Etanercept, infliximab and adalimumab for the treatment of rheumatoid arthritis (including a review of existing guidance no.36)

Joint submission to the National Institute for Health and Clinical Excellence by:

- Arthritis Care
- Arthritis Research Campaign
- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing Rheumatology Forum

Under the auspices of the Arthritis and Musculoskeletal Alliance

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Executive Summary

This joint submission by ARMA, Arthritis Care, ARC, BHPR, BSR, NRAS, PCR and the RCNRF outlines the main issues of concern to both people with rheumatoid arthritis (RA) and the health professionals treating them in relation to TNF-α inhibitors. This approach reflects our shared belief that the best management of RA is achieved through a partnership between people with RA and the people who treat them.

Our submission draws on recent research, clinical evidence and the experience of people with RA to outline the impact of RA on the individual and health services. It describes the impact of the introduction of TNF-α inhibitors and notes the changes in evidence and experience since NICE’s original guidance was issued in 2002.

There are a number of key issues and concerns shared by people with RA and health professionals, which we believe must be considered by NICE as it reviews TNF-α inhibitors.

The impact of the introduction of TNF-α inhibitors on people with RA, clinical practice and health services has been significant and extremely positive. In summary, the key impacts are:

- TNF-α inhibitors have proved to be very effective in treating severe RA.
- Studies show that TNF-α inhibitors are a cost-effective method of treating RA.
- Clinical experience in the NHS has reflected favourable efficacy and safety data from clinical trials.
- TNF-α inhibitors have been shown to work more quickly than traditional DMARDs.
- In short, the introduction of TNF-α inhibitors has improved the lives of thousands of people in England and Wales, and has had a positive impact on health service provision.

Research and clinical practice since the NICE guidance of 2002 have shown that TNF-α inhibitors are more effective than previously predicted.

- Studies have shown that people with RA who fail to respond to one TNF-α inhibitor often respond to another.
- In some people with RA and co-morbidity it may be appropriate to use a TNF-α inhibitor prior to the failure of two DMARDs.
- Significant advantages have been shown in the use of combination therapies which include a TNF-α inhibitor in the treatment of early RA.

We believe that people should continue to have access to TNF-α inhibitors on a basis of clinical need. In addition we ask that NICE guidance be amended in accordance with the BSR guidelines, in particular to reflect:

- Where one TNF-α inhibitor fails, patients should be able to try another.
- The NICE guidance should be amended to include adalimumab.
- In some circumstances a TNF-α inhibitor should be considered in the treatment of early RA.
Consensus Statement

Rheumatoid Arthritis in Context

Introduction
The use of TNF-α inhibitors represents a major advance in the treatment of rheumatoid arthritis (RA). Previous NICE guidance on this topic has improved the lives of thousands of people with RA in the UK. A growing body of evidence supports the clinical effectiveness of these drugs. In addition we believe that the treatments have had a positive impact on service provision as well as people’s everyday lives. This submission summarises our hopes for the future in prescribing TNF-α inhibitors based on our organisations’ experience and advances in the research on the treatments.

What is RA?
Rheumatoid arthritis is a chronic, unpredictable and destructive disease affecting 1% of the adult population in the UK, (approximately 400,000 people). It is the most common potentially treatable form of disability in the UK. The main symptoms are pain, immobility, stiffness, impaired function, tiredness and depression. The pain, in particular, can be excruciating, making activities of daily life a significant challenge. ‘Flares’ – acute episodes characterised by extreme pain and inflammation – are a key feature of the condition, and in some cases may be interspersed with periods of relative inactivity in the disease.

The precise cause of the disease is unknown, but essentially it is an autoimmune disease in which the joints are damaged. This results in the severe disability and deformity of joints often seen in people with severe RA.

What is Severe RA?
Approximately 10% of those with RA have the condition in a particularly severe form. This manifests itself as relentless pain and swelling, often in many joints. It causes significant disability and loss of function, meaning that simple daily tasks, including self-care, can become impossible without assistance. Severe RA can also result other complicating factors that add to the risk and burden of the disease.

Severe RA is associated with a high level of mortality. 30% of people with severe RA will die within 5 years, a figure comparable with triple vessel Coronary Heart Disease or stage III Hodgkin’s Disease. On average, someone with RA can expect to live 5 years less than someone without the disease. Much of this is accounted for by the markedly reduced life expectancy of the population with severe RA.

In order to control the disease people with severe RA will usually require treatment with aggressive drug regimens and may require multiple joint replacements. All of these carry risks of side-effects and complications. However, for the individual with severe RA there are few options; thus the benefits of gaining some control of their disease will usually outweigh the risks related to their treatment.

The impact of RA on the individual, society and health services
Other aspects of this submission go into more detail on the impact of RA on the individual, health services and society but to serve as illustrations:

- The debilitating symptoms of RA lead to many limitations on the individual’s personal and work life, sometimes leading to the breakdown of relationships and loss of employment.
• The costs of treating RA are high and as the disease progresses, further physical staffing and resources are needed. The disease requires input from a wide array of secondary care specialties.
• The total UK costs, including indirect costs and work related disability, are estimated to be approximately £3.8-4.75 billion per year.

Changes in the treatment of people with RA
Evidence gathered since the 2002 NICE guidance, has emphasised the importance of early treatment of RA with disease-modifying drugs (DMARDs) and continual efforts to suppress the disease process as fully as possible, in order to reduce the risk of disease progression.
• Disease modifying anti-rheumatic drugs (methotrexate, sulfasalazine, leflunomide, gold, anti-malarials, azathioprine and penicillamine) are used to slow the progress of the disease. Use of DMARDs is correlated with decreased long-term disability, can reduce joint damage in a significantly greater proportion of cases than placebo and is cost-effective. However the later such drugs are introduced, the longer it takes to bring active disease under control, and the worse the outcome.
• A substantial minority (~15%) of patient with RA do not respond to conventional anti-rheumatic drugs and have relentless disease.
• The clinical practice of a decade or more ago in which six or more DMARDs were used sequentially over 5–10 years is now recognised as thoroughly inadequate, as there is less chance of a good response with increasing duration of disease and each successive DMARD. The strategy is also associated with long-term morbidity and work disability. A further consequence is that individuals with RA require costly orthopaedic surgery, nursing and allied health professional support in hospital and residential care.
• Much has improved over the last 20 years for individuals with RA as a result of a more aggressive approach to treatments using conventional DMARDs. However, there remain an important minority of patients who have a poor prognosis from the disease. There is a tremendous need for new improved drugs in these patients, and this is where TNF-α inhibitors have had considerable impact since their introduction 4 years ago.

The impact of the introduction of TNF-α inhibitors
Rheumatologists, healthcare professionals and many people with RA who have received TNF-α inhibitors have seen the benefits of these therapies and are aware that they represent a major advance in the management of this potentially severely disabling disease.

The impact of TNF-α inhibitors on people living with RA
The impact of the treatments on the lives of people with RA can not be underestimated. The improvement to their general health and reduction in disease activity are significant. This improved health leads to many other benefits in their own lives and to wider society as illustrated by a recent survey of people with RA receiving TNF-α inhibitors, conducted by Arthritis Care and NRAS.
• 31% of those surveyed said that the treatments had transformed their lives. A further 37% believed them to be a lot better than their previous treatments.
• Respondents stated that they were again able to be more active on a day to day basis; to be spontaneous, independent and able to socialise; and they could think about returning to work.

The impact of TNF-α inhibitors on clinical practice
In clinical practice TNF-α inhibitors have shown the following benefits:

- They act more quickly than traditional DMARDS.
- Treatment response is maintained in most patients, unlike conventional DMARDs.
- The group of patients with the poorest prognosis in the past i.e. those that have failed to respond to many or all of the traditional DMARDs, can still respond well to TNF-α inhibitors.
- Clinical experience in the NHS has reflected favourable efficacy and safety data from clinical trials. Although there are some concerns about infections including TB and some uncommon complications, the drugs have generally been well-tolerated with few side effects.
- Due to the greater than predicted effectiveness, withdrawal rates have been lower than estimated.
- The therapies often enable other potentially harmful drugs such as NSAIDs, steroids or concomitant DMARDs to be reduced or withdrawn.
- Patients not only benefit from improvement in pain and disability but also experience improved sense of well-being and increased energy levels.
- Recent studies indicate that the use of TNF-α inhibitors minimises the risk of disease progression. Specifically, TNF-α inhibitors can prevent or reverse radiographic deterioration, which is associated with joint destruction. This may eventually decrease the need for orthopaedic surgery. This feature of the drugs importantly differentiates them from methotrexate, which was hitherto considered to be the gold standard for the treatment of RA.

The impact of TNF-α inhibitors on health services

The introduction of TNF-α inhibitors has led to some changes in staffing needs.

- More specialist practitioner time is required to monitor disease activity to ensure selection of appropriate patients for both the initiation and continuation of treatments. However, it is thought that this should have less of an impact on services in the future, as specialist practitioners develop long term strategies to deliver these drugs to their patients.
- Nursing time is also required to teach patients the technique of subcutaneous injection (etanercept and adalimumab) and for supervising infusions of infliximab. The latter have to be given in a hospital environment because of the potential risk of anaphylaxis with intravenous protein use.
- As with the introduction of any new class of therapeutic agent, rheumatologists and other health professionals have to devote some time to the education of consultant colleagues, junior hospital staff, GPs and paramedical staff on the possible complications of treatment.
- The role of physiotherapists and occupational therapists is changing as patients on TNF-α inhibitors have increased mobility and consequently, changing needs. Fewer in-patients services and less medical equipment in the home etc. are needed, but there is an increasing role for preventative education and support in the community, including work adaptations.
- TNF-α inhibitors have a positive impact on staff morale, as staff are able to provide better treatment for their patients and reduce waiting lists and provide quicker access for urgent patients, through effective management of RA.

The costs of TNF-α inhibitors

We acknowledge that TNF-α inhibitors are relatively expensive. However, NICE determined in 2002 that they are cost effective, and most studies suggest an incremental cost-effectiveness ratio that is comparable with other drugs that have been approved by NICE. It is anticipated that the impact of TNF-α inhibitors on
slowing progression of the disease will have beneficial long-term consequences for health care expenditure, e.g. reducing co-morbidity, hospital admission and reducing the number of orthopaedic surgical operations. We have observed a significant reduction in rheumatology in-patient admissions in parallel with the advent of TNF-α inhibitors. Furthermore, if the societal impact of the therapies is considered they demonstrate even greater cost-benefit.

**Advances in understanding the effects of TNF-α inhibitors**

**Sequential use of TNF-α inhibitors**
A number of recent studies have demonstrated that people with RA who fail to respond to one TNF-α inhibitor often respond to another, in line with previous anecdotal experience^{11,12,13}. Thus a change from one TNF-α inhibitor to another can bring active rheumatoid disease under control.

**Failure of a single DMARD**
Whilst the overwhelming majority of patients going onto TNF-α inhibitors will have failed on at least two DMARDs, there may be occasions when the use of these drugs could be justified at an earlier stage in their disease. Some patients may have very aggressive early disease where rapid control is paramount or contraindications to conventional DMARDs such as abnormal liver function tests.

**Use of TNF-α inhibitors in the treatment of early RA**
Recent studies indicate that early use of TNF-α inhibitors minimises the risk of disease progression^{6,8,14}, and by extrapolation could eventually reduce morbidity and the need for services such as orthopaedic surgery. A number of studies comparing the use of methotrexate alone with the combined use of methotrexate and etanercept, infliximab or adalimumab in the treatment of early RA have shown significant advantages in using combination therapies. Significant radiographic as well as clinical and functional benefits have been demonstrated.

**Prevailing Concerns**
- Increasing experience has led to revision of the BSR guidelines on the use of TNF-α inhibitors in RA. Nevertheless the criteria for the use of TNF-α inhibitors in England and Wales remain amongst the most stringent in Europe.
- We are aware that some people with RA are not receiving TNF-α inhibitors in line with NICE guidance because of local funding constraints. In short, post-code prescribing still prevails in some areas. There is a great need for more emphasis to be given to the effective implementation of NICE decisions.
- There is concern from clinicians and patients alike that the ways we currently measure the efficacy of treatment, e.g. DAS and HAQ scores, do not adequately reflect the impact that the treatment is having on people’s general condition and on their lives.

The rheumatology community has taken a responsible approach to the implementation of the NICE 2002 guidance and nearly 8000 people on TNF-α inhibitors have been registered with the BSR Biologics Register. This ensures long-term evaluation of the benefits and possible hazards of such treatment. This responsible approach and the level of clinical awareness that has been raised about the treatments have led to a considerable improvement in service delivery and the quality of life for people with RA. We believe that there is sufficient evidence to extend the use of TNF-α inhibitors in specific circumstances and we believe that there would be significant negative consequences if the access to TNF-α inhibitors were to be further restricted in comparison with the NICE 2002 Guidance.
Conclusion

TNF-α inhibitors have proved to be highly effective in the management of rheumatoid arthritis. Indeed their success has exceeded initial expectations. Benefits are being reaped by patients, service providers and society at large. We believe that people with RA should continue to have access to these treatments. We believe that NICE guidance should be amended in accordance with the revised BSR guidelines. In particular adalimumab should be included in the guidance, and where one TNF-α inhibitor fails, patients should be able to try another. Furthermore there may be circumstances in which the use of a TNF-α inhibitor should be considered in the treatment of early RA, i.e. after failure of methotrexate when used as the first DMARD, or in people with poor prognosis RA (people with early disease who have high functional impairment and disease activity scores; high acute phase reactants; erosions at presentation) in whom it is not appropriate to use methotrexate.

References

Update on the British Society for Rheumatology (BSR) guidelines for prescribing TNF α blockers in adults with Rheumatoid Arthritis (update of previous guidelines April 2001)

J Ledingham, C Deighton on behalf of the British Society for Rheumatology (BSR) Standards, Guidelines and Audit working Group (SGWAG)

Introduction

These guidelines have been developed for use by prescribing secondary care Rheumatologists. They are intended to indicate which adult patients with Rheumatoid Arthritis (RA) may benefit from the anti TNF therapies, precautions that need to be taken in their use, and to highlight potential side-effects from these therapies. The previous guidelines applied to the then available anti TNF therapies (Etanercept and Infliximab) (1). These current guidelines would apply to these two products together with Adalimumab which is a newly licensed anti TNF therapy for RA. This is a rapidly changing field with new data emerging each month, so that it is vital that clinicians keep up to date with this area of practice. These guidelines can only incorporate information that was available to them at the time of their completion.

The guidelines have been drawn up by the above working party and have been approved by the BSR Standards Guidelines and Audit Working Group. National Institute of Clinical Excellence (NICE) guidelines, Medline literature searches for published data on the anti-TNF drugs and data from the pharmaceutical companies producing anti-TNF agents have been used to draw together the updated guidelines. The guidelines were subject to a consultation process at the BSR Annual Meeting 2004 and feedback was received from BSR members, allied health professionals, patient representatives and members of the pharmaceutical industry. The BSR SGAWG will be responsible for initiating a further update of these guidelines in the future and for auditing their use.

The anti TNF therapies are not necessarily the only treatment option available to patients who are eligible for treatment according to these guidelines – the potential risks versus the benefits need to be considered for each individual case. There will be circumstances in which Rheumatologists will feel that there are other drugs that may be equally likely to produce a good clinical response.

In the UK all patients commenced on the following anti-TNF therapies need to be registered on the BSR biologics register (BSRBR): etanercept, infliximab, adalimumab and anakinra. It is currently intended that data be collected on 4000 patients per anti-TNF therapy. Thereafter the BSR would recommend continued data collection, in the same format as for the BSRBR, at a local level. These guidelines will be updated as other Anti-TNF treatments are included in the register. For further clarification before registration, please contact [Contact Information], BSRBR Study Coordinator, arc Epidemiology Unit, Stopford Building, The University of Manchester, Oxford Road, Manchester, M13 9PT.

Adverse Incidence/serious side affects arising whilst on anti TNF therapy should be notified immediately via the yellow card system, but also to the BSRBR via the 6 monthly review sheets. Rheumatologists have responsibility for supplying updated
information to the BSRBR as required and as requested. Written consent will be sought from patients for their participation in this study via the BSRBR.

**Eligibility for treatment with biologics therapies:**

Patients must:

1. fulfil the 1987 criteria of the American College of Rheumatology classification criteria for a diagnosis of Rheumatoid arthritis
2. have active RA (have a DAS28 score of >5.1). Measurements of disease activity should be made at 2 points, 1 month apart confirming on-going active disease.
3. have failed standard therapy as defined by:
   - Failure to respond or tolerate adequate therapeutic trials of at least 2 standard DMARDs (IM Gold, Hydroxychloroquine, Sulphasalazine, Penicillamine, Azathioprine, Methotrexate or Leflunomide). One of the failed or not tolerated therapies must be Methotrexate.
   - Adequate therapeutic trial is defined as:
     - Treatment for at least 6 months, with at least 2 months at a standard target dose unless significant toxicity limited the dose tolerated
     - Treatment for less than 6 months where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses.

There may be circumstances when other DMARDs are relatively contraindicated, so that anti-TNF therapy may be considered very early in the course of the disease, and in patients in whom Methotrexate has not been used. There is data to support these approaches with anti-TNF therapies working well in trials of early RA and in DMARD naïve patients. However it is anticipated that in clinical practice it will be rare that circumstances arise necessitating use of anti-TNF therapy as a first line therapy.

**Exclusion criteria**

Reference should be made to the individual drug data sheets, but important exclusions include:

1. Women who are pregnant or breast feeding (see below).
2. Active infection
3. Septic arthritis of a native joint within the last 12 months*
4. Sepsis of a prosthetic joint within the last 12 months or indefinitely if the joint remains in situ*.
5. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure (CCF) (see below).
6. Clear history of demyelinating disease (see below)

*Based on opinion, but no good evidence

1. Extreme caution needs to be taken in those patients who are prone to infection, e.g. chronic leg ulcers, persistent or recurrent chest infections, indwelling urinary catheters. Patients infected with Tuberculosis, Hepatitis B and C, and HIV are discussed below.

Recent information from the BSR Biologics Register suggests that there may be higher levels of mortality in patients with pulmonary fibrosis treated with infliximab. At present there is more follow-up data available on infliximab treated patients than for
the other biologics. Increased mortality in patients with pulmonary fibrosis could occur with other biologics agents. Until further information is available, caution is needed when exposing RA patients with pulmonary fibrosis to anti-TNFα drugs. Such patients should be monitored closely for infection and any deterioration in pulmonary function.

Criteria for withdrawal of therapy
2. Inefficacy as indicated by failure of the DAS 28 score to improve by >1.2 or to reduce to a score of ≤3.2 after 3 months of therapy. However if other changes in therapy have occurred within the first 3 months (e.g. the treatment has allowed a reduction in steroid dose) treatment may be continued for a further three months, but should not be maintained for more than 6 months if the DAS 28 responses are not achieved (this statement is based on opinion rather than evidence).
3. Severe intercurrent infection (temporary withdrawal).

Which anti-TNF therapy should be used?

There is no current evidence to suggest that any type of anti-TNF therapy is more efficacious than the others (29-30). Selection of an anti-TNF agent will be based on patient preference and practical issues relating to drug administration and delivery. Etanercept and Adalimumab do not require co-prescription with Methotrexate, so that this is an attractive option in patients intolerant of this drug.

Should a patient who is failing to respond to one anti-TNF therapy have their treatment changed to an alternative anti-TNF agent?

There are a limited number of studies that have suggested that some patients who have shown no, or only partial response to anti-TNF therapy, can benefit from transferring to an alternative type of anti-TNF therapy. The current evidence suggests that Infliximab can be useful when Etanercept has failed, and vice versa (31-32). There is also evidence for Adalimumab substitutions (currently in abstract form (33-38)).

Can DMARDs other than methotrexate be used in combination with anti-TNF therapies?

There are some published papers and abstracts highlighting that Infliximab may be combined with Leflunomide. The combination is efficacious, however widespread use may be limited by adverse events which were common, and in some cases severe (39). A pilot study using Infliximab with Azathioprine suggests the combination is clinically beneficial in severe RA refractory to Azathioprine alone, but this has only been published in abstract form (40). Until further evidence is forthcoming, Methotrexate must remain the preferred drug for co-prescription with Infliximab.

Although it is not necessary to co-prescribe Methotrexate and Etanercept, studies have addressed the possibility that the two together may be more efficacious than the individual agents (41-43). There is good evidence to support this (42,43). In patients with inadequate response to Etanercept, the addition of Methotrexate is a useful option, and vice versa. Adalimumab has been shown to be useful in patients with an inadequate response to Methotrexate (44). To ensure maximum efficacy, Adalimumab should be administered in combination with Methotrexate.
Is there a place for alteration in the dose or the frequency of administration of anti-TNF therapy?

Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or reduced frequency of treatment, and in the absence of large trials each patient needs to have their regime tailored individually. Likewise there may be a proportion of patients on Infliximab who would benefit from an increase in dose or in frequency of treatment when partial response only has been achieved with recommended dosage regimes (7, 45-47). Adalimumab is licensed for weekly use for patients failing to respond to fortnightly injections.

In the absence of definitive data the routine use of regimes which depart from those that are recommended cannot be supported as a general policy, and the majority of patients should stay on the recommended regimes.

Potential adverse effects related to TNF therapy and guidance related to these:

1. Serious infections, excluding Tuberculosis

A number of serious infections including some fatalities have been reported in association with the anti-TNF therapies (7-24, 48-53).

Guidelines

- Anti-TNF therapy should not be started in the presence of serious infections.

- Anti-TNF should be discontinued in the presence of serious infections, but can be recontinued once the infection has completely resolved.

- The effects of anti-TNF are unknown for patients with HIV. There is a case report of a HIV patient with reactive arthritis receiving Infliximab without any deleterious effects (54), but further data is needed. Infliximab has been used in 6 advanced HIV patients and there are abstracts reporting the use of Infliximab in small numbers of HIV positive Crohn’s disease sufferers without any obvious deleterious effects. (55-57) However, until large scale controlled studies are performed, anti-TNF therapy cannot currently be advised in patients who are HIV positive.

- Reports on the effects of anti-TNF therapy on Hepatitis B patients are contradictory. There are case reports of severe hepatitis reactivation (58,59), with a more recent case report of no deleterious effects of anti-TNF therapy over 1 year (60). Until more definitive data is available, anti-TNF therapy should be avoided in patients with Hepatitis B infection.

- Although larger and longer term studies are needed, initial reports on the use of Infliximab on patients infected with Hepatitis C suggest no deterioration in hepatitis or viral load (60-62). Similar data are also available in abstract form for Etanercept (information from the drug company). However, there is a single published case of hepatitis C activation in a rheumatoid arthritis patient on Etanercept (63). Anti-TNF therapy may be used with caution in these patients.

2. Tuberculosis
There have been a large number of cases of tuberculosis (TB) reported in association with the use of Infliximab, and studies that demonstrate a significantly higher rate of TB in patients on this treatment compared with controls (64-66). Cases of TB have also been reported in association with Etanercept (64,67) and Adalimumab (68). Reactivation of latent TB is highest in the first twelve months of treatment, so particular vigilance is required during this time (64,66). With Infliximab, the majority of cases occurred within 3 cycles of treatment, with a median of 12 weeks after starting treatment, suggesting reactivation of latent TB as the main factor predisposing to TB (64,66) in these cases.

Guidelines

a) Prior to commencing treatment with anti-TNF, all patients should be screened for TB in accordance with the British Thoracic Society (BTS) guidelines (see appendix 1). Active TB needs to be adequately treated before anti-TNF therapy can be started.

b) Prior to commencing anti-TNF therapy consideration of prophylactic anti-TB therapy (as directed by the British Thoracic Society guidelines) should be given to patients with evidence of potential latent disease (past history of TB treatment or abnormal chest x-ray raising the possibility of TB) after consultation with a local TB specialist.

c) All patients commenced on anti-TNF therapies need to be closely monitored for TB. This needs to continue for 6 months after discontinuing Infliximab treatment due to the prolonged elimination phase of Infliximab.

d) Patients on anti-TNF therapy who develop symptoms suggestive of TB, should receive full anti-TB chemotherapy, but may continue with their anti-TNF therapy if it is clinically indicated (see the BTS guidelines on Tuberculosis screening that accompanies this guideline).

e) Anti-TNF therapy should only be resumed in accordance with the BTS guidelines and after agreement in collaboration with a TB specialist.

3. Surgical Procedures

Treatment with Infliximab, Etanercept and Adalimumab should be withheld for 2 to 4 weeks prior to major surgical procedures. Treatment may be restarted postoperatively if there is no evidence of infection and once wound healing is satisfactory (information provided by the drug companies).

4. Vaccination

The effects of anti-TNF therapies are unknown for most primary vaccinations and live attenuated vaccinations. A study on pneumococcal vaccination suggested patients on anti-TNF may not respond adequately to the vaccination (69). If live vaccines are required they should ideally be given 4 weeks prior to commencing treatment or 6 months after the last infusion of Infliximab (or potentially earlier if risks from not vaccinating are high) or 2-3 weeks after the last dose of Etanercept (information available from the drug companies). Since no data are available, concurrent administration of live vaccines and Adalimumab is not recommended (information available from the drug company). The BSR has a policy document on the use of
vaccinations in patients on immunosuppressive therapy (70), and until further evidence is available these recommendations should be adhered to in patients on anti-TNF therapy.

5. Malignancy

There have been number of malignancies, including lymphoma, reported from studies and post-marketing surveillance in association with the anti-TNF therapies (62).

Guidelines
a) There is no evidence currently for an increase in risk of solid tumours or lymphoproliferative disease with the anti-TNF therapies above that which would be expected in the Rheumatoid Arthritis population (72-74).

b) Patients should be investigated for potential malignancy if clinically suspected and consideration should be given to stopping anti-TNF treatment if malignancy is confirmed.

c) The effects of anti-TNF therapies are as yet unknown in patients with pre-existing malignancy or lymphoproliferative disease. Caution should be exercised in the use of anti-TNF therapies in patients with previous malignancy. The potential benefits of treatment need to be considered against the risks related to potential recurrence of the specific malignancy. If patients have been free of any recurrence of their malignancy for 10 years there is no evidence for a contra-indication to anti-TNF therapy.

d) The effect on pre-malignant conditions such as Barrett’s oesophagus, cervical dysplasia and large bowel polyps of anti-TNF therapies is unknown. Caution should be exercised in the use of anti-TNF therapies in such patients.

6. SLE syndromes and autoimmunity

Rare cases of SLE syndromes have been reported in association with the anti-TNF therapies (7,8,28,75-81). Symptoms resolved on discontinuing therapy – usually within 6 weeks to 14 months. There have been no fatalities or cases of major organ involvement in association with SLE like syndromes developing in association with the anti-TNF therapies. There is no evidence that developing ANA, DNA or anticardiolipin antibodies whilst on anti-TNF therapies increases the risk of developing clinical SLE type syndromes.

Guidelines
If symptoms of a SLE like syndrome develop whilst on anti-TNF therapies:

a) anti-TNF treatment should be discontinued.

b) appropriate treatment should be initiated for the clinical symptoms and signs.
7. Congestive cardiac failure (CCF)/cardiovascular disease (CVD)

Following an increase in reported mortality and hospitalization in the Infliximab treated group in a placebo controlled trial in patients with cardiac failure, warning statements were issued in November 2001 with regard to the use of Infliximab in patients with CCF/CVD \(^{(82,83)}\). This is usually with high dose regimes (such as 10 mg/kg). Etanercept may also adversely affect congestive cardiac failure \(^{(82,84)}\). A more recent study suggests that heart failure may be more common in patients with rheumatoid arthritis than controls, and that anti-TNF may actually ameliorate heart failure in RA \(^{(85)}\).

**Guidelines**

a) Anti-TNF therapy should not be initiated in patients with New York Heart Association (NYHA) grade 3/4 CCF. It should be used in caution in patients with mild CCF.

b) Patients should be carefully monitored for CCF whilst being treated with any anti-TNF therapy. If symptoms and signs of CCF are stable, treatment should still potentially be discontinued if the benefit of the anti-TNF therapy is only limited.

c) Anti-TNF therapy should be discontinued if CCF increases whilst on treatment.

8. Demyelination and neurological complications

There are a number of reports of demyelination and acute neurological complications in association with the anti-TNF therapies. The cases reported thus far have usually responded to discontinuation of anti-TNF therapy and treatment for the acute demyelination when clinically indicated \(^{(7,28,86-88)}\).

**Guidelines**

1. Anti-TNF therapy should not be given when there is a clear history of demyelinating disease.

2. Anti-TNF therapy may be best avoided if there is a possible history of demyelinating disease or a strong family history of demyelination.

3. Anti-TNF therapy should be withdrawn if demyelination occurs.

4. If a patient develops signs of demyelination whilst on anti-TNF therapy they should be referred to a neurologist for specialist investigation.

9. Haematological complications

There have been a few reports of haematological complications arising in patients treated with all three anti-TNF therapies \(^{(7,28,89-93)}\). Pancytopenia was fatal in some patients treated with Etanercept and Infliximab. No fatalities are reported from pancytopenia with Adalimumab. Most patients were taking other potentially myelotoxic drugs and/or Prednisolone at the time of the haematological abnormalities.
**Guidelines**

If haematological complications arise whilst on anti-TNF therapies, these agents should be discontinued. Checking a full blood count periodically, and immediately if the patient is unwell, is recommended.

**10. Pregnancy and Lactation**

There are no formal clinical studies of anti-TNF therapy in pregnancy or lactation. Animal models suggest no teratogenicity or risk of miscarriage. Some patients have become pregnant whilst taking anti-TNF therapy. There is no data to suggest any risk to the fetus, but insufficient data to warrant continuation of the therapy during pregnancy (95-97 and information from the drug companies).

Because immunoglobulins are excreted in breast milk, the manufacturers of anti-TNF therapies advise no breast feeding. Due to the long half-life of Infliximab it is recommended that patients do not breast feed until 6 months has elapsed from the last infusion.

**Guidelines**

Safety of the anti-TNF therapies is unknown/has not been established through pregnancy or lactation.

It is recommended that:

a) pregnancy should be avoided whilst on anti-TNF therapies and effective contraception is strongly recommended to prevent pregnancy in women of child-bearing potential.

b) breast-feeding should be avoided with anti-TNF therapies.

c) consideration should be given to stopping anti-TNF therapy if a patient becomes pregnant on treatment.

d) Infliximab is discontinued for 6 months before a female patient becomes pregnant or a male patient fathers a child. No data is currently available with regard to how long it takes for Etanercept to be cleared from the reproductive organs. Abbott Laboratories recommend that Adalimumab is discontinued for 5 months before a female patient becomes pregnant or a male patient fathers a child. The effect of Adalimumab on sperm has not been studied so no specific recommendations can be made.

**Acknowledgements**

The Authors would like to thank Rebecca Astbury for her secretarial support, and the Medical Information Departments of Schering-Plough, Wyeth and Abbott Pharmaceutical Companies. Thanks also to Mrs Ailsa Bosworth, Chair of the National Rheumatoid Arthritis Society (NRAS) for reading and offering comment on the guideline from the patient perspective during development.

**Working party of the British Society for Rheumatology 2003-2004**
Dr Jo Ledingham (Chair)
Consultant Rheumatologist, Queen Alexandra Hospital, Portsmouth.

Dr Chris Deighton
Consultant Rheumatologist, Southern Derbyshire Acute Hospitals NHS Trust.
**Appendix 1**  
**Conflict of Interest**

The Working Party was set up independently of any input or funding from the manufacturers of the new biologic therapies.

Members of the Working Party were asked to clarify their relationships with the manufacturers of the new biologic therapies. Members were asked to declare if they, as individuals, had been sponsored to attend scientific or other meetings in the past 24 months or if they had a direct financial stake in the manufacturing companies. They were also asked if their units had received funding from the manufacturers to take part in clinical trials of the new biologic therapies. Organisations were asked to declare if they had received sponsorship from manufacturers of the new biologic therapies for activities related to the new therapies (either educational or promotional) or for activities not related to the new therapies.

The following replies were received:

- The following Working party members have received funding from pharmaceutical companies involved in producing biologic therapies to attend scientific meetings: A Bosworth
- BSR has established a register which is funded by the manufacturers of biological therapies; training for rheumatologists in data collection has also been funded by these manufacturers

**References**


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Arthritis Care & National Rheumatoid Arthritis Society
Submission to NICE Review of TNF-α inhibitors for people with Rheumatoid Arthritis

1. Introduction

1.1 As members of the Arthritis and Musculoskeletal Alliance (ARMA) Arthritis Care (AC) and the National Rheumatoid Arthritis Society (NRAS) welcome the opportunity to respond to the NICE review of TNF-α inhibitors for people with Rheumatoid Arthritis (RA). AC and NRAS work to support those affected by RA and other related conditions. A vital part of the individual's care is based upon achieving the right balance between self management of their condition and receiving appropriate help and support at the time it is required. This can only be achieved by the ability to access the most effective treatments and appropriate healthcare services so that they can enjoy the optimum quality of life possible when living with a chronic disease.

1.2 Arthritis Care and NRAS believe that people should have access to the most effective treatments irrespective of cost or where they live. This is particularly relevant, given that post code prescribing of TNF-α inhibitors is still happening in a number of areas in the UK.

In support of our submission we will focus on the importance of people with RA being able to carry out normal daily living activities to illustrate the positive impact that TNF-α inhibitors can have on the quality of an individual’s life.

2. For more detailed information about Arthritis Care and the National Rheumatoid Arthritis Society, please see Appendix 3 of the submission.

3. Rheumatoid Arthritis

3.1 Rheumatoid arthritis is a painful, chronic and usually progressive autoimmune disease. In recent years it has become clear that much of the damage with rheumatoid arthritis can happen in the first months and years of the condition. This is why it is vital to have early diagnosis and treatment, to minimise damage to the joints and reducing the potential for long term disability. The nature of this disease, the symptoms and statistics have been well documented by the professional organisations involved in the ARMA submission and therefore both AC and NRAS felt it would be more appropriate for our submission to focus on what impact the disease has upon the individual and what matters most to them.

3.2 We would also like to highlight the importance of studies such as the Sture study (Appendix 2) which shows that many of the cost implications related to RA are not always fully identified or considered when evaluating new therapies.

4. The Impact of Rheumatoid Arthritis

4.1 Some of the key symptoms which people with RA constantly struggle to
cope with are:

Pain, can be constant, can be extreme
Fatigue
Tiredness
General feelings of being unwell (flu-like symptoms)
Lack of sleep
Feelings of isolation
Depression
Stiffness, particularly in the morning
Lack of mobility and function such as doing up shoe laces
For some, side effects of different drugs can be debilitating

4.2 For many, the above symptoms lead to:

Loss of self confidence
Loss of self esteem
Depression
Changes to body image
Loss of opportunity to do things others take for granted
Loss of employment or reduced working hours
Financial difficulties
Dependence upon social services
Loss of ability to complete education or pursue educational interests
Dependence on others to help with daily living activities
Loss of ability to maintain satisfactory sexual relationship with partner
Disruption and damage to personal relationships because partners have to become carers and also often reduce their working hours
Surgery

4.3 For some there are the additional problems of co-morbidities which can make life very restricted indeed.

5. The Joint Submission

5.1 As part of this submission, Arthritis Care and NRAS were keen to explore the views of the members of AC and NRAS. An email inviting 750 members of NRAS who had RA (varying ages, sexes and length of time with the disease) to complete a survey (see Appendix 3) located on AC’s website, was sent out.

5.2 AC emailed 7,500 of its members with the same request, however AC was unable to identify how many of these members had RA (as this data is not held on their database) which is why a larger number were emailed. People who were taking TNF-α inhibitors were invited to go to a link on AC’s website to complete the survey attached in Appendix 3.

5.3 The questionnaire was specifically targeted at people who were either currently taking TNF-α inhibitors or had taken them in the past. A minority of people taking part in the survey had Psoriatic Arthritis, Ankylosing Spondylitis, Juvenile Idiopathic Arthritis or ‘other condition’. However, the majority - 83% - of those who responded (81 people in total) had RA. To comply with data protection legislation, the surveys were completed anonymously.

5.4 The response rate is likely to have been affected by the timescale to carry
out this work which had to be extremely tight and the questionnaire was available for completion for a period of 10 days.

5.5

It is worth noting that the group of people who took part in this survey represent a cohort of patients who are computer literate, probably reasonably knowledgeable about their disease and likely to be pro-actively self managing by the very fact that they are members of either AC or NRAS.

5.6

In addition to carrying out the above survey, AC and NRAS held a Focus Group in London in which 8 people took part. All were female and 7 out of the 8 were in their middle years and 1 was younger. 7 out of the 8 were currently being treated with different TNF-α inhibitors for RA and 1 person had taken them in the past for RA but had had to withdraw from treatment due to side effects. 7 out of the 8 had had the disease for many years and had sustained significant joint damage with a number having undergone surgery. No-one in the group was relatively newly diagnosed and therefore the fact that the members of the Focus group could be described as having long term, active disease with sustained damage is relevant. Two members of the Focus group had been on TNF-α inhibitors for 3 months and 4 months respectively and therefore were not able to give as much feedback as the rest of the group who had been on treatment for more than 1 year (with the exception of the younger participant who was no longer on treatment).

5.7

It is important to note that the outcomes of the questionnaire and the Focus Group also reflect the experiences of both Arthritis Care and NRAS communicating on a daily basis with people who are taking this class of drug.

6. Findings from the Questionnaire

6.1

‘Which aspects of the disease do you most want the anti-TNF alpha to help you with?’

43% wanted the TNF-α inhibitors to provide relief from inflammation in the joints with 30% specifically citing ‘seeking pain relief’. This reflected the views of the focus group.

‘For me dealing with inflammation was the key. It would lead to pain and fatigue control.’

‘It brought down the inflammation, I had more energy’

‘for me pain and inflammation’

‘Can you tell us about the good and the poor effects that these treatments have on treating the symptoms?’

6.2

51% of people felt that TNF-α inhibitors helped with inflammation and 22% felt it helped with pain.

6.3

In the Focus Group, talking this question through in detail, the benefits had been considerable. For example, personal hygiene for one lady had improved hugely, for others, the ability to do some cleaning around the
house, being able to work again, etc. Many felt that TNF-α inhibitors had
given them back their lives. They were more able to be spontaneous,
independent, could once again think about returning to work, planning a
holiday, do more activities in the day and were able to socialise, etc.

'My health has improved so much that I am thinking
about looking for work'

'All my lumps have gone and I have all the
movement back in my hands'

35% of the people that responded in the questionnaire felt that TNF-α
inhibitors had not helped them with their fatigue, with 26% saying that they
did not help when dealing with sleep disturbance. Interestingly 20% of the
respondents found that TNF-α inhibitors did not help with their pain.
However, it should be remembered some individuals with difficulties in
access to treatment may raise expectations above those patients who have
had a structured pathway in their care with TNF-α inhibitors.

How does anti-TNFα treatment compare to other
drugs you have taken for your condition?

37% of the respondents felt that TNF-α inhibitors were a lot better at
treating their RA, with 31% saying it had transformed their life. 11% found
no difference in their RA when compared with other medications.

'My daughter says I am less grumpy now.’

'Somewhere between a lot better and transforming my
life'

'I have noticed I have a lot more mobility’

What effect has the treatment had on your disease?

32% felt that TNF-α inhibitors enabled them to do more for themselves and
not feel so dependent on others. 19% of respondents felt their condition
had improved so much they were thinking of returning to work. 18% felt
that the treatment allowed them to do more for their family.

Only 10% felt there had been no noticeable difference in their quality of life.

'A lot better – transformed my life, I have done a lot of
things I would not have been able to do before’

'I am now doing voluntary work and am able to cope
better’

'I used to go to bed when my daughter went, now I stay
up till 10.30 – 11 o’clock!’

Discussions within the focus group highlighted the important issue of
employment. Although some of the group had found employers who had
been helpful and recognised the problems with RA, others had
experienced difficulties with their employers in the past, having to face discrimination due to lack of awareness and understanding. One of the group lost her job because of her RA which had left her feeling ‘very raw’ (this was prior to commencing treatment on Anti-TNFα). Approximately half of the group felt they had lost a lot of self confidence in relation to employment and were wary of making commitments that they could not honour.

6.9 The questionnaire and the focus group identified very few negative aspects of taking TNF-α inhibitors. Such comments related to a variety of side effects which a minority of people had experienced. There were a very few examples of people who had experienced adverse reactions resulting in them being admitted to Accident and Emergency.

6.10 These comments reflect the concern people have about taking any toxic drugs, and the fact that many of those with RA have learnt to cope with these challenges when receiving high doses of drugs such as Methotrexate. In the Focus group, any minor side effects were tolerated well because of the benefits of being on the drug. The majority who took part in both the questionnaire and the focus group did not experience side effects at all (see section 7.00).

6.11 What is the most important difference the anti-TNF treatment has made on your long-term health?

42% of those that answered this question felt the greatest difference was enabling them to feel better within themselves, with 17% stating that taking TNF-α inhibitors ensured they could continue going to work/remain in education/socialising.

‘without this treatment, I would be getting very very depressed’

‘more mobility’

‘I feel re-assured, I feel the future has more prospects’

6.11 What impact does anti-TNFα have on family, friends or employers?

28% felt they were easier to live with due to their lack of pain, with 22% stating that it was easier to do things for themselves around the home (the importance of regaining independence is a goal we hear over and over again). 20% felt the medication had given them back their lives and as a result, their close personal relationships had improved, with 18% saying they had more energy to socialise. 10% felt there had been little or no effect on their family, friends or employers.

‘Anti-TNF has made me a lot easier to live with, and I don’t have to put up a front now’

‘If I had had it years before, I would have been able to stay on at work’

‘close relationships have improved’
Which side effects experienced are the most intolerable?

52% of the people responding to the questionnaire had no side effects when taking TNF-α inhibitors, with 18% stating that increased minor infections were the most intolerable.

Which side effects experienced are the easiest to deal with?

52% of people who responded to the questionnaire had no side effects when taking TNF-α inhibitors. 16% found injection site reaction easiest to deal with, with 12% stating that they found increased minor infections although most felt these were not a major problem.

How did people think they would feel if they had not had access to anti-TNF treatment?

Respondents were asked to comment in an open question.

The overwhelming response was that they felt that their RA would be far worse without TNF-α inhibitors. Some felt that access to the drug earlier might have helped reduce joint damage and therefore the amount of surgery they had experienced. Others commented that they thought they would have had less mobility, more depression, greater dependence on others, would have had to deal with higher levels of inflammation, and would have had to give up/or stay off work.

'I think I may have given up on work as I had gone through all the DMARDS'

'I had my hips replaced and they were talking about my knees, my knees are fine now'

'I have stopped taking co-proxamol and my steroids are reducing'

However their were a small number of comments where some of the respondents felt nothing much had changed whilst taking TNF-α inhibitors and they had seen no real benefits from taking the medication.

How does the drug fit into a person’s life?

82% of the respondents felt that taking TNF-α inhibitors fitted into their life with no difficulty, with 17% saying for them there was some difficulty and only 2% said they had great difficulty. This reflected the views of the focus group.

Is the drug easy or difficult to use?

48% of the people who answered the questionnaire found it easy to use TNF-α inhibitors, with 35% stating it was quite easy. 5% of respondents had to have someone else inject them, with only 5%
needing help to get to the hospital for the infusion/monitoring. The focus group generally found the drug easy to use, but sometimes had difficulty self injecting (particularly where they had a lot of damage to their hands).

‘The design of the handle can make it difficult to inject myself.’

6.18 Participants were asked about the time or costs involved in taking anti-TNFα drugs

51% of the people that responded had their TNF-α inhibitors delivered and self injected so had no real costs, with 29% saying that injecting themselves meant that the medication fitted into their lifestyles. 6% needed to take time off work to have their infusions of TNF-α inhibitors, with 5% needing a carer to accompany them to hospital. Again this reflected the views expressed in the focus group.

6.19 It is important to mention here that to stress that patient choice should be respected and taken into account when determining which of the TNF-α inhibitors is likely to be the most appropriate for that individual. This is a decision which should be taken in consultation with support and information from their health professionals.

8. Conclusions

8.1 The key themes that emerged from the questionnaire and focus group, which reflect the experiences of both Arthritis Care and NRAS, were the importance of people maintaining their independence, reducing their need for hospital admissions/visits, social and employment issues and the impact on family and friends.

8.2 For most people with RA, ensuring that they can remain as independent as possible is very much a priority. The findings from the questionnaire reflected this. For the majority of the population, being able to carry out normal daily living activities is taken for granted, whereas for many people with severe RA, just being able to wash and take care of personal hygiene can be extremely challenging and sometimes impossible. Having access to a treatment that can enable one to remain independent can make a massive difference in someone’s life.

8.3 Employment and socialising was another important theme that emerged for many people with RA. For a significant number of people the negative impact it has on their employment and ability to socialise can be devastating. It can lead to people being unable to continue to work, which can be due both to the disease and/or the lack of understanding or preparedness of the employer to adapt the workplace or work practices to assist. The ability to enjoy a normal social life is a distant memory for many people with RA. Going out for an evening often results in ‘suffering’ more greatly the next day. You effectively ‘pay’ for an evening’s entertainment and such is the cost that many would prefer not to go out at all. TNF-α inhibitors had enabled many people to continue to work and socialise.
The impact on the family and friends of people living with RA can be enormous. Findings from the questionnaire and focus group indicate that for the majority, TNF-α inhibitors have helped to relieve the burden of not only the painful symptoms and progression of their disease but the restrictions it imposes on family and friends and the damage it can do to close relationships. Indeed in many circumstances family members also had to play a role as a carer particularly for such issues as getting to hospital (where parking access for disabled people is somewhat limited) as well as undertaking shopping etc for them.

However it must be noted that for a small minority of people who responded in both the questionnaire and focus group, TNF-α inhibitors had not particularly improved their quality of life and for a very few there had been adverse effects of taking the medication. TNF-α inhibitors like any treatment, has side effects and as such patient safety is key and needs to be monitored accordingly.

There can be no doubt however, from a patient perspective, that access to TNF-α inhibitors are a critical and very important aspect of treatment given that the most appropriate effective DMARDs have failed. The value to the individual and wider society in giving someone back their independence, ability to work, take part in education, look after their family and maintain their close relationships outweighs the pure cost of the drug. There are potential gains to the health service which might include less surgery for joint replacements, less emergency admissions to hospital, and in the long term less reliance on healthcare services.

For many who took part in both the survey and the Focus Group, serious joint damage had been sustained prior to starting on TNF-α inhibitors. The guidelines effectively select the most seriously ill patient. Arthritis Care and NRAS have been impressed by the evidence of efficacy in treating early RA with TNF-α inhibitors. The ability to put the disease into remission for long periods is no longer a distant dream for people with this devastating disease but is now a reality. Fewer operations, fewer other drugs, greater independence and quality of life are goals that those of us with this disease cannot put too high a value on.

One important caveat is that there has been a great contribution made by the healthcare professionals and patients working together in the management and assessment of those eligible to receive . This has been important to ensure that patients play a vital part in their management, not only in having a voice to receive the appropriate treatments but also to be active and responsible participants in their care.

Patients receiving these therapies should be educated and informed to ensure they take responsibility for reporting side effects and comply with advice given, manage their therapies effectively and recognise that should treatment fail they will not continue.

AC and NRAS believe that patients and their clinicians should be able to try other TNF-α inhibitor when one has failed. The evidence so far shows that there are some aspects of these therapies that are not fully understood about individual responses to one TNF-α inhibitor where another has failed. Provided the eligibility and reviewing processes are taken into account we believe this will be a valuable way of using these therapies in
the care of those with RA.
Appendix 1 – STURE Study

Although our focus in this submission is from the patient's perspective with a particular focus on enhancing outcomes and improving quality of life, we would like to highlight the importance of studies such as the Sture study (van Vollenhoven RF, et al. *Arthritis Rheum*. 2002;46:S535.) which shows that many of the cost implications related to RA are not always fully identified or considered when evaluating new therapies.

AC and NRAS would like to highlight how relevant this study is to both organisations and their members.

**Does treatment with biological agents improve economic productivity, as assessed by work-force participation?**

**A study on 296 patients by the Stockholm TNFα registry (TURE)**

Treatment with infliximab or etanercept results in significant increases in work force participation: data from the Stockholm TNFα antagonist registry (TURE)

- Costs of rheumatoid arthritis are mostly indirect costs, i.e., loss of economic productivity
- During treatment with the biological agents etanercept and infliximab, work-force participation increased significantly compared to baseline
- Work-force participation was noted to increase mostly during the second year of treatment, suggesting slowly incremental benefits (whereas clinical benefits are mostly constant over time)
- Gains in employability may result in significant economic benefits for individual and society
- These gains may offset at least part of the costs of these treatments

After excluding old-age pensioners and the permanently disabled, an increase in work-force participation is seen from 18.5 (±1.31) hours/week at baseline to 26.0 (±2.5) hours/week after 2 years, a statistically significant increase of 7.5 hours worked per week, or 41%.

When analyzing only those patients who were on sick leave at baseline, an increase in work-force participation is seen from 8.55 (±1.07) hours/week at baseline to 20.0 (±3.48) hours/week after 2 years, a statistically significant increase of 11.45 hours worked per week, or 134%.

For further details or a full copy of the above slide presentation from which the above extracts were taken, please contact either AC or NRAS.
Appendix 2

Anti-TNF Questionnaire

We would like to ask for your help in putting together our submission to NICE who are in the process of reviewing the current guidance for the prescription of anti-TNF drugs. We need to let them know what the patients think about these drugs and we would like to hear what you have to say about them.

If you are currently taking a TNF or have taken a TNF in the past we would be most grateful if you would email or write to us at the above address and tell us about your experiences. In writing to us could you please consider the following:

**Question 1**
What type of condition do you have?

| Rheumatoid Arthritis | Ankylosing Spondylitis | Psoriatic Arthritis | Idiopathic Juvenile Arthritis | Other |

**Question 2**
Which of the aspects of the disease do you most want the anti-TNF to help you with?

| Pain | Fatigue | Inflammation | Mobility | Lack of sleep |

**Question 3**
Which symptom is the drug particularly good at treating?

| Pain | Fatigue | Inflammation | Mobility | Lack of sleep |

**Question 4**
Which symptom is the drug particularly poor at treating?

| Pain | Fatigue | Inflammation | Mobility | Lack of sleep |

**Question 5**
How does the anti-TNF treatment compare to other drugs you have taken for your condition?

| A lot worse | Slightly | No difference | Slightly | A lot | Transformed |
Question 6
What effect(s) has the treatment had on your disease?
Please tick no more than THREE.

- There has been no noticeable change in my quality of life
- I have a little more mobility but still no discernable improvement in ability to carry out daily living activities or walk distances
- My disease has improved so much I can think about returning to work/education
- I can now do sporting activities again which I couldn’t do before
- I can do more for myself and don’t feel so dependent
- I can do more for my family and don’t feel so dependent

What, if any, have been the negative impacts of the anti-TNF treatment? (Please use no more than 50 words)

Question 7
What is the most important difference the anti-TNF treatment has made on your long-term health?

<table>
<thead>
<tr>
<th>No difference so far</th>
<th>Feel better in myself</th>
<th>Potential for less surgery</th>
<th>Decreased dependency on others</th>
<th>Enabled return to work/education/socializing</th>
<th>Sleep better</th>
</tr>
</thead>
</table>

Question 8
How has taking the drug impacted on others i.e. your family, friends or employers?

- Little or no effect
- The time off taken for assessments/monitoring/ hospital visits has been a problem
- It is easier to do things for myself and in the home
- It has given me some of my life back and my close relationships have improved
- Less pain means I am easier to live with
- I have more energy for socializing

Question 9
Of the side effects you may have experienced, which do you find most intolerable?

Suggest the following:

I have Skin Injection Headaches Nausea Increased Serious reaction,
no side effects | rash | Skin rash | Injection Site reaction | Headaches | Nausea | Increased minor infections (e.g. colds) | Serious reaction, e.g. anaphylactic shock, TB etc. (please specify)
---|---|---|---|---|---|---|---

**Question 10**
Of the side effects you may have experienced, which do you find easiest to accept?

**Question 11**
How do you think you would be if you had not had access to anti-TNF treatment?  
(Please use no more than 50 words)

**Question 12**
How does taking this drug fit into your life?

<table>
<thead>
<tr>
<th>With no difficulty</th>
<th>With some difficulty</th>
<th>With great difficulty</th>
</tr>
</thead>
</table>

**Question 13**
Do you find it is easy or difficult to use this drug?

<table>
<thead>
<tr>
<th>Easy</th>
<th>Quite Easy</th>
<th>Someone else has to inject me</th>
<th>Quite difficult</th>
<th>Very difficult</th>
<th>I need help to get to the hospital for my infusion/monitoring</th>
</tr>
</thead>
</table>

**Question 14**
In relation to the time or costs involved in taking anti-TNF drugs, please select from the list below those statements that apply to you (if any).

- I have home delivery and inject myself so no real costs are incurred
- I find the time taken to inject myself is easy to fit into my lifestyle
- I find the time taken to inject myself is difficult to fit into my lifestyle
- My carer has to do my injection
- My carer has to accompany me to the hospital
- I have to incur significant costs to get to the hospital
- I have to take time of work to have my infusion
Question 15
In considering all the above can you explain to us briefly (no more than 100 words) what you were like before you were taking an anti-TNF and how it has changed your life (either for the better or for the worst)

Thank you for taking the time to complete this questionnaire.

We really do need your input so please contact us so that we can be fully representative of our members' views.

Many thanks and best wishes
THE ARTHRITIS RESEARCH CAMPAIGN SUBMISSION TO NICE ON THE REAPPRAISAL OF ETANERCEPT, INFLIXIMAB AND ADALIMUMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

About the Arthritis Research Campaign

The Arthritis Research Campaign (arc) is the 4th largest medical research charity in the UK and the major provider of funding for research into arthritis and musculoskeletal disease, with a current expenditure of over £22 million a year [1]. Our income is provided entirely by voluntary donations from the public and we receive no Government support. Our mission is to advance the understanding, prevention and treatment of arthritis and associated rheumatic conditions. About one third of our research budget, of approximately £20 million, provides support for our 2 research institutes, the Kennedy Institute, Imperial College London (where TNF-α inhibitors were originally developed for the treatment of RA) and the Epidemiology Unit, University of Manchester. The remaining two thirds of the budget provides competitive peer-reviewed “response mode” grant funding to universities and hospitals within the UK, including a major initiative to support multicentre randomised clinical trials.

About our submission

The Arthritis Research Campaign is presenting this submission as part of a joint submission with Arthritis Care, BHPR, BSR, NRAS, PCR, and the RCN Rheumatology Forum, which is co-ordinated by ARMA. We will concentrate on the recent key research evidence for the clinical effectiveness of TNF-α inhibitors published since our last NICE submission in 2000.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common and severe of the inflammatory rheumatic joint diseases. It affects approximately 1% of the adult population in the UK resulting in chronic pain, permanent disability, shortened life expectancy and huge economic consequences to society in terms of work loss and the costs of health care and social care [2,3].

TNF-α inhibitors

The development of the biologic agents and in particular those that target TNF-α, such as etanercept, infliximab and adalimumab, have proved to be a major advance in the treatment of RA. There are several cohorts of patients with longstanding, established chronic disease, both in North America and Europe, that have now been treated continuously for over 7 years with considerable benefit and several published studies have now established that combination therapy with TNF-α inhibitors and methotrexate is more efficacious than either drug alone [4]. This holds true for longstanding standard DMARD unresponsive disease, but is especially marked in methotrexate naive patients with early erosive rheumatoid arthritis [5]. There is
growing evidence from open clinical trials that patients who do not respond to infliximab, may respond to etanercept or vice versa [6,7]. Furthermore, there is data that suggests that it may be possible to identify subgroups of non-responding patients who may either show a late clinical improvement with infliximab or a good response when switched to etanercept [8].

An important observation from many studies is the arrest of structural damage by combination therapy and data is now emerging suggesting that damage may even be reversed [9,10,11]. Since structural damage is, in the long term, a determinant of disability and the need for surgery, this observation has significant implications since it distinguishes the actions of TNF-α inhibitors from those of methotrexate.

Very impressive data is emerging that, in early RA, combination therapy can induce remission of disease in up to 50% of patients. At 2 years, functional and quality of life benefits were sustained with methotrexate alone, despite withdrawal of infliximab [12]. These data may have significant implications for the optimal cost-effective use of the biologic therapies. In the BeSt trial in Leiden it was possible to discontinue TNF-α inhibitors in about 40% of patients at 6 months and maintain remission on methotrexate alone. This study has not been published in full, but it supports the possibility that initial therapy with TNF-α inhibitors in early rheumatoid arthritis may prove to be a potentially cost effective approach to the treatment of severe disease [13].

Some safety concerns about the biologic agents remain, but these are being addressed in ongoing observations and registers in both Europe and North America. The current opinion is that, in appropriate patients, benefit clearly exceeds risk.

**Concluding Statement**

There is overwhelming and growing clinical evidence that the TNF-α inhibitors are not only highly effective in the treatment of RA but can halt or even reverse structural damage and induce remission. They must remain available as treatment option to patients in the UK as they are in most of Europe and North America.

**References**

3. Arthritis: The Big Picture, Arthritis Research Campaign, 2002


BRITISH HEALTH PROFESSIONALS IN RHEUMATOLOGY SUBMISSION TO
NICE ON THE REAPPRAISAL OF TNF-α INHIBITORS IN RA.

This submission accompanies that of the British Society of Rheumatology (BSR), this document focuses on the implications of the continuing use of TNF-α inhibitors for allied health professionals (AHPs) (e.g. specialist practitioners, physiotherapists, occupational therapists and podiatrists) working within the field of Rheumatology. As yet there is little published evidence to draw on with regard to either the short or long term effects on the services provided by these allied health professionals. This document is therefore based largely on the opinion of AHPs working in the field.

Specialist Practitioners.
These are usually specialist nurses or physiotherapists working in an extended role. As the number of patients being treated with biologic agents grows so does the workload involved in screening, monitoring, data entry, managing a helpline and general administrative tasks. It is essential that sufficient posts are funded to keep pace with the growing numbers and that job plans include sufficient time for administration. The morale and job satisfaction of these practitioners is high as they see patients responding to treatment but when patients fail to respond the disappointment is great. Patients then require increased levels of support as they seek to come to terms with this and to find hope for the future; frequent clinic visits are often required to try and regain some measure of disease control.

Physiotherapists.
As many patients with severe rheumatoid arthritis treated with biologic agents are enabled to live more normal lives, acute flares of the disease requiring admission to hospital become more rare. The role of the physiotherapist for RA patients will change for those responding to TNF-α inhibitors as their potential for physical activity increases. Many will have become deconditioned over the years, losing muscle strength, joint mobility and general cardiovascular fitness. Physiotherapists are well placed to supervise appropriate exercise programmes, to rebuild confidence and encourage patients to adopt lifestyles that are healthier than have previously been possible.

Occupational Therapists.
Eventually there is likely to be less demand for major equipment and home adaptations for people with rheumatoid arthritis, although there are many patients with end stage disease who will continue to require these services for the foreseeable future. Less inpatient services will be needed as admissions for RA patients become fewer, but as there is already a shortage of Rheumatology Occupational therapists it is unlikely that this will result in the need for fewer posts. More likely there will be a redirecting of resources to education and offering preventative provision to a wider variety of clients than is currently possible. OTs may also be able to use their expertise to liaise with employers and disability employment officers to support clients in the workplace. Many of these interventions will be less of a financial burden than those currently required.

Podiatrists
Podiatry resources for rheumatology are already stretched in most areas and fall short of what is required, the growing number of patients on TNF-α inhibitors presents an expansion of the role of the podiatrist and further pressure on their services. Poor foot health is prevalent in RA patients, particularly those with co morbidities [1,2]
The effect of TNF-α inhibitors is to mask early signs of infection when wounds do occur and infection can develop rapidly [3.4]. Patients should therefore be screened for potential sites of infection and educated with regard to footcare. Facilities also need to be in place for quick access for review. Clinical experience suggests that a number of patients responding well to TNF-α inhibitors are experiencing foot related pain due to their increased mobility and resultant increased functional stresses. Podiatry service needs therefore include:

- Locally agreed foot screening tool for use within MDT with prompt access to podiatry for assessment if risk factors identified.
- Patient education with regard to footcare.
- Footwear services.
- Appropriate and timely service access as per ARMA Standards of Care, which reflects the tissue viability and functional needs of the individual.
- Education for wider podiatry community to ensure they are updated with regard to the issues affecting this group of patients.

References.
Introduction

Rheumatoid arthritis (RA) is the most common potentially treatable cause of disability in the western world (1). TNF-α inhibitors have had a substantial impact on addressing this, and have heralded a new era in the management of chronic inflammatory arthritis. They are now well established in the management of RA, and the BSR wishes to support their continuing and extended use. In order to achieve this, the submission will present information under the following headings:

- The impact of RA on the individual and society
- RA and secondary care
- Drug treatments for RA
- TNF-α inhibitors in RA
- Updated BSR guidelines for TNF-α inhibitors in RA
- Health Economic Analyses of TNF-α inhibitors in RA
- The likely impact of limiting access to TNF-α inhibitors

The impact of RA on the individual and society

RA has an incidence of 9 new cases per 100,000 population per annum and a prevalence of 300-600/100,000 (2,3). The disease has a major impact on the lives of those affected:

- 16% have marked functional loss and 10% require home adaptation or wheelchair by 5 years (4). The disease places a tremendous burden on family members who provide care for RA patients (5,6).
- Work disability is 25-33% at 2 years, 80% at 20 years (4, 7-9). This accounts for a large fraction of the indirect costs of RA (10). Employer expenditure on RA employees is three times greater than that spent on the rest of the workforce (11).
- Average life expectancy is reduced by approximately 5 years (12) and the quality of life during this abbreviated life span is also reduced (13,14).

Apart from loss of earnings and cost of medication, home adaptations, transport, etc for the patient, the disease also has major financial implications for the community at large:

- Direct cost in UK is estimated at £3,250 per annum; indirect cost is approximately £3,420 per patient per annum (15). The economic burden of RA significantly exceeds that of osteoarthritis and hypertension (16)
- Direct costs: 30-65% due to hospitalisation; 5-30% due to drugs (15,17,18).
- These costs are skewed so that costs are much greater in late disease (>10 years) and overall some 20% of RA patients incur some 80% of the costs (15,17,19). Costs increase and the quality of life decreases as RA progresses (14).
- In late RA the costs of nursing home care in UK (approximately £188m per annum) are similar to those of joint replacement (16)
- Total UK costs including indirect costs and work disability are estimated to be approximately £3.8 - 4.75 billion (15)
RA and secondary care

Patients with RA constitute 12% of new patient referrals to Rheumatology services, but 42% of follow-up patients (20), reflecting the serious and chronic nature of the condition. In well-controlled RA the average outpatient review is six to twelve-monthly but for inadequately controlled RA the frequency of follow-up increases. There is also a requirement for extra urgent appointments for disease flares. Although the number of RA patients admitted to hospital has decreased over recent years, refractory cases are still admitted to control disease through pulsed intravenous steroids and immunosuppressive and multidisciplinary therapy (specialist nurses, physiotherapists, occupational therapists and social workers); for treatment of complications of the disease such as vasculitis, multi-organ involvement, leg ulcers, septic arthritis and osteonecrosis, and for the management of iatrogenic disorders such as blood dyscrasias.

The morbidity and increased mortality associated with RA have an impact on the work of other secondary care specialties.

- RA places heavy demands on the orthopaedic services: 8% of patients require joint replacement within 5 years and 25% within 20 years; half of these require additional joint replacements (4,21,22).
- Many RA patients also need surgical appliances e.g. crutches, walking aids, collars and footwear. Occupational therapists often need to organise wheelchairs or home adaptations e.g. special seating, walk-in showers or stair-lifts.
- Pain is a disabling symptom that can lead to depression and an increased burden on the individual's ability to cope with activities of daily living and result in heavier use of healthcare resources particularly if patients fail to get appropriate pain management advice (23-25).
- Depression is common in active RA and antidepressants, with or without counselling are often required (26).
- Patients with RA have an increased incidence of infection (12,27) and of lymphoma (28) which require specialist care.
- Patients who have more than 30 joints involved have a 5-year mortality comparable with patients with 3-vessel coronary heart disease or stage III Hodgkin's disease (29).
- Patients with severe RA place a heavy nursing burden on health professionals. Severe disease also causes distress and frustration to staff having to care for severely disabled patients.

Drug treatments for RA

There is a close correlation between joint damage and disability in RA. Average disability scores are 25% of maximum in early disease rising to 50% of maximum after 20 years in patients treated with conventional anti-rheumatic drugs (22). Disease modifying anti-rheumatic drugs (DMARDs - antimalarials, azathioprine, gold, leflunomide, methotrexate, penicillamine, sulphasalazine) are used to slow down the progress of the disease. A meta-analysis of 66 trials in 5343 patients showed that these drugs can improve symptoms, signs and investigations of inflammation (30). This has been confirmed in subsequent trials (31-37). DMARD use correlates with decreased long-term disability (32), can reduce joint damage in a significantly greater proportion of cases than placebo (33,37-41) and is cost-effective (42).
The quality of evidence for the effectiveness of conventional treatments for RA has been reviewed (43). Over the past 15 years rheumatologists have treated patients more aggressively based on new clinical evidence:

- Joint damage occurs early in RA (44) and DMARD treatment can reduce joint damage (14,31,33,36-38,45). A widely held concept is that early in the disease process there is a “window of opportunity” where therapeutic intervention has a disproportionately positive impact on outcome (46-48). Therefore all patients are now treated with such drugs at the time of diagnosis.
- The effectiveness of a “saw-tooth” strategy i.e. when the disease flares up in a patient on a DMARD an alternative is introduced at once (49).
- Combinations of DMARDS, with or without steroids, are more effective than single agents (50-52).

By treating RA more aggressively and early in the disease process the joint damage, and hence disability, systemic complications and joint failure resulting in the need for joint replacement surgery can be reduced.

A substantial minority of patient with RA do not respond to conventional anti-rheumatic drugs and have relentless disease. Such patients incur the greatest direct and indirect costs as a result of their need for medical, orthopaedic, nursing and residential care plus loss of employment. Costs are 10-20x greater in the most severe 20% compared with the least severe quintile (53,54), and are related to the level of disability as measured by the HAQ questionnaire (54). Morbidity and mortality are also related to the severity of the disease (54).

Consequently, although the treatment of RA has improved substantially over the past 20 years with conventional DMARDs, there is still a minority of patients who have a poor prognosis from the disease There is a tremendous need in these patients for new improved drugs, and this is where TNF-α inhibitors have had considerable impact since their introduction 4 years ago.

**TNF-α inhibitors in RA**

There is considerable evidence to support the efficacy of all three available TNF-α inhibitors. This applies to diminished disease activity, increased functional ability, stopping or even reversing radiological progression, and improving energy levels and sense of well-being. This is true for both established and early rheumatoid arthritis. The individual drug companies and arc will provide detailed evidence for this. In clinical practice, TNF-α inhibitors offer the following benefits:

- They act quickly, unlike traditional DMARDs. Data from Derby in 99 patients shows that over 3 months the Disease Activity Scores (DAS) for the 3 drugs dropped by between 2.2 to 2.8 (abstract accepted for BSR Annual Meeting 2005). Data from Prof Scott in Norwich in 163 patients shows a similar mean drop in DAS from 7.1 to 5.1, with tender joint counts dropping from 21.7 to 11.3, and swollen joint counts from 13.9 to 5.8. The Ritchie articular index dropped from 33.4 to 15.8. The data from Norwich shows that not only were these decreases in various scores occurring quickly over 3 months, but they were also maintained at 12 months. All these decreases in scores represent clinically highly significant improvements.
- They are well tolerated with few side effects – withdrawal rates have been far lower than initially predicted highlighting just how effective they have been in those patients eligible for treatment. Only 10% of the Derby and Norwich patients have stopped TNF-α inhibitors due to lack of efficacy or intolerance.
• They often enable other potentially harmful drugs such as NSAIDs, steroids or concomitant DMARDs to be reduced or withdrawn. In Derby 41.7% of patients on steroids were able to decrease their dose of steroids in the first 3 months of treatment (range of decrease 0.4 to 6.25mg of prednisolone daily), and 22% in Norwich (mean decrease 4.23mg/day). In Norwich, 36% of patients (42 out of 130) have been able to reduce their dose of concomitant methotrexate by a mean dose of 7.7mg/week, and 11 out of 35 patients have stopped their other DMARDs (Gold in 6, cyclosporin in 2 and sulphasalazine in 2).

• Patients not only benefit from improvement in pain and disability but also experience improved sense of well-being and increased energy levels. A study from Canada on improvement of health-related quality of life showed significant improvements on adalimumab with QALYs gained per year of 0.145 and 0.104 in two analysed trials (55). A qualitative study from Newcastle showed that patients’ experience of TNF-α inhibitors was good, particularly in terms of physical function and sense of well-being (56). In Norwich a pain visual analogue score dropped from a mean of 70.5 to 36.6 at 3 months, and this was maintained at 12 months. The mean Health Assessment Questionnaire scores decreased from 2.2 to 1.8 at 3 months, with a further drop to 1.6 at 12 months. The visual analogue scores for global health dropped from a mean of 63.1 to 33.3 at 3 months, and this was also maintained at 12 months.

• The group of patients with the poorest prognosis in the past i.e.: those that have failed to respond to many or all of the traditional DMARDs can still respond well to the TNF-α inhibitors. This is certainly the clinical experience of the physicians in Derby and Norwich.

• Patients with RA have a greater risk of cardiovascular morbidity and mortality which may be related to the proatherogenic changes of IL6 and CRP which are increased by TNF-α inhibitors. A recent study from the Netherlands showed that anti-TNF increased HDL-cholesterol levels, raising the possibility that needs further longitudinal data that TNF-α inhibitors may improve the cardiovascular risk profile of RA patients (57).

Updated BSR guidelines for TNF-α inhibitors in RA

In 2001 the BSR produced guidelines for the use of TNF-α inhibitors in RA. These were accepted by NICE, and included in their original guidance. In 2004 the BSR updated the guidelines (see appendix 1). Based on increasing evidence from the literature, and increasing experience in clinical practice, 6 major changes to the use of TNF-α inhibitors were incorporated into the new 2004 guidelines. These are summarised below, and reference is made to further evidence that was not included in or has appeared since the guidelines were updated:

1. Adalimumab was introduced as the third TNF-α inhibitor that has efficacy equal to the other two available agents.
2. There are some circumstances under which TNF-α inhibitors would be used prior to failure of two DMARDs. This was based on two points:
   a. Increasing evidence to support the efficacy of this approach in early aggressive disease.
      i. The Early Rheumatoid Arthritis Study compared etanercept with methotrexate. More rapid control of disease activity was achieved with etanercept, although the groups converged at 12 months (58). A 12 month open-label extension of this study
showed significant differences in x-ray erosion scores, ACR20 improvement criteria, and functional improvement (59). This suggests that rapid and sustained suppression of the disease in the first year may lead to ongoing benefits in the second year.

ii. A comparison of infliximab and methotrexate versus methotrexate alone in active RA with a mean disease duration of under one year demonstrated significantly greater clinical, radiographic and functional benefits in the combination group (60).

iii. A further comparison of infliximab and methotrexate versus methotrexate alone in active RA with a mean disease duration of under one year showed a significant reduction in MRI evidence of synovitis and erosions at 1 year (61). At 2 years functional and quality of life benefits were sustained despite withdrawal of the infliximab therapy.

iv. There is data for the efficacy of adalimumab compared with methotrexate in the treatment of early RA, though currently this is only available in abstract form (62).

It is envisaged that in the near future there will be more evidence to support the early use of anti-TNF therapy, and the pressure to introduce this approach into clinical practice will increase.

b. Contraindications to other DMARDs, particularly where a rapid therapeutic response was required. Data from Derby and Norwich Rheumatology units were referred to above, and demonstrate the rapid speed of efficacy of these drugs seen in patients in clinical practice. Abnormal liver function tests are not uncommon in early inflammatory arthritis, and may contraindicate the use of drugs such as methotrexate and sulphasalazine. Although other DMARDs such as gold injections, hydroxychloroquine and cyclosporine may be used with caution in patients with abnormal liver function, these often take time before they are effective.

3. The new guidelines recognised that some patients improve clinically but this cannot be recorded as a significant fall in DAS scores. For some of these patients they may have been able to reduce other therapy such as steroids and concomitant DMARDs, and it was recommended that such patients should be allowed to continue with their a further three month trial of TNF-α inhibitors. This illustrates some of the drawbacks of DAS estimates, in that they are not sensitive to other useful outcomes, such as decreasing other potentially harmful medication. Data from Derby and Norwich summarised above illustrates the extent to which other potentially harmful drug therapy withdrawal is possible in clinical practice. This is a valuable clinical outcome for which a DAS score improvement of less than 1.2 should not necessarily lead to withdrawal of TNF-α inhibitors.

4. Patients who fail on one TNF-α inhibitor should be entitled to a trial with a further TNF-α inhibitor. This is in keeping with the significant differences between the drugs in their structure, pharmacokinetics and clinical properties (63). The updated guidelines quote the available evidence for switches in TNF-α inhibitors improving efficacy following inadequate response to the first drug. There is evidence that switches from any of the TNF-α inhibitors to one of the others can be helpful. Recent data adds to that in the updated BSR guidelines:

   a. A retrospective study of 20 patients switching from etanercept to infliximab due to lack of efficacy showed improvement that was similar to infliximab patients with no prior TNF-α inhibitor (64).
b. A recent study from Leeds showed that 68% of a group of non-responders to infliximab when switched to etanercept showed an ACR20 response and decreased CRP at 12 weeks (65).

c. Data from Norwich in 38 patients switching from one TNF-α inhibitor to another mainly due to lack of efficacy (61%), or side effects (34%) and in the remaining cases patient preference and drug availability. 27 out of 38 (71%) showed a clinical response at 3 months, and 74% of these continued to show a response at a mean follow-up of 11 months.

d. Data from Cannock Chase Hospital is available in 24 patients switching from infliximab to etanercept, and 23 from infliximab to adalimumab. Reasons for switching were loss of efficacy (21 patients), lack of efficacy (1), infusion reaction (13), and miscellaneous causes (12). 10 out of 19 patients in whom data was available showed significant improvement on switching to etanercept, and 14 out of 21 on switching to adalimumab (abstract to be presented at the Midland Rheumatology Society Meeting, 25th February 2005).

5. In some circumstances it may be appropriate to increase (or decrease) the dose or frequency of TNF-α inhibitor treatment in order to obtain optimal control of disease activity. A recent study from Belgium in a large out-patient sample of 511 out-patients showed that the 22% of patients losing response to infliximab over a 22 week period could be improved by increasing the dosage of the drug by 100mg (66). Data from Norwich shows that in 133 RA patients treated with infliximab 19 (14%) had flares or an inadequate response that required an increase in infusion frequency. 74% of patients responded to infusions when the frequency was reduced to 6 or 7 weekly. In the United States the Food and Drug Administration has further approved that the dosage of infliximab can be increased to 10mg/kg and the doses can be given as often as every four weeks to optimise patient outcome (information based on the US package insert dated June 2002).

6. The co-prescription of DMARDS with TNF-α inhibitors other than methotrexate can be safe and effective. A recent paper has confirmed that the administration of leflunomide with infliximab is safe and efficacious (67). An abstract from the ReAct study of adalimumab suggests that it is as effective in combination with other DMARDs as with methotrexate in treating rheumatoid arthritis (68).

Based on the clinical experience gained over the last 4 years of use of the TNF-α inhibitors the BSR would strongly oppose any steps that would render TNF-α inhibitors less available to RA patients. We would argue that these therapies should have an expanded role in the management of aggressive RA. The updated 2004 BSR guidelines attempt to address these areas.

Health economic analyses of TNF-α inhibitors in RA

TNF-α inhibitors are expensive, but there are a number of independent studies that have suggested that their use is cost effective:

- In an editorial in 2001 Lambert pointed out that the economic consequences of failing to slow disease progression in RA far outweigh the cost of any currently available therapy for the disease, including TNF-α inhibitors (69).
- A study of infliximab showed acceptable cost-effectiveness ratios (<$US50,000 per QALY gained) when compared to methotrexate monotherapy in patients who had not responded to previous DMARD therapy (70).
A study of etanercept and methotrexate showed this combination to be more effective than other DMARDs at a cost of $34,800 to achieve an ACR70 over a 6 month period. An ACR70 represents a dramatic decrease in disease activity (71).

A study of infliximab over 54 weeks suggested a cost-effectiveness ratio of $9100 per QALY gained when compared to methotrexate alone. This study applied a societal perspective and included indirect and productivity costs (72).

A study of Infliximab over a 2 year period suggested a cost per QALY gained of £29,900 (73).

A study of etanercept estimated the cost per QALY of £16,330 (74).

A Swedish study showed that patients improving on infliximab and etanercept within 3 months of treatment incurred a cost per QALY of €36 900 to €43 500, with the greatest gains for those with more severe disease (75).

A further Swedish study on adalimumab showed similar results, with the cost per QALY of €35 000 to 42 000 (76).

One study suggested high costs per QALY for use of infliximab and etanercept, but did not address potential effects on joint replacement, hospitalisation, mortality, or all aspects of quality of life (77). The model used has been criticised based on assumptions of both estimates of withdrawal rates and disability progression, and HAQ improvement achieved by responders (78). In conclusion, most studies suggest an incremental cost-effectiveness ratio that is in keeping with other drugs that have been approved by NICE, and a study that suggested high costs per QALY has been heavily criticised.

As experience of these drugs increases, and with appropriate funded data collection processes, it will be possible to collect further information on their impact on

- ability to keep working. An important recent study from Finland has shown that prompt induction of remission translates into maintenance of work capacity (79). Failure to achieve an ACR20 at 6 months carries a high risk for work disability. This strongly supports the need for aggressive early intervention.
- hospital admissions
- orthopaedic surgery,
- morbidity and mortality from other drugs such as other DMARDs, steroids, and NSAIDs.
- disability with attendant need for Disability Living Allowance, aids, appliances and home adaptations
- quality of life of RA patients and their families
- morale of rheumatology staff, and their ability to provide better care for other patients with reduced waiting lists for new patients, and quicker access for urgent patients

Other implications of TNF-α inhibitor use

TNF-α inhibitors have other workload implications:

- There are additional staffing costs for specialist practitioners (nurses or physiotherapists) to monitor disease activity to ensure selection of appropriate patients for both the initiation and continuation of treatment.
- Nursing time is required to teach patients the technique of subcutaneous injection (etanercept and adalimumab) and for supervising infusions of infliximab. The latter have to be given in a hospital environment because of the potential risk of anaphylaxis with intravenous protein use.
- Periodic blood tests are required but the vast majority of patients eligible for these drugs will already be having regular blood tests to monitor conventional second-
line drugs for toxicity. The monitoring requirements for TNF-α inhibitors are less stringent than for most DMARDS (leflunomide, methotrexate, azathioprine and gold) so there may be a net decrease in the number of tests performed with cost savings.

• Submission of data to the BSR Register of patients on TNF-α inhibitors requires funded medical, nursing and clerical input.
• As with the introduction of any new class of therapeutic agent, rheumatologists have to devote some time to the education of consultant colleagues, junior hospital staff, GPs and paramedical staff on possible complications of treatment. Rheumatologists have considerable experience in monitoring conventional second-line agents for adverse events and have pioneered the use of telephone help-lines and nurse practitioners for this purpose. This infrastructure, present in most rheumatology units, will need expanding but can be applied to TNF-α inhibitors.

The likely impact of limiting access to TNF-α inhibitors

We have concerns about the likely effects of decreasing access to these agents and would highlight that this would result in a lost opportunity to reduce the long term complications of RA with all the consequent loss of impact on primary as well as secondary care services and on the indirect costs to the community of RA:

• Doctors are duty-bound to treat their patients to the best of their ability and are frustrated by their inability to use treatments of proven efficacy. We have ethical concerns that patients with active and progressive arthritis who have failed to respond to all conventional second-line drugs might be denied an effective treatment. All rheumatologists have such patients.
• The patient community is only too aware of the great success that these drugs have had in many of their fellow sufferers. Patients are already concerned that access to these drugs is limited.
• Many other countries around the world have much less stringent criteria for eligibility for TNF-α inhibitors than the UK. The 2001 World health Organisation Collaborating Centre consensus meeting on anti-cytokine therapy identified appropriate patients as those who had failed DMARDs and had unacceptable disease activity defined as 5 swollen joints plus an elevated ESR of more than 28mm/hr or a CRP of more than 20mg/l (80). In order to achieve a DAS score of 5.1, UK RA patients need considerably more disease activity than these recommendations. An abstract from the BSR Biologics Register presented at the recent BSR meeting demonstrated that UK patients going onto anti-TNF have a mean disease duration of 14 years, a DAS of 6.7 and a Health Assessment Questionnaire (HAQ) score of 2.1 (81). This translates into well-established disease with high levels of disease activity and disability. The abstract went on to reveal that a high HAQ score associated with a poor anti-TNF response. This argues for a greater emphasis on the use of anti-TNF earlier in the disease, and in patients who have accumulated less damage. Most European countries require a DAS score of more than 3.2, which is much less restrictive than the 5.1 in the United Kingdom. The Irish Rheumatology Society has recently released anti-TNF guidelines which are much less restrictive than the UK guidelines. Further limits to anti-TNF usage would be met by an angry response from patients and the Rheumatology community.

Concluding Statement
RA can have a devastating effect on the individual affected, their families, and society in general. TNF-α inhibitors have rapidly become established as highly efficacious drugs in the treatment of this disease. The drugs are expensive, but uncontrolled RA is very costly also. Current drug treatments can be effective, especially when used early and aggressively in the course of the disease. However, despite these improvements a minority of patients still do very badly. The original BSR guidelines for the use of TNF-α inhibitors provided a framework for clinicians to use these drugs appropriately, and secured the agreement of NICE. The updated guidelines seek to extend some of the indications for these drugs based on increased scientific and clinical evidence over the past 4 years. Most health economic analyses place the TNF-α inhibitors in the cost per QALY range that NICE has previously found acceptable for other drugs. It is the hope of rheumatological care teams and their patients that NICE will support the continuing use of TNF-α inhibitors in RA, and allow their use to be extended.

References


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PCR submission to NICE

The PCR fully endorse the ARMA submission.

The PCR supports the use of Biologics within the BSR Guidelines.

RA is a chronic disease with a major effect on all aspects of a patient’s life including their partner, friends, relatives and carers. These problems have been well illustrated by patients from NRAS and highlight the long-term costs to the NHS and society as a whole.

This group of patients do well on Biologics – again illustrated by NRAS.

Some comments:

- Early referral and treatment is essential to prevent long-term disability. This may be more easily obtained with practice based commissioning.
- The PCR would support early use of Biologics in appropriate patients. This would necessitate early referral and treatment with DMARDs if disability is to be minimised.
- The aim of treatments is to:
  - Alleviate pain and suffering
  - Maintain function and mobility
  - Maintain work capacity
  - Maintain activities of daily living and quality of life
  - Reduce and slow joint damage
- Importantly evidence now shows that Biologics are superior to methotrexate in producing a clinical response, reducing disability and improving quality of life. They also reduce radiological progression; this may be a marker for predicting long-term outcomes.
- While taking into account patient choice, doctors need to be in a position of being able to prescribe biologics solely on clinical need, and not restricted by postcode prescribing or budgetary constraints

These comments are made with the ultimate goal of achieving and maintaining remission and preventing disability: this will give the best value for the individual and society.
The Royal College of Nursing Rheumatology Forum submission to NICE as a member of the Arthritis and Musculoskeletal Alliance on the reappraisal of anti-Tumour Necrosis Factor alpha blockers adalimumab, etanercept and infliximab in the treatment of Rheumatoid Arthritis.

The Royal College of Nursing Rheumatology Forum (RCNRF) represent members of the RCN who have an interest in rheumatology. There are approximately 1,400 members of this forum representing a wide range of nursing roles including nurse consultants, ward and community nurses. The RCNRF undertake a number of initiatives to support nurses in delivering care to those with musculoskeletal conditions. These include preparing guidelines, disseminating good practice and running educational events.

Nurses and practitioners are an integral part of the team providing support to those being assessed, treated and monitored with TNF-\(\alpha\) inhibitors.

Pain, fatigue, depression and disability have a significant consequence on those with Rheumatoid Arthritis and their quality of life and ultimately use of healthcare resources. Treatments that address these symptoms are imperative if we are to reduce the downward spiral of progressive disability and other co-morbidities such as cardiovascular disease. The ability of individuals to participate more fully in their own care and activities of daily living has the potential to enable some patients to return to work or at the very least be more independent and in some cases potentially release carers to return to work.

In the last four years clinical experience has enabled patients and healthcare professionals to recognise the importance of these treatments. In addition to the already recognised and demonstrated criteria to measure benefits of treatment smaller qualitative studies (accepting limitations in transferability and possibly robustness) have highlighted the fact that we need further research to gain a wider global understanding of the measures we should use to capture the patients experience of reductions in symptoms, in addition to the already clearly demonstrated benefits based upon the current criteria for evaluating\(^1,2\) One such measure is that of fatigue.

Anecdotal, experience highlights some omissions from the current guidelines that should be considered. These include the fact that patients receiving treatment with TNF-\(\alpha\) inhibitors often have an improvement in symptoms (pain being one of the most significant) that potentially can enable them to reduce their non-steroidal anti-inflammatories, analgesics and possibly reduce oral steroids. These reductions have a benefit in reduced prescribing costs and risks related to these therapies. Due to the current restrictions on prescribing (in the criteria) patients are often reluctant to attempt any reduction in their medications in case it should adversely affect their disease activity score (DAS) and threaten their eligibility to continue treatment.

In addition, early evidence appears to show significant radiological benefits to those treated with TNF-\(\alpha\) inhibitors. It is hoped that as part of the overall
review NICE will consider less stringent disease activity criteria used by our European partners and still demonstrate the value of treatment.

Nurses and allied healthcare professionals have directed their efforts since the first NICE guidance to ensuring patients are empowered and effectively managed according to the current guidelines. This has had an impact on services but one that is achievable if services can begin to look at a long term strategy of delivering these therapies to eligible patients. Practitioners have also had to undertake additional work to ensure that the detailed data required by NICE and the BSR has been collected for the BSR BR. It is hoped that the NICE review will have access to this data.

The RCN Rheumatology Forum developed a guidance document for practitioners to support good practice and adherence to BSR/NICE guidance (RCN, 2003). This has supported practitioners in identifying key factors to consider in relation to eligibility criteria and aided transparency in the patient’s pathway of care.  

Beyond the Pain

The Social & Psychological Impact of RA

A report by NRAS

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3 Conclusions, implications and recommendations

4 National Rheumatoid Arthritis Society
Preface

Rheumatoid arthritis (RA) is a devastating disease that can cause severe pain and disability to those affected. However the physical symptoms of RA such as pain, lack of mobility and tiredness can have a significant and wide-reaching effect on all aspects of a person’s life, affecting their relationships with partners and family, limiting their career progress and ability to work and impacting on their emotional and psychological well-being and state of mind.

The National Rheumatoid Arthritis Society (NRAS) is the only patient led group focusing specifically on RA. Our aim in conducting this survey was to explore in depth the social and psychological impact of RA by talking to the people who live with this disease every day of their lives. By understanding the full impact of living with RA, we can campaign to improve services in the areas which will benefit RA patients and their carers most and ensure that people have access to the treatments and services which will allow them to live their lives as fully as possible.

We would like to thank all our members who gave up their time to participate in this survey and talked in great detail about very personal areas of their lives including their relationships, sex lives, careers and self-image.

Ailsa Bosworth

Chairman of NRAS
1 Introduction

1.1 What is rheumatoid arthritis?

The word rheumatoid arthritis takes its origins from the Greek words arthron (joint) and itis (inflammation). Symptoms include pain, swelling, and stiffness in inflamed joints.

Rheumatoid Arthritis (RA) is a chronic, progressive and disabling disease affecting between 0.5 – 1% of the UK adult population. It is an incredibly painful condition, which can cause disability and ultimately can seriously affect a person's ability to carry out everyday tasks. The disease can progress slowly or very rapidly, causing inflammation, swelling and stiffness and damaging cartilage and bone around the joints. Any joint may be affected but it is commonly the hands, feet and wrists.

It affects approximately 3 times more women than men and onset is generally between 30 – 50 years of age although you can get the disease at any age. There are around 12,000 children under the age of 16 with the juvenile form of the disease. It has no known cause or cure although if diagnosed and treated early with appropriate drugs, the prognosis is significantly better today than it was 20 years ago. RA is a lot more common than Multiple Sclerosis; however, awareness of the severity of the condition tends to be restricted to those who are directly or indirectly affected. NRAS is working hard to make politicians and the general public more aware of this serious and common disease.

1.2 Survey methodology and demographics

The National Rheumatoid Arthritis Society (NRAS) commissioned a survey of its members to establish a clear and up to date picture of the social and psychological impact of RA, focusing on issues such as personal relationships, careers and self image. The survey was supported by an educational grant from Wyeth.

A quantitative study was undertaken in September and October 2003.

Market researchers from an independent agency conducted individual, structured telephone interviews with 200 NRAS members using a 56-item questionnaire developed in consultation with expert advisors to NRAS (Dr Bruce Kirkham, Consultant Rheumatologist at Guy's Hospital, London, Dr Ernest Choy, Consultant Rheumatologist, King's College Hospital, London and Susan Oliver, Independent Nurse Specialist Rheumatology).

Most respondents (85%) were female. Just over half (56%) had had RA for less than 10 years. The average length of time from onset of the disease was 11.8 years. The average length of time since diagnosis was 10.6 years, and the average age at diagnosis was 42.8. Just under half of respondents (49%) were registered as disabled. Of the total sample, a significant minority (34%) remained in work and 25% lived alone.
2 Key findings

2.1 RA and working life

Work disability can be an expensive consequence of RA, which translates into less income for patients and less productivity for society. Indeed, it is estimated that 9.4 million working days are lost because of RA, representing £833 million in lost production. Inflammatory arthritis also accounts for 1.9 million GP consultations and 45,887 hospital admissions per annum.\(^2\)

However the impact of RA on working life affects more than just economics. Of those surveyed, 88% felt that having a job helps them cope with their disease. Among working respondents (34% overall), 85% felt that their RA had reduced their choice of occupation and 63% felt that their career progress had been hampered by their RA. The proportion that felt their potential to succeed at work had been seriously reduced by RA was highest in younger age groups, with 75% of 25-34 year olds believing this to be true.\(^5\)

However, most (63%) of those working said their employer was sympathetic to their condition.\(^5\)

- 88% of working respondents felt that having a job helps them cope with RA\(^5\)
- 63% of working respondents felt RA had affected their career progress \(^5\)
- 85% of working respondents felt RA had limited their career choice \(^5\)
- The incidence of depression was higher amongst non-workers (70%) than workers (47%) \(^5\)

*Being in employment has a number of benefits for people with RA, therefore people with RA should receive the most effective treatments and support at an early stage to allow them*
to stay in work for as long as possible. Given that 63% of those working said their employer was sympathetic, people should consider informing their employer about their disease as soon as possible after diagnosis and work together to accommodate any changes necessary to enable that person to stay in work for longer.

2.2 RA and self image

The physical damage caused by RA and the limitations it produces can take an understandable toll on the self esteem and confidence of some individuals. Though nearly all respondents agreed that there were many people worse off than themselves, many felt that RA had had a detrimental impact on their self image. Half of respondents said that their condition caused them to feel a lack of confidence and embarrassment and 58% said they felt very unattractive because of their RA either sometimes or all of the time.

Many respondents expressed how tired, angry and worthless they felt as a result of having RA. Indeed, the main anxieties respondents felt in relation to their condition were being dependent on other people and their declining mobility. Two-thirds (65%) of those questioned “hated” being dependent on other people and 57% felt frustrated at not being able to get around. Just under half of the sample felt that they were not contributing to their family because of their RA. However an overwhelming majority of 90% said they could rely on their family and friends to help them.

- 50% said that RA has decreased their confidence and caused them embarrassment
- 58% said RA made them feel very unattractive some or all of the time
- 65% hated being dependent on others
- 57% felt frustrated at not being able to get around
- 90% said they could rely on their family and friends to help them

As well as causing significant physical pain and impaired mobility, RA also has a huge impact on a person’s self-esteem causing them to feel frustrated, dependent and unattractive at times. A low self-image can impact negatively on relationships and performance at work, so it is important that people with RA are able to
discuss these feelings with appropriate healthcare professionals.

“I FEEL THAT PEOPLE LOOK AT YOU DIFFERENTLY. I WANT TO FEEL LIKE EVERYONE ELSE”

“THE DEFORMITY OF MY HANDS CAN BE EMBARRASSING”

2.3 RA and depression

Almost two-thirds (62%) of respondents believed they had suffered from depression. The rate of self-reported depression was higher among non-working respondents (70%) compared to working respondents (47%), supporting the previous finding that work is believed to help in coping with RA. Only 5% of those reporting depression thought that their RA was unconnected. Over three-quarters of the sample reporting depression due to RA thought that pain and chronic tiredness had contributed to their depression (79% and 88% respectively); 50% said feeling isolated had contributed and 79% said that being unable to lead a normal life had contributed to feeling depressed.5

A significant minority (24%) had taken no steps to counteract their depression. The remainder had tried a variety of strategies, including: consulting a doctor
(57%), taking antidepressant medication (37%), talking to friends and family (22%), consulting a psychiatrist (7%), counselling (7%), support groups (4%), positive thinking (3%), new activities (3%), hypnosis (2%), therapy (2%), lifestyle changes (2%), painkillers (2%), vitamin supplements (2%), prayer (2%), consulting psychiatric nurse (2%), relaxation and yoga (2%), sleeping pills (1%), time off work (1%).

- 62% believed they had suffered from depression
- 83% said their depression was due to their RA
- Rates of depression were higher among non-working respondents than working respondents
- Pain, chronic tiredness, feeling isolated and being unable to lead a normal life were cited as principal contributory factors

The daily pain experienced by people with RA is a major cause of depression. To reduce this, rheumatologists should ensure that people with RA are receiving the most appropriate and effective treatments as early as possible in their disease. If people with RA have concerns or worries, both in terms of the symptoms of their disease and also the wider impact (including depression and relationship problems), they should highlight this to their rheumatology care team as early as possible so that appropriate advice and support can be arranged.
"I AM ANGRY THAT I HAVE NOT BEEN ABLE TO HAVE CHILDREN DUE TO MY CONDITION AND MY MEDICATIONS"

2.4 Self-management and treatment

Joint deterioration and erosion can be seen very early on when x-rays are taken of affected joints. While this can usually be reduced with appropriate treatment, delays in receiving treatment mean further disease progression, which can result in irreversible joint damage. Patients at all stages of the disease benefit from treatment, however, any hope of slowing or moderating this damage lies in early management and aggressive treatment with a complex regimen of drug treatment and therapy to reduce long term disability. Early, treatment using a single DMARD (Disease Modifying Anti-Rheumatic Drug) such as methotrexate or a combination of DMARDs is now accepted best practice in the treatment of RA and these drugs may be supplemented by simple analgesics and/or NSAID (non-steroidal anti-inflammatory drugs).\textsuperscript{1}

The recent introduction of biologic treatment for RA has transformed the quality of life of some patients who failed to respond to traditional therapies. These complex drugs block the action of particular target molecules or cells that are believed to be important in the joint inflammation process.\textsuperscript{1} The molecules targeted include tumour necrosis factor and interleukin-1 and the drugs can be given either by infusion (drip) into a vein or self-administered injection.
Most respondents (89%) used pharmacological treatments to help them control their symptoms, and 64% said they used diet and exercise programmes in addition to their drug treatment. The vast majority (95%) thought that medication, above other methods, had the most impact on their condition. The most commonly prescribed treatments were methotrexate (51%), prednisolone (30%) and COX 2 inhibitors (21%). Most (81%) respondents felt that their healthcare professionals involved them in treatment decisions. The majority (93%) thought this had a positive impact on their condition. Only a small percentage of respondents use alternative therapies such as evening primrose (4%) or a medical herbalist (1%) or self-help programmes (3%).

Prescribed medication is the most important factor in disease control for people with RA; therefore it is vital that they receive the most appropriate and effective medication as early as possible.

2.5 RA and relationships

Given that RA affects self esteem, confidence, emotional and psychological well-being and work opportunities, it is not surprising that 78% of respondents believed that their condition had had an impact on their relationships. For 37% of respondents, this impact was either “major” or “considerable”.

WHAT SINGLE ASPECT HAS THE MOST IMPACT ON YOUR DISEASE?

Prescribed medication is the most important factor in disease control for people with RA; therefore it is vital that they receive the most appropriate and effective medication as early as possible.

2.5 RA and relationships

Given that RA affects self esteem, confidence, emotional and psychological well-being and work opportunities, it is not surprising that 78% of respondents believed that their condition had had an impact on their relationships. For 37% of respondents, this impact was either “major” or “considerable”.
Having RA can complicate sexuality because of its association with pain, fatigue and depression. Though 44% said that their condition never threatens their relationship with their partner, 27% felt that it did. And 12% felt that their RA had made it impossible to begin a new relationship. Almost a quarter (23%) said that their condition makes it impossible to have sex, with 48% citing pain as the main barrier to a sex life. Almost half (49%) said they felt having RA inhibits their partner during sexual activity. That said, 73% said they felt their partner understood the impact of RA on their sexual desires.5

Less than half of all respondents (48%) felt they were able to discuss any problems with their sex life with a healthcare professional. This figure rose to 57% in those aged 25-34.5

• 78% felt RA had an impact on their relationships 5
• 37% said this impact was major or considerable 5
• Nearly 20% of single respondents agreed that their disease was the main reason for breaking up their relationship 5
• Among divorced respondents this figure rose to 25% 5
• 38% of 25-34 year olds said RA makes it impossible to have a lover 5
• 23% said RA prevented sexual activity 5
• 49% felt that RA inhibited their partner during sex 5

“I FEEL LESS SEXUALLY ATTRACTIVE TO MY HUSBAND”

There are significant barriers to young people with RA being able to begin and maintain a lasting and meaningful relationship, but these
Barriers may be decreased with the right treatment at the right time. Problems achieving and maintaining a loving sexual relationship with their partner are an added burden for people of any age with RA and although the survey revealed that 73% felt their partner understood the impact of RA on their sexual desires, they should also consider their partner’s needs and fears.

People with RA and their partners should have access to support and advice from their rheumatology care team about the issues that RA may raise in terms of their relationships and sex at an appropriate stage in the development of their disease.

3 Conclusions, implications and recommendations

As these survey findings show, RA has a significant and far-reaching impact on almost every aspect of a person’s life and also the life of their partner and their family.

• Treatments for RA can help improve mobility and reduce pain associated with the disease and even halt disease progression. More importantly, improved disease control can help give a person their life back by freeing them of living with constant pain, immobility or tiredness. Therefore it is vital that people with RA should receive the most effective treatments as early as possible, to allow them to work and interact fully with family and friends. The ability to get an early diagnosis is therefore clearly vital.

• Depression caused by pain, fatigue and feelings of dependence is particularly prevalent in people with RA. Early and effective treatment and holistic intervention can help prevent depression which, if left untreated, can also become a debilitating and chronic disease.

• Relationships and sex can be a problem for people of all ages with RA. For young people who have not yet settled down with a partner this presents a major barrier to establishing a lasting relationship. However these barriers can be decreased with effective treatment. People with RA should have access to support and advice from their rheumatology care team about the issues that RA may raise in terms of their relationships and sex.

As these results demonstrate, everyone involved in the life of a person with RA including rheumatologists, specialist nurses, carers, employers and the
patients themselves have an important role to play in tackling the social and psychological impact of RA.

“I HAD TO GIVE UP WORK AND FIND IT DIFFICULT TO CONTRIBUTE TO THE FAMILY”
“I HAVE TO LIVE FOR THE DAY, UTILISE EVERY MOMENT”

4 National Rheumatoid Arthritis Society (NRAS)

NRAS is committed to providing help and advice to people with RA and their carers and families.

National Rheumatoid Arthritis Society
Briarwood House
11 College Avenue
Maidenhead
Berkshire SL6 6AR
Tel: 01628 670606
Fax: 01628 638810
Email: enquiries@rheumatoid.org.uk
www.rheumatoid.org

Registered Charity No: 1086976

2 Arthritis Research Campaign. The Big Picture, 2003
3 Arthritis Research Campaign, Rheumatoid Arthritis, 2003
4 http://www.mssociety.org.uk/what_is_ms/index.html
5 National Rheumatoid Arthritis Society. Beyond the Pain - The Social & Psychological Impact of RA, October 2003

Sponsored by an educational grant from Wyeth. ZENB 404/01/04
APPENDIX B
ABOUT THE ORGANISATIONS PARTICIPATING IN THIS SUBMISSION

Arthritis and Musculoskeletal Alliance
41 Eagle Street, London, WC1R 4TL
Tel: 020 7841 5191  Fax: 020 7242 3277
E-mail: apage@rheumatology.org.uk
Website: www arma uk net
Registered Charity No: 1054784

ARMA - The Arthritis and Musculoskeletal Alliance - is the UK umbrella association bringing together support groups, professional bodies and research organisations in the field of arthritis and other musculoskeletal conditions.

ARMA aims to:
• Raise awareness of the need for high quality services for those with arthritis and other musculoskeletal conditions
• Promote the development of treatment, prevention, rehabilitation and relief
• Foster co-operation, understanding and mutual support between all individuals and organisations concerned with these conditions
• Provide a forum for the exchange of ideas and information between member organisations

Arthritis Care
18 Stephenson Way, London NW1 2HD
Tel: 020 7380 6500  Fax: 020 7380 6505  Helplines: 0808 800 4050
Email: Helplines@arthritiscare.org.uk
Website: www.arthritiscare.org.uk
Registered Charity No: 206563

Arthritis Care is the leading membership organisation working with people with arthritis and musculoskeletal conditions. Arthritis Care has 70,000 supporters and has a network of over 7,000 volunteers, all of whom live with, or are affected by some form of arthritis. AC works across all communities to support those with arthritis manage their condition. This is achieved by campaigning providing, information, training and support services. The AC Helplines receive on average 8,000 calls per year. These are monitored and there has been an increasing amount of calls concerning the anti-TNFα therapies. People want a range of information from general information about what the drugs are. They have often read about them and want to know how to access them, often having not consulted their rheumatologist.

Arthritis Research Campaign (ARC)
Copeman House, St Mary’s Court, St Mary’s Gate, Chesterfield S41 7TD
Tel: 01246 558033  Fax: 01246 558007
Email: info@arc.co.uk
Website: www.arc.org.uk
Registered Charity No: 207711

The Arthritis Research Campaign (arc) was founded in 1936 and is the fourth largest medical research charity in the UK. We are the major provider of funding for research into arthritis and musculoskeletal disease in the UK, with a current expenditure of over £22 million a year. Our income is provided entirely by voluntary donations from the public and we receive no Government support. Our mission is to advance the understanding, prevention and treatment of arthritis and
associated rheumatic conditions and this is achieved by supporting the highest quality basic and clinical research into these diseases and disseminating the results of that research. About one third of our research budget, of approximately £20 million, provides support for our 2 research institutes, the Kennedy Institute, Imperial College, London (where TNF-alpha blockers were originally developed for the treatment of RA) and the Epidemiology Unit, University of Manchester. The remaining two thirds of the research budget provides competitive peer reviewed “response mode” grant funding to universities and hospitals within the UK, through a portfolio of grant schemes including projects, programmes, fellowships and clinical trials. Approximately £1 million a year is used to provide information and education about the rheumatic diseases to medical professionals, patients and the general public.

British Health Professionals in Rheumatology (BHPR)
41 Eagle Street, London WC1 4TL
Tel: 020 7242 3313 Fax: 020 7242 3277
Website: www.rheumatology.org.uk
Registered Charity No: 10000668
The British Health Professionals in Rheumatology exists to unite and support members of the multi-disciplinary team (MDT) in delivering best quality care which meets the needs of individuals with musculoskeletal conditions (MSCs).

Aims of BHPR

- To promote the key role of the multi-disciplinary team (MDT) in delivering best quality care for people with musculoskeletal conditions
- To support Health Professionals / allied care workers in their role as members of the MDT
- To inform, influence and facilitate health policy and practice to address the needs of people with musculoskeletal conditions
- To be a viable and effective organisation with its own unique identity.

British Institute of Musculoskeletal Medicine (BIMM)
34 The Avenue, Watford, Herts WD17 4AH
Tel: 01923 220 999 Fax: 01923 249 037
Email: info@bimm.org.uk
Website: www.bimm.org.uk
BIMM is a professional organisation of doctors interested in diagnosis and management of musculoskeletal disorders, concentrating on manual treatments and injections for non-inflammatory spinal, joint and soft tissue lesions. They expect to keep systemic drug treatment to a minimum, but await with interest advances in this aspect of disease management. The Institute is involved in the education of doctors and the general population in such matters. BIMM organises regular conferences and additional courses of instruction for Registered Medical Practitioners who wish to further their knowledge in this field of practice. Some members are also involved in research.

National Rheumatoid Arthritis Society (NRAS)
Unit B4, Westacott Business Centre, Westacott Way, Littlewick Green, Maidenhead SL6 3RT
Tel: 01628 823524 Fax: 0845 458 3971
The NRAS is the only patient led charity in the UK specifically for people with rheumatoid arthritis, their families and carers. NRAS have a national network of volunteers who themselves have RA and provide peer to peer support, helping to facilitate the networking of people with RA and working with NRAS and health professionals to encourage and promote self-help. NRAS have an annual award (Patients in Focus) for rheumatology health professionals to reward and publicise best practice in patient centred initiatives.

Our website has received over 100,000 visits and the number of calls to our helpline is increasing month on month. Anti-TNFα treatment is one of the subjects we are frequently asked about in letters, emails and through our help line.

Primary Care Rheumatology Society (PCR)
PO Box 42, Northallerton, North Yorkshire DL7 8YG
Tel: 01609 774 794  Fax: 01609 779 940
Email: helen@pcrsociety.freeserve.co.uk
Charity Registration No. 327583
The Primary Care Rheumatology Society (PCR) was founded in 1986. The PCR seeks to improve GPs’ knowledge and understanding of rheumatology and hence the care GPs provide to arthritis patients. The PCR’s membership consists of GPs with an interest in arthritis. The PCR has a high and growing reputation, both nationally and abroad. The PCR’s work on rheumatoid arthritis (RA) and its separate guidelines for managing RA and osteoporosis have all been critically acclaimed. The Society’s diploma in musculoskeletal medicine now run by Bath University is well established and attracts primary care physicians from around the globe. The Society runs an annual conference for its members to learn, keep up to date and exchange information.

The PCR has worked with ARMA on its submission.

Royal College of Nursing
20 Cavendish Square, London W1G 0RN
Tel: 020 7409 3333  Fax: 020 7647 3425
Website: www.rcn.org.uk
The Royal College of Nursing is a Professional Organisation that represents its nursing members in all fields of care. The wider scope of the RCN is to support and advise nurses in their professional roles ensuring they are empowered to provide high quality care.

The RCN Rheumatology Forum (RCNRF) works to improve standards of care for those with all forms of musculoskeletal conditions. This is achieved by supporting nurses in their nursing roles providing clinical expertise and high standards of professional care.

The RCNRF hold educational events each year, prepare and distribute newsletters on key issues in care and disseminate best practice, act as an advisory and supporting group providing expert resource for nursing within the specific specialist area of rheumatology. This involves representation at working parties, supporting medical and therapy colleagues and patients in the development of documents and standards for musculoskeletal services.
The Forum members also work as a member of the Arthritis and Musculoskeletal Alliance to enhance awareness and the provision of care by working as a member of the wider professional and patient groups in raising awareness and developing standards of care.
## APPENDIX C
### JOINT SUBMISSION STEERING GROUP MEMBERSHIP

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Position</th>
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<tbody>
<tr>
<td>Ms Ailsa Bosworth</td>
<td>Chief Executive, NRAS</td>
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<td>NRAS</td>
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<tr>
<td>Dr Robin Butler MD FRCP</td>
<td>Consultant Rheumatologist, Oswestry</td>
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<td>ARMA</td>
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<tr>
<td>Ms Patricia Cornell</td>
<td>Senior Rheumatology Practitioner</td>
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<td>RCN</td>
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<tr>
<td>Dr Chris Deighton</td>
<td>Consultant Rheumatologist, Derby</td>
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<tr>
<td>BSR</td>
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<tr>
<td>Dr Madeleine Devey</td>
<td>Scientific Advisor, ARC</td>
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<tr>
<td>ARC</td>
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<tr>
<td>Dr John Dickson MRCGP FRCP (Glas) FRCP (Lond)</td>
<td>Business Manager of PCR</td>
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<td>PCR</td>
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<tr>
<td>Ms Christine Donohoe</td>
<td>Rheumatology Nurse Specialist, PAHNT</td>
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<td>PAHNT</td>
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<tr>
<td>Dr Ian Griffiths</td>
<td>Consultant Rheumatologist, Newcastle</td>
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<td>BSR Biologics Register</td>
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<tr>
<td>Mrs Lindsey Hawley</td>
<td>Senior Rheumatology Practitioner, Dorset</td>
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<tr>
<td>BHPR</td>
<td></td>
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<tr>
<td>David Isenberg</td>
<td>Academic Director of Rheumatology, UCL</td>
</tr>
<tr>
<td>BSR</td>
<td>President of BSR</td>
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<tr>
<td>Dr Jo Ledingham</td>
<td>Consultant Rheumatologist, Portsmouth</td>
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<tr>
<td>BSR</td>
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<tr>
<td>Ms Rahana Mohammed</td>
<td>Policy and Campaigns Manager, England</td>
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<tr>
<td>Arthritis Care</td>
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<tr>
<td>Ms Susan Oliver RGN MSc</td>
<td>Chair of RCNRF</td>
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<tr>
<td>RCN</td>
<td>Independent Nurse Specialist in Rheumatology</td>
</tr>
<tr>
<td>Ms Abigail Page</td>
<td>Policy and Campaigns Officer</td>
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<tr>
<td>ARMA</td>
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<tr>
<td>Prof David Scott</td>
<td>Consultant Rheumatologist, Norwich</td>
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<tr>
<td>RCP</td>
<td>Honorary Professor UEA</td>
</tr>
<tr>
<td>Ms Margaret Somerville MSc</td>
<td>Clinical Research Manager (Rheumatology), Norwich</td>
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<tr>
<td>BA(Hons)</td>
<td>Deputy Secretary BHPR</td>
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<td>BHPR</td>
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Mr Michael Wright FRCP  British Institute of Musculoskeletal Medicine
representative to ARMA
APPENDIX D
DECLARATION OF INTERESTS
Members of the steering group were asked to clarify their and their organisations’ relationships with the manufacturers of the products being appraised by NICE:

**Personal:** Members were asked to declare if they had been sponsored to attend scientific or other meetings in the past 24 months or if they had a direct financial stake in the manufacturing companies; clinicians were also asked if their units had received funding from the manufacturers to take part in clinical trials.

**Organisational:** Members were asked to declare any support or support in kind their organisations had received from manufacturers of these products.

Replies were received as follows:

**Personal**
- Ms Ailsa Bosworth received support from Schering Plough to attend EULAR 2004.
- Dr Robin Butler stated that his unit received funding from Schering Plough, Wyeth and Abbott for nursing time to assist with assessment of patients and administration of TNF inhibitors. He also received funding from Abbott to attend scientific or other meetings in the past 24 months.
- Ms Patricia Cornell stated that her medical unit received funding from the manufacturers of biologic therapies to take part in trials of CAREDERA II involving Anakinra within the department.
- Dr Chris Deighton stated that his Rheumatology unit in Derby received support from Aventis, Pfizer, Abbott, Schering Plough, Wyeth and MSD for meetings and refreshments in the departments, speakers’ expenses, and travel for some colleagues to international Rheumatology meetings.
- Dr John Dickson received funding from the above manufacturers of biologic therapies to attend ACR 2004 and EULAR 2004. He has also received honoraria from Wyeth.
- Ms Christine Donohoe received support from the above manufacturers of the biologic therapies to attend the BSR conference in 2004.
- Dr Ian Griffiths stated that his unit received funding from the above manufacturers of the biologic therapies for multicentre RCT of Etanercept vs. Sulphasalazine. His unit also received 0.5WTE support for two years from Schering Plough for a nurse to collect data for the BSR Biologics Register.
- Ms Lindsey Hawley received donations from Wyeth and Abbott towards Rheumatology practitioner funding to attend BSR/BHPR conferences. Her unit received funding from Schering Plough for a sprint nurse to administer Remicade infusions and for some equipment for day case room. Wyeth funded a short term post for a practitioner to identify suitable patients for anti TNF treatments, and Abbott funded some software for monitoring patients on anti-TNF treatments.
- Ms Susan Oliver received honoraria from the above manufacturers of the biologic therapies. She also received funding to attend scientific and other meetings, and for nursing training and education study days.
- Dr David G I Scott stated that his unit received funding from Wyeth, Schering Plough and Abbott for the EABARG Study, Peripheral Clinics and the AS Study respectively. His unit also received sponsorship from Schering Plough and Wyeth to attend BSR AGM 2005 and RA study day. He received funding from Schering Plough, Wyeth and Abbott to attend ACR 2003 and 2004, EULAR 2005. He received honoraria from Wyeth and Schering Plough.
- Ms Margaret Somerville stated that her unit received funding from Abbott for AS clinical trial Adalimumab 2004-5, and from Wyeth for Early RA study commencing April 2005.
Organisational

- ARC received an unsolicited donation from Wyeth of £1,200 in 2003. ARC also receives a small proportion of royalties in respect of Infliximab from the Kennedy Institute of Rheumatology Trust.
- ARMA received unrestricted educational grants to support the Standards of Care project from Abbott Laboratories, Schering Plough and Wyeth. ARMA were also seconded a staff member from Schering Plough to carry out a piece of research.
- Arthritis Care received educational grants from Royal Pharma, Wyeth, Schering Plough, MSD and Pfizer Ltd for research, publications and events.
- BSR received sponsorship from Abbott, Wyeth and Schering Plough for Exhibition Stand sales and Satellite Symposia. Abbott also sponsored a prize.
- Centre for Rheumatology, UCL: Prof David Isenberg (Director) acts as scientific advisor to Abbott, but does not receive any funding for this work. None of his activities are related to the use of the TNF alpha blockers but rather to the use of new drugs in the treatment of systemic lupus erythematosus.
- Norfolk and Norwich University Hospital received sponsorship from Wyeth for a research grant, and from Schering Plough for nurse support.
- NRAS has received sponsorship from Abbott towards their newsletters, and from Schering Plough and Wyeth for the Volunteer Network and Helpline respectively in 2004.
- The PCR received support from Chemedica, Q-Med, Pfizer, Novartis, Servier, MSD, Wyeth and Novartis for its conference in November 2004.
- The RCN received sponsorship from the above manufacturers of the biologic therapies for support for Rheumatology Conferences.
- St Mary’s Hospital and Portsmouth Hospitals NHS Trust received sponsorship from Wyeth, Schering Plough and Abbott to attend educational meetings.