

# GUIDELINES FOR PRESCRIBING TNF- $\alpha$ BLOCKERS IN ADULTS WITH RHEUMATOID ARTHRITIS

## *Report of a Working Party of the British Society for Rheumatology*

The news of treatment advances is always exciting for people with arthritis and those treating them. Any new treatment will have undergone a long development process including small-scale volunteer trials on normal subjects and then limited clinical trials. If a new drug passes these hurdles and is shown to be efficacious and safe in the short term, it may be granted a product licence for general use. Its acceptance as part of the range of treatment options used to treat people with arthritis will then depend on whether wider use proves its effectiveness and on whether, in the long term, efficacy outweighs risk.

This report relates to a new class of therapy, the **tumour necrosis factor (TNF- $\alpha$ ) blockers**. Trials have shown these to be effective in rheumatoid arthritis and two drugs of this class were licensed for treatment of rheumatoid arthritis in 2000\*. Further guidelines may be required over time to assist with the introduction of other new treatments.

## **Background**

Rheumatoid arthritis affects some half a million people in the UK causing persistent pain and disability. The secondary care costs for the first five years of disease have been estimated at £22 million<sup>1</sup> with the majority of costs generated by a small proportion of patients with severe disease. Costs rise substantially in late disease due to the need for operations and institutional care with a total annual cost to society of over one billion pounds<sup>2 3</sup>. Tumour necrosis factor (TNF- $\alpha$ ) blockers have the potential to produce radical relief of patients' symptoms and improve their prognosis. Potential long-term benefits could include:

- reduced need for joint replacement surgery
- reduced demands on physiotherapy, occupational therapy and podiatry
- reduced demands on medical and nursing services
- reduced needs for other medicines
- reduced demands on social services and carers
- improved quality of life
- increased prospect of remaining in work
- increased life expectancy

As a result, significant savings in medical, social services and welfare benefits budgets could be achieved, although, at the same time, the treatments will involve significantly higher demands on the drugs budget. Ideally, these treatments should be available to all patients who might benefit from them.

---

\* One of the two available drugs, infliximab, was launched for use in Crohn's disease, an inflammatory disorder of the intestine, in September 1999

The development of these new therapies presents all those concerned with the welfare of people with arthritis with some significant challenges. In the short term, because of their cost, there is a danger that people's access to the new treatments will be determined more by where they happen to live than by clinical need - so called 'postcode prescribing'. To avoid this, there is a need for national guidelines to provide guidance to clinicians and health planners as to when to prescribe the new therapies *on clinical grounds* and to explain to people with arthritis in a clear and accessible way the basis on which these decisions are being made.

In the medium term, if the treatments prove their worth in general use, there will be a need to argue for a further increase in expenditure. Careful monitoring of the medical, social and economic impact of the new treatments will be an essential part of this approach, in other words what the Government calls 'joined up thinking'. The National Institute of Clinical Excellence (NICE) is undertaking an assessment of these new treatments in 2001. Further evidence from trials in progress must also be monitored.

### **National Guidelines**

The following guidelines are recommended to ensure that the new treatments are introduced in as systematic and planned a way as possible to ensure the greatest possible benefit to people with arthritis. They have been developed by a Working Party set up by the British Society for Rheumatology with representation from patients (Arthritis Care), research (the Arthritis Research Campaign), public health and general practice and have been drawn up on the basis of published trial data. A graded list of the scientific papers we have examined is appended, along with a list of members of the Working Party. Any potential conflict of interest in the Party drawing up the guidelines has been stated.

The guidelines have been developed for use by prescribing clinicians and for consideration by commissioners of secondary care rheumatology services. They are intended to indicate which patients may benefit from the new therapies. It is important to stress that clinical recommendations for use can only be based on the clinical evidence available. As current trials have been carried out in circumscribed study populations, these guidelines necessarily involve restricting access to these new treatments in the short term. However, the new therapies are not necessarily the only available treatment option for patients who *do* satisfy these guidelines. The risks and potential risks, as well as the benefits must be considered. There will be circumstances in which the rheumatologist feels that there is another lower cost drug(s) which is equally likely to produce a good clinical response in the individual patient, in which case this should be discussed with the patient.

### **Registry**

The situation with respect to the availability and use of biologic agents will evolve. It is meanwhile necessary to establish a review system that will monitor use, benefit and side effects; there are various models for organisation and sponsorship but there are compelling arguments for developing a specialty-run register.

The BSR & EULAR are supporting the establishment of a Registry of all patients who are treated with the new biologic agents. An appropriate control group of untreated patients will also be recruited. The aim of this Registry is to study the short-term and long-term toxicity of these agents - in particular the incidence of serious infections, the development of malignancy, and mortality. For the first three years after initial treatment patients should be followed using patient completed diaries and via their hospital records for the development of serious infections. Monitoring for malignancy and mortality will be continued for at least five years via the NHS Central Registry. Rheumatologists will be contacted on a six-monthly basis for details of the total dose and mode of administration of the new therapies. Approval for the establishment of this Registry has been obtained from the NorthWest Multi-Centre Research Ethics Committee (MREC). Informed consent will be sought from patients for their participation in this follow-up study.

The guidelines recommend careful clinical monitoring of patients. For this reason it is recommended that the new treatments will only be prescribed in the secondary care sector at this stage.

**These guidelines will be reviewed and revised by the BSR as new evidence becomes available and will be posted on the BSR website.**

## **British Society for Rheumatology Working Party on New Treatments**

### **Working Party Membership**

**Dr Andrew Bamji (CHAIR)** (Consultant Rheumatologist, Queen Mary's Hospital, Sidcup; Chairman, Clinical Affairs Committee, British Society for Rheumatology)

**Ms Jean Bradlow** (Assistant Director of Public Health, Oxfordshire Health Authority)

**Dr Robin Butler** (Consultant Rheumatologist, Robert Jones & Agnes Hunt Hospital, Oswestry; Honorary Secretary, British Society for Rheumatology)

**Dr David Doyle** (Consultant Rheumatologist, Whipps Cross Hospital, London; Secretary, Joint Specialty for Rheumatology Committee of the Royal College of Physicians and British Society for Rheumatology; Honorary Officer, British League Against Rheumatism; Trustee & Chairman, Arthritis Care Medical Advisory Committee)

**Ms Sophie Edwards** (External Relations Manager, British Society for Rheumatology; Chief Executive, British League Against Rheumatism)

**Dr Jane Griffin** (Consultant Rheumatologist, Chase Farm Hospital, Enfield; Clinical Affairs Committee, British Society for Rheumatology; Arthritis Care Medical Advisory Committee)

**Mr Richard Gutch** (Chief Executive, Arthritis Care)

**Dr Brian Hazleman** (Consultant Rheumatologist, Addenbrookes Hospital, Cambridge; President, British Society for Rheumatology)

**Dr Gill Hosie** (President, Primary Care Rheumatology Society)

**Mr Fergus Logan** (Chief Executive, Arthritis Research Campaign)

**Dr Tom Palferman** (Consultant Rheumatologist, Yeovil District General Hospital, Yeovil; Vice-Chairman, Clinical Affairs Committee, British Society for Rheumatology)

**Dr Duncan Porter** (Consultant Rheumatologist, Gartnavel General Hospital, Glasgow)

**Dr David Rampton** (Consultant Gastroenterologist, Barts & the London NHS Trust, London; Reader in Gastroenterology, Barts & the Royal London School of Medicine and Dentistry, London; British Society of Gastroenterology)

**Professor Deborah Symmons** (Consultant Rheumatologist, East Cheshire NHS Trust; Professor of Rheumatology and Musculoskeletal Epidemiology, ARC Epidemiology Unit, Manchester)

### **References**

1. Cooper NJ, Mugford M, Scott DGI, Barrett EM, Symmons DPM. Secondary health service care and second line drug costs of early inflammatory polyarthritis in Norfolk, UK. *J Rheumatol* 2000, 27: 2115-2122
2. Pugner KM, Scott DL, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. *Semin Arthritis Rheum* 2000, 29: 305-320
3. McIntosh E. The cost of rheumatoid arthritis. *Br J Rheumatol* 1996, 35: 781-790

# **GUIDELINES FOR PRESCRIBING TNF- $\alpha$ BLOCKERS IN ADULTS WITH RA**

## **Introduction**

### **Prevalence and incidence of Rheumatoid Arthritis**

Rheumatoid Arthritis (RA) is the commonest inflammatory polyarthropathy in the UK, with an annual incidence of new cases of approximately 54/100,000/year for women and 25/100,000 for men<sup>i</sup>. It is a chronic disorder, with a course that often exceeds 20 years, and a prevalence of established disease of approximately 500-600/100,000<sup>ii</sup>. In a Health Authority area with a population of 500,000 adults, approximately 250 new cases each year, and 3000 prevalent cases, may be expected.

### **Clinical impact of disease**

RA varies in its clinical manifestations and severity, but in many cases, it is a progressive, destructive and disabling condition. In an inception cohort of newly diagnosed RA patients, 44% of patients became unable to work, as a result of their RA, over the ensuing 10 years<sup>iii</sup>. With increasing age and disease duration, an increasing proportion of patients require major joint surgery, such that after 20 years of disease, approximately 25% of RA patients will have undergone joint replacement surgery.<sup>iv</sup> Patients with RA have increased mortality rates; this is most marked in patients attending specialist rheumatology clinics, increasing with disease severity and disease duration<sup>v</sup>. In the most severely affected RA patients, mortality is increased to a degree that is comparable to that seen in triple vessel coronary artery disease<sup>vi</sup>.

### **Economic impact of RA**

In 1992, the total economic impact of RA in England was estimated to be £1.3 billion<sup>vii</sup>, of which approximately half was due to indirect costs of loss of production. The direct costs were attributed to hospitalisation, outpatient care, drugs, residential care and social services provision, with hospitalisation consuming the largest proportion of expenditure. The costs associated with RA rise steeply with disease severity – when compared to patients with mild disease, patients with severe RA consume 20 times more resources.<sup>viii</sup> Therapy that substantially reduces long term disease progression could be expected to reap cost savings in the long term – for example, by reducing the number of joint replacements required - which should be offset against the short term costs associated with therapy.

### **Therapy for RA**

Modern management of RA revolves around the early diagnosis, and early use of disease modifying anti-rheumatic drugs (DMARDs) in an attempt to suppress joint inflammation, thereby limiting the amount of joint damage that accrues over the long course of the disease. Newly diagnosed RA patients are usually treated with either sulphasalazine or methotrexate, which are of equal efficacy in early RA.<sup>ix</sup> Patients with a poor response to initial therapy are changed to an alternative DMARD, or are commenced on combination DMARD therapy, but a proportion of patients respond sub-optimally to all currently available DMARDs, whether used singly or in combination.

## TNF- $\alpha$ blockers

There are two compounds licensed for use in the treatment of active RA in the UK and USA. Etanercept (*Enbrel*, Wyeth) is a recombinant human TNF receptor:Fc fusion protein consisting of a dimer of the extracellular portion of two p75 receptors fused to the Fc portion of human IgG1. It is administered subcutaneously at a dose of 25mg twice weekly. Infliximab (*Remicade*, Schering-Plough) is a chimeric human-murine monoclonal antibody administered by slow intravenous infusion at weeks 0, 2, 6 and 8 weekly thereafter at a dose of 3mg/kg, and is used in combination with oral methotrexate.

## Clinical efficacy - monotherapy

In Europe, the disease activity score (DAS 28) is a validated instrument which is often used to assess disease severity and response to treatment<sup>x</sup>. Response to therapy in RA is also often described using American College of Rheumatology definitions of ACR 20 (20% improvement in a selection of measures of disease activity), ACR 50 (50% improvement) and ACR 70 (70% improvement) response. Response rates are influenced by the study population. ACR response rates to sulphasalazine, methotrexate, leflunomide, infliximab and etanercept are shown below:

## Examples of Double blind Randomised Controlled Trials of anti-TNF monotherapy comparison with sulphasalazine, methotrexate (MTX) and leflunomide

Drug	No of patients	Disease duration	Assessment period	ACR 20 response	ACR 50 response	ACR 70 response
Etanercept 25mg <sup>xi</sup>	78	11 yrs	6 months	59%	40%	<b>15%</b>
Etanercept 10mg <sup>xx</sup>	208	11yrs	12 months	60%**	33%**	16%**
Etanercept 25mg <sup>xx</sup>	207	12yrs	12 months	72%	48%**	26%**
Infliximab 3mg/kg <sup>xii</sup>	14	7.8 yrs	4 months	55%*	42%*	
Infliximab 10mg/kg <sup>xii</sup>	15	9.7 yrs	4 months	60%*	36%*	
SASP 2g/day <sup>xiii</sup>	133	7.4 yrs	6 months	<b>56%</b>	30%	
Leflunomide <sup>xiv</sup>	182	7.0 yrs	12 months	52%	34%	20%
MTX 7.5-20mg/wk <sup>xx</sup>	217	12yrs	12 months	65%	42%**	21%**
MTX 7.5-15mg/wk <sup>xiv</sup>	182	6.5 yrs	12 months	46%	23%	9%

\* Paulus response

\*\* estimated from figure

In a randomised-controlled trial, which compared etanercept with methotrexate in patients with RA of less than 3 years duration who had not previously received methotrexate, etanercept acted significantly more rapidly to decrease symptoms and signs of active RA. However the proportions of patients achieving ACR 20, 50 or 70 responses at 12 months did not differ significantly between the groups. Although both etanercept and infliximab appear to be more effective than standard therapy, their use cannot be justified in patients who might respond equally well to much cheaper conventional therapy with sulphasalazine or methotrexate with which there is extensive long-term clinical experience.

### Clinical efficacy – combination therapy

Most interest has focussed on patients who have proved themselves to be resistant to standard DMARD therapy. These are the patients with the most severe disease, with high morbidity and mortality, associated with high cost of care. Trials that have studied the benefits of adding TNF- $\alpha$  blockers to patients with continuing disease activity despite adequate therapy with methotrexate are shown below:

Examples of Double blind Randomised Controlled Trials of addition of TNF- $\alpha$  Blockers to patients with inadequate response to MTX – comparison with cyclosporin

Drug added	No of patients	Disease duration	Assessment	ACR 20 response	ACR 50 response	ACR 70 response
Etanercept 25mg <sup>xv</sup>	59	13 yrs	6 months	71%	39%	15%
Infliximab 3mg/kg /4 wk <sup>xvi</sup>	86	7.2 yrs	6 months	53%*	29%	11%
Infliximab 3mg/kg/8 wk <sup>xvi</sup>	86	8.4 yrs	6 months	50%*	27%	8%
Infliximab 10mg/kg/4 wk <sup>xvi</sup>	81	8.7 yrs	6 months	58%*	26%	11%
Infliximab 10mg/kg/8 wk <sup>xvi</sup>	87	9.0 yrs	6 months	52%*	31%	18%
Infliximab 3mg/kg/4 wk <sup>xxi</sup>	86	9yrs	54 weeks	48%	34%	17%
Infliximab 3mg/kg/8 wk <sup>xxi</sup>	86	10yrs	54 weeks	42%	21%	10%
Infliximab 10mg/kg/4 wk <sup>xxi</sup>	81	12yrs	54 weeks	59%	38%	19%
Infliximab 10mg/kg/8 wk <sup>xxi</sup>	87	11yrs	54 weeks	59%	39%	25%
Cyclosporin 2.5-5mg/kg/day <sup>xvii</sup>	75	11.2 yrs	6 months	48%		

\* approximate ACR response rate (read from figure)

It has proved difficult to reproduce the results obtained with cyclosporin, because of drug toxicity. Methotrexate and TNF- $\alpha$  blockers are synergistic and the data show that combining the two agents in methotrexate-resistant patients results in a substantial response rate.

### **Quality of life**

Infliximab (3mg/kg every four weeks or 10mg/kg every four or eight weeks) plus methotrexate had a significantly greater effect on arthritis-specific function as assessed by the HAQ than did methotrexate alone<sup>xxi</sup>. The combination also had significantly greater beneficial effect on scores for the physical component of the SF-36 General Health Survey questionnaire than methotrexate alone, and for the vitality and social-functioning subscales of the mental component of the SF-36<sup>xxi</sup>.

### **Radiological outcome**

There is now evidence that both etanercept and infliximab will improve radiological outcome. The mean increase in erosion score at 12 months was 0.47 for etanercept compared with 1.03 for methotrexate ( $p = 0.002$ )<sup>xx</sup>. There was no deterioration in erosion score in 72% of etanercept-treated patients compared with 60% of those given methotrexate. The rates of joint space narrowing were low and prevented by both drugs. Patients who had the best clinical responses had the smallest amount of radiological progression.

There was a 9-10% deterioration in total radiographic score in patients given methotrexate alone over 54 weeks whereas there was no significant change in groups who received infliximab as well as methotrexate<sup>xxi</sup>. The rate of progression of joint damage was reduced in those patients on infliximab who failed to show a clinical response as well as in those who did.

### **Toxicity**

In post-marketing use in the USA, serious infections and sepsis, including some fatalities, have been reported. Many of these events occurred in patients predisposed to infections, such as those with advanced or poorly controlled diabetes. There have been a few reports of tuberculosis in patients treated with infliximab, and of blood dyscrasias and demyelination with etanercept.

Injection site reactions are common with etanercept and infusion-related events including headache, diarrhoea, rash, fever, chills, urticaria and dyspnoea have been reported with infliximab.

There is a theoretical risk of immunosuppression and malignancy as a result of the mode of action of TNF- $\alpha$  blockers but there are as yet no long term studies to quantify these risks.

Effects on pregnancy are unknown.

### **Eligibility for treatment with biologic therapies**

All patients must satisfy the 1987 criteria of the American College of Rheumatology Classification criteria for a diagnosis of Rheumatoid Arthritis<sup>xviii</sup>.

## 1. Active RA

The method used to assess disease activity must be strictly defined, objective and robust. Candidate measures include:

- Composite disease activity score (DAS) – based on 28 joint swelling count, 28 joint tenderness count, ESR and patient global assessment of disease activity. This score is used in the EULAR definition of “good response” and “remission”. Good response to therapy includes two components – (1) improvement relative to the past (a fall in DAS by > 1.2) and (2) improvement to a level of low activity (DAS < 3.2). A score of >5.1 indicates a high activity of disease.
- Multiple measures of disease activity – e.g. ACR core measures of disease activity. This assesses response to treatment in comparison with baseline, but has the disadvantage that it does not give an overall score which could be used as an entry criterion for treatment. The definition of improvement (ACR 20% or 50% improvement) does not include a component relating to the achievement of low disease activity.

Measurements of disease activity should be made at two points, one month apart. In busy outpatient follow-up clinics there are obviously workload implications for the introduction of formal disease scoring.

### **Recommendation:**

**The Working Party favours use of the 28 joint DAS score. A DAS28 score of >5.1 indicates highly active disease eligible for treatment.<sup>x xix</sup> It is important in relation to the proposed Register (see below) that all prescribing doctors use the same system so that information from different centres is comparable.**

## 2. Failure of standard therapy

Patients must have had adequate therapeutic trials of at least 2 standard DMARDs (IM gold, hydroxychloroquine, sulphasalazine, penicillamine, azathioprine, methotrexate or leflunomide, of which methotrexate must have been one). An adequate therapeutic trial would be defined as:

- Treatment for at least 6 months, with at least 2 months at standard target dose (unless significant toxicity limited the dose tolerated).
- Treatment for < 6 months, where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses (appendix 1).

## 3. Exclusion criteria

Reference should be made to the drug data sheet but important exclusions include:

Women who are pregnant or breastfeeding; effective contraception must be practised.

Active infection

Patients at high risk of infection including

- Chronic leg ulcers
- Previous tuberculosis (*Note:* patients with previous TB may be eligible if they have completed a full course of anti-tuberculous therapy within the modern antibiotic era, but

measures should be taken to prevent the reactivation of tuberculosis and the risk / benefit for the patient should be considered before starting treatment)

- Septic arthritis of a native joint within the last 12 months
- Sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ
- Persistent or recurrent chest infections
- Indwelling urinary catheter

Multiple sclerosis

Malignancy or pre-malignancy states excluding:

- Basal cell carcinoma
- Malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high)

#### **4. Criteria for withdrawal of therapy**

Treatment will be withdrawn in the event of adverse events:

- malignancy
- severe drug related toxicity
- pregnancy (temporary withdrawal)
- severe intercurrent infection (temporary withdrawal)

inefficacy:

- lack of response, but not within the first three months of treatment. A response is defined as improvement in the DAS28 score by  $>1.2$ , or the achievement of a DAS28 score of  $< 3.2$ .

Re-administration of infliximab after a drug free interval of 2-4 years has been associated with a delayed hypersensitivity reaction in a significant number of patients with Crohn's disease. Although this has not been reported in RA, consult the data sheet when readministration after an interval is being considered.

#### **Central registry of data**

Any clinician prescribing these medications must (with the patient's permission) undertake to register the patient with the Central Registry and forward information on dosage, outcome and toxicity on a six-monthly basis.

#### **Review of guidelines**

These guidelines will be revised and updated by the BSR

- One year from introduction, or
- With the appearance of new data that requires incorporation

***Working Party of the British Society for Rheumatology, 2<sup>nd</sup> April 2001***

## APPENDICES

### **Appendix 1: Definitions of “standard target” and “therapeutic” doses.**

“Standard target” doses of standard DMARDs that should be reached before a treatment is deemed ineffective.

- Hydroxychloroquine 6.5mg/kg/day
- Sulphasalazine 40 mg/kg/day in divided doses
- IM gold 50 mg/week
- Penicillamine 500-750 mg/day
- Azathioprine 2 mg/kg/day in divided doses
- Methotrexate 20 mg/week

Doses of standard DMARDs deemed to be “therapeutic”

- Hydroxychloroquine 200-400mg/day
- Sulphasalazine 2 g/day in divided doses
- IM gold 50 mg/week
- Penicillamine 500-750 mg/day
- Azathioprine 100 mg/day in divided doses
- Methotrexate 7.5 mg/week

### **Appendix 2: Data to be collected by Central Registry**

#### **Baseline**

Age  
Gender  
Post Code (for social deprivation index)  
Details of RA duration and severity  
Co-morbidity

Medication  
Smoking status  
Baseline outcome data

- HAQ score
- SF36
- DAS28 score

#### **Six-monthly**

Record of episodes of intercurrent illness

- Surgery
- Serious infection
- Malignancy
- Hospitalisation

Drug toxicity  
Cumulative dosage of biologic therapy  
Outcome data

Six-monthly returns would continue for 3 years after treatment starts, regardless of whether or not it is continued. Thereafter returns will be made on an annual basis.

### Appendix 3: Supporting Evidence

The conclusions in the report were based on the following scientific literature on TNF- $\alpha$  Blockers which was identified by Medline search. Articles published only in abstract form were not considered. The quality of the evidence is graded as follows and indicated by a letter after each reference. Grade A: randomised controlled trial or meta-analysis of randomised controlled trials. Grade B: controlled trial or quasi-experimental study or well-designed descriptive study. Grade C: expert committee report.

Bathon JM, Martin RW, Fleischmann RM et al.

A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.

New Engl J Med 2000; 343: 1586-1593 [A]

Elliot MJ, Maini RN, Feldmann M et al.

Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumour necrosis factor  $\alpha$

Arthritis Rheum 1993, 36: 1681-1690 [B]

Elliot MJ, Maini RN, Feldmann M et al.

Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor  $\alpha$ (cA2) versus placebo in rheumatoid arthritis

Lancet 1994, 344: 1105-1110 [A]

Elliot MJ, Maini RN, Feldmann M et al.

Repeated therapy with monoclonal antibody to tumour necrosis factor  $\alpha$ (cA2) in patients with rheumatoid arthritis

Lancet 1994, 344: 1125-1127 [B]

Furst DE, Breedveld FC, Burmester G-R et al.

Access to disease modifying treatments for rheumatoid arthritis patients

Ann Rheum Dis 1999, 58 (Suppl. 1): 1129-1130 [C]

Furst DE, Keystone E, Maini RN, Smolen JS

Recapitulation of the round table-discussion – assessing the role of anti-tumour necrosis factor therapy in the treatment of rheumatoid arthritis

Rheumatology 1999, 38 (Suppl. 2): 50-53 [C]

Kalden-Nemeth D, Grebmeier J, Antoni C et al.

NMR monitoring of rheumatoid arthritis patients receiving anti-TNF $\alpha$  monoclonal antibody therapy

Rheumatol Int 1997, 16: 249-255 [B] \*

Lipsky PE, Van Der Heijde DMFM, St Clair EW et al.

Infliximab and methotrexate in the treatment of rheumatoid arthritis.

New Engl J Med 2000; 343: 1594-1602 [A]

Maini RN, Breedveld FC, Kalden JR et al.

Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor  $\alpha$  monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis

Arthritis Rheum 1998, 41: 1552-1663 [A]

Maini RN, St Clair EW, Breedveld F et al.

Infliximab (chimeric anti-tumour necrosis factor  $\alpha$  monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial

Lancet 1999, 354: 1932-1939 [A]

Moreland LW, Baumgartner SW, Schiff MH et al.

Treatment of rheumatoid arthritis with a recombinant human tumour necrosis factor receptor (p75)-Fc fusion protein

N Engl J Med 1997, 337:141-147 [A]

Moreland LW, Schiff MH, Baumgartner SW et al.

Etanercept therapy in rheumatoid arthritis

Ann Intern Med 1999, 130: 478-486 [A]

Rankin EEC, Choy EHS, Kassimos D et al.

The therapeutic effects of an engineered human anti-tumour necrosis factor  $\alpha$  antibody (CDP571) in rheumatoid arthritis

Br J Rheumatol, 1995, 34: 334-342 [A]

Weinblatt ME, Kremer JM, Bankhurst AD et al.

A trial of etanercept, a recombinant tumour necrosis factor receptor:Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate

N Engl J Med 1999, 340: 253-259 [A]

\* the patients in this report were included in the study reported by Elliott et al. (Lancet 1994, 344: 1105-1110)

#### **Appendix 4: Declaration of Interest statement**

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 units in which the following WP members work have received funding for taking part in clinical trials of the new biologic therapies: Dr David Doyle, Dr David Rampton, Dr Brian Hazleman
- The following WP members have received funding from pharmaceutical companies involved in producing biologic therapies to attend scientific meetings in the past 24 months: Dr Robin Butler, Dr Jane Griffin, Dr David Rampton, Dr Duncan porter. Dr Gill Hosie reported that she was in the process of applying for funding to attend an event.
- The following organisations represented on the WP have received sponsorship for educational (i.e. non-promotional) activities relating to the new biologic therapies: Arthritis Care, British Society for Rheumatology, BLAR
- The following organisations represented on the WP have received sponsorship for activities not relating to the new biologic therapies: British Society for Rheumatology, Arthritis Care
- BSR is establishing a register which is expected to be funded by the manufacturers of the therapies; training for rheumatologists in data collection is also to be funded by the manufacturers
- Dr Deborah Symmons declared that her unit has been sponsored by a manufacturer of a new biologic therapy to conduct secondary analysis of data from a longitudinal study for use in pharmacoeconomic modelling.
- Dr Brian Hazleman attended an advisory panel meeting prior to the establishment of the WP but resigned on joining the Party.
- No WP members declared a direct financial stake, such as personal shareholding, in companies manufacturing the new biologic therapies.
- Dr Andrew Bamji, Dr Tom Palferman, Dr Jean Bradlow, Ms Sophie Edwards, & Mr Fergus Logan declared they had no conflict of interest.

## **Appendix 5:**

*The following were shown a draft version of the first edition (Apr 2000) of the guidelines*

### **BSR COUNCIL**

Dr D Bax; Dr A Behn; Dr A Crisp; Dr W Dodds; Dr I Griffiths; A Hakim; Dr P Helliwell; Dr N Hurst; Prof. D Isenberg; Prof MIV Jayson; Dr R Jubb; Dr T Kennedy; Dr G Kingsley; Dr P Maddison; Prof W Ollier; Dr M O'Sullivan; Prof G Panayi; Dr DL Scott; Dr M Seifert; Dr E Tunn; Prof P Woo

### **BSR CLINICAL AFFAIRS COMMITTEE**

R Hull; T Kennedy; M Webley (BMA Central Cons. M. S Comm); R Ellis (BIMM); Ms P Biddle (BHPR)

### **REGIONAL GROUP CHAIRS**

Dr A Bell, Northern Ireland; Dr A Bradlow, Oxford; Dr J Carty, Trent; Dr O Duke, SWTRHA; Dr C Holland, Northern; Dr C Hutton, South Western; Dr B Kidd, NETRHA; Dr G Kitas, West Midlands; Dr M Martin, Yorkshire; Dr A MacDonald, Scotland; Dr R Moots, Mersey; Dr N Sheehan, East Anglia; Dr P Prouse, Wessex; Dr E Smith, North Western; Dr P Williams, SETRHA; Dr W Williams, Wales; Dr A Young, NWTRHA

### **OTHER NATIONAL AND INTERNATIONAL EXPERTS**

Prof P Emery, Rheumatologist, University of Leeds, UK; Prof R N Maini, Rheumatologist, Kennedy Institute of Rheumatology, UK; Prof D Blake, Royal National Hospital for Rheumatic Diseases, Bath, UK; Prof D G I Scott, Rheumatologist, Norfolk & Norwich Healthcare NHS Trust, UK; Prof J Smolen, Rheumatologist, University of Vienna, Austria; Prof R Sturrock, University of Glasgow, UK; Prof L Van Der Putte, Rheumatologist, University Hospital Nijmegen, Netherlands; Prof M Weinblatt, Rheumatologist, Brigham Women's Hospital, Boston, USA

*The British Society for Rheumatology  
41 Eagle Street London WC1R 4TL  
Tel: + 44 (0)20 7242 3313  
Fax: + 44 (0)20 7242 3277  
Email: [bsr@rheumatology.org.uk](mailto:bsr@rheumatology.org.uk)  
WWW: <http://www.rheumatology.org.uk>*

Registered Charity Number: 1067124

## References

- <sup>i</sup> Wiles N, Symmons DPM, Harrison B, Barrett E, Barrett JH, Scott DGI, Silman AJ. *Arthritis Rheum* 1999; 42: 1339-46
- <sup>ii</sup> Silman A, Hochberg M. *Epidemiology of the rheumatic diseases*. Oxford University Press, 1994.
- <sup>iii</sup> Sokka T et al. Work disability in RA 10 years after the diagnosis. *J Rheumatology* 1999;26:1681-5
- <sup>iv</sup> Wolfe F et al. The long term outcomes of rheumatoid arthritis. *Arthritis Rheum* 1998;41:1072-82
- <sup>v</sup> Wolfe et al. The mortality of rheumatoid arthritis. *Arthritis Rheum*. 1994;37:481-94
- <sup>vi</sup> Pincus T. The underestimated long term medical and economic consequences of RA. *Drugs* 1995;50 (supp 1):1-14
- <sup>vii</sup> McIntosh E. The cost of rheumatoid arthritis. *Br J Rheumatol* 1996;35:781-90
- <sup>viii</sup> Jonsson B et al. Locomotor status and costs in destructive RA. *Acta Orthop Scand* 1992;63:207-12
- <sup>ix</sup> Dougados M et al. Combination therapy in early RA. AN RCT of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;58:220-5
- <sup>x</sup> van Gestel AM, Haagsma CJ, van Riel PLCM. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998, 41; 1845-1850
- <sup>xi</sup> Moreland et al. Etanercept therapy in rheumatoid arthritis. *Ann Intern Med* 1999;130:478-86
- <sup>xii</sup> Maini et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis monoclonal antibody combined with low dose methotrexate in RA. *Arthritis Rheum* 1998;41:1552-63
- <sup>xiii</sup> Smolen et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind randomised trial. *Lancet* 1999;353:259-66
- <sup>xiv</sup> Strand V, Cohen S, Schiff M et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arth Intern Med* 1999, 159 : 2542-2550.
- <sup>xv</sup> Weinblatt et al. Trial of etanercept, a recombinant TNF receptor:Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate. *NEJM* 1999;340:253-259
- <sup>xvi</sup> Maini et al. Infliximab (chimeric anti-TNF monoclonal antibody) versus placebo in RA patients receiving concomitant: a randomised phase III trial. *Lancet* 1999;354:1932-39
- <sup>xvii</sup> Tugwell et al. Combination therapy with cyclosporin and methotrexate in severe RA. *NEJM* 1995;333:137-41
- <sup>xviii</sup> Arnett FC, Edworthy SM, Block DA et al. The ARA 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988, 31: 315-324
- <sup>xix</sup> Prevoo MLL, van't Hoff MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PLCM. Modified Disease Activity Scores that include twenty-eight joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
- <sup>xx</sup> Bathon JM, Martin RW, Fleischmann RM et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *New Engl J Med* 2000; 343: 1586-1593
- <sup>xxi</sup> Lipsky PE, Van Der Heijde DMFM, St Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *New Engl J Med* 2000; 343: 1594-1602