

## **GUIDELINES FOR PRESCRIBING ANAKINRA IN ADULTS WITH RHEUMATOID ARTHRITIS**

### **Therapy for RA**

Modern management of rheumatoid arthritis (RA) revolves around the 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 comparable efficacy in early RA.<sup>1</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.

Over the past 10-15 years, there has been a great deal of research into the aetiology, pathogenesis and management of patients with rheumatoid arthritis. Particular focus has examined the role of cytokines in the pathogenesis and progression of the clinical features of rheumatoid arthritis including joint inflammation and cartilage destruction. Cytokines are regulatory proteins and their functions include effects on systemic immune and inflammatory reactions and also on responses at the site of tissue inflammation and injury. Amongst this network of cytokines, two have been identified which are believed to play major roles in the pathogenesis and progression of the disease, namely tumour necrosis factor alpha (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ).

Recently TNF- $\alpha$  blockers have been licensed for the treatment of RA and the BSR has produced guidelines on their use (available on the BSR website at [www.rheumatology.org.uk](http://www.rheumatology.org.uk)). In brief they are recommended for patients who still have active disease (defined as a DAS28 score >5.1 on two occasions at an interval of one month) despite adequate trials of treatment with two second-line drugs including methotrexate.

### **Anakinra**

IL-1 is a pro-inflammatory cytokine which plays an important role in tissue remodelling and inflammation, and which is believed to contribute to the pathogenesis of RA. IL-1 $\alpha$  and IL-1 $\beta$  are abundant in biopsies of synovial tissue in patients with RA and elevated levels of IL-1 $\beta$  are found in the plasma of patients with active disease. IL-1 $\beta$  has several pro-inflammatory effects including an increase in collagenase production by chondrocytes in cartilage and the activation of osteoclasts in bone. It is believed that IL-1 plays an important role in the cartilage destruction and joint erosion in RA.

A naturally occurring interleukin-1 receptor antagonist (IL-1Ra) modulates the activity of IL-1 *in vivo*. Anakinra (*Kineret*, Amgen) is a recombinant form of human IL-1Ra which binds to the IL-1 Type 1 receptor (IL-1 R1) and competitively prevents binding of IL-1. When bound to the IL-1 type 1 receptor anakinra does not itself activate the IL-1R accessory protein, so no signal transduction occurs.

Anakinra is licensed for use in Europe and in the USA. In Europe it is licensed for “the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients

with an inadequate response to methotrexate alone”. The licensed dose is 100mg daily by subcutaneous injection, and treatment “should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis”.

### 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>ii</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) compared with baseline. Response rates are influenced by the characteristics of the study population and by the number of DMARDs with which patients have previously been treated, and it is therefore difficult to compare ACR response rates in various studies. Although anakinra is licensed in the UK for use in combination with methotrexate, Table 1 illustrates that there are also published data on its use as monotherapy. ACR response rates to anakinra, sulphasalazine, methotrexate, leflunomide, infliximab and etanercept are shown below:

**Table 1. Examples of Double blind Randomised Controlled Trials of monotherapy with Anakinra compared with TNF- $\alpha$  blockers, Sulphasalazine (SASP), Methotrexate (MTX) and Leflunomide**

Drug	No of patients	Disease duration	Assessment period	ACR 20 response	ACR 50 response	ACR 70 response
Anakinra 30mg <sup>iii</sup>	119	4.3 yrs	6 months	39%	¶	¶
Anakinra 75mg <sup>iii</sup>	116	4.2 yrs	6 months	34%	¶	¶
Anakinra 150mg <sup>iii</sup>	116	3.9 yrs	6 months	43%	¶	¶
Anakinra <sup>iv</sup> 30mg	81	#	11 months	41%	Φ	Ψ
Anakinra <sup>iv</sup> 75mg	79	#	11 months	51%	Φ	Ψ
Anakinra <sup>iv</sup> 150mg	73	#	11 months	47%	Φ	Ψ
Etanercept 25mg <sup>v</sup>	78	11 yrs	6 months	59%	40%	15%
Etanercept 10mg <sup>vi</sup>	208	0.9 yr	12 months	60%**	33%**	16%**
Etanercept 25mg <sup>vi</sup>	207	1 yr	12 months	72%	48%**	26%**
Infliximab 3mg/kg <sup>vii</sup>	14	7.8 yrs	4 months	55%*	42%*	¶

Infliximab 10mg/kg <sup>vii</sup>	15	9.7 yrs	4 months	60%*	36%*	¶
SASP 2g/day <sup>viii</sup>	133	7.4 yrs	6 months	44%	30%	¶
Leflunomide <sup>ix</sup>	182	7.0 yrs	12 months	52%	34%	20%
MTX 7.5- 20mg/wk <sup>vi</sup>	217	1 yr	12 months	65%	42%**	21%**
MTX 7.5- 15mg/wk <sup>ix</sup>	182	6.5 yrs	12 months	46%	23%	9%

\* Paulus response      \*\* estimated from figure      ¶ Not stated  
 # Mean 4.1 yrs      Φ Mean 18%      Ψ Mean 3%

It is difficult to compare studies carried out by different teams in different patient groups. The method of analysis, e.g. by intention to treat or study of completers, can also make comparisons difficult. The data published by Bresnihan et al.<sup>iii</sup> and Nuki et al.<sup>iv</sup> may however suggest that anakinra is somewhat less effective than etanercept and infliximab in reducing clinical symptoms and signs of active RA.

### Clinical efficacy – combination therapy

Most interest has focused 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 anakinra or TNF- $\alpha$  blockers to patients with continuing disease activity despite therapy with methotrexate are shown below:

**Table 2. Examples of Double blind Randomised Controlled Trials of addition of Anakinra and 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
Anakinra 0.1mg/kg <sup>x</sup>	74	8.8 yrs	6 months	30 %	20 %	7 %
Anakinra 0.4mg/kg <sup>x</sup>	77	7.0 yrs	6 months	36 %	11 %	2 %
Anakinra 1mg/kg <sup>x</sup>	59	6.5 yrs	6 months	42 %	24 %	10 %
Anakinra 2mg/kg <sup>x</sup>	72	8.0 yrs	6 months	35 %	17 %	7 %
Anakinra 100mg <sup>xi</sup>	250	10.8 yrs	6 months	38 %	17 %	6 %
Etanercept 25mg <sup>xii</sup>	59	13 yrs	6 months	71%	39%	15%
Infliximab 3mg/kg /4 wk <sup>xiii</sup>	86	7.2 yrs	6 months	53%*	29%	11%

Infliximab 3mg/kg/8 wk <sup>xiii</sup>	86	8.4 yrs	6 months	50%*	27%	8%
Infliximab 10mg/kg/4 wk <sup>xiii</sup>	81	8.7 yrs	6 months	58%*	26%	11%
Infliximab 10mg/kg/8 wk <sup>xiii</sup>	87	9.0 yrs	6 months	52%*	31%	18%
Infliximab 3mg/kg/4 wk <sup>xiv</sup>	86	9yrs	12 months	48%	34%	17%
Infliximab 3mg/kg/8 wk <sup>xiv</sup>	86	10yrs	12 months	42%	21%	10%
Infliximab 10mg/kg/4 wk <sup>xiv</sup>	81	12yrs	12 months	59%	38%	19%
Infliximab 10mg/kg/8 wk <sup>xiv</sup>	87	11yrs	12 months	59%	39%	25%
Cyclosporin 2.5-5mg/kg/day <sup>xv</sup>	75	11.2 yrs	6 months	48%	¶	¶

\* approximate ACR response rate (read from figure) ¶ Not stated ¶¶

It has proved difficult to reproduce the results obtained with cyclosporin<sup>xv</sup>, because of drug toxicity<sup>xvi</sup>. The data show that combining methotrexate and TNF- $\alpha$  blockers in methotrexate-resistant patients results in a substantial response rate. As with monotherapy, the response rates to anakinra appear to be slightly lower than with TNF- $\alpha$  blockers, which might be for the reasons discussed under Table 1.

### Quality of life

Anakinra had a significantly ( $p=0.001$ ) greater effect on arthritis-specific function as assessed by the HAQ score than did placebo<sup>iii</sup>. When given with methotrexate it had a significantly greater effect on the HAQ than did methotrexate alone:  $p=0.036$  for 1mg/kg and  $p=0.0005$  for 2mg/kg anakinra<sup>x</sup>. In the confirmatory efficacy study patient function as measured by the HAQ showed an improvement of -0.29 in the Anakinra group at 24 weeks<sup>xi</sup>. This was 61% greater than that seen in the placebo treated group ( $P = 0.017$ ). This degree of improvement in HAQ score is considered to be of clinical relevance.

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>xiii</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>xiv</sup>.

### Radiological outcome

It is not possible to make meaningful comparisons between the studies of the effect of biological agents on radiological progression in RA. The paper by Bathon et al. (Table 3) concerned subjects with early RA, whereas Lipsky et al. (Table 4) studied subjects who had had an inadequate response to methotrexate. Both of these used the modified Sharp method for scoring radiological progression and compared TNF- $\alpha$  blocker with methotrexate, whereas that by Jiang et al. (Table 5) used the Larsen and Genant scoring systems and compared anakinra with placebo. Radiological data for leflunomide, methotrexate and sulphasalazine are shown in Table 6; the Sharp method was used in these studies<sup>xviii</sup>.

Table 3. Radiological data (modified Sharp method) at 1 year from Bathon et al.<sup>vi</sup>

	No of patients	Erosion	Total score
Etanercept 25mg	207	0.47	1.0
Methotrexate	217	1.03	1.59

Table 4. Radiological data (modified Sharp method) at 54 weeks from Lipsky et al.<sup>xiv</sup>

	No of patients	Erosion	JSN #	Total score
Infliximab				
3mg/kg x 8/52	71	0.2	1.1	1.3
3mg/kg x 4/52	71	0.3	0.7	1.6
10mg/kg x 8/52	77	0.2	0	0.2
10mg/kg x 4/52	66	-0.7	0	-0.7
Methotrexate	64	4.0	2.9	7.0

# Joint space narrowing

Table 5. Radiological data (Genant method) at 24 weeks from Jiang et al.<sup>xvii</sup>

	No of patients	Erosion	JSN #	Total score
Anakinra				
30mg	86	1.07	0.80	1.87
75mg	83	1.30	0.57	1.86
150mg	79	1.15	0.67	1.81
All doses	248	1.18	0.68	1.85
Placebo	78	1.91	1.62	3.52

# Joint space narrowing

Table 6. Radiological data (Sharp method) at 6 or 12 months from Sharp et al.<sup>xviii</sup>

Study	No of patients	Duration	Erosion	JSN #	Total score
MN 301					
Leflunomide	87	6 months	0.63	0.60	1.23
SASP	84	6 months	0.92	1.40	2.32

US 301					
Leflunomide	131	1 year	0.23	0.31	0.53
MTX	136	1 year	0.48	0.41	0.89
MN 302					
Leflunomide	302	1 year	1.00	1.48	2.48
MTX	324	1 year	0.54	1.08	1.62

# Joint space narrowing

Anakinra in all doses improved radiological outcome compared with placebo <sup>xvii</sup>. By the Genant method there was a 38% reduction in erosion score; a 58% reduction in joint space narrowing; and a 47% reduction in total score. The Larsen erosive joint count method showed a 45% reduction compared with placebo. Deterioration in erosion score occurred in 44% anakinra-treated patients versus 58% in the placebo group. Figures for deterioration in joint space narrowing were 37% versus 56%, and for total score 52% versus 67% respectively.

Both etanercept and infliximab 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>vi</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>xiv</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.

There is evidence that all the drugs listed in Tables 3-6 have a beneficial effect on joint damage. The anakinra study includes a placebo group and clearly demonstrates its efficacy in this regard.

#### **Toxicity (data from Summary of Product Characteristics)**

Anakinra therapy is associated with an increased risk of serious infections compared with placebo (1.8% versus 0.7% for placebo). The risk of serious infection was greater in those with a history of asthma than in those without such a history. Neutropenia ( $<1.5 \times 10^9/l$ ) was seen in 2.4% of patients treated with anakinra compared with 0.4% of those given placebo. The manufacturer recommends neutrophil counts before starting treatment; monthly for the first six months of treatment; and quarterly thereafter.

Injection site reactions are the most common adverse event, typically being seen in the first four weeks of therapy in up to 70% of subjects, but they lead to discontinuation of therapy in fewer than 7% of cases. Headache occurs in up to 12%.

Effects on pregnancy are unknown, but the manufacturer states that the use of anakinra in pregnant women is not recommended.

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

Overall the toxicity observed is very similar to that seen with other biological agents, whether used alone or in combination with methotrexate.

There is limited experience of its use in combination with TNF- $\alpha$  blockers but the SPC does note a 7% incidence of serious infections in a pilot study in 58 patients. In the US the package insert states that combined use of anakinra and TNF- $\alpha$  blockers “should only be done with extreme caution and when no satisfactory alternative exists”. Further clinical studies are in progress.

### **Eligibility for treatment with Anakinra**

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

#### **1. Active RA**

The method used to assess disease activity must be strictly defined, objective and robust. As for TNF- $\alpha$  blockers we recommend the DAS28 score. This composite disease activity score (DAS) is 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.

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.

#### **2. Failure of standard therapy**

As for TNF- $\alpha$  blockers patients must have had adequate therapeutic trials of methotrexate and at least one other standard DMARD (IM gold, hydroxychloroquine, sulphasalazine, penicillamine, azathioprine or leflunomide). 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 Summary of Product Characteristics (SPC) but important exclusions include:

Persistent neutropenia ( $<1.5 \times 10^9/l$ )

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

The SPC states that “physicians should exercise caution when administering anakinra to patients with a history of recurring infections or with underlying conditions which may predispose to infections”. Patients defined as being at high risk of infection in the BSR TNF- $\alpha$  blocker guidelines were as follows:

- 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

The crude incidence rates for malignancy were the same in anakinra- and placebo-treated patients, and did not differ from the general population. It is unknown if anakinra will increase the risk of malignancy in the longer term. We consider it unwise to administer anakinra to people with malignant disease. The BSR TNF- $\alpha$  blocker guidelines recommended that TNF- $\alpha$  blockers should not be used in malignancy or pre-malignancy states other than:

- 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 should be withdrawn in the event of adverse events:

- serious infection
- persistent neutropenia ( $<1.5 \times 10^9/l$ )
- 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  $>1.2$ .

#### **BSR Biologics Register of data**

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

## Overall conclusions:

- Anakinra is a novel therapy which is indicated for use in conjunction with methotrexate in patients with active RA which is not adequately controlled by methotrexate
- The use of anakinra has been shown to retard radiological deterioration in comparison with placebo
- The relative efficacy of anakinra and TNF- $\alpha$  blockers in retarding radiological progression is not clear, and no firm conclusion can be reached in the absence of a head to head trial of such agents
- The effect of anakinra on symptoms and signs of RA may be less pronounced than with TNF- $\alpha$  blockers, but no firm conclusion can be reached in the absence of a head to head trial of such agents
- The relative toxicity of anakinra and TNF- $\alpha$  blockers is not clear, and no firm conclusion can be reached on available evidence
- There are insufficient data for us to provide clear guidance on the relative merits of using anakinra and TNF- $\alpha$  blockers in patients whose RA remains active despite treatment with methotrexate. The choice between anakinra, etanercept and infliximab will have to be made on the basis of tolerance, or lack of tolerance of methotrexate; perceived differences in the likely efficacy and relative risk of toxicity in individual patients; and the relative suitability and convenience, for the both the patient and the rheumatology unit, of self-administered injection as opposed to intermittent infusion of biological agent
- Criteria for eligibility, exclusion, monitoring, and withdrawal of anakinra therapy have been suggested above
- The long-term safety profile of anakinra is unknown, and it is vital that physicians register treated patients with the BSR Biologics Register
- In common with the American College of Rheumatology<sup>xx</sup>, the British Society for Rheumatology supports the use of anakinra in patients with RA who have an inadequate response to methotrexate

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

***Working Party of the British Society for Rheumatology, August 2002***

**British Society for Rheumatology Working Party on Anakinra**

**Working Party Membership**

**Dr Robin Butler (CHAIR)** (Consultant Rheumatologist, Robert Jones & Agnes Hunt Hospital, Oswestry)

**Professor George Nuki** (Professor of Rheumatology, University of Edinburgh)

**Dr Peter Prouse** (Consultant Rheumatologist, North Hampshire Hospital, Basingstoke & Honorary Secretary, British Society for Rheumatology)

**Professor David GI Scott** (Professor of Rheumatology, University of East Anglia & President of BSR)

**Professor Bryan Williams** (Professor of Rheumatology, University of Cardiff)

## 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 400mg or 6.5mg/kg/day
- Sulphasalazine 2-4g/day in divided doses
- IM gold 50 mg/week
- Penicillamine 500-750 mg/day
- Azathioprine 2 mg/kg/day in divided doses
- Methotrexate 15-25 mg/week
- Leflunomide 20mg/day
- Cyclosporin 3mg/kg/day

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
- Leflunomide 10mg/day
- Cyclosporin 2mg/kg/day

### **Appendix 2: Data to be collected by BSR Biologics Register**

#### **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 Anakinra and 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.

American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines  
Guidelines for the management of rheumatoid arthritis  
Arthritis Rheum 2002; 46: 328-346 [C]

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]

Bresnihan B, Alvaro-Gracia JM, Cobby M et al.  
Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist  
Arthritis Rheum 1998; 41: 2196-2204 [A]

Cohen S, Hurd E, Cush J et al.  
Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate  
Arthritis Rheum 2002; 46: 614-624 [A]

Confirmatory efficacy study (990145).  
[www.fda.gov/ohms/dockets/ac/01/briefing/3779b1\\_01\\_Amgen.pdf](http://www.fda.gov/ohms/dockets/ac/01/briefing/3779b1_01_Amgen.pdf) [A]

Dayer J-M, Bresnihan B  
Targeting Interleukin-1 in the treatment of rheumatoid arthritis  
Arthritis Rheum 2002; 46: 574-578 [C]

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]

Jiang Y, Genant H, Watt et al.

A multicenter double-blind dose-ranging, randomised, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis  
Arthritis Rheum 2000; 43: 1001-1009 [A]

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]

Nuki G, Bresnihan B, Bear MB et al.

Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human IL-1 receptor antagonist) in patients with rheumatoid arthritis  
Arthritis Rheum 2002 (in press) [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: G Nuki, P Prouse; D Scott, B Williams
- The following WP members have received funding from pharmaceutical companies involved in producing biologic therapies to attend scientific meetings in the past 24 months: R Butler, G Nuki, P Prouse, D Scott, B Williams
- The British Society for Rheumatology has received sponsorship for educational (i.e. non-promotional) activities relating to the new biologic therapies:
- 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
- The following WP members have acted as medical advisers to manufacturers of biological agents: D Scott, B Williams
- No WP members declared a direct financial stake, such as personal shareholding, in companies manufacturing the new biologic therapies.

*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

---

<sup>i</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>ii</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>iii</sup> Bresnihan B, Alvaro-Gracia JM, Cobby M et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998, 41: 2196-2204

<sup>iv</sup> Nuki G, Bresnihan B, Bear MB et al.  
Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human IL-1 receptor antagonist) in patients with rheumatoid arthritis  
*Arthritis Rheum* 2002 (in press)

<sup>v</sup> Moreland LW, Schiff MH, Baumgartner SW et al.  
Etanercept therapy in rheumatoid arthritis  
*Ann Intern Med* 1999, 130: 478-486

- 
- <sup>vi</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>vii</sup> 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
- <sup>viii</sup> Smolen J, Kalden JR, Scott DL et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind randomised trial. *Lancet* 1999, 353:259-266
- <sup>ix</sup> Strand V, Cohen S, Schiff M et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999, 159: 2542-2550
- <sup>x</sup> Cohen S, Hurd E, Cush J et al.  
Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate  
*Arthritis Rheum* 2002, 46: 614-624
- <sup>xi</sup> Confirmatory efficacy study (990145).  
[www.fda.gov/ohms/dockets/ac/01/briefing/3779b1\\_01\\_Amgen.pdf](http://www.fda.gov/ohms/dockets/ac/01/briefing/3779b1_01_Amgen.pdf)
- <sup>xii</sup> 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
- <sup>xiii</sup> 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
- <sup>xiv</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
- <sup>xv</sup> Tugwell P, Pincus T, Yocum D et al. Combination therapy with cyclosporin and methotrexate in severe RA. *N Engl J Med* 1995, 333: 137-141
- <sup>xvi</sup> Kvien TK, Zeidler HK, Hannonen P et al.  
Long term efficacy and safety of cyclosporin versus parenteral gold in early rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 511-516
- <sup>xvii</sup> Jiang Y, Genant H, Watt et al. A multicenter double-blind dose-ranging, randomised, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis Rheum* 2000, 43: 1001-1009
- <sup>xviii</sup> Sharp JT, Strand V, Leung H et al.

Treatment with leflunomide slows radiographic progression in rheumatoid arthritis  
Arthritis Rheum 2000, 43: 495-505

<sup>xix</sup> Arnett FC, Edworthy SM, Block DA et al. The ARA revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988, 31: 315-324

<sup>xx</sup> American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis Arthritis Rheum 2002; 46: 328-346