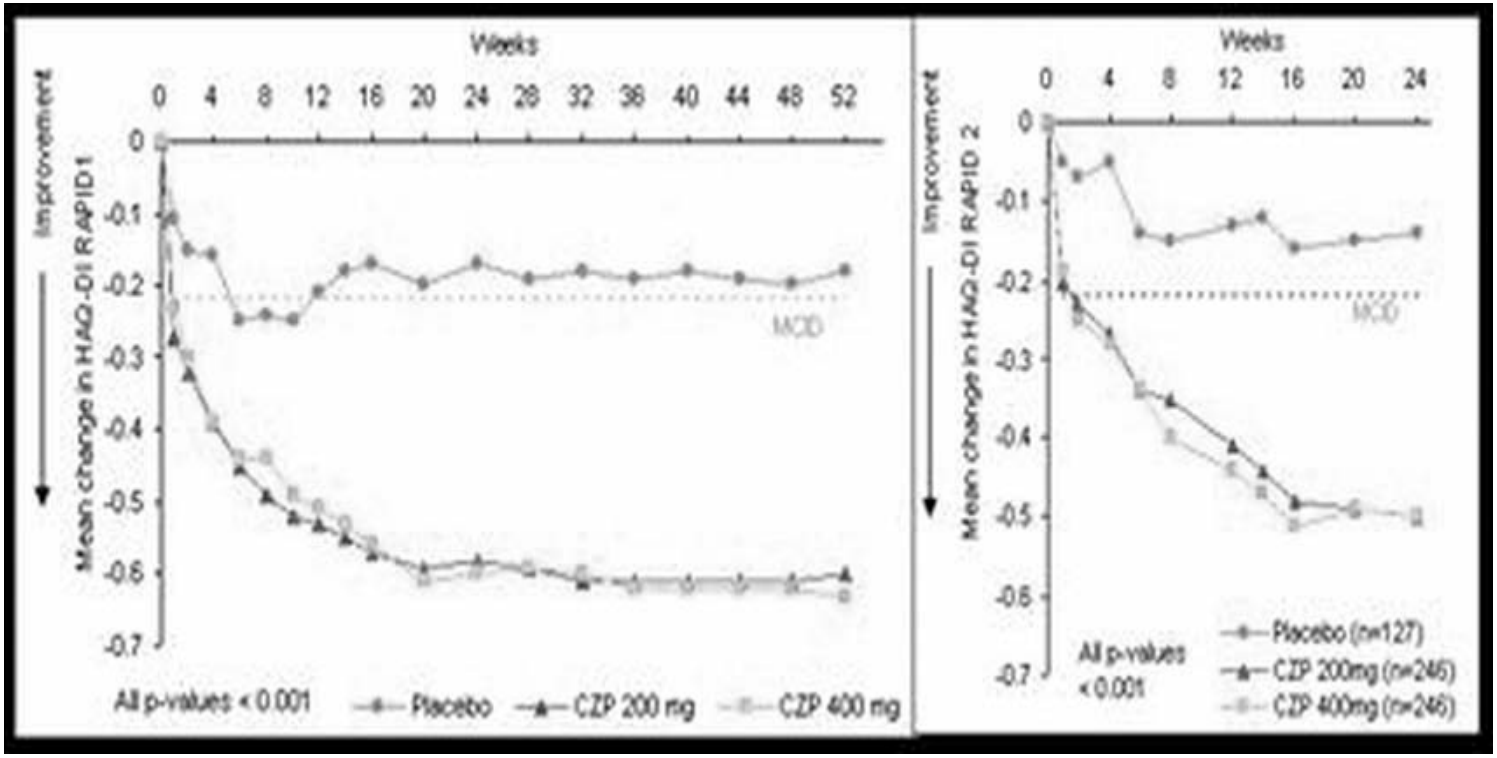
Background: CZP, the first PEGylated anti-TNF Fab' fragment, has been shown to significantly improve physical function and HRQoL in patients with active RA in 2 phase III RCTs.(1)
Objectives: To assess the kinetics of achievement of clinically meaningful differences in physical function and HRQoL after treatment with CZP.
Methods: RAPID 1 and 2 were phase III RCTs which assessed the efficacy and safety of CZP (400 mg at Weeks 0, 2 and 4, followed by 200 mg or 400 mg every 2 weeks) or placebo, added to stable-dose MTX in patients with RA for 24 weeks (RAPID 2) or 52 weeks (RAPID 1). Physical function was assessed by the Health Assessment Questionnaire-Disability Index (HAQ) and HRQoL by Short Form-36 Health Survey (SF-36). Adjusted mean changes from baseline (BL) were analyzed using ANCOVA with LOCF imputation. Minimum Clinically Important Differences (MCID) were defined as ≥ 0.22 for the HAQ and ≥ 2.5 for the SF-36 Physical and Mental Component Summary scores (PCS, MCS).
Results: 982 and 619 patients were randomised in RAPID 1 and 2, respectively. As early as Weeks 1 or 2 until endpoint in both RCTs, adjusted mean changes from BL in HAQ in patients treated with CZP were significantly different compared to placebo ($p<0.001$) and exceeded the MCID threshold (figure). After 52 weeks of CZP treatment in RAPID 1, 83% (200mg) and 86% (400mg) of those patients remaining on treatment with non-missing data had improvements in HAQ ≥ MCID; 90.3% (200mg) and 78.9% (400mg) at 24 weeks in RAPID 2. From the first assessment (Week 12) until endpoint in both RCTs, adjusted mean changes from BL in SF-36 PCS and MCS scores in patients receiving CZP at both doses were significantly different compared to placebo ($p<0.001$) and exceeded the MCID threshold.



Conclusion: In patients with active RA, CZP 200 mg or 400 mg every 2 weeks with MTX results in clinically meaningful improvements in physical function by Week 2 and HRQoL as early as at the first assessment at Week 12. Improvements in both patient reported outcomes were sustained for up to 1 year, regardless of dose regimen.

References: 1 Strand et al. Poster presented at the American College of Rheumatology (ACR) 71st Annual Meeting; November 6-11, 2007; Boston, Massachusetts.

Ann Rheum Dis 2008;67(Suppl II):331

[FRI0117] THE EFFECT OF ANTI-TNF THERAPY ON FUNCTION AND QUALITY OF LIFE IN PORTUGAL

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Background: Rheumatoid Arthritis (RA) is a chronic and debilitating disease that affects function and quality of life. No former study has ever been undertaken in Portugal to evaluate the effect of anti-TNF therapy on these outcomes.
Objectives: To study the effect of anti-TNF therapy on function and quality of life in Portuguese rheumatoid arthritis patients.
Methods: 1044 RA patients have been participating in a semi-annual on-going longitudinal study (NDB-Portugal) since 2003. Several aspects of their disease, such as medication socio-demographic and clinical characteristics, including pain, function and quality of life measures have been collected. Generalized estimating equations were used to univariately and then multivariately determine whether anti-TNF therapy affects function (measured by HAQ) and quality of life [measured by EuroQoL and by the SF-36 Physical component scale (PCS) and mental component scale (MCS)], adjusting for potential confounders. Predictor variables were 6 month-lagged to reflect prior clinical and drug history
Results: Table 1 shows the results of the final multivariate GEE models for HAQ and EuroQoL. Aside from the significant predictors, other covariates were included in the models but not shown because of non-significance, such as age and marital status. HAQ improvement was noted in those treated with biologics, but did not reach statistical significance. Furthermore, males and higher educational level predicts better functional and quality of life scores. We included steroid use in the models but these also showed little effect on HAQ and quality of life.

Table 1

Variables	Multivariate HAQ β (95%CI)	Multivariate EUROQOL β (95%CI)
Biologics	-0.08 (-0.21, 0.04)	0.01 (-0.05, 0.06)
Prednisone use	0.09 (0.00, 0.19)	-0.06 (-0.11, -0.01)
Sex (males vs. females	-0.37 (-0.52, -0.23)	0.09 (0.04, 0.15)
Educational level (>12 vs. reference: 0-3)	-0.61 (-0.84, -0.38)	0.20 (0.11, 0.30)
Disease duration (years)	0.01 (0.01,0.02)	0.00 (0.00, 0.00)
Total lifetime comorbidity score	0.04 (0.02, 0.07)	-0.05 (-0.07, -0.03)

Conclusion: Anti-TNFs as well as male sex and higher educational levels improve function and quality of life among RA patients in Portugal.

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Date: Friday, June 13, 2008
Session Info: RA – Anti-TNF therapy

[FRI0135] INFLUENCE OF AGE ON THE OUTCOME OF ANTI-TNF-ALPHA THERAPY IN RHEUMATOID ARTHRITIS

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Background: Elderly patients represent an increasing proportion of the rheumatoid arthritis (RA) patient population. Physiological changes related to aging might decrease the effectiveness of anti-TNFalpha treatment in the elderly RA patient. It is unclear whether this indeed occurs, and how large the effect of age would be.
Objectives: To investigate the influence of age on the effectiveness and tolerance of anti-TNFalpha therapy in a prospective observational cohort of RA patients during the first year of anti-TNFa treatment.
Methods: The DREAM (Dutch Rheumatoid Arthritis Monitoring) Register, started in February 2003, was used for analysis. In total, 607 patients were categorized into three groups according to their age at the initiation of anti-TNFalpha therapy: 130 aged under 45 years, 318 aged between 45-65 years and 159 patients older than 65. Effectiveness was analyzed after 12 months of anti-TNFalpha therapy using the DAS28, the improvement in DAS28, the EULAR criteria for clinical response and remission, improvement in functional capacity (HAQ) and health-related quality of life outcomes (SF-36). Tolerance of anti-TNFalpha was investigated by drug survival analysis and Cox proportional hazard methods. Treatment decisions after the cessation of anti-TNFalpha therapy were analyzed.
Results: Elderly patients had higher DAS28 at baseline then younger patients (5.59 vs. 5.29 and 5.13, $p<0.005$). Improvement in disease activity and physical functioning was significantly less in elderly patients, corrected for baseline variables and confounders. Elderly patients reached the EULAR categories of good-responders (19% vs. 28% and 39%, $p<0.005$) and remission (9% vs. 19% and 30%, $p<0.005$) less often than younger patients. Drug survival, co-medication use and tolerance were comparable between the 3 age

groups. Following the discontinuation of the first anti-TNFa agent, significantly less elderly patients received new DMARD therapy or a second anti-TNFalpha agent when compared to younger ones.
Conclusion: Despite comparable tolerance and co-medication use as in younger patients, anti-TNFalpha therapy appeared to be less effective in elderly RA patients. High baseline disease activity and less aggressive pharmacotherapy after stopping anti-TNFalpha treatment suggest a conservative approach for elderly RA patients that may be improved.

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[FRI0082] HEALTH-RELATED QUALITY OF LIFE IN ITALIAN PATIENTS WITH RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS, AND PSORIATIC ARTHRITIS: A COMPARISON WITH THE GENERAL POPULATION

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Background: Consideration of health-related quality of life (HRQOL) has become increasingly important in decisions regarding resource allocation, intervention design, and treatment of individuals with chronic disease. HRQOL is most often recognized as an individual's perception of his or her own health that can clearly and directly affect physical or mental health. Thus, HRQOL is predictive of morbidity and mortality.
Objectives: To compare the health-related quality of life (HRQL) score between patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) and the general population.
Methods: Of the 1121 patients with chronic inflammatory rheumatic diseases (IRD) invited to undergo a complete medical history, a careful clinical examination and radiological evaluation, 799 patients (71.3%) (469 with RA, 164 with SA, 65 with axial PsA and 101 with peripheral PsA) accepted the invitation to participate by completing the questionnaires and the physical and radiological evaluation. For comparison were used 1579 healthy controls. The HRQL was evaluated with a validated Italian version of the Medical Outcome Study Short-Term 36 (SF-36), using physical (PCS) and mental (MCS) component summary scales. Comparison were performed with respect to sex and age, and standardized difference scores (s-scores) were calculated for comparison with the norm.
Results: The four rheumatic disease groups, compared to controls, significantly impaired all eight health concepts of the SF-36 ($p<0.0001$) in both component summary scores (PCS and MCS) ($p<0.0001$). Overall, the dimensions typically affected by chronic IRD were physical functioning, limitations due to physical function, and bodily pain. The SF-36 scores decreased (indicating a linear decline in HRQL), especially in the physical dimension, with increasing age in all categories of IRD. The disease with the worst HRQL for those dimensions was RA. The mean PCS score of RA patients was 32.5 (SD = 5.9), approximately two standard

deviations below the mean observed in the Italian general population. Significant differences were found between men and women only in AS group concerning role limitations due to physical function (p=0.011), and for general health (p=0.031), with women reporting worse health than men. Regarding the HRQL dimensions involving mental health problems, patients with PsA (both peripheral and axial PsA) score generally lower than the controls. In patients with AS the physical domain due to role function-physical aspect and bodily pain is more impaired than the mental one.
Conclusion: Chronic IRD conditions have a clearly detrimental effect on the HRQL in both sex and in age groups, and physical domain is more impaired than mental and social ones. The SF-36 may be used as generic instrument to measure HRQL. Longitudinal studies are, also, needed to examine how these quality of life measures change over time and respond to clinical and public health interventions.

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SAT0461] UTILITY AND QUALITY OF LIFE ANALYSIS: CONSIDERATIONS ON TREATMENT GOALS IN RHEUMATOID ARTHRITIS

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Background: In rheumatoid arthritis (RA), ambitious treatment strategies call for aggressive reduction of the inflammatory disease load, but it is unclear whether the aim of therapy should be remission or the mere presence of low disease activity suffices.
Objectives: To assess the value of achieving remission, as compared to low disease activity, from a patient-based utility analysis.
Methods: We retrieved data from an observational database of RA outpatients. Differences in utility scores between groups of disease activity were assessed in a Generalized Linear Model (GLM). For the main analysis, we identified patients who had achieved low disease activity and subsequently remission (CDAI≤2.8) during therapy, after an initial moderate disease activity state (CDAI≥10). We ascertained corresponding HAQ values in the course of these visits. From these we derived utility scores (transformation from HAQ to the Health Utility Index-3, HUI-3 1) and quality of life scores (QoL2). We assessed the changes in these indicators from moderate disease activity (MDA), to (LDA) and subsequent remission (REM).
Results: GLM was performed using data from 1106 patients (9287 visits). The analyses revealed significant differences of HAQ and HAQ-derived utility-scores between each group of disease activity (p<0.01). We then identified 67 patients (75.8% female, 60.7% seropositive) who had experienced a stepwise improvement during therapy from MDA to LDA and remission. The average time of observation analysed was 3.2 years. CDAI decreased from 15.7±5.9 (MDA) to 5.2±2.1 (LDA) and 0.8±0.9 (remission). The corresponding difference in HAQ was significant for the comparison of MDA-visits vs. remission-visits (p<0.01), aswell as for MDA compared to LDA visits (p=0.03). These changes implicate an increase in utility (HUI III, 0-1 scale) from 0.6±0.2 in MDA to 0.7±0.1 in

remission (p=0.01, Tab. 2).
The improvement from MDA to low disease activity resulted in significant amelioration of HUI III and QoL, as did the improvement from MDA to remission. Comparing utilities between LDA and remission did not show significant differences, although there was a trend for improvement (p=0.098).

Table 1. Improvement of HUI III and QoL when ameliorating from medium disease

	MDA	LDA	REM	p-value		
				MDA→LDA	MDA→REM	LDA→REM
QoL	0.57±0.21	0.70±0.15	0.74±0.15	0.014	0.001	n.s.
HUI III	0.57±0.18	0.68±0.13	0.72±0.13	0.014	0.001	n.s.

Conclusion: HAQ based evaluation of utility and quality of life in patients with RA indicates that there is a significant difference between moderate disease activity and remission, and even between moderate and low disease activity state. Only a trend toward better utility scores emerged when low disease activity and remission were compared. Nevertheless, although the differences were small, costs accumulate over time, and the high p-value related to achievement of remission implies the importance of aiming therapy at remission.
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OP-0095] FATIGUE REDUCTION AND PHYSICAL FUNCTION IMPROVEMENTS ASSOCIATED WITH INCREASED PRODUCTIVITY AT WORK AND AT HOME IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) patients experience fatigue and decreased physical function which significantly impact their everyday lives. This affects their ability to carry out paid work and household activities and is thus associated with substantial economic costs. The extent to which fatigue or impaired physical function influence productivity is poorly understood. Certolizumab pegol (CZP), the first PEGylated, Fc-free anti-TNF, reduces RA signs and symptoms and also improves physical function and reduces fatigue.
Objectives: To quantify the change in work productivity within and outside the home associated with meaningful improvements in physical function or reduction of fatigue in RA patients treated with CZP.
Methods: Physical function and fatigue were assessed in the RAPID 1 and 2 trials using the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the Fatigue Assessment Scale (FAS), respectively. Clinically meaningful improvement in HAQ-DI was ≥0.22 points (1) and for FAS was ≥1.0 point.(2) Productivity within and outside the home was evaluated with the Work Productivity Survey (WPS-RA). Improvements in productivity were compared between responders and non-responders at wk 12, irrespective of treatment assignment, using a non-parametric bootstrap-t method.
Results: For patients employed outside home, meaningful improvement in physical function was associated with a decrease in absenteeism; responders gained 1.95 ($p \leq 0.05$) and 0.58 (NS) additional work days/month compared to nonresponders. Physical function improvements were also associated with a decrease in presenteeism, a reduction of 3.26 to 4.50 work days/month with low productivity was observed in responders compared to nonresponders ($p \leq 0.05$). Meaningful reduction in fatigue in employed patients was related to a decrease of 2.68 (NS) to 3.37 ($p \leq 0.05$) work days/month with low productivity compared to non-responders. For all patients (regardless of employment status), meaningful improvement in physical function was associated with a gain of 2.11 to 4.74 additional household work days/month ($p \leq 0.05$) and a decrease of 1.89 to 3.40 household work days/month with low productivity compared to nonresponders ($p \leq 0.05$). Meaningful reduction in fatigue was related to a gain of 2.41 to 3.16 additional household work days/month ($p \leq 0.05$) and a decrease of 3.59 to 3.69 household work days/month with low productivity compared to nonresponders ($p \leq 0.05$).

Difference in productivity improvement at week 12

Difference in days/mo (resp vs non-resp)	HAQ-DI		FAS	
	RAPID1	RAPID2	RAPID1	RAPID2
Employed patients (n)	(190)	(218)	(190)	(218)
# work days gained	1.95*	0.58	-0.85	-0.41
# work days -reduced productivity	-3.26*	-4.50*	-2.68	-3.37*

All patients (n)	(449)	(560)	(449)	(560)
# household work days gained	4.74*	2.11*	3.16*	2.41*
# household work days -reduced productivity	-3.40*	-1.89*	-3.59*	-3.69*

*p<0.05.

Conclusion: Meaningful reduction in fatigue in RA patients was associated with improved work productivity at home, whereas physical function improvements were associated with increased productivity both at work and at home.
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6. Evaluation of assessment tools. The Disease Activity Assessment:

The DAS 28 has some limitations but also can be considered an important tool that includes patient reported aspects (global health) and observed actively swollen joints together with tenderness on palpation or movement. It has been shown to be a useful tool to guide the targeted management of RA as advocated in NICE RA management guidelines (2009) and used as components of assessment is valuable and vital tool. It does have to be considered in the round with consideration to the strengths and weaknesses of such a tool. There appears to be some uncertainty in small study (n=511)exploring the DAS-ESR against the DAS-CRP that there was variability in the discrimination of patients with low Disease activity using the DAS-ESR and there was larger fluctuations in the relationship between the two scores at lower end of the scale showing there many be some inherent uncertainties at the lower values of DAS28 (Taylor et al, 2008) We would advocate clarity for future assessment processes that the DAS28-CRP should be recommended to ensure clarity and consistency for future evidence.

Efficacy review time frames of the DAS

Original evidence for the first TNF appraisal considered data from the BSRBR. This data was based upon patients being assessed every three months for eligibility to stay on TNF therapy. Hyrich et al (2007) states the slightly more than one-third of patients discontinued their primary anti-TNFa therapy during the follow up period. This cessation of treatment requires further analysis – e.g. of the 60% who discontinued due to inefficacy were evaluated at the specified 3 month time frame and discontinued due to lack of efficacy at this time point ? In the last two to three years evidence has grown to confirm that the most effective period to review

efficacy is six months. It is noted in a recent prepared paper by the BSRBR (Hyrich updated analysis 2009).That the number of patients that were determined by 6 months was 86% (although this probably still includes patients who were stopped due to inefficacy at the 3 months evaluation time frame). Hyrich does note that that patient who continued treatment and were classified as non responders continued to show improvements in their HAQ score of the following 12 months.

It will be important that evidence reviewed takes into account the different review time frames, longer disease duration of this patient group and number of failed DMARD (having more sustained long term disease).

The other component to consider in this review is the number of patients receiving concomitant DMARD – shown to enhance efficacy of the TNF.

a. Recognition of the limitations in relation to the DAS 28 that was not specifically designed to measure criteria in relation to eligibility and cessation of treatment. The fact that for some patients the DAS will fail to reflect the reason for the clinicians' decision to treat – for example frequent use of high dose steroids, systemic or specific organ damage related to the RA.
b. Clarification of how patients who fail DAS 28 Criteria but have active systemic disease (such as rheumatoid lung) are to be considered. We would hope that exception reporting will not be the route we will have to use regularly to negotiate with PCTs as the additional paperwork and time taken with such negotiations results inequity of care across the country.
c. ESR or CRP blood test to support DAS scores
d. The DAS was historically calculated using the ESR. In recent years the DAS 28 has been validated to use CRP rather than ESR. This is another area for the appraisal committee to review and consider particularly as ESR may be raised for a number of other non disease activity related issues. A sub-analysis of those assessed using an ESR DAS versus the CRP DAS are different or demonstrated difference in treatment response (Taylor et al, 2008). .

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Abstracts from Eular 2008/2009

THU0158] PATIENTS WITH MODERATE RHEUMATOID ARTHRITIS ACHIEVE BETTER DISEASE ACTIVITY STATES WITH ETANERCEPT TREATMENT THAN PATIENTS WITH SEVERE RHEUMATOID ARTHRITIS

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Background: Patients (pts) with rheumatoid arthritis (RA) in clinical trials typically have severe disease activity, yet most pts in clinical practice have more moderate disease.
Objectives: To examine clinical and radiographic responses to methotrexate (MTX), etanercept (ETN), and combination ETN and MTX in pts with moderate vs severe RA in early and late disease.
Methods: Data from TEMPO (3 treatment arms) and ERA (2 treatment arms) trials were analyzed. Pts were classified by DAS28 with moderate (>3.2 and ≤5.1) or severe (>5.1) RA. Outcomes included DAS28 remission (<2.6), DAS28 low disease activity (≤3.2), Total Sharp Score (TSS) progression, no radiographic progression (annualized change in TSS <0.5 and ≤0), HAQ score, ACR scores, change from baseline in TSS, and change in TSS for pts with radiographic progression (TSS >0) at months 6 and 12.
Results: The analyses included 41 and 636 pts with moderate and severe disease, respectively, from TEMPO and 65 and 349 pts, respectively, from ERA. In all treatment arms, more pts with moderate disease achieved DAS28 remission than pts with severe disease (Table). Similar results were seen in all treatment arms for low disease activity: 12 months of treatment resulted in DAS28 low disease activity in 68% and 36% of pts with moderate and severe disease, respectively, in TEMPO and 55% and 27% of pts in ERA (P<0.05 for each). Differences in DAS28 low disease activity were significant in each treatment group at months 6 and 12, with the exception of the ETN group in TEMPO. While ACR 20 and 50 responses were generally numerically greater in the severe disease group, ACR 70 responses were significantly greater in the moderate vs the severe group in the combination treatment arm only (71% vs 33% at 6 months and 65% vs 40% at 12 months; P<0.05 for both). A greater percentage of pts with moderate than severe disease had a HAQ score ≤0.5, although not all treatment groups showed statistically significant differences. Pts with severe disease activity, while not achieving a better disease state, had greater changes from baseline in DAS28 and HAQ scores. No significant differences emerged between pts with moderate vs severe disease activity in terms of radiographic outcomes, although progression of TSS changes tended to be greater for severe vs moderate pts.

Percentage of Patients in DAS28 Remission at 12 Months

	TEMPO Moderate	TEMPO Severe	ERA Moderate	ERA Severe
MTX	44	15*	33	15*
ETN	38	17	47	14*
ETN+MTX	77	35*		
Total	56	22*	40	14*

*P<0.05 moderate vs severe.

Conclusion: Treatment with high-dose MTX and/or ETN resulted in greater improvements in clinical efficacy measures in pts with severe disease activity; however, more pts with moderate RA achieved a lower disease activity state.
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7. Treatment options in biologic therapies

The option to have clarity about the treatment options for those who fail their first TNF inhibitor is essential. As part of this issue it is also essential that nurses ensure that patients are adequately assessed and screened as well as preparing the patient psychological for their new treatment. We feel there are opportunities to further develop a strong patient centred approach that enhances the patients' ability to sustain positive outcomes, including more positive health seeking behaviours, return to social participation (including work activities) and realistic expectations of their treatment. The first step in this approach has to be a clear and transparent pathway of effective treatments. Working with our primary care colleagues we can optimise patient expectations in the early stages of their disease and consider the global needs of the patient as outlined in the NICE RA management guidelines. With these factors in mind it is essential that we have treatments that are effective and enable joint destruction to be kept at bay. We do not wish to treat sub optimally and watch as the visible signs of joint destruction appear whilst the individual faces the erosion of their personal independence, social benefits of work, family and carer activities.

There are a number of treatments being considered in this multiple technology appraisal and each has its own individual merits for patients. Yet we recognise it is difficult to predict which therapy will be the best first or even second option for anyone patient.

a. Abatacept. This therapy is unique in its therapeutic target and to date clinicians have had virtually no clinical experience because of the cost effective nature in the negative appraisal. We would welcome an opportunity to have this therapeutic target to be available in some way to patients – particularly as the international evidence on effectiveness continues to grow and appear very favourable to improving long term outcomes. The time frame for efficacy appears to continue over time.
b. TNF inhibitors. The evidence continues to support the benefits of these therapies, including radiological and safety data. The evidence also from the BSRBR needs to consider the numbers of patients who were not prescribing concomitant therapy and who had long standing disease, and were assessed for efficacy at 3 rather than the current 6 months. The new generation of TNF inhibitors will add to the options for patients.
c. Rituximab. Rituximab is an excellent drug that provides immense benefit to many patients and has the advantage of less frequent treatments. However it needs to be clarified what is the repeat time frame and what will be the re-treatment criteria. We would also welcome evidence that can dispute or support the issue related sero-negative treatment benefits as this will have implications for some patients and their options in the treatment pathway. .
d. Tocilizumab has a new therapeutic target and early evidence appears promising. As for Abatacept it is vital that we gain sound clinical knowledge of these therapies with robust assessment and treatment criteria to be able to adequately review the benefits to patients in daily clinical practice.

References in relation to this section have not been submitted as they are being submitted by the BSR and also the individual companies.

In conclusion

We welcome this whole pathway approach to review the treatment options for patients with RA. It is imperative that sufficient evidence is sought to ascertain the wider costs and longer term costs of RA as outlined for example in the National Audit Office Report (2009).

It would be helpful if the appraisal committee would enhance their usual approach to provide patient information on the guidance to include a simple visual flow chart for patients who will need real clarity about access to therapies when their treatments have failed.

Nurses are actively involved in the assessment, management and administration of biologic therapies. Over the last seven or eight years we have seen significant benefits to patients lives as a result of biologic therapies including reduction in pain, fatigue, sleep, joint changes as well as improvements in quality of life, social participation and the self esteem of the individuals who have received

these therapies, particularly those that have been proactively managed based upon a targeted approach. This approach is advocated in the NICE RA management guidelines and rewards of this approach will continue to be capitalised upon with less patients failing treatment and be left to languish on sub-optimal treatment. We recognise the physical components of this assessment are significant and vital. However, the final word must go to the social and psychological implications that have the strong potential to change the patient from the proactive self managing person with a positive view about improving their general health, contributing in society and looking forward to a future of reasonable health to somebody who becomes hopeless and helpless, with the effects of poor disease control resulting in the double jeopardy of RA, co-morbidities and physical decline.. Not only will the patient have the disabling disease contributing to increasing risks related to morbidity and mortality but also the financial burden of job losses and resulting in depression poor health behaviours (lack of exercise, poor diet, social isolation).

Nurses would welcome the opportunity to continue a rigorous assessment and review process provided that this enables us to provide education and support to patients based upon a transparent and equitable approach that will be applied to all patients in England and Wales.

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