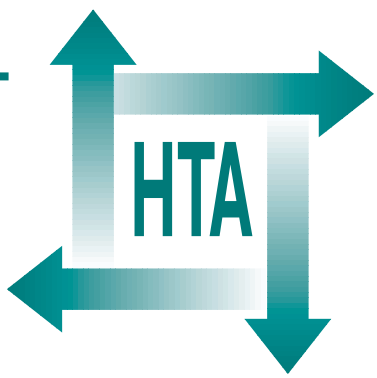
*Health Technology Assessment* 2002; Vol. 6: No. 21

# The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation

P Jobanputra
P Barton
S Bryan
A Burls

**Health Technology Assessment**
**NHS R&D HTA Programme**





**How to obtain copies of this and other HTA Programme reports.**
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

**Contact details are as follows:**

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

**Payment methods**

*Paying by cheque*
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

*Paying by credit card*
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

*Paying by official purchase order*
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

**How do I get a copy of *HTA on CD*?**

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

---

The website also provides information about the HTA Programme and lists the membership of the various committees.

# The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation

P Jobanputra[1,2*]
P Barton[1,3]
S Bryan[1,3]
A Burls[1]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK
[2] Department of Rheumatology, Selly Oak Hospital, University Hospital Birmingham NHS Trust and Royal Orthopaedic Hospital NHS Trust, Birmingham, UK
[3] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK

[*] Corresponding author

**Declared competing interests of the authors**: P Jobanputra is engaged in a multi-centre clinical trial of etanercept, sponsored by Wyeth Laboratories

Published September 2002

This report should be referenced as follows:

Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(21).

*Health Technology Assessment* is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

# NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/18/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

**Criteria for inclusion in the HTA monograph series**
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.



The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278



Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

T

# Contents

# List of abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| ANA | anti-nuclear antibodies |
| anti-dsDNA | anti-double stranded DNA (antibodies) |
| ARA | American Rheumatism Association |
| ATTRACT | Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy |
| BPM | Birmingham Preliminary Model |
| BSR | British Society for Rheumatology |
| CI | confidence interval |
| CRP | C-reactive protein |
| DAS | Disease Activity Score |
| DMARD | disease-modifying anti-rheumatic drug |
| EMS | early morning stiffness* |
| EQ-5D | EuroQol-5 dimensions |
| ESR | erythrocyte sedimentation rate |
| FDA | Food and Drug Administration (USA) |
| HAQ | Health Assessment Questionnaire |
| HLA | human leucocyte antigen |
| ICER | incremental cost-effectiveness ratio |
| IgG | immunoglobulin G |
| IgG1 | immunoglobulin G (class 1) |
| IgM | immunoglobulin M |
| IL-1 | interleukin-1 |
| IL-6 | interleukin-6 |
| IL-10 | interleukin-10 |
| IL-1ra | interleukin-1 receptor antagonist |
| i.m. | intramuscular/ly |
| i.v. | intravenous/ly |
| MTX | methotrexate* |
| NICE | National Institute for Clinical Excellence |
| NNT | number-needed-to-treat |
| NOAR | Norfolk Arthritis Register |
| NSAID | non-steroidal anti-inflammatory drug |
| PEG | polyethylene glycol |
| PSS | Personal Social Services |
| QALY | quality-adjusted life-year |
| RA | rheumatoid arthritis |
| RCT | randomised controlled trial |
| RD | risk difference |
| RF | rheumatoid factor |
| RR | relative risk |
| SD | standard deviation |
| SE | standard error |
| SEM | standard error of the mean |
| SF-36 | Short Form with 36 items |
| SJC | swollen joint count* |
| SLE | systemic lupus erythematosus |
| SMD | standardised mean difference |
| SMR | standardised mortality ratio |
| sTNFR | soluble tumour necrosis factor receptor |
| sTNFR1 | soluble tumour necrosis factor receptor type 1 (55 kd) |
| sTNFR2 | soluble tumour necrosis factor receptor type 2 (75 kd) |
| TACE | TNFα converting enzyme |
| TJC | tender joint count* |
| TNF | tumour necrosis factor |

*continued*

*continued*

| | |
|---|---|
| TNFα | tumour necrosis factor alpha |
| TNFβ | tumour necrosis factor beta (or lymphotoxin) |
| TNFR | tumour necrosis factor receptors |
| TNFR1 | tumour necrosis factor receptor type 1 (55 kd cell surface receptor for TNFα) |
| TNFR2 | tumour necrosis factor receptor type 2 (75 kd cell surface receptor for TNFα) |
| URTI | upper respiratory tract infection |
| UTI | urinary tract infection |
| VAS | visual analogue scale |
| WMD | weighted mean difference |

* Used only in tables

# Executive summary

## Background

This report reviews the evidence for the clinical effectiveness and cost-effectiveness of etanercept and infliximab, agents that inhibit tumour necrosis factor alpha (TNFα) when used in the treatment of rheumatoid arthritis (RA) in adults and referred to as anti-TNFs. RA is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Key aims of treatment include:

- control of joint pain and inflammation
- reduction in joint damage and disability
- improvement in physical function
- maintenance or improvement in quality of life.

Drugs that have been shown to, or have the prospect of, inhibiting joint destruction are known as disease-modifying anti-rheumatic drugs (DMARDs). There are around eight DMARDs currently in common use in the UK. These drugs are not always effective, or they lose effectiveness with time, and they may cause adverse effects, leading to a low likelihood of long-term drug use for a disease with a lifelong course. New DMARDs are therefore of great importance and several new agents have appeared in recent years.

TNFα is a cytokine that plays an important role in mediating joint inflammation. Its actions may be inhibited by infliximab (Remicade®, Schering-Plough, Welwyn Garden City), a monoclonal antibody that binds to soluble and cell-bound TNFα, and by etanercept (Enbrel®, Wyeth Laboratories, Maidenhead), a manufactured receptor for TNFα. Both agents are licensed for use in the UK for the treatment of RA. Infliximab is given by intravenous infusion at 0, 2 and 6 weeks and then at 8-weekly intervals. It is only licensed for use concomitantly with methotrexate. Etanercept is given by twice-weekly subcutaneous injection and can be given for an indefinite period.

## Methods

A systematic review of the literature was undertaken, together with a meta-analysis of clinical effectiveness data. The literature review was based on a search of a range of databases and contact with leading researchers and industry. Industry submissions to the National Institute for Clinical Excellence, including economic models, were also reviewed in detail. A preliminary incremental cost analysis was carried out using a simulation model developed specifically for this purpose.

## Results

### Number and quality of studies

Six randomised controlled trials (RCTs) of etanercept in patients with RA, involving a total of 1710 patients (1230 of whom received etanercept), were identified. Five of these compared etanercept to placebo; one compared etanercept to methotrexate. Four RCTs of infliximab in patients with RA, involving 630 patients (497 of whom received infliximab), were identified. All compared infliximab to placebo. Some of the smaller studies showed either poor comparability of the baseline characteristics of patients, or large losses to follow-up, especially from the placebo group. However, these flaws in quality affected only small numbers of patients and all trials were given high quality scores.

### Direction of evidence

Both etanercept and infliximab improve the outcomes in adults with RA when compared to placebo. Only one trial directly compared a DMARD with an anti-TNFα agent. This study failed to demonstrate a convincing treatment difference between etanercept and methotrexate.

### Size of treatment effect

Anti-TNFs are very effective, as demonstrated by a number-needed-to-treat (NNT) of 2 to produce a 20% improvement in American College of Rheumatology (ACR) score (ACR20), a composite score that includes measures of tender and swollen joints and other measures of disease. NNT for a 50% improvement in ACR score was 4 and NNT for 70% improvement was 8. Both anti-TNF agents consistently and rapidly improved all relevant clinical outcomes and also reduced joint damage assessed radiographically. These findings are very unlikely to have occurred by chance. Serious adverse events occurred infrequently and were comparable to placebo.

### Costs

An incremental economic analysis was undertaken to estimate the additional costs and quality-adjusted life-year (QALY) gains associated with the use of either etanercept or infliximab, either as the third DMARD in a sequence of DMARDs or separately as last-resort therapy (i.e. used last in a DMARD sequence). A simulation model was constructed that considered improvements in quality of life but assumed no effect of either etanercept or infliximab on mortality or the need for joint replacement. For use as the third DMARD in a sequence of DMARDs, the Birmingham Preliminary Model gave a base-case incremental cost-effectiveness ratio of approximately £83,000 per QALY for etanercept and approximately £115,000 per QALY for infliximab. These figures reduced to £72,000 per QALY for etanercept, and £95,000 for infliximab, if they were used last in the sequence of DMARDs. Sensitivity analysis in the latter case gave figures ranging from £47,000 to £128,000 for etanercept and £62,000 to £169,000 for infliximab. It should be stressed that these figures do not include all benefits. Further research is needed on the effect of all DMARDs on joint replacement, hospitalisation, mortality and quality of life.

## Conclusions

### Recommendations for research

Further research and development of economic models is necessary to reflect clinical practice more accurately. Future models need to include other aspects of RA, such as disease complications, to improve current models.

Comparative studies of anti-TNF agents and other DMARDs (new and old) should be carried out, as only one study included in this review compared anti-TNF directly with another DMARD. This showed equivalent efficacy. Such direct comparisons have a potential for informing practice, especially where therapeutic choices that take cost into account are to be made.

Studies of the quality of life of RA patients in the long term and the impact of DMARDs and other interventions on quality of life are needed. Also needed are studies of the impact of DMARDs on joint replacement, and other disease and drug-related morbidity, and on mortality.

# Chapter 1
# Introduction

## Aims of the review

- To provide a background on rheumatoid arthritis (RA), including epidemiology, current therapeutic options, and impact of disease on individuals and health services.
- To conduct a systematic review and meta-analysis of the clinical benefits and hazards of using etanercept and infliximab in RA.
- To review the economic evidence about the cost-effectiveness of these agents compared with other treatment options.
- To describe other agents targeted against tumour necrosis factor (TNF), which are currently unlicensed but that may be licensed in the future for the treatment of RA, and to outline areas for research.

## Background

### Description of underlying health problem

#### *Clinical features of RA*

RA is characterised by pain, swelling and stiffness of synovial joints. These symptoms are often worse in the morning and after periods of inactivity.

Synovial joints are the most mobile joints. They have a capsule and an internal lining of synovial membrane that holds a small amount of viscous synovial fluid. An inflammatory reaction, increased cellularity of synovial tissue and joint damage are the pathological hallmarks of RA.

RA causes inflammation of synovial joints but may also affect other organ systems. For example patients may develop lymph node enlargement, anaemia, a raised platelet count, pulmonary disease such as pleurisy or interstitial lung disease, pericarditis, vascular inflammation (vasculitis), skin nodules, and eye diseases such as reduced tear production or inflammation. Patients may also experience lethargy, weight loss and fever. RA is therefore regarded as a systemic illness, with a potential for severe disability and life-threatening complications. Disease severity can be variable. For instance 18% of a community cohort of patients with RA were in 'remission off treatment' after 3 years' follow-up. By contrast, 47% of patients were classified as having moderate disability as rated by a Health Assessment Questionnaire (HAQ) score of greater than 1.0, and 25% of patients had a joint replaced within 22 years of disease onset.[1,2] (Details of the HAQ are given in appendix 1.)

Symptoms of RA may begin overnight or evolve over weeks, months or years.[3] Common patterns of disease are:

- Disease of small or medium joints, particularly metacarpophalangeal and proximal interphalangeal joints of the hands, and metatarsophalangeal joints of the feet, wrists and ankles. There may also be variable large joint disease.
- Predominantly large joint disease.
- Disease involving only a few joints, or sometimes only one joint.
- Less common presentations include pain and stiffness affecting the shoulder and hip girdles (polymyalgic presentation); systemic symptoms such as weight loss and joint pain without a true arthritis; and intermittent short-lived attacks of arthritis ('palindromic rheumatism').

The clinical course of RA and the responses of any one individual to disease are also variable. Pain and disability of early RA is linked to disease severity and to measures of psychological distress.[4] RA may follow three broad patterns: progressive disease with significant functional limitations in time, intermittent disease (where disease is punctuated by partial, or complete, remissions), and disease with long clinical remissions.[5]

#### *Diagnosis of RA*

RA is diagnosed from a constellation of clinical and laboratory or radiographic abnormalities. Diagnosis may be obvious in some but in others it may be more difficult and require a period of clinical observation. Classification criteria for RA have been devised. Most contemporary research studies of RA include patients who satisfy such criteria. The most recent criteria, formulated by the American Rheumatism Association (ARA) in 1987, are shown in *Table 1*.[6] These criteria were derived from a group of typical patients who had been diagnosed with RA and had well-established

***TABLE 1*** *Revised 1987 ARA criteria for classification of RA*

| Criteria | Definition |
|---|---|
| 1. Morning stiffness | Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement |
| 2. Arthritis of three or more joints | At least three joint areas have simultaneously had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are (right or left): PIP, MCP, wrist, elbow, knee, ankle and MTP joints |
| 3. Arthritis of hand joints | At least one joint area swollen as above in wrist, MCP or PIP joints |
| 4. Symmetrical arthritis | Simultaneous involvement of the same joint areas (as in 2) on both sides of the body (bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry) |
| 5. Rheumatoid nodules | Subcutaneous nodules, over a bony prominence, or extensor surface or in juxta-articular regions, observed by a physician |
| 6. Serum rheumatoid factor | Demonstration of abnormal amounts of serum 'rheumatoid factor' by any method that has been positive in less than 5% of control subjects |
| 7. Radiographic changes | Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) |
| *A patient is said to have RA if he or she satisfies at least four of the above seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded* | |

*Adapted from Arnett* et al., *1988*[6]

*MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal*

disease. However, they have limited utility in routine practice and most clinicians diagnose RA without formal reference to such criteria. Also, many patients do not meet formal criteria, at least early in disease.[7,8] Criteria were also developed as an algorithm (*Figure 1*), and these are more readily met in clinical practice.[9]

Two diagnostic tests are included in the criteria: rheumatoid factor (RF) and X-ray changes. RF, measured in routine blood samples, is a circulating immunoglobulin M (IgM) autoantibody that is directed against immunoglobulin G (IgG) molecules. It occurs in approximately 60% of patients with early RA. Early in disease radiographs may show soft tissue swelling and reduced bone density around affected joints. Later there may be evidence of joint damage such as joint erosions (focal loss of bone and cartilage, often near the joint margin) or a reduced joint space (indicating diffuse cartilage loss). With continued joint damage there may be extensive joint destruction, features of joint deformity or instability, and bony ankylosis. With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. At an earlier stage surgical treatment such as removal of synovial tissues (synovectomy) or other soft tissue procedures such as tendon release or repair may also be necessary.

### *Epidemiology*

RA affects around 0.5–1% of the population worldwide. Recent estimates in Western populations indicate an annual incidence of 0.5 per 1000 population and a point prevalence of 8 per 1000 population.[10] Therefore there are likely to be 476,000 patients with RA in the UK, or approximately 421,520 in England and Wales (population 52,690,000).[11] This means that an average health authority with a population of half a million has 4000 patients with RA. The incidence of RA in the UK appears to have declined in recent decades.[10] Prevalence increases with age so that at age 65 it is six times as prevalent as at age 25. Peak age of onset is in the sixth decade and RA is more common in women than men by a ratio of 2.5 to 1.

### *Aetiology*

No single cause has been identified for RA. It appears to be a multifactorial disease in which there are important genetic and environmental influences:

- Genetic influence is estimated at 50–60%.[12] Much of this contribution comes from the human leucocyte antigen (HLA) region of chromosome 6, particularly HLA-DR4. HLA plays a key role in immune function and regulation. The only known function of DR is in presentation of peptides to T cells for mounting an immune response to particular

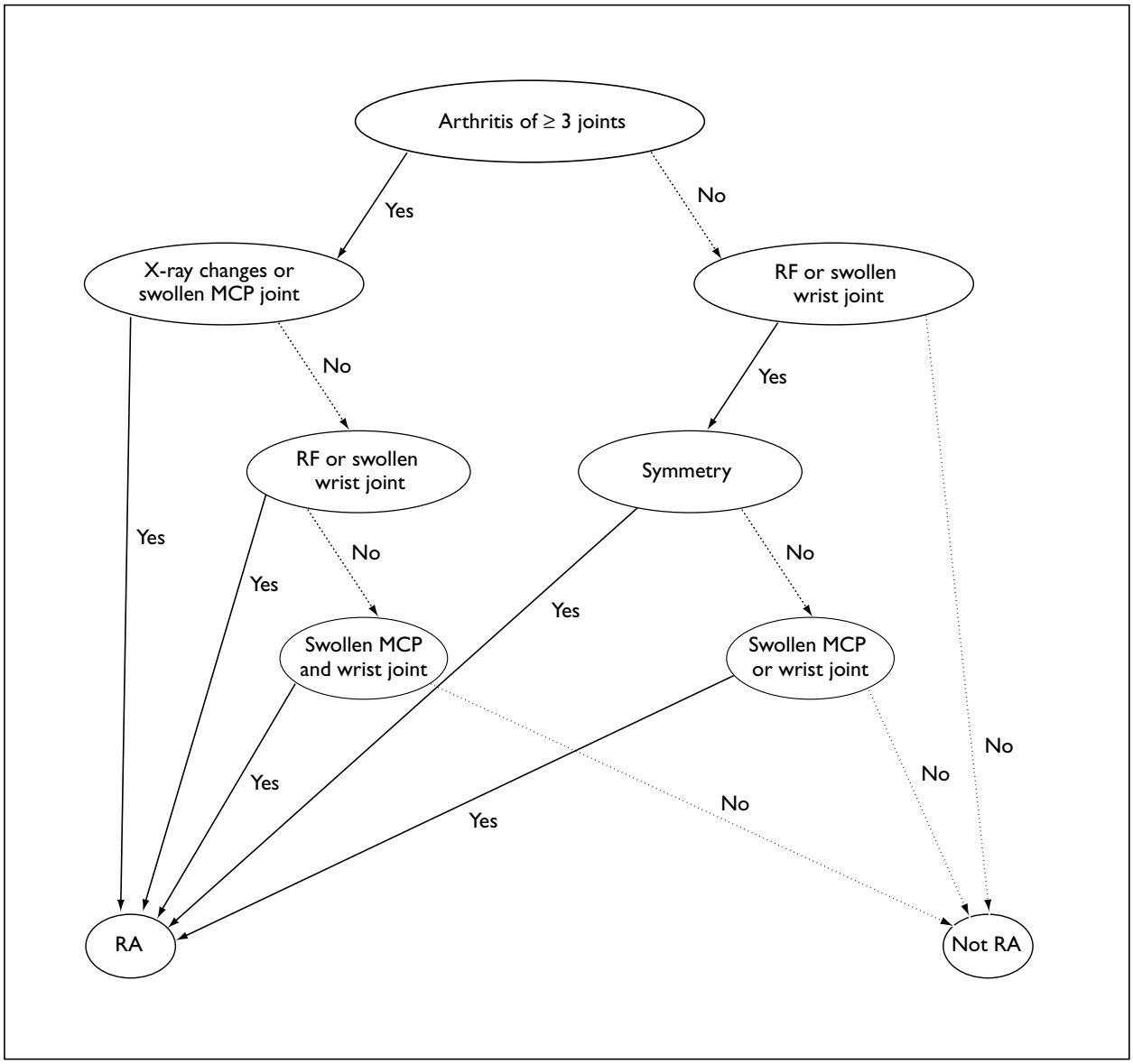



***FIGURE 1*** *1987 ACR decision tree algorithm for classification of RA (adapted from Arnett* et al.*, 1988[6] (MCP, metacarpophalangeal)*

antigens. Recently a gene for tumour necrosis factor receptor (TNFR) has been linked to RA.[13]

- The occurrence of RA in both of a pair of identical twins is 12%.[10] A family history of RA increases the risk of an individual developing disease by 1.7 times that of the expected population rate.[10]
- Infectious agents such as mycobacteria, Epstein–Barr virus and parvovirus have been suspected as causal agents but without any conclusive or convincing evidence.[14,15]
- Lifestyle factors such as diet, occupation or smoking are not causally linked to RA.
- Sex hormones are implicated because there is an increased incidence in women and RA improves in pregnancy in many cases, and relapses post-partum. Nulliparous women, women in the post-partum period and women who have an early menarche have a greater risk of developing RA.[10]
- RF, an autoimmune response to IgG, is a key feature of RA. High levels are relatively specific for RA but RF may also occur in other chronic diseases and is absent in around 30% of patients with established RA. Other auto-antigens have been proposed but as yet no single antigen has been incriminated in causing disease.[16–18]

### *Pathology*

The pathological hallmark of RA is synovial hyperplasia and an inflammatory reaction of synovial tissues. This is accompanied by an inflammatory exudate into the joint cavity. Synovial fluid in RA is highly cellular and contains predominantly poly-

morphonuclear cells with lesser numbers of T cells and macrophages. The normal joint lining layer consists of a one or two cell layer thickness of fibroblast-like cells without a basement membrane. These cells lie on an interstitium of connective tissue with a few blood vessels and deeper fibroblasts. In disease, the lining layer is increased up to a ten cell layer thickness. There are more blood vessels and populations of activated cells such as fibroblasts, T lymphocytes, plasma cells (antibody-producing cells) and cells resembling macrophages. Aggregates of lymphoid tissue resembling lymph nodes may also be found in synovial tissues.

Cytokines, small peptides that mediate signals between cells primarily in a localised environment, and their receptors, are produced in greater quantities in inflamed synovial tissues. Erosion, or destruction, of cartilage and bone commonly occurs where synovial tissue meets cartilage and bone. This occurs through the combined actions of 'invasive' synovial tissue (pannus) and resident cartilage and bone cells. Erosions may be seen on X-rays and are useful in diagnosis. Erosions, and loss of cartilage in a synovial joint, are rarely reversible. Such damage therefore compromises the structure and function of a normal joint.

### *Role of TNF*

Almost all biological processes involve cytokines, especially normal immunity and inflammation. Cytokines are multifunctional and highly expressed in RA tissues.[19–21] TNF appears to be a key cytokine in RA. Two forms of TNF are recognised – TNFα and TNFβ (or lymphotoxin). Synovial fluid and tissue levels of TNFα are increased in RA and serum levels are increased in 50% of cases.[22] Some cytokines, such as interferon-γ, interferon-β, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6) and TNF can augment inflammation. Others such as interleukin-4 (IL-4), interleukin-10 (IL-10) and transforming growth factor have anti-inflammatory properties. Cytokines that augment inflammation, especially those produced by macrophages (IL-1, IL-6, TNFα and interleukin-8 (IL-8)) are found in abundance in RA tissues. TNFα appears to regulate production of a variety of proinflammatory agents including IL-1, which has a key role in mediating joint damage.[21]

TNF was described in 1975 as a soluble factor that induced necrosis of tumours. Subsequently TNFα was identified as a catabolic hormone and an important mediator of endotoxic shock.[23] Release of large amounts of TNF can lead to cardiovascular collapse. Release of lower levels for a prolonged period may cause wasting, anaemia, fever and bone resorption. TNFα has a half-life of 6–7 minutes and is produced largely by activated macrophages. Its production can comprise as much as 1–2% of protein released by activated cells.[24] TNFα is one of a family of ten related molecules that bind to structurally related receptors. Of this family, only TNFα and lymphotoxin (TNFβ) are secreted.[23] Lymphotoxin is now known to have two forms, lymphotoxin-α and lymphotoxin-β. Other members of this family, including nerve growth factor, are transmembrane proteins that act during cell-to-cell contact. Mice that have the lymphotoxin-α gene deleted lack important lymphoid tissues such as lymph nodes, Peyer's patches and splenic white pulp, but have a normal thymus.

TNFα is synthesised as an inactive prohormone. In its active secreted state three identical subunits combine to form a trimer. TNFα is released by activated macrophages as a single unit (monomer) by the actions of TNFα converting enzyme (TACE).[25] TNFα and lymphotoxin-α signal to cells by binding to two cell receptors. These receptors are known by their molecular size as the 55-kd TNF (TNFR1) and the 75-kd TNF (TNFR2) receptor. Two cell-surface receptors, either TNFR1 or TNFR2, combine when TNFα binds to the cell surface. This binding triggers a variety of biological processes, including:

- increased passage of immune cells (e.g. polymorphs and lymphocytes) across the endothelium of blood vessels
- activation of immune cells
- release of other cytokines, especially those that promote inflammation
- release of potentially deleterious enzymes that can contribute to local tissue destruction.

TNFα has a greater affinity for TNFR1 than for TNFR2. It is believed that TNFR2 functions by passing on bound TNFα to TNFR1 when circulating levels of TNFα are low. However, TNFR2 is also able to mediate the biological activity of TNFα. Mice lacking TNFR1 are highly susceptible to infection by *Mycobacteria* and *Listeria monocytogenes*. Experiments with knockout mice indicate that the TNF/TNFR1 interaction is critical for the formation of lymphoid tissues and resistance against bacterial, parasitic and viral infections. The role of TNFR2 is less clear from such studies. It appears that expression of TNFR2 is restricted to endothelial and haemopoietic cells whereas virtually all cell types express TNFR1.[26] Both TNFα and lymphotoxin-α bind to TNFR1 and TNFR2 with similar affinity and have similar

biological effects. However, different cell types produce these two cytokines: lymphotoxin-α is produced primarily by lymphocytes, TNFα by macrophages. Also, unlike TNFα, lymphotoxin has not been detected in synovial fluid or in serum of patients with RA, but messenger RNA has been found.[21,22]

The extracellular sections of TNFR may be shed as a result of the actions of enzymes similar to TACE. These soluble TNF receptors (sTNFRs) are natural inhibitors of TNF and have a half-life of seconds or minutes.[25] Levels of sTNFR are raised in RA, after surgery in normal people, in AIDS and in osteomyelitis, suggesting that they serve as acute phase proteins.[27,28] The level of circulating sTNFR in RA correlates with disease activity and levels in synovial fluids are two- or three-fold higher than those found in serum. Levels of IL-1 receptor antagonist (IL-1ra), another natural cytokine inhibitor, and of cytokines with anti-inflammatory activity such as IL-10, are also elevated in RA. This suggests that in RA there is an imbalance between agents that promote inflammation and those that inhibit it, leading to chronic inflammation. Interestingly, chronic TNF stimulation suppresses T cell function but anti-TNF therapy in RA improves immune cell function.[28] In addition, anti-TNF therapy in RA reduces egress of immune cells across the endothelium of blood vessels and this effect appears to be linked to clinical response.[29]

### *Goals of management*

Effective treatment of RA and osteoarthritis was the subject of a recent workshop involving a committee of the Royal College of Physicians and the British Society for Rheumatology (BSR).[30] The Scottish Intercollegiate Guidelines Network (SIGN) has also examined the management of early RA in detail.[31] The goals of treating RA may be summarised as follows:

- to control symptoms of joint pain and inflammation
- to minimise loss of function and to maintain or improve quality of life
- to reduce the risk of joint damage and disability
- to treat extra-articular complications of RA
- to have well informed and satisfied patients and carers.

Other guidelines list similar principles of management.[32] There is general agreement that a long-term treatment plan is required, and that this needs repeated re-evaluation in the light of clinical parameters and patient preferences.[33] Clinicians recognise that many factors need to be considered during this interaction with patients.[34] These include:

- Discussion of therapeutic options, including drug and non-drug treatments, as well as an appreciation of risks and benefits. This includes an awareness of the hazards of untreated disease and of rare potentially life-threatening adverse events with some drugs, such as pneumonitis with methotrexate.
- Modes of drug administration and monitoring needs to ensure safe use of particular drugs.
- Assessment of psychosocial factors such as available social support, adjustment to disease, needs of dependants and effect on employment and employability.
- Educational needs of patients and carers.
- Co-morbidity that may influence drug use and prognosis. For instance nearly a third of RA patients have co-existing cardiovascular disease at diagnosis.[35]
- Drug costs.

### *Current drug therapy for RA*

Conventional drug therapy for RA relies on varying combinations of the following four classes of drugs:

- non-steroidal anti-inflammatory drugs (NSAIDs)
- analgesics
- corticosteroids such as prednisolone and methylprednisolone
- disease-modifying anti-rheumatic drugs (DMARDs), including sulphasalazine, methotrexate, gold preparations, penicillamine, azathioprine, hydroxychloroquine, leflunomide and cyclosporin A.

Daily pain control and stiffness are managed by NSAIDs, low-dose prednisolone (for example prednisolone 10 mg or less), analgesics or a combination of these. The risks and benefits of NSAIDs are well recognised and have been reviewed extensively.[31,36] Corticosteroids may be given in varying doses by mouth, or as injections into joints, intramuscular (i.m.) injections or intravenously (i.v.). This is often done for short-term control of disease or for acute relapses, as 'bridge therapy' or 'step-down therapy', to allow rapid control of disease whilst awaiting the effects of DMARDs.[37] The benefit of corticosteroids on symptoms of RA does not appear to be sustained in randomised trials. However, in clinical practice, a significant proportion of patients are maintained on corticosteroids long term, indicating sustained benefit for some patients.[37,38] Long-term therapy may also be justified on the grounds that low-dose prednisolone prevents joint damage.[39]

### *DMARDs*

DMARDs are slow-acting drugs that provide symptomatic relief and may take several weeks or months to work. They also have a potential for inducing disease remission and for reducing the risk of joint damage in progressive RA. Remission may be achieved in a small proportion of patients. The mode of action of many DMARDs is not fully understood but many appear to act by immune suppression. Methotrexate and leflunomide, a newly available DMARD, are anti-metabolites.[40] However, methotrexate probably functions as an anti-inflammatory drug in the low doses used in rheumatic diseases, through a variety of cellular enzymes and mediators. Methotrexate binds and inactivates dihydrofolate reductase, an enzyme that has a key role in purine and DNA synthesis.[41] Leflunomide binds to dihydroorotate dehydrogenase, an enzyme with a key role in pyrimidine synthesis.

It is generally accepted that patients with RA should be treated with DMARDs soon after diagnosis. This advice is based on randomised trials and patient cohorts showing that patients in whom DMARDs are delayed have worse outcomes.[31,42,43] Benefits of DMARDs include:

- improved symptoms of arthritis, overall well-being and physical function
- improved blood parameters such as reduced anaemia and acute phase responses
- slowing of radiological damage associated with RA.

DMARDs are usually given with NSAIDs, analgesics, corticosteroids, or a combination, at least initially. As disease control is achieved, doses of other drugs may be reduced, or drugs discontinued, while maintaining therapy with DMARDs. Comparisons between DMARDs indicate that oral gold, azathioprine and hydroxychloroquine are less effective than other agents.[31,40,44] The remaining drugs appear to have comparable efficacy. A meta-analysis of treatment termination rates showed that continued drug use 60 months after starting a DMARD was 36% for methotrexate, 23% for i.m. gold, and 22% for sulphasalazine. Median time for drug use for these agents was 41, 24 and 18 months, respectively, underlining a key limitation of DMARDs – relatively short-term use, or drug survival, of a DMARD for a disease with a lifelong course.[45]

DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preference, complicating co-morbidity or a combination of these.[46] DMARD toxicity varies from relatively minor adverse reactions to life-threatening events such as bone marrow suppression. Felson and colleagues, in a meta-analysis that examined the balance between toxicity and efficacy, concluded that, in the context of clinical trials, anti-malarial drugs and methotrexate had the most favourable profile.[47] Sulphasalazine and methotrexate had similar efficacy but sulphasalazine had slightly higher toxicity. Anti-malarials were particularly safe. On these grounds any one of hydroxychloroquine, methotrexate or sulphasalazine might be considered for first use in newly diagnosed RA. However, methotrexate might be regarded as the standard against which other drugs should be judged, at least on the grounds that long-term therapy is most likely with methotrexate.

DMARDs are conventionally used in sequence. Thus a patient who fails one drug has that drug substituted by another DMARD. Increasingly, combinations of DMARDs are used, although evidence in favour of combining DMARDs is limited.[48,49] DMARDs may be combined at the outset or they may be added sequentially following initial therapy with one agent. A recent study failed to demonstrate superiority of combination therapy over a single agent in early RA of poor prognosis.[50] This practice appears to be based on the idea that additive therapy is more effective and that in some patients there has been at least a partial response to the initial DMARD.[51] This strategy is described as a 'step-up' approach. Most studies supporting use of combination therapy either in a 'step-up' approach or in parallel comparisons of combination therapy versus single agents have not been replicated and have involved fewer than 100 patients in each treatment arm.[48] Tugwell estimated in 1996 that trials involving 3000 patients or more would be needed to determine whether there is a clinically important difference between combination therapy and single DMARDs.[52] Preferred DMARD combinations include methotrexate with hydroxychloroquine or cyclosporin A.[53,54]

An analysis of sequential use of DMARDs suggests that there may be reduced likelihood of sustained therapy with each successive DMARD.[55] Other studies indicate that such differences are not statistically significant. It does appear, however, that the prospect of prolonged therapy for a DMARD is greatest if that DMARD is the drug first used in a sequence of DMARDs.[56] The choice

of initial DMARD does not seem to be relevant, suggesting that failure to respond to methotrexate, or any other specific DMARD, is not a marker for a resistant form of RA.[55]

Patients whose disease is well controlled, or in remission, while taking DMARDs often seek to reduce their medication. Discontinuing treatment increases the risk of relapse and guidelines advocate sustained long-term therapy.[57,58] However, it is not widely acknowledged that only around 60% of patients are fully compliant with DMARD therapy and that nearly a quarter are consistently non-compliant.[59]

Disease in some patients appears to be resistant to conventional approaches. However, there is no clear definition of 'resistant RA'. Criteria for 'refractory' RA have recently been proposed.[60] The following demands must be met, according to the criteria described:

- Patients have used at least three DMARDs including methotrexate (> 15 mg/week) and sulphasalazine (dose > 2 g/day) for a minimum of 6 months unless there was toxicity. Lack of efficacy is defined by failure to improve the Disease Activity Score (DAS) by > 0.6 (discussed below).
- Patients have persistently active disease (DAS > 3.7) despite therapy.

In support of these suggestions the authors showed that 61 (29%) of 210 patients from an inception cohort, followed for a mean of 9 years, used three or more DMARDs but that 34 were controlled on therapy and 27 (12.9%) met their criteria for refractory RA.[60]

### *Toxicity of DMARDs*

The high rate of discontinuation of DMARDs, and the fact that significant proportions of patients discontinue because of drug toxicity, are key concerns in rheumatology. In general, drug toxicity arises during the first months of therapy. After 24 months drug cessation is as likely to be a result of loss of efficacy as toxicity.[56] Treatment cessation because of toxicity is more likely with i.m. gold than with sulphasalazine or methotrexate.[45] Clearly all toxicity is not the same.[47] For instance, many patients may stop taking a drug because of a rash or diarrhoea. Another drug may cause fewer minor adverse reactions but might carry the risk of respiratory failure in a smaller proportion of patients. Such a drug may be much less desirable despite equivalent efficacy. Adverse reactions to commonly used DMARDs are listed in *Table 2*.

### *Assessment of response to DMARDs*

The ultimate goal of treating any disease is complete remission. For RA this is currently an unrealistic goal. Modern clinical trials assess the response of a patient to therapy using a composite measure that combines several measures of disease activity (appendix 2). The American College of Rheumatology (ACR) definition of improvement and the DAS are two of the most commonly used measures. The ACR response, for example, requires an improvement in:[62]

- tender joint count
- swollen joint count
- at least three of:
  - global disease activity assessed by observer
  - global disease activity assessed by patient
  - patient assessment of pain
  - physical disability score (e.g. HAQ)
  - acute phase response (e.g. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)).

Response is defined as ACR20, ACR50 or ACR70, where the figures refer to percentage improvement in the clinical measures shown above. This creates a dichotomous outcome of responders and non-responders. Achieving an ACR20 response has been regarded as a low hurdle but in clinical practice patients who fail to achieve this may still gain a worthwhile clinical response, especially in early RA.[63,64]

### Perspective of regulatory agencies

Guidance produced by the Food and Drug Administration (FDA) for products or devices intended for RA treatment lists six specific aspects of disease that might be targeted by a product.[65] A product may satisfy some or all such claims. This guidance gives an insight into the demands placed on new therapies. Brief details are shown in *Table 3*. A European group described similar but simpler guidance. Drugs were classified into three possible categories: symptom-modifying, inflammation-modifying or structure-modifying.[67] The European Agency for Evaluation of Medicinal Products classification scheme for anti-rheumatic therapies includes the following categories:[68]

- Symptom-modifying anti-rheumatic drugs (SMARDs). This requires improved swollen joint counts, morning stiffness and physical function.
- Disease-modifying anti-rheumatic drugs (DMARDs). This requires improved swollen and tender joint counts and physical function.

***TABLE 2*** *Toxicity of commonly used DMARDs*

| Drug | Common | Uncommon | Rare or very rare |
|---|---|---|---|
| Azathioprine | Nausea, rash, hypersensitivity, mouth ulcers | Leucopenia, infection | Lymphoma (long-term use) |
| Cyclosporin A | Headaches, hypertension, renal impairment, depression, nausea, paraesthesiae, tremor, hypertrichosis, gingival hyperplasia, depression | Incipient renal failure, gout | Malignancy |
| Gold | Rash and pruritis, diarrhoea (especially oral gold), mouth ulcers, thrombocytopenia, proteinuria | IgA deficiency, reduced Igs, neutropenia, cholestatic jaundice | Marrow aplasia, pneumonitis, exfoliative dermatitis |
| Hydroxy-chloroquine | Nausea, diarrhoea, rash, headache, dizziness, blurred vision | Muscle weakness | Retinal toxicity |
| Leflunomide | Hypertension, nausea, diarrhoea, mouth ulcers, abnormal LFTs, headache, dizziness, hair loss, rash | Hypokalaemia, taste disturbance, tendon rupture, anxiety, weight loss | Severe abnormality of LFTs, Stevens–Johnson syndrome, leucopenia (< 2.0), pan-cytopenia, agranulocytosis (very rare) |
| Methotrexate | Abdominal pain, nausea, diarrhoea, abnormal LFTs, neutropenia, macrocytosis, subcutaneous nodules, altered mood | Pancytopenia, pneumonitis, herpes zoster | Lymphoma, liver failure, unusual and severe infections |
| Penicillamine | Altered taste or loss of taste, nausea, mouth ulcers, rash or pruritis, proteinuria, thrombo-cytopenia (dose related) | Glomerulonephritis | Myaesthenia, polymyositis, SLE, aplasia, neutropenia |
| Sulphasalazine | Nausea, rash, discoloured urine, leucopenia, fever, mouth ulcers, dizziness, oligospermia, raised MCV | Neutropenia, agranulo-cytosis, abnormal LFTs, reduced Igs | Pneumonitis |

*Data are collated from a variety of sources, primarily Denman.[61] The term 'common' indicates occurrence in approximately 1–10% of patients; 'uncommon' 0.1–1%; 'rare or very rare' < 0.1%. IgA, immunoglobulin A; Igs, immunoglobulins; LFT, liver function test; MCV, mean corpuscular volume; SLE, systemic lupus erythematosus*

- Disease-controlling anti-rheumatic drugs (DCARTs). This requires improved physical function, morning stiffness and prevention of structural damage, as shown in *Table 3*.

### *Non-drug therapy*

Contemporary treatment of RA requires input from a multi-disciplinary team of health professionals.[31,69] This includes:

- Occupational therapy and physiotherapy, to provide education and optimise, and improve, functional limitations through exercise regimes, aids and appliances. Patients and health professionals value hydrotherapy, but research studies are reported to be of poor quality.[70]
- Podiatry to assist with lower limb mobility by local measures and advice on footwear.
- Dietetics to assess nutrition in those with systemic disease, to give guidance to those choosing diet as therapy and to provide advice for those with weight problems. Diets and dietary supplements have a limited role in RA management.
- Advice on appropriate use of complementary therapies.
- Enabling patients and carers through education.[71]
- Hospitalisation in those requiring intensive treatment, or for severe RA.[72]

### *Prognosis*

The impact of RA on an individual can be viewed from a variety of perspectives including employment status, economic costs to the individual or society, quality of life, physical disability, life expectancy, medical complications such as radiographic damage or the need for surgery, and so on. Understandably, factors that can predict longer-term outcomes at diagnosis are of great interest to patients and doctors. In general, persistent disease activity is associated with poorer outcomes but studies show an inconsistent relationship with specific markers. This probably reflects differences in settings and in selection of patients. Inception cohorts of patients with RA provide the most robust assessment of prognosis. A few well-

***TABLE 3*** *New product claims for treatment of RA (summarised from FDA guidance)*

| Claim | Description |
|---|---|
| 1. Reduction in signs and symptoms of RA | Improvement in clinical end-points, e.g. validated composite end-points such as ACR20* or well-accepted measures, e.g. counts of tender and swollen joints, pain, and physician and patient global assessments. Trial duration ≥ 6 months unless the product belongs to a well-characterised pharmacological class (such as NSAIDs), when 3 months is accepted |
| 2. Major clinical response | 70% improvement in ACR definitions for therapeutic effect.* Statistically significant improvement in ACR70 response rates, compared to background therapy, for a continuous period of 6 months |
| 3. Complete clinical response | Remission (see below) and no progression of disease on radiographs by defined methods, for a continuous period of 6 months. Trials of at least 1 year duration are envisaged and trials aiming to show this level of response should use complete clinical response or treatment failure as the primary outcome measure |
| 4. Remission | Defined as joint morning stiffness of < 15 minutes, no fatigue, no symptoms of joint pain, no joint tenderness or pain on motion, no swelling of joints or tendon sheaths, and ESR < 20 or 30 depending on sex.[66] Trial duration 1 year |
| 5. Prevention of disability | Studies of 2–5 years' duration. Measurement of validated disability outcomes is required, e.g. the HAQ. Improvement in symptoms or signs must also be demonstrated either concomitantly or in previous studies. Stability in measures of health-related quality of life using generic and validated measures, such as SF-36, is also required |
| 6. Prevention of structural damage | Slowing radiographic progression does not define patient benefit, therefore concomitant or previous benefit in symptoms, signs, clinical response or disability are required. Progression on X-rays may be defined as slowing or prevention of disease-related X-ray changes using a validated index. Trial duration ≥ 1 year |

*SF-36, Short Form with 36 items*

* *The ACR definition of improvement as defined on page 7*

studied outcomes and their predictors are discussed briefly below.

- **Disability** can be difficult to predict within 5 years of diagnosis, as the functional status of individuals is labile.[73] At 5 years, disability (HAQ > 1) is predicted by age at symptom onset, a high disability score at presentation (a tautology), rheumatoid nodules, female sex, psychological status and joint tenderness.[74–76] Accuracy of 76% is reported for a combination of these factors (excluding female sex).[74] Physical function of patients followed soon after disease onset and, defined by ACR classification for function (appendix 3), is normal in up to 40% of patients at 5 years. Moderate or severe disability occurs in 15.4%.[75]
- **Loss of employment** is related to type of employment, and other aspects of the workplace such as pace of work, physical environment, physical function, education and psychological status.[77,78] Work disability is not necessarily linked to measures of disease activity such as tender or swollen joint count. It occurs in 40% of patients 5 or more years after diagnosis and, in as many as a third, 2 years after diagnosis. Rates of work disability are substantially greater than in controls in some studies, but not all.[79] Manual workers, not surprisingly, suffer most limitations.[75]
- **Serial measures of disease activity and severity** may predict radiographic damage. Markers linked to greater radiographic damage include positive RF, age, disease duration and extent of disease.[80] The predictive value of such factors for erosions on X-rays approaches 80% in some studies, although there is considerable variation between studies.[1] Genetic markers have been shown in some studies to predict radiographic damage, however others suggest that this may not be the case.[81] Clinical trials of DMARDs usually measure radiographic damage in the small joints of hands and feet. The degree of small joint damage correlates with extent of large joint damage and both correlate with physical function.[82,83]
- **Major joint replacement surgery** (including hip, knee, shoulder and elbow replacements) was required in 8% of RA patients 5 years after diagnosis.[75] With longer follow-up 25% of patients had total joint arthroplasty within

22 years of disease onset.[2] Hospitalisation for medical treatment of RA shows considerable variation between centres as a result of availability of inpatient facilities.[75] However, medical treatment of severe RA in hospital can lead to better outcomes up to 2 years after hospitalisation, compared with routine outpatient care.[72]

- **Mortality** may be increased in RA. A standardised mortality ratio (SMR) of 1.82 (range 0.87–3) was reported in a recent review.[84] Wolfe reported an SMR of 2.26 from a large cohort of US patients.[77] This study indicated that skin nodules, greater physical disability and treatment with steroids were associated with increased mortality. Deaths from infection, lymphoma or leukaemia, and deaths related to the digestive system, were found in greater than expected proportions. The death rate at 5 years in a large British cohort of patients seen in hospital was 10.7%, whereas the rate for an inception cohort of primary care patients with RA was 13% after median follow-up of 6.9 years.[75,85] The latter study (the Norfolk Arthritis Register or NOAR) found that cardiovascular disease was the most common cause of death. Mortality was not increased in patients satisfying the ACR criteria for RA but patients who were positive for RF had an increased all-cause mortality (SMR 1.5, 95% confidence interval (CI), 1.1 to 2.1).

### *Burden of illness*

Many medical aspects of the burden of RA have been reviewed. The illness is associated with a substantial economic burden in some studies. Medication costs account for 8–24% of medical costs, physician visits 8–21% and hospitalisation 17–88%. It is unclear whether indirect costs exceed direct medical costs overall, but it appears that patients and families, rather than healthcare services, incur a majority of the economic costs early in disease.[86] Mean annual direct and indirect costs for the year 1996 were reported at £3575 and £3638 per patient, respectively.[87] Inevitably, in a disease characterised by lifelong pain, discomfort and physical impairment, the burden on individuals and families is increased. Economic disadvantage, for example because of work disability, or limited access to resources such as aids and appliances, can have a substantial impact on the ability of an individual to function independently.[88]

## Current service provision

Joint pain is the leading reason for referral to hospital outpatient services, with an annual rate of referral exceeding 40 per 1000 population.[89] Most patients with RA are referred to hospital services but up to a quarter of patients with early inflammatory arthritis (not necessarily RA) are managed in primary care without specialist referral.[1] The BSR and other organisations recognise a significant shortfall in rheumatology service provision. A recent assessment of needs indicated that one whole-time consultant rheumatologist was required per 85,000 population, implying a need for 650 whole-time equivalents in rheumatology for the UK. In 1990 there were 250 whole-time equivalents, with an estimated annual consultant expansion rate of 3%.[90,91] Prolonged waiting times for patients to be seen in hospitals, and opinions of general practitioners and patient groups, provide support for the view that rheumatology provision is insufficient.[92,93]

The majority of patients followed up in a hospital rheumatology department have RA or another type of inflammatory arthritis or connective tissue disease. A significant proportion of such patients may also require inpatient treatment. However, there are considerable variations in inpatient facilities for patients with rheumatic disease. This may account for variations in hospitalisation rates for RA.[90]

## Description of new intervention

### *Identification of patients and criteria for treatment*

The limitations of current therapies for RA were described earlier. These limitations provide a context in which new treatments for RA should be viewed. Rigid criteria for the use of any specific treatment in any one individual are inappropriate.[94,95] This is especially true for RA where, in addition to considering a patient's perspective, significant co-morbidity is likely to influence therapeutic choices. A BSR committee issued guidelines in 2000 on the appropriate use of etanercept and infliximab.[96] The motive for producing these guidelines was the cost of these new therapies and concerns about equitable access. No such guidance was issued on leflunomide, a new, much cheaper DMARD, licensed at around the same time as anti-TNF agents. The BSR committee recommended that etanercept and infliximab should only be used if the following criteria were met:

- Patients satisfy the 1987 ACR classification criteria for RA.
- Patients have highly active RA based on a DAS score of > 5.1 (using DAS28, appendix 2).

- Patients must have failed treatment with methotrexate and at least one other DMARD (from a list including i.m. gold, hydroxychloroquine, sulphasalazine, penicillamine, azathioprine, methotrexate and leflunomide). Treatment with each DMARD should be for at least 6 months. A 'standard target dose' for a minimum of 2 months is stipulated unless toxicity requires discontinuation.
- Clinicians must register treated patients, with consent, in a central registry and provide data on drug dose, outcome and toxicity on a quarterly basis.[97]

The stated purpose of the patient registry is to study drug safety, the incidence of serious infections, malignancy and mortality in treated patients. The guidelines state that a group of 'untreated controls' will also be studied but no further details are provided. It is proposed that patients are monitored for at least 5 years and the goal is to recruit all patients treated with anti-TNF agents. Training for clinicians to participate in this registry has begun. The sources of funding for this study are not stated and physicians contributing patient data will not be reimbursed or receive support for data gathering. It is also not stated how complete participation is to be ensured or how standards for data recording are to be maintained and audited. This is especially important because many thousands of patients may be eligible for anti-TNF therapies (see page 13). It is also unclear whether those contributing data, and the public, will have open access to the data.

The ACR, motivated by similar concerns of cost and equity, formed a 'blue ribbon committee' to discuss new therapies.[98] This committee acknowledged that access to prescription drugs was a matter for shared responsibility between many interested parties. This committee, like the BSR, recognised the need for a sound basis in evidence for any new treatments. It recommended flexibility and recognised the unique nature of each case and the impact of physician–patient judgement in decision-making. The ACR committee also recommended ongoing evaluation of approved therapies but made explicit mechanisms by which research should be regulated, and reviewed, and also recommended open access for participants and the public. The ACR committee drew back from listing criteria for use of biological therapies in RA and affirmed its view that 'the judgement of the individual rheumatologist should be the sole criterion that governs access to therapy'. In doing so the committee recognised that such a stance could be viewed as self-serving.

### *Description of technology*

Etanercept (Enbrel®, Wyeth Laboratories, Maidenhead) and infliximab (Remicade®, Schering-Plough, Welwyn Garden City) are two newly licensed biological agents that aim to reduce the actions of circulating TNF in human diseases. Etanercept is classified as an sTNFR, infliximab is a selective immunosuppressive agent.

**Etanercept**

Etanercept is a combination protein consisting of the extracellular portion of two of the 75-kd TNF receptors (TNFR2) for TNF combined with a human Fc portion of human IgG1 (class 1) (IgG1). It is produced in cultured, genetically engineered Chinese hamster ovary cells. The active substance is manufactured at Boehringer Ingelheim Pharma, Germany. Assembly, labelling and release are by Wyeth Laboratories, UK or Wyeth Medica, Ireland.

Etanercept binds soluble and cell-bound TNFα and lymphotoxin by competing with TNFRs. It has a 50-fold higher affinity for TNF than monomeric TNFR, *in vitro*. It is distributed to bone, liver, spleen and kidney and probably penetrates synovial tissue. Breakdown and clearance are believed to occur through proteolysis with recycling or elimination of by-products in bile or urine. In RA, it is administered as a twice-weekly subcutaneous injection of 25 mg and may be given for an indefinite period. Patients or caregivers are expected to administer etanercept and so appropriate instruction, supervision, and facilities for disposal of needles and syringes are necessary to ensure safe use.

Peak plasma concentration is reached in 48 hours, with slow clearance from the body (half-life 70 hours). Clearance is slower in RA patients. No dose changes are recommended for patients with renal or hepatic failure, in elderly patients or in those of a particular race or gender. With repeated dosing patients may have a two to five times increase in serum levels. Co-administration with methotrexate does not affect etanercept concentrations but data on methotrexate concentrations is not available in humans (animal studies show no effect). No specific blood or other toxicity monitoring is required. Laboratory studies indicate that delayed-type hypersensitivity, immunoglobulin levels and cell populations of immune cells are not affected by treatment.[99] However, concerns about the possibility of altered immune responses to malignancy and infections remains.

Etanercept is indicated for the following patient groups:

- RA patients, to reduce signs and symptoms in those with moderately or severely active RA. It may be used in combination with methotrexate for patients who have had an inadequate response to methotrexate alone. The recommended dose is 25 mg given twice weekly as a subcutaneous injection.
- Juvenile idiopathic or chronic arthritis patients with polyarticular disease who have had an inadequate response to one or more DMARDs. The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg/dose) twice weekly.

**Infliximab**

Infliximab is a chimeric human-murine monoclonal antibody directed against TNFα. The TNFα binding region is murine and comprises 30% of the amino acid sequence of infliximab. The remainder is a human IgG1 heavy chain and kappa chain constant region. Infliximab is secreted by mouse myeloma cells and is manufactured by continuous cell perfusion cell culture. Harvests are purified and undergo various quality control and safety procedures. The recombinant antibody is manufactured in production batches and each vial is presented as a sterile powder to be reconstituted for i.v. use.

The recommended dose of infliximab for RA is 3 mg/kg body weight given as an i.v. infusion followed by further infusion, at the same dose, 2 and 6 weeks later. Thereafter infusions are given at 8-week intervals. Freshly reconstituted infliximab is diluted to a volume of 250 ml using 0.9% sodium chloride and the infusion is administered i.v. over at least 2 hours using a low-protein-binding filter.

Infliximab levels are related to the dose administered and have a rapid effect on TNFα levels. For example, TNFα levels detected in 54% of patients before treatment with infliximab fell to below detection limits 1 hour after infusion of infliximab but peaked from 72 hours to 2 weeks after infusion.[100] Peak concentrations and persistently detectable TNFα levels are greater when patients are treated with high-dose infliximab. This is attributed to the presence of infliximab–TNFα complexes. The half-life of infliximab is estimated to be 8–10 days, although it has been detected for up to 28 weeks after infusion (mean 12 weeks). No data on metabolism and excretion are available, but it is assumed that infliximab is eliminated as though it were a native antibody. Patients in specific risk categories, for example those with renal or liver failure, have not been studied. Methotrexate marginally increased plasma concentrations of infliximab for unexplained reasons.

Infliximab binds with high affinity to cell-bound TNFα and soluble TNFα monomers and trimers and forms stable complexes. Infliximab inhibits binding of TNFα to TNFR1 and TNFR2 and it may dissociate TNFα already bound to TNFR. Unlike etanercept, infliximab does not bind or inhibit lymphotoxin. Short-term studies suggest that infliximab does not cause generalised immune suppression.[101] Infliximab is indicated for the following patient groups:

- RA patients, to reduce signs and symptoms in those who have had an inadequate response to methotrexate. The data sheet stipulates use of infliximab with methotrexate (dose unspecified).
- Crohn's disease, to reduce signs and symptoms in those who have not responded adequately to conventional therapy. Safety and efficacy have been established for single infusion only.
- Crohn's disease patients with enterocutaneous fistulae, to reduce number of draining fistulae for patients that do not respond adequately to conventional therapy. Safety and efficacy established for three doses only.

***Degree of diffusion***

There appears to be great variation in the use of these therapies across the UK. Some health authorities have agreed specific criteria for use of these agents with local hospital trusts, and have agreed specific funding. Preliminary information provided by Wyeth Laboratories indicates that 23% of 123 health authorities had approved funding for the year 2000/2001 and that a further 14% might do so for the current financial year. Other health authorities have not approved funding and have indicated that funding is, in the first instance, the responsibility of hospital trusts, resulting in very limited access for some patients. Approximately 600 patients have been treated with infliximab (for either Crohn's disease or RA) (Quartey P, Schering-Plough Ltd: personal communication, March 2001) and around 700 patients with etanercept (Reynolds A, Wyeth Laboratories: personal communication, April 2001). It is unclear whether these numbers represent patients treated in clinical trials, routine practice or both. Currently, this represents an approximate annual cost for etanercept of £6.3 million. In view of the demand for etanercept and, at present, limited capacity for

production, Wyeth Laboratories has introduced a quota system for each country. Treatment is available for 500–600 patients per annum in the UK. Priority is being given to children and juveniles. It is believed that production needs will be met by the end of 2002 (Reynolds A, Wyeth Laboratories: personal communication, May 2001).

### *Anticipated costs*

In order to estimate anticipated costs a number of assumptions are required. Using the prevalence of RA as a starting point and assuming that 25% of these patients are not seen in secondary care, we estimate that 316,140 patients with RA are known to hospital departments (see page 2).[1] Accepting Kroot and colleagues' definition of 'resistant RA', that is patients who have active disease despite use of three DMARDs, and using their data, 12.8% of patients known to hospital departments might be considered eligible for anti-TNF therapy.[60] Young and colleagues applied the BSR guidelines (which suggest that patients failing to respond to sulphasalazine and methotrexate should be treated, i.e. failing two DMARDs) to a long-term cohort of over a thousand RA patients followed for 5 years after diagnosis. They estimated that 8% of patients continued to have active RA or poor function, despite therapy with at least two DMARDs (Young A, Early Rheumatoid Arthritis Study Group, Rheumatology Department, City Hospital, St Albans, Hertfordshire: personal communication, April 2001). It is difficult to extrapolate from this data of patients with early disease to the population found in rheumatology clinics.

A local audit indicates that 6.2% of patients seen in a hospital rheumatology department might be eligible for anti-TNF therapy.[102] Accepting that 6.2% of RA patients attending hospital departments are eligible the total figure for England and Wales is 19,600 potential patients. This equates to approximately 186 patients for an average health authority with a population of half a million or 37 patients per 100,000 population. These figures are eroded further by examining actual activity of hospital departments and it has been estimated that as few as nine patients per 100,000 population might be eligible. Accepting the lower estimate yields a potential cost of drugs, in England and Wales, of £38 million per annum, with an upper estimate exceeding four times this amount (estimating drug costs at £8000 per patient per annum). An estimate from Norway in 1999 suggested a potential cost of anti-TNF therapies of between US$450,000 and US$3 million per 1 million population, equating to around US$24–158 million for England and Wales.[103]

# Chapter 2

# Effectiveness

## Methods of reviewing effectiveness

### Search strategy

The following databases and resources were examined:

- MEDLINE (Ovid)
- EMBASE (Ovid)
- Science Citation Index
- Cochrane Library
- National Research Register
- Abstracts from meetings of the ACR and the Annual European Congress of Rheumatology for the years 1999 and 2000. Abstracts from the combined meeting of the BSR and the Scandinavian Society for Rheumatology 2001
- Manufacturer and sponsor submissions to the National Institute for Clinical Excellence (NICE)
- FDA website
- *Scrip*.

Searches were based on medical subject headings and keywords that encompassed rheumatoid arthritis, tumour necrosis factor, tumour necrosis factor receptors, anti-TNF, quality of life, etanercept and infliximab (see appendix 4).

### Inclusion and exclusion criteria

#### *Inclusion criteria*

All randomised controlled trials (RCTs) comparing etanercept or infliximab with any agent including placebo in RA.

#### *Exclusion criteria*

- Trials of etanercept or infliximab in childhood arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis.
- Articles reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms.
- Observational studies of anti-TNF therapies that did not include a control group.

### Quality assessment strategy

The quality of RCTs was assessed by examining methods of randomisation, concealment of allocation, blinding, losses to follow-up, and methods of analysis. The Jadad checklist was used for this purpose.[104] Two reviewers independently examined trial quality. Disagreements were resolved by consensus.

### Data extraction strategy

Data was extracted independently by two reviewers. A third reviewer resolved any discrepancies. One reviewer screened foreign language publications using English abstracts, if available. Translations were obtained where necessary.

Data extraction focused on clinical outcomes. This included tender and swollen joint scores, physician and patient global assessments, acute phase protein responses, disability scores and composite scoring systems, such as the ACR response criteria and DAS score (appendix 2), which encompass such measures. Data on validated radiographic outcomes were also extracted (appendix 5). The characteristics of patients included in studies were sought in order to allow comparisons between studies to assess the baseline comparability of groups and to judge relevance to routine care. Data on adverse events and other clinically relevant laboratory tests were also extracted, for example, data on anti-double stranded DNA (anti-dsDNA) antibodies were described. Pharmacokinetic data were not abstracted. Additional data on adverse events was sought from reports of post-marketing surveillance or other safety data, in order to obtain a complete picture of potential adverse events.

## Results

### Quantity and quality of research available

An appreciation of the importance of TNF in disease pathogenesis, and favourable results from early trials after initial disappointing results with other biological therapies, has generated a large number of publications.[105] Identified reports included many reviews, news articles, observational studies and studies investigating TNF-related disease mechanisms as well as a small number of clinical trials of anti-TNF therapy. Many identified reports of clinical trials were available as published abstracts only, but unpublished data from key trials were kindly supplied by industry contacts.

## Identified studies, inclusions and exclusions

In total, 118 potentially relevant reports were identified – 34 published reports, 80 abstracts, identified by hand searches, and four internal reports supplied by industry (three from Wyeth Laboratories and one from Centocor, not including submissions to NICE). Data from some studies were presented at more than one meeting, resulting in more than one identified abstract for the same study. In other cases several abstracts presented subsets of data or details of a specific outcome. Where identical data was presented at more than one meeting only the most recent abstract was included. In other cases abstracts were included if pertinent outcome data, not found in other sources, was presented. Efficacy data from the open-label extension phase of blinded studies, or studies that were unblinded for safety or ethical reasons, were excluded.

Ten RCTs of anti-TNF therapy were included in all, four of infliximab and six of etanercept. A flow diagram illustrating these figures is shown in *Figure 2*. Results of MEDLINE and EMBASE searches are shown in appendix 4. A list of included and excluded reports, with a brief comment and reasons for exclusion, is shown in appendix 6. Two preliminary studies that explored optimal doses of anti-TNF agent,

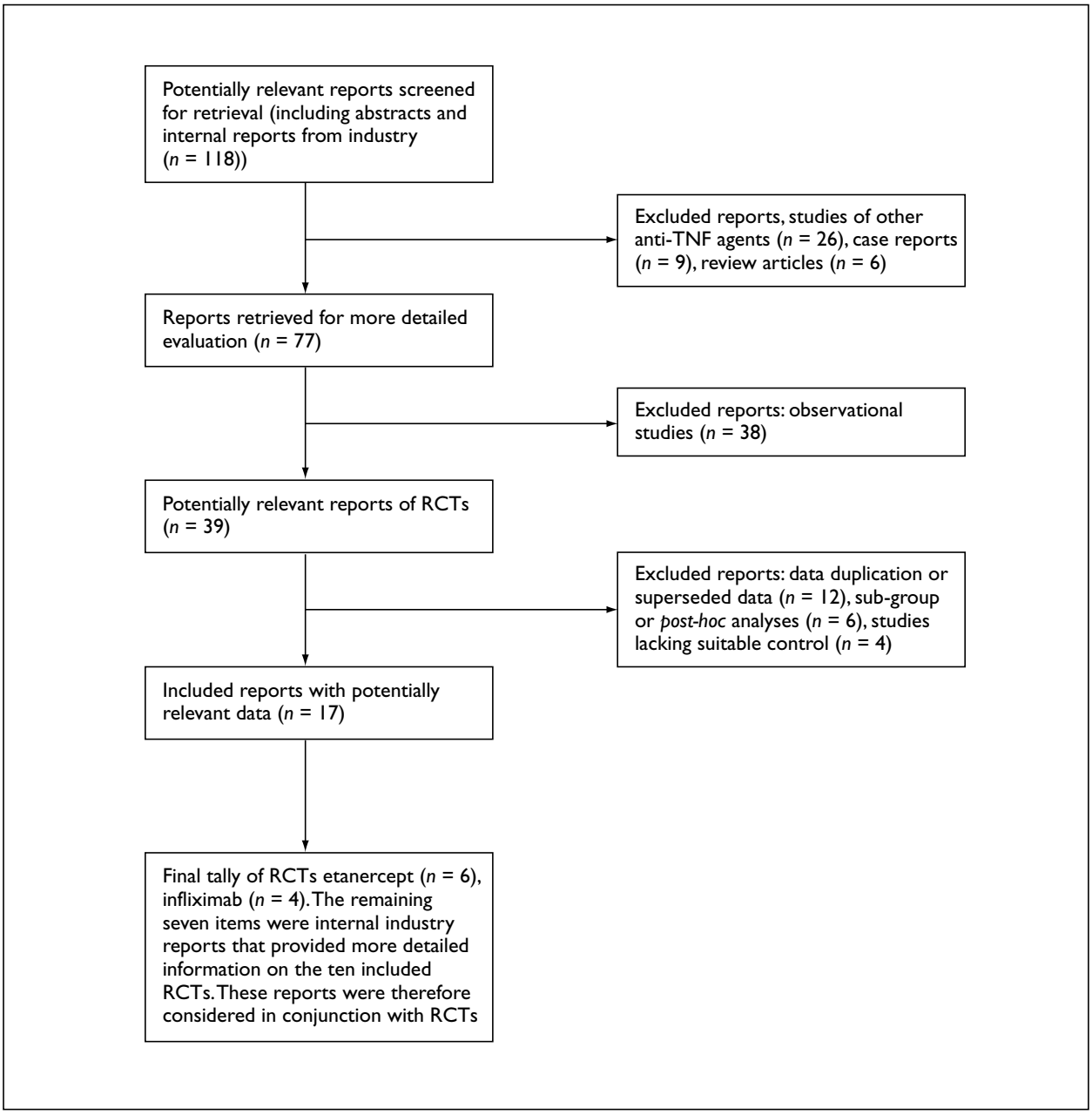



***FIGURE 2*** *Flow diagram for identified reports*

and each including fewer than ten patients in each treatment arm (the Kavanaugh[106] and Moreland[107] studies) are summarised in the text below but data were not tabulated. Key data for the other eight trials is described in a commentary and summarised in a series of tables. The section on adverse events describes data from post-marketing surveillance and other experiences.

Among excluded studies were clinical trials of several anti-TNF agents that have the potential for use in RA. These included:

- D2E7, a fully human anti-TNFα monoclonal antibody[108]
- A recombinant soluble TNF receptor (TNFR1), a natural inhibitor of TNF, attached to a high molecular weight polyethylene glycol (PEG) molecule designated PEG sTNFR1 and developed by Amgen Inc.[109]
- CDP571, a humanised anti-TNFα monoclonal antibody[110]
- A polyclonal antibody against TNFα[111]
- Lenercept, a dimeric human TNFR1 fused with an IgG1 protein.[112]

Additional trials of anti-TNF agents, identified as currently in progress, are listed in appendix 7.

## Infliximab studies – quality and efficacy

Four trials were identified: Elliott and colleagues (1994),[113] Maini and colleagues (1998),[114] Kavanaugh and colleagues (2000),[106] and the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) (1999, 2000).[115,116] All trials were of high quality and scored 5/5 on the Jadad scale. Study characteristics and key data are described below and presented in a series of tables. Data from Kavanaugh (2000)[106] is not tabulated. Additional data on adverse events is reported in a separate section.

### *Elliott and colleagues (1994)[113]*

**Population**

Patients who had failed at least one DMARD and had joint erosions were recruited. Patients taking a DMARD at recruitment had to withdraw from therapy at least 4 weeks before entry. In total, 73 patients from four centres, randomised to three groups, were included. Included patients had six or more swollen joints. Mean disease duration exceeded 7 years and patients had received a mean of three previous DMARDs (*Table 4*). Patients taking low-dose prednisolone (≤ 12.5 mg/day) were allowed to continue at a stable dose. The proportions of patients taking steroids were not given. Of the patients treated with placebo, 71% were RF-positive, compared with 96% receiving 1 mg/kg and 75% of patients given 10 mg/kg.

**Interventions**

- Single i.v. infusion of 0.1% albumin (as placebo) – 24 patients
- Single i.v. infusion infliximab 1 mg/kg – 25 patients
- Single i.v. infusion infliximab 10 mg/kg – 24 patients

**Study duration and key outcomes**

Four weeks, at which time Paulus20 (appendix 2) response was assessed.

**Main efficacy results**

When treated with infliximab 10 mg/kg, infliximab 1 mg/kg and placebo, 79%, 44% and 8% of patients, respectively, met Paulus20 response criteria ($p < 0.0001$ infliximab 10 mg/kg, and $p = 0.0083$ 1 mg/kg compared with placebo, *Table 5*). Swollen joint counts improved by 38% with infliximab 1 mg/kg and by 59% with infliximab 10 mg/kg. Other measures such as ESR improved to a lesser extent (*Table 6*).

**Adverse events**

Overall there were few adverse events (*Table 7*). Intravenous infusions did not lead to haemodynamic problems or fever. One injection-site reaction, and one patient who developed rigors, believed to be related ('reasonably related') to the infusion, occurred in the group treated with infliximab 1 mg/kg. Five infections (25%) were reported in the group given infliximab 1 mg/kg. By contrast only one infection (4%) was reported in the groups treated with placebo and infliximab 10 mg/kg. Two severe adverse events were reported in this study. One patient treated with infliximab 1 mg/kg developed pneumonia. Another, treated with infliximab 10 mg/kg, developed a pathological fracture of the clavicle 1 week after the infusion, believed to be unrelated to treatment. No other serious adverse events were described.

**Comment**

This was the first randomised trial of an anti-TNF agent for RA.

### *Maini and colleagues (1998)[114]*

**Population**

Patients who had taken methotrexate at a dose of 7.5–15 mg/week for at least 6 months were recruited. Concomitant DMARDs other than methotrexate, if any, were withdrawn at least

***TABLE 4*** *Description of included studies – infliximab*

| Study and description | Interventions and patient characteristics | | | | | |
|---|---|---|---|---|---|---|
| | **Interventions** | **No. of patients** | **Mean age (years)** | **Mean disease duration (years)** | **No. of previous DMARDs** | **On steroids** |
| ***Elliott* et al., *1994*[113]** | | | | | (mean) | |
| Study duration 4 weeks | Placebo, single i.v. infusion of 0.1% albumin | 24 | 48 | 9 | 3.7 | Not |
| Placebo-controlled RCT | Infliximab single i.v. infusion 1 mg/kg | 25 | 56 | 7.5 | 2.8 | reported |
| in 4 centres of single infusion of infliximab (2 different doses) | Infliximab single i.v. infusion 10 mg/kg | 24 | 51 | 7.3 | 3.1 | |
| ***Maini* et al., *1998*[114]** | | | | | (median) | |
| Study duration 26 weeks | Placebo 0.1% albumin + MTX 7.5 mg/week | 14 | 49 | 7.6 | 2 | 50% |
| Placebo-controlled RCT | Infliximab i.v. 1 mg/kg + MTX 7.5 mg/week | 14 | 54 | 14.3 | 2 | 43% |
| in 6 centres of infliximab | Infliximab i.v. 1 mg/kg, no MTX | 15 | 49 | 7.6 | 3 | 67% |
| (5 infusions, weeks 0, 2, | Infliximab i.v. 3 mg/kg + MTX 7.5 mg/week | 15 | 59 | 12.1 | 2 | 60% |
| 6, 10 and 14) with or | Infliximab i.v. 3 mg/kg, no MTX | 14 | 47 | 7.8 | 2.5 | 50% |
| without MTX | Infliximab i.v. 10 mg/kg + MTX 7.5 mg/week | 14 | 50 | 11.1 | 2 | 29% |
| | Infliximab i.v. 10 mg/kg, no MTX | 15 | 56 | 9.7 | 2 | 60% |
| ***ATTRACT, 1999, 2000*[115–119]** | | | | | (mean) | |
| Study duration | Placebo (0.1% albumin or saline) + | 88 | 51 | 11 | 2.5 | 64% |
| 12 months | MTX 15 mg/week | | | | | |
| International, placebo- | Infliximab i.v. 3 mg/kg every 8 weeks + | 86 | 56 | 10 | 2.8 | 63% |
| controlled RCT | MTX 15 mg/week | | | | | |
| (34 centres) of infliximab | Infliximab i.v. 3 mg/kg every 4 weeks + | 86 | 51 | 9 | 2.6 | 54% |
| and concomitant MTX | MTX 15 mg/week | | | | | |
| (median dose is quoted) | Infliximab i.v. 10 mg/kg every 8 weeks + | 87 | 55 | 11 | 2.5 | 58% |
| | MTX 15 mg/week | | | | | |
| | Infliximab i.v. 10 mg/kg every 4 weeks + | 81 | 52 | 12 | 2.5 | 65% |
| | MTX 15 mg/week | | | | | |

*Details from Kavanaugh* et al., *2000*[106] *are not tabulated. This study is described on page 22*

4 weeks before entry. In total, 101 patients were randomised to seven treatment groups. At least six swollen and six tender joints were required for entry. Patients taking more than 7.5 mg of prednisolone a day were excluded. Mean disease duration ranged from 8 to 14 years and age from 47 to 59 years. At entry, 29–67% of patients were taking steroids; 71–93% of patients were RF-positive. Patients had tried a median of two DMARDs (excluding methotrexate) at entry.

**Interventions**

- Methotrexate tablets 7.5 mg/week and placebo infusions – 14 patients
- Methotrexate 7.5 mg/week and infliximab 1 mg/kg infusions – 14 patients
- Placebo tablets and infliximab 1 mg/kg – 15 patients
- Methotrexate 7.5 mg/week and infliximab 3 mg/kg infusions – 15 patients
- Placebo tablets and infliximab 3 mg/kg infusions – 14 patients
- Methotrexate 7.5 mg/kg/ week and infliximab 10 mg/kg – 14 patients
- Placebo tablets and infliximab 10 mg/kg infusions – 15 patients

All patients received five i.v. infusions at weeks 0, 2, 6, 10 and 14.

**Study duration and key outcomes**

Twenty-six weeks – the primary efficacy measure was the total time, in weeks, that a patient showed a response to therapy as measured by Paulus20.

**Main results**

Approximately 60% of patients given infliximab 1 mg/kg without methotrexate showed an initial Paulus20 response. However, this was lost by week 8. Thus only 7% of patients met Paulus20 criteria compared with 21% for patients who had infliximab 1 mg/kg and methotrexate, at week 26. Median duration of response for infliximab 1 mg/kg without methotrexate was 2.6 weeks

**TABLE 5** *Percentage of patients showing ACR or Paulus response and discontinuing therapy – infliximab*

| Study and description | ACR20/Paulus | ACR50/Paulus | ACR70 | DAS28* | Drug cessation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Any reason | Lack of efficacy | Toxicity |
| ***Elliott* et al., *1994*,[113] *4-week data*†** | | | | | | | |
| Placebo infusion x 1, *n* = 24 | 8 | 8 | – | – | Not available | Not available | Not available |
| Infliximab infusion 1 mg/kg x 1, *n* = 25 | 44 | 28 | – | – | | | |
| Infliximab infusion 10 mg/kg x 1, *n* = 24 | 79 | 58 | – | – | | | |
| ***Maini* et al., *1998*,[114] *26-week data*** | | | | | | | |
| Placebo + MTX 7.5 mg/week, *n* = 14 | 7 | 0 | – | – | 57 | 57 | 0 |
| Infliximab 1 mg/kg + MTX, *n* = 14 | 21 | 21 | – | – | 7 | 0 | 7 |
| Infliximab 1 mg/kg, no MTX, *n* = 15 | 7 | 7 | – | – | 47 | 33 | 13 |
| Infliximab 3 mg/kg + MTX, *n* = 15 | 47 | 40 | – | – | 0 | 0 | 0 |
| Infliximab 3 mg/kg, no MTX, *n* = 14 | 21 | 14 | – | – | 14 | 7 | 7 |
| Infliximab 10 mg/kg + MTX, *n* =14 | 57 | 50 | – | – | 14 | 7 | 7 |
| Infliximab 10 mg/kg, no MTX, *n* = 15 | 33 | 20 | – | – | 20 | 13 | 7 |
| ***ATTRACT study, 2000*,[116] *54-week data*** | | | | | | | |
| Placebo + (MTX all patients), *n* = 88 | 17 | 8 | 2 | 22 | 50 | 36 | 8 |
| Infliximab 3 mg/kg every 8 weeks, *n* = 86 | 42 | 21 | 10 | 52 | 27 | 20 | 6 |
| Infliximab 3 mg/kg every 4 weeks, *n* = 86 | 48 | 34 | 17 | 59 | 23 | 12 | 11 |
| Infliximab 10 mg/kg every 8 weeks, *n* = 87 | 59 | 39 | 25 | 68 | 15 | 7 | 5 |
| Infliximab 10 mg/kg every 4 weeks, *n* = 81 | 59 | 38 | 19 | 60 | 20 | 9 | 10 |

* *DAS for 28 defined joints, see appendix 2. Data from Antoni* et al., *2000*[118]

† *Paulus data were supplied by authors, figures are not available in the published report.*[120] *Quoted figures are Paulus response rates for both Maini* et al.[114] *and Elliott* et al.[113] *(appendix 2). These are similar to ACR response rates*

***TABLE 6*** *Percentage change in measures of disease activity – infliximab*

| Study and description | SJC | TJC | Pain score patient | Global score | | CRP | ESR | HAQ | EMS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Patient | Physician | | | | |
| ***Elliott* et al., *1994,*[113] *4-week data*** | | | | | | | | | |
| Placebo infusion x 1, *n* = 24 | 0 | 7 | –1 | 0 | 3 | 3 | –3 | – | 5 |
| Infliximab 1 mg/kg x 1, *n* = 25 | 38 | 41 | 36 | 19 | 19 | 13 | 10 | – | 30 |
| Infliximab infusion 10 mg/kg x 1, *n* = 24 | 59 | 61 | 63 | 28 | 39 | 45 | 32 | – | 94 |
| ***Maini* et al., *1998,*[114] *6-week data**** | | | | | | | | | |
| Placebo + MTX 7.5 mg/week, *n* = 14 | –6 | 11 | – | – | – | –33 | – | – | – |
| Infliximab 1 mg/kg + MTX, *n* = 14 | 75 | 71 | – | – | – | 56 | – | – | – |
| Infliximab 1 mg/kg, no MTX, *n* = 15 | 53 | 67 | – | – | – | 17 | – | – | – |
| Infliximab 3 mg/kg + MTX, *n* = 15 | 63 | 57 | – | – | – | 71 | – | – | – |
| Infliximab 3 mg/kg, no MTX, *n* = 14 | 59 | 71 | – | – | – | 11 | – | – | – |
| Infliximab 10 mg/kg + MTX, *n* = 14 | 70 | 85 | – | – | – | 71 | – | – | – |
| Infliximab 10 mg/kg, no MTX, *n* = 15 | 68 | 57 | – | – | – | 38 | – | – | – |
| ***ATTRACT study, 2000,*[116] *54-week data**** | | | | | | | | | |
| Placebo/MTX (*n* = 88 at baseline, *n* ≈ 69 week 54) | 29 | 45 | 22 | 18 | 35 | 30 | 16 | 18 | 52 |
| Infliximab 3 mg/kg every 8 weeks/MTX (*n* = 86 at baseline, *n* ≈ 77 week 54) | 55 | 59 | 43 | 42 | 53 | 59 | 45 | 28 | 69 |
| Infliximab 3 mg/kg every 4 weeks/MTX (*n* = 86 at baseline, *n* ≈ 80 week 54) | 57 | 58 | 44 | 42 | 62 | 57 | 40 | 29 | 73 |
| Infliximab 10 mg/kg every 8 weeks/MTX (*n* = 87 at baseline, *n* ≈ 82 week 54) | 65 | 66 | 53 | 51 | 59 | 64 | 44 | 35 | 74 |
| Infliximab 10 mg/kg every 4 weeks/MTX (*n* = 81 at baseline, *n* ≈ 74 week 54) | 67 | 65 | 42 | 39 | 58 | 74 | 41 | 29 | 73 |

*SJC, swollen joint count; TJC, tender joint count; EMS, early morning stiffness*

* *The 6-week time point was chosen because figure 2 in this study shows placebo data terminating at 6 weeks. Data at 6 weeks were estimated from figure 2 of this study*

† *Percentage change is calculated by subtracting mean population scores at the end of the study from baseline scores and dividing by mean baseline scores for that group. Therefore figures shown are not directly comparable with figures shown in the ATTRACT study,*[116,121] *which describes mean changes for individual patients and then reports a median for each treatment group*

*Negative values indicate worsening, (–) shows unavailable data*

***TABLE 7*** *Infliximab – summary of key adverse events in clinical trials*

| Event | Study and treatment group | |
|---|---|---|
| | **Elliott *et al.*, 1994,[113] 4-week data** | |
| | **Placebo group (*n* = 24)** | **Infliximab groups (*n* = 49)** |
| Any infection | 4% | 12% |
| Pneumonia, injection-site reaction, pathological fracture, rigors | 0 | 1 patient (2%) each |
| | **Maini *et al.*, 1998,[114] 26-week data** | |
| | **Placebo group (*n* = 14)** | **Infliximab groups (*n* = 87)** |
| Serious infections: endophthalmitis, septicaemia | 0 | 1 patient each |
| Infections needing antibiotics | 3 patients (21%) | 28 patients (32%, $p = 0.54$) |
| Infusion reactions: urticaria, pruritis, chills | 0 | 6% |
| Rash – ceased therapy | 0 | 1 patient |
| Anti-dsDNA antibodies‡ | Not reported | 8% |
| SLE | 0 | 1 patient (1%) |
| Malignancy | 0 | 0 |
| Deaths | 0 | 1 patient |
| | **ATTRACT studies, 1999, 2000,[115,116] 54-week data** | |
| | **Placebo group (*n* = 88)** | **Infliximab groups (*n* = 340)** |
| Serious infections* | 8% | 6% |
| Infections needing antibiotics | 35% | 44% |
| Sinusitis | 6% | 17% |
| Infusion reactions | | |
| Hypotension | 2.3% | 2.3% |
| Urticaria | 0% | 1.2% |
| Dyspnoea | 0% | 0.6% |
| ANA† | 26% | 62% ($p \leq 0.002$) |
| Anti-dsDNA antibodies‡ | 0% | 10% ($p \leq 0.013$) |
| SLE | 0% | 1 patient |
| Malignancy | 0% | 5 patients (1.5%) |
| Deaths | 3% | 1% |

*ANA, anti-nuclear antibodies; anti-dsDNA, anti-double stranded DNA*

* *Serious infections are described as bacterial infections, bronchitis, cellulitis, fungal infections, herpes zoster, peritonitis, pneumonia, pyelonephritis, UTI, sepsis and tuberculosis*

† *Values are % of patients who were initially negative for ANA and who had a positive test (serum titre of at least 1:320) at any time during the study*

‡ *Maini* et al., *1998 measured antibodies by Farr assay and positive tests (≥ 10 units/ml) were confirmed by* Crithidia *test. In ATTRACT, values are % of patients who were initially negative for serum antibodies against ds-DNA and who had a positive* Crithidia *test and Farr assay (≥ 25 IU/ml) at any time during the trial*

compared with 16.5 weeks for infliximab 1 mg/kg with methotrexate ($p = 0.006$). Patients given methotrexate and placebo injections had a median Paulus20 response of 0 weeks. Similar proportions of patients receiving infliximab 3 or 10 mg/kg with methotrexate achieved a Paulus20 response (49% and 59%, respectively, *Table 5*). Responses were sustained for between 10 weeks and at least 18 weeks. There was a poor dose–response relationship but responses were more durable with infliximab 10 mg/kg and methotrexate, so that 50% of patients still showed a Paulus50 after 26 weeks (3 months after the final infusion) compared with approximately 20% of

patients with infliximab 1 mg/kg (with methotrexate). Over a third of patients treated with placebo or with infliximab 1 mg/kg without methotrexate discontinued therapy because of inefficacy (*Table 5*).

**Adverse events**
More patients receiving placebo discontinued treatment than those receiving active therapy (*Table 5*). Therefore, as a result of longer follow-up, more minor adverse events were recorded in the groups treated with infliximab (83% compared with 57% for placebo). Five patients (6%) treated with infliximab withdrew as a result of reactions during the infusion. Urticaria, pruritis and chills were the reported reactions (*Table 7*). One patient withdrew because of a rash after the fourth infusion and another because of a urinary tract infection (UTI) and vaginitis. Infections, mostly minor events such as coughs and upper respiratory tract infections (URTIs), were more common in infliximab groups (28 patients of 87, 32%, compared with 3 of 14, 21%, placebo patients). Other common minor adverse events potentially related to treatment were headache (13%), diarrhoea (9%), rash (7%), pharyngitis (7%), rhinitis (7%) and UTI (5%).

One patient, given infliximab 3 mg/kg, developed bacterial endophthalmitis 9 weeks after the final infusion and following cataract surgery. This patient lost his eye. A second patient, given 10 mg/kg infliximab, withdrew after the third infusion because of lack of efficacy but 15 weeks later died of septicaemic shock as a result of bacterial infection. Anti-dsDNA antibodies developed in 8% of patients treated with infliximab and one patient, treated with 3 mg/kg, developed clinical evidence of SLE. Anti-dsDNA antibodies disappeared on cessation of infliximab after 10 weeks.

**Comment**
A total of 57% of patients treated with placebo (with methotrexate) and 40% of patients treated with infliximab 1 mg/kg (without methotrexate) discontinued treatment within 8 weeks of the study (*Table 5*). Thus only three and four patients, respectively, remained in the study at 26 weeks. Parameters of disease such as tender and swollen joint counts were presented as medians in graphs but graphs were terminated when patients ceasing therapy exceeded 50%. It appears therefore that patients who terminated treatment were not followed for the duration of the study, or were excluded from analysis. Finally the maximum dose of methotrexate used in this study in most cases was below 12.5 mg. This reflects practice at the time of the study. In contemporary practice the dose range for methotrexate is between 7.5 and 25 mg/week.

### *Kavanaugh and colleagues (2000)*[106]

**Population**
Patients who had taken methotrexate for at least 3 months, and at a stable dose of 10 mg/week in the 4 weeks before screening, were recruited. A total of 28 patients were randomised to four treatment groups (seven in each arm) at three study centres. Patients had a mean age of 46 years, mean disease duration of 6 years and had been established on methotrexate for at least 3 months (a stable dose of 10 mg/week at entry). Patients taking more that 7.5 mg of prednisolone a day were excluded. At least five patients (71%) in each treatment arm were RF-positive. At entry, 29% of placebo-treated patients took corticosteroids compared with 71–86% given infliximab.

**Interventions**
All patients received methotrexate 10 mg/week, folic acid 1 mg/day and:

- Single i.v. infusion of 0.1% albumin (as placebo) – 7 patients
- Single i.v. infusion infliximab 5 mg/kg – 7 patients
- Single i.v. infusion infliximab 10 mg/kg – 7 patients
- Single i.v. infusion infliximab 20 mg/kg – 7 patients

**Study duration and key outcomes**
Twelve weeks blinded phase, open-label phase 28 weeks. The primary efficacy measure was ACR20 response at any stage over 12 weeks.

**Main results**
One placebo-treated patient (14%) gained an ACR20 response during the study period and at 12 weeks. By comparison 81% of patients treated with infliximab (all dose groups combined) gained ACR20 at some stage and 52% at the 12-week assessment. Mean ACR50 responses for all infliximab-treated groups at 12 weeks was 29%.

**Adverse events**
Minor events were common with infliximab (95%) and placebo (71%). Four patients (19%) given infliximab had temporary infusion-related events including dry mouth, anxiety, dizziness, headache, nausea and bruising. Three patients (43%) treated with placebo and five patients (24%) treated with infliximab had one or more infections requiring antibiotics. Reported infections were septic bursitis, URTI, and fever with

cough in the placebo group, and sinusitis, bronchitis, ulcerative stomatitis and mastitis in the infliximab groups. In the open-label extension of this study 23 patients were treated. Three withdrew because of adverse events. One developed cellulitis in the infusion arm, another developed dizziness, amnesia, headache and apathy, and a third developed skin vasculitis and a positive test for anti-dsDNA antibodies. In the last case the rash and anti-dsDNA antibodies cleared spontaneously after 11 weeks. Ten patients had infections needing antibiotics including three with bronchitis, two UTIs and two URTIs.

**Comment**
Small numbers of patients as this was a preliminary trial of safety and efficacy.

### *ATTRACT studies*[115,116]

**Population**
Patients who had taken methotrexate for at least 3 months, and at a stable dose of 12.5 mg/week or more in the 4 weeks before screening, were recruited. In total, 428 patients were randomised to five treatment groups at 34 study centres. Patients taking more than 10 mg of prednisolone a day were excluded. At entry 81% of patients were RF-positive, 54–65% took oral corticosteroids (*Table 4*) and 86% had taken methotrexate for more than 1 year. Median disease duration was 7 or more years, and mean previous DMARD use 2.5 (excluding methotrexate). Mean swollen joint count at entry was 20 (out of 66), mean ESR of at least 49 mm/hour. Patients had substantial functional limitations at study entry as indicated by an ARA functional class III (appendix 3) or worse in 49% of patients and a history of joint replacement in 23% of patients.

**Interventions**
Methotrexate 12.5 mg/week or more and:

- Saline or 0.1% albumin infusions – 88 patients
- Infliximab 3 mg/kg every 8 weeks – 86 patients
- Infliximab 3 mg/kg every 4 weeks – 86 patients
- Infliximab 10 mg/kg every 8 weeks – 87 patients
- Infliximab 10 mg/kg every 4 weeks – 81 patients

All patients had three i.v. infusions at weeks 0, 2 and 6. Thereafter infusions were given at 4-week intervals. Those allocated to 8-weekly infusions of active therapy received placebo infusions at alternate visits.

**Study duration and key outcomes**
The three stated objectives of this study were to evaluate safety and efficacy of infliximab in RA after 30 weeks, to evaluate effect of treatment on joint damage at 54 weeks and to show improved physical function at 102 weeks.[117]

**Main results**
For ethical reasons this trial was unblinded for patients treated with placebo when the 54-week data were analysed.[117] Of 28 patients treated with placebo who entered year 2 (out of the original 88 allocated placebo), 14 completed through to week 102 compared with between 47 and 59 patients in the active treatment arms.[121] Therefore only the 54-week data are described. ACR20 response, the primary efficacy measure, was highest for infliximab 10 mg/kg, given either every 4 weeks or every 8 weeks, 59% in both cases compared with 17% for placebo ($p < 0.001$, *Table 5*). Response rates for infliximab, at all doses, exceeded placebo ($p < 0.001$ in all cases). ACR50 responses were 21–39% for infliximab groups and 8% for placebo. ACR50 response for infliximab 10 mg/kg, 4-weekly or 8-weekly, was significantly better than ACR50 response for infliximab 3 mg/kg every 8 weeks ($p = 0.02$ and 0.008, respectively (*Table 5*)). Improvement in individual measures of disease activity are shown in *Table 6*. Levels of serum RF were reduced by approximately 40% with infliximab. Mean HAQ scores improved by 0.3 with placebo and by 0.5 or 0.6 with infliximab. Short Form with 36 items (SF-36) physical component summary scales improved from a mean of 27.1 (standard deviation (SD) 8.2) to 31.5 (SD 10.8, 66 patients evaluated at week 54) for placebo, compared with a population norm of 50 ± 10. Infliximab patients improved from 25.2 to 26.5 before treatment to between 33.0 and 36.5 after treatment. Differences in SF-36 physical component scales were statistically significant when comparing placebo and infliximab ($p < 0.015$) except where patients had infliximab 3 mg/kg every 8 weeks. The mental component of SF-36 was not significantly improved by any intervention. However, the subscales for 'vitality' and 'social functioning' were significantly improved.

**Radiographic data**
Data from radiological scores are summarised in *Table 8*. Patients treated with placebo showed significantly more progression in total radiological scores ($p < 0.001$, van der Heijde modification of Sharp score, appendix 5) than those treated with infliximab. Radiographic scores for placebo worsened by 9% or 10% but scores for infliximab groups were not significantly different over 54 weeks. Differences were maintained when scores for joint space narrowing, erosions and for X-rays of hands and feet were studied

***TABLE 8*** *Radiological outcomes – etanercept and infliximab*

| Study and intervention | Total score | | Erosion | | Joint space narrowing | | Other radiological outcome | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Mean change from baseline | Baseline | Mean change from baseline | Baseline | Mean change from baseline | | |
| ***ATTRACT study, 2000,[116] 54-week data*** | 0–440 | | 0–280 | | 0–160 | | Major progression* | Improvement† |
| Placebo, *n* = 64 | 82 | 7 | – | 4 | – | 2.9 | 31% | 14% |
| Infliximab 3 mg/kg every 8 weeks, *n* = 71 | 79 | 1.3 | – | 0.2 | – | 1.1 | 8% | 44% |
| Infliximab 3 mg/kg every 4 weeks, *n* = 71 | 71 | 1.6 | – | 0.3 | – | 0.7 | 13% | 48% |
| Infliximab 10 mg/kg every 8 weeks, *n* = 77 | 67 | 0.2 | – | 0.2 | – | 0 | 1% | 39% |
| Infliximab 10 mg/kg every 4 weeks, *n* = 66 | 76 | –0.7 | – | –0.7 | – | 0 | 0% | 55% |
| ***Etanercept ERA trial, 2000,[122] 52-week data*** | 0–398 | | 0–230 | | 0–168 | | No progression‡ | Improvement† |
| MTX (20 mg/week by week 8), *n* = 217 | 12.9 | 1.7 | 7.5 | 1.1 | 5.4 | 0.6 | 56% | 18% |
| Etanercept 10 mg twice a week, *n* = 208 | 11.2 | 1.4 | 6.1 | 0.8 | 5.0 | 0.7 | 62% | 21% |
| Etanercept 25 mg twice a week, *n* = 207 | 12.4 | 0.8 | 6.4 | 0.4 | 6.0 | 0.4 | 62% | 21% |
| ***Etanercept ERA trial, 2000,[123] 104-week data*** | 0–398 | | 0–230 | | 0–168 | | No progression‡ | Improvement† |
| MTX (20 mg/week by week 8), *n* = 213 | 12.9 | 3.2 | 7.5 | 1.9 | 5.4 | 1.3 | 51% | 18% |
| Etanercept 10 mg twice a week, *n* = 199 | 11.2 | 2.5 | 6.1 | 1.4 | 5.0 | 1.1 | 53% | 21% |
| Etanercept 25 mg twice a week, *n* = 204 | 12.4 | 1.3 | 6.4 | 0.7 | 6.0 | 0.7 | 63% | 21% |

*In the ATTRACT study the van der Heijde modification of the Sharp scoring system was used.[124] The Etanercept ERA trial used the modified Sharp method[125]*

* *Major progression defined as those with changes from baseline that exceeded 95% CI of the mean score for the two readers*

† *Improvement in total radiological scores*

‡ *No progression is defined as a change of < 0.5 units. Figures shown are for the total Sharp score. Percentages of patients showing no progression for erosion score for MTX, etanercept 10 mg and etanercept 25 mg were 60%, 66% and 72% at year 1 and 58%, 60% and 70% at year 2. For joint space narrowing figures were 76%, 79% and 81% at year 1 and 69%, 73% and 78% at year 2*

independently. The authors emphasised, in *post hoc* analyses, that radiographic improvements were also seen for patients not showing a clinical response. The proportion of patients showing 'major progression' and those showing 'improvement' confirmed the favourable effect of infliximab compared with placebo (*Table 8*).

**Adverse events**
Minor events were common with placebo/methotrexate (94%) and with infliximab/methotrexate (95%). Infusion-related reactions such as headache and nausea were common, especially after the first infusion. Hypotension developed in eight infliximab-treated patients (2.3%) and two (2.3%) placebo-treated patients (*Table 7*). Four patients (1.2%) treated with infliximab developed urticaria and two (0.6%) developed dyspnoea. Two of these patients ceased treatment because of urticaria and dyspnoea, respectively. No patient treated with placebo had urticaria or dyspnoea related to infusions.

Serious infections, defined as those that were life-threatening or that required hospital treatment, occurred in 8% placebo/methotrexate compared with 6% of infliximab-treated patients. Infections that were treated with antibiotics occurred in 35% of placebo-treated patients versus 44% for infliximab. Sinusitis was more common with infliximab (17% versus 6%). There were eight deaths in total and they occurred in 3% of placebo/methotrexate patients compared with 1% for infliximab. Deaths were mostly from cardiopulmonary disease. Malignancies were reported in 5 of 340 infliximab-treated patients and none treated with placebo (88 patients). One was a recurrence of carcinoma of the breast, one patient developed squamous cell carcinoma and melanoma, one patient in each case developed basal-cell carcinomas, rectal carcinoma, and a B-cell lymphoma.

No patient treated with placebo/methotrexate developed anti-dsDNA antibodies but 26% had anti-nuclear antibodies (ANA). By contrast, 7–11% of infliximab-treated patients had anti-dsDNA antibodies and 53–68% ANA. One patient treated with infliximab was diagnosed as having drug-induced SLE.

**Comment**
Patients entering this study may, at best, be characterised as partial responders to methotrexate and potentially were not gaining any benefit at all from methotrexate. Therefore this study might be regarded as a comparison of infliximab against placebo, at least for a proportion of patients. It should be noted however that more than 54% of patients in each group were taking oral corticosteroids. Only 44 (50%) patients randomised to placebo infusions completed study treatment to 54 weeks. By contrast 15–27% of patients treated with infliximab had ceased therapy by week 54. Treatment cessation by week 54 was mainly a result of inefficacy (*Table 5*). Details of the numbers of patients assessed at week 54 shows that between 6% and 26% fewer patients completed assessments, for different treatment groups, at this time point compared with the numbers at study entry. Thus 69 patients treated with placebo were evaluated for swollen and tender joints at week 54 compared with 88 entering the placebo arm. In analysis it was assumed that patients who discontinued treatment for any reason (including deaths) were non-responders for ACR response criteria. For calculation of other outcomes the last observation was carried forward and used as the study end-point value.

A sensitivity analysis by reclassifying patients who discontinued medication as non-responders is described in the 30-week report of the ATTRACT study.[115] Similar sensitivity analysis is not reported in the published report of the 54-week data.[116]

Percentage change for individual parameters of disease activity are shown in *Table 6*. Figures in this table are not comparable to figures shown, for example, in the ATTRACT study, where the percentage change was calculated for each individual patient.[115] Figures shown in *Table 6* are derived by calculating percentage change in disease parameters for the mean scores for the group rather than individual patients. This was done to allow comparisons with etanercept studies. Actual mean scores for disease parameters, for patient groups, at baseline and after treatment for infliximab and etanercept, are shown in appendices 8 and 9.

## Adverse events – infliximab: additional information

Data from post-marketing reports of adverse events with infliximab (including patients treated for Crohn's disease) includes 46 deaths, 27 (59%) of which were attributed to infections. Unusual infections that have been identified include two patients with listeria infection, 28 patients with tuberculosis (two of whom died), five with pneumocystis carinii infection, six patients with aspergillosis, three with histoplasmosis, one with septic arthritis due to coccidiomycosis and three systemic candidal infections.[126] Centocor representatives indicated that 115,000 patients have been treated with infliximab and that in many

cases, where unusual infections occurred, patients were being treated with other immunosuppressive agents such as corticosteroids and azathioprine concurrently.[126] Tuberculosis occurred within the first 4 months of therapy and preliminary reports suggest 'unusual presentations' including extra-pulmonary tuberculosis.[127] Tuberculosis associated with infliximab was highlighted in a recent report from the Committee on Safety of Medicines.[128] The data sheet for infliximab highlights the need for caution if patients have chronic infection or a history of recurrent infections.[101] No specific pretreatment screening procedures or requirements for monitoring on treatment such as chest radiographs or anti-dsDNA antibody measurements are stipulated in the data sheet.

Patient samples from three clinical trials of infliximab have been tested in detail for anti-dsDNA antibodies.[129] Anti-dsDNA antibodies developed in approximately 7% of patients treated with infliximab but clinical SLE occurred in only 1 of 156 treated patients. Anti-dsDNA antibodies associated with infliximab are of IgM class whereas patients with idiopathic SLE usually have both IgG and IgM class anti-dsDNA antibodies. In an analysis of approximately 880 patients treated with infliximab, three patients (0.3%) developed SLE or a related clinical syndrome but none had life-threatening disease.[130]

## Etanercept studies – quality and efficacy

Six studies were included: Moreland and colleagues (1996),[107] (1997)[131] and (1999);[132] Weinblatt and colleagues (1999);[133] The European Etanercept Investigators Group study;[134,135] and the Etanercept Early RA (ERA) trial.[122,123,136] All trials were of high quality and scored 5/5 on the Jadad scale. Study characteristics and outcomes are described below. Key data from all studies, except Moreland (1996),[107] are tabulated. Additional data on adverse events is reported in a separate section.

### *Moreland and colleagues (1996)[107]*

**Population**

Patients who had failed at least one DMARD, and had at least five swollen joints and nine tender joints were included. Prednisolone dose at entry was 10 mg or less and patients taking a DMARD at recruitment had to withdraw therapy 4 weeks before entry if on methotrexate and 6 weeks for other DMARDs. Sixteen patients at a study centre with a mean age of 53 years were included.

Mean disease duration was 8.5 years. The mean ESR, swollen and tender joint count at baseline were 38 mm/hour, 24 and 43, respectively.

**Interventions**

Four cohorts of four patients each; three received active therapy and one placebo.

- Single i.v. infusion 4 mg/m$^2$, twice-weekly etanercept 2 mg/m$^2$
- Single i.v. infusion 8 mg/m$^2$, twice-weekly etanercept 4 mg/m$^2$
- Single i.v. infusion 16 mg/m$^2$, twice-weekly etanercept 8 mg/m$^2$
- Single i.v. infusion 32 mg/m$^2$, twice-weekly etanercept 16 mg/m$^2$

**Study duration and key outcomes**

Four weeks double-blind phase and open-label extension. Phase I dose-finding and safety study.

**Main results**

The trial was too small to demonstrate any statistically significant improvements in outcomes between the intervention and placebo, even when all intervention groups were combined. The direction of change was consistent with a treatment effect for all outcomes measured (CRP, ESR, swollen and tender joint counts and morning stiffness).

**Adverse events**

All patients completed 4 weeks of treatment. Eight patients had mild injection-site rashes.

**Comment**

This was a small preliminary trial of safety and efficacy. Randomisation was not described. Each cohort was recruited sequentially and the dose of anti-TNF increased. There is doubt over the baseline comparability of the placebo and the intervention groups, with the former having more severe disease – for example, they had a mean disease duration of 12 years compared to just 4 years in the intervention group and a mean total joint score of 88 compared to 61 in the intervention group.

### *Moreland and colleagues (1997)[131]*

**Population**

Patients who had failed at least one DMARD, and had at least 10 swollen joints and 12 tender joints were included. Patients on DMARDs at recruitment had a 4-week washout before entry. In total 180 patients, randomised to four groups, were recruited. Disease duration exceeded 5 years in over 71% of patients. Patients had previously used between one and four DMARDs, at least 27% of patients had received methotrexate, and 59–77% were taking oral corticosteroids at study entry. Included patients had to take a stable dose of NSAIDs and prednisolone (≤ 10 mg/day of prednisolone) for 4 weeks prior to

study entry, throughout the study and the follow-up periods. The proportions of RF-positive patients in each group were not reported. Mean age of patients was between 52 and 55 years.

**Interventions**
Subcutaneous injections, twice weekly, were given in each case.

- Placebo – 44 patients
- Etanercept 0.25 mg/m$^2$ – 46 patients
- Etanercept 2 mg/m$^2$ – 46 patients
- Etanercept 16 mg/m$^2$ – 44 patients

**Study duration and key outcomes**
Twelve weeks – primary efficacy measures were swollen joint count, tender joint count, and total count of swollen or tender joints. Secondary efficacy measures were pain, quality of life, duration of morning stiffness, ESR, CRP, and physician and patient global evaluations.

**Main results**
Swollen joint counts improved by an average of 24% for each placebo-treated patient compared with 16%, 32% and 58% with increasing doses of etanercept. Similarly, tender joint counts improved by an average of 28% for each placebo-treated patient compared with 25%, 46% and 64% for etanercept groups. Changes in other parameters of disease activity, shown as percentage change in group mean scores, are presented in *Table 9*.

ACR20 responses for placebo were 14% and for etanercept 33%, 46% and 75% with increasing dose. ACR responses began by 1 month and continued to rise to 3 months. For instance, ACR20 responses for etanercept 16 mg/m$^2$ increased from 59% after 1 month, to 68% after 2 months and 75% after 3 months. ACR50 response for placebo was 7% compared with 57% for etanercept 16 mg/m$^2$ ($p < 0.001$), at 3 months. Only 52% of placebo-treated patients completed the study compared with 61%, 78% and 93% for etanercept doses of 0.25, 2 and 16 mg/m$^2$, respectively (*Table 10*). Most patients discontinued therapy because of inefficacy.

**Adverse events**
Reactions related, or potentially related, to etanercept were injection-site reactions, consisting of local erythema with or without discomfort, and URTIs. Proportions of patients experiencing reactions were not reported and no serious infections, haematological or biochemical abnormalities were reported. Tests for autoantibodies such as anti-dsDNA antibodies were not done. Injection-site reactions did not occur persistently in individual patients and reactions usually resolved within 3 days. One patient withdrew from the study because of injection-site reactions caused by etanercept. There was one death, in a patient given placebo, but details were not provided.

**Comment**
When patients withdrew from the study the last available value was used as the 3-month value. Patients were categorised as non-responders for ACR20 and ACR50 if they had dropped out prior to study completion.

### *Moreland and colleagues (1999)*[132]

**Population**
Patients who had failed to respond to more than one but fewer than four DMARDs were recruited. Patients on DMARDs at recruitment had a 4-week washout before entry. At least 10 swollen joints and 12 tender joints were required at entry. In total, 234 patients participated at 13 North American study centres. Patients had used a mean of three or more DMARDs (at least 87% had received methotrexate previously). Mean age was between 51 and 53 years. Mean disease duration at entry was 12 years. Steroids were used by 58% of placebo patients at study entry compared with 66% for etanercept 10 mg and 81% for etanercept 25 mg. Patients taking more than 10 mg of prednisolone were excluded. Mean daily corticosteroid dose was between 6.8 and 7.5 mg. Proportions of patients taking NSAIDs were 84% for placebo, 67% for etanercept 10 mg and 67% for etanercept 25 mg. Proportions of RF-positive patients were 79%, 82% and 79%, respectively. Patients had a mean of 25 swollen joints at entry, and a mean ESR of at least 35 mm/hour.

**Interventions**
Subcutaneous injections, twice weekly, were given in each case.

- Placebo – 80 patients
- Etanercept 10 mg – 76 patients
- Etanercept 25 mg – 78 patients

**Study duration and key outcomes**
Six months – primary efficacy end-points were ACR20 and ACR50 at 3 and 6 months.

**Main results**
ACR20 responses at 6 months were 11% for placebo, 51% for etanercept 10 mg, and 59% for etanercept 25 mg ($p < 0.001$ etanercept versus placebo). ACR50 responses were 5%, 24% and 40%, respectively ($p < 0.001$ etanercept versus

***TABLE 9*** *Percentage change in measures of disease activity – etanercept*

| Study | SJC | TJC | Pain score patient | Global score | | CRP | ESR | HAQ | EMS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Patient | Physician | | | | |
| ***Moreland* et al., *1997*[131] *** | | | | | | | | | |
| Placebo twice a week, *n* = 44 | 23 | 24 | 5 | 7 | 16 | 33 | 0 | 3 | 16 |
| Etanercept 0.25 mg/m$^2$ twice a week, *n* = 46 | 21 | 25 | 19 | 18 | 24 | 41 | 11 | 10 | –23 |
| Etanercept 2 mg/m$^2$ twice a week, *n* = 46 | 29 | 47 | 31 | 33 | 40 | 44 | 25 | 11 | 50 |
| Etanercept 16 mg/m$^2$ twice a week, *n* = 44 | 54 | 57 | 51 | 51 | 58 | 75 | 40 | 23 | 78 |
| ***Moreland* et al., *1999*[132]** | | | | | | | | | |
| Placebo twice a week, *n* = 80 | –7 | 6 | –22 | –3 | 2 | –207 | –18 | 6 | –23 |
| Etanercept 10 mg twice a week, *n* = 76 | 44 | 44 | 39 | 31 | 33 | –18 | 10 | 33 | 34 |
| Etanercept 25 mg twice a week, *n* = 78 | 47 | 56 | 53 | 46 | 44 | 31 | 18 | 31 | 13 |
| ***Weinblatt* et al., *1999*,[133] *24-week study*** | | | | | | | | | |
| Placebo + MTX, *n* = 30 | 35 | 39 | 21 | 33 | 38 | 38 | 17 | 27 | 26 |
| Etanercept 25 mg twice a week + MTX, *n* = 59 | 70 | 75 | 64 | 67 | 67 | 77 | 40 | 47 | 89 |
| ***The European Etanercept Investigators Group, 1999*[137]** | | | | | | | | | |
| Placebo, *n* = 105 | 18 | 16 | 2 | 3 | 7 | –33 | –20 | –6 | 4 |
| Etanercept 10 mg/week, *n* = 122 | 39 | 42 | 34 | 32 | 34 | 29 | 16 | 22 | 25 |
| Etanercept 10 mg twice a week, *n* = 110 | 50 | 48 | 44 | 42 | 44 | 33 | 19 | 33 | 28 |
| Etanercept 25 mg/week, *n* = 111 | 55 | 52 | 43 | 40 | 46 | 40 | 23 | 33 | 15 |
| Etanercept 25 mg twice a week, *n* = 111 | 55 | 58 | 48 | 45 | 51 | 35 | 29 | 32 | 33 |
| ***Etanercept ERA trial, 2000*,[122] *52-week data*** | | | | | | | | | |
| MTX (20 mg/week by week 8), *n* = 217 | 58 | 60 | 57 | 52 | 58 | 75 | 49 | 50 | 84 |
| Etanercept 10 mg twice a week, *n* = 208 | 54 | 58 | 43 | 38 | 52 | 76 | 31 | 36 | 73 |
| Etanercept 25 mg twice a week, *n* = 207 | 63 | 65 | 54 | 46 | 63 | 75 | 41 | 53 | 74 |

*Data shown are for differences between group means (or medians if means were not available), not average change per patient as reported in some studies (Moreland* et al., *1997*[131]*).*

[*] *Percentage improvement from baseline was calculated as the mean of the change in individual patients rather than the difference between group means at baseline and 3 months*

***TABLE 10*** *Percentage of patients showing ACR response and discontinuing therapy – etanercept*

| Study and intervention | ACR20 | ACR50 | ACR70 | ACR-N | Drug cessation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Any reason | Lack of efficacy | Toxicity |
| ***Moreland* et al., *1997*[131]** | | | | | | | |
| Placebo twice a week, *n* = 44 | 14 | 7 | – | – | 48 | 43 | 0 |
| Etanercept 0.25 mg/m$^2$ twice a week, *n* = 46 | 33 | 9 | – | – | 39 | 35 | } 1 patient |
| Etanercept 2 mg/m$^2$ twice a week, *n* = 46 | 46 | 22 | – | – | 22 | 17 | |
| Etanercept 16 mg/m$^2$ twice a week, *n* = 44 | 75 | 57 | – | – | 7 | 5 | |
| ***Moreland* et al., *1999*[132] *** | | | | | | | |
| Placebo twice a week, *n* = 80 | 11 | 5 | 1 | – | 67 | 53 | 4 |
| Etanercept 10 mg twice a week, *n* = 76 | 51 | 24 | 9 | – | 32 | 21 | 7 |
| Etanercept 25 mg twice a week, *n* = 78 | 59 | 40 | 15 | – | 24 | 15 | 3 |
| ***Weinblatt* et al., *1999*, [133] *24-week study*** | | | | | | | |
| Placebo + MTX, *n* = 30 | 27 | 3 | 0 | – | 20 | 13 | 3 |
| Etanercept 25 mg twice a week + MTX, *n* = 59 | 71 | 39 | 15 | – | 3 | 0 | 3 |
| ***The European Etanercept Investigators Group*, [137] *3-month data*** | | | | | | | |
| Placebo, *n* = 105 | 12 | 5 | 1 | – | 19 | 14 | 1 |
| Etanercept 10 mg/week, *n* = 122 | 47 | 22 | 4 | – | 7 | 4 | < 1 |
| Etanercept 10 mg twice a week, *n* = 110 | 63 | 28 | 9 | – | 8 | 4 | 2 |
| Etanercept 25 mg/week, *n* = 111 | 59 | 26 | 10 | – | 9 | 3 | 3 |
| Etanercept 25 mg twice a week, *n* = 111 | 70 | 34 | 13 | – | 5 | 2 | 4 |
| ***Etanercept ERA trial*, [122] *52-week data*** | | | | | | | |
| MTX (20 mg/week by week 8), *n* = 217 | 65 | 43 | 22 | 29 | 21 | 4 | 10 |
| Etanercept 10 mg twice a week, *n* = 208 | 61 | 32 | 16 | 29 | 20 | 7 | 4 |
| Etanercept 25 mg twice a week, *n* = 207 | 72 | 49 | 25 | 35 | 15 | 5 | 5 |

[*] *Paulus response rates were also available in this study. Paulus20 were 16%, 64% and 68% at 6 months for placebo, etanercept 10 mg and etanercept 25 mg, respectively. Paulus50 were 8%, 42% and 55%, respectively. Figures are slightly greater than equivalent ACR responses*

placebo). Swollen joint counts increased with placebo by 7% and decreased by 45% and 47% with increasing dose of etanercept ($p < 0.001$). Details of changes in other measures of disease activity are shown in *Table 9*. 'Minimal disease', defined as patients with fewer than five tender or swollen joints, occurred in 3% of placebo patients, 14% etanercept 10 mg and 17% etanercept 25 mg ($p < 0.005$ etanercept versus placebo).

Responses were noticeable within 2 weeks and appeared to plateau at 3 months. Etanercept response was not related to body weight, use of NSAIDs or use of corticosteroids. A total of 54 patients (67%) on placebo withdrew, compared with 24 (32%) on etanercept 10 mg and 19 (24%) on etanercept 25 mg (*Table 10*). Lack of efficacy accounted for most withdrawals.

Quality of life data from this study was reported in greater detail in a separate publication.[138] This included details of HAQ responses, SF-36 data for a subset of 48 patients, and an overall self-assessment scale ('Feeling thermometer'). 'Feeling thermometer' responses were rated on a scale of 0 for worst imaginable health and 100 for best imaginable health. SF-36 data was incomplete as measurements only began after the trial was under way. 'Feeling thermometer' responses showed baseline values of 47, 46 and 50 for placebo, etanercept 10 mg and 25 mg, respectively. Values improved to 55, 66 and 69, respectively ($p = 0.019$ etanercept 10 mg versus placebo, $p = 0.054$ etanercept 25 mg versus placebo).

**Adverse events**
Injection-site reactions were the most common adverse event and occurred in 13% on placebo, 43% etanercept 10 mg, and 49% etanercept 25 mg ($p < 0.001$ etanercept versus placebo). Most reactions were classified 'mild', consisting of local erythema, itching and pain and lasted for a median of 3 days. Patients experienced reactions with fewer than one in ten injections and efficacy was not influenced by local reactions. Some patients were prescribed topical steroids or antihistamines.

Infections, mainly URTIs, were common and occurred in 16% of patients on placebo, 29% etanercept 10 mg and 33% etanercept 25 mg. After allowing for early withdrawals in the placebo group no differences in infection rates were noted between groups. Other adverse events such as headaches, rhinitis, diarrhoea and sinusitis were similar across groups when expressed as events/patient-year.

No haematological or biochemical abnormalities were noted. Measurement of autoantibodies showed that 1% of patients on placebo were newly positive for anti-dsDNA antibodies compared with 9% for etanercept 10 mg and 4% etanercept 25 mg. Using the (more specific) *Crithidia luciliae* assay, one patient, on etanercept 10 mg, tested positive. This patient was noted to have a pre-existing overlap syndrome of RA and SLE, and improved in this study.

**Comment**
When patients withdrew from the study the last available value was carried forward for statistical analysis. Patients were categorised as non-responders for ACR20 and ACR50 if they had dropped out prior to study completion.

### *Weinblatt and colleagues (1999)[133]*
**Population**
Patients who had active disease despite using methotrexate for at least 6 months (dose range 15–25 mg/week, but as low as 10 mg if poorly tolerated) were recruited. The dose of methotrexate was kept stable 4 weeks before study entry and all patients received folic or folinic acid to reduce methotrexate toxicity. Concomitant therapy with other DMARDs was discontinued 4 weeks before study entry, except for hydroxychloroquine and sulphasalazine, which were discontinued 2 weeks prior to entry. At least six swollen and six tender joints were required and stable doses (for at least 4 weeks before entry) of steroids (prednisolone ≤ 10 mg/day) and NSAIDs were permitted. In all, 89 patients participated at seven US study centres. Mean age of patients given placebo was 53 years and 48 years for etanercept. Disease duration, NSAID use, and previous DMARD use was comparable in the two groups (*Table 11*). At baseline, 70% of placebo patients were on steroids and 90% were RF-positive. By comparison, 53% of etanercept patients were on steroids and 84% were RF-positive. Mean dose of methotrexate at baseline was 18 mg for placebo, 19 mg for etanercept patients. Mean duration of methotrexate was 35 months for placebo patients and 58 months for etanercept patients. Median number of swollen joints at baseline was at least 17, and median ESR was 36 mm/hour placebo and 25 mm/hour etanercept group.

**Interventions**
- Methotrexate and placebo injections twice weekly – 30 patients
- Methotrexate and etanercept 25 mg injections twice weekly – 59 patients

**TABLE 11** *Description of included studies – etanercept*

| Study and description | Interventions and patient characteristics | | | | | |
|---|---|---|---|---|---|---|
| | **Interventions** | **No. of patients** | **Mean age (years)** | **Mean disease duration (years)** | **Mean no. of previous DMARDs** | **On steroids** |
| ***Moreland* et al., *1997*[131]**<br>Multicentre RCT of etanercept at 3 doses.<br>Study duration 12 weeks | Placebo s.c. twice a week | 44 | 55 | 71% > 5 years | 34% MTX* | 66% |
| | Etanercept s.c. 0.25 mg/m$^2$ twice a week | 46 | 54 | 76% > 5 years | 41% MTX* | 59% |
| | Etanercept s.c. 2 mg/m$^2$ twice a week | 46 | 52 | 80% > 5 years | 30% MTX* | 65% |
| | Etanercept s.c. 16 mg/m$^2$ twice a week | 44 | 52 | 80% > 5 years | 27% MTX* | 77% |
| ***Moreland* et al., *1999*[132,138]**<br>RCT in 13 centres of etanercept at 2 doses.<br>Study duration 26 weeks | Placebo s.c. twice a week | 80 | 51 | 12 | 3.0 | 58% |
| | Etanercept s.c. 10 mg twice a week | 76 | 53 | 13 | 3.4 | 66% |
| | Etanercept s.c. 25 mg twice a week | 78 | 53 | 11 | 3.3 | 81% |
| ***Weinblatt* et al., *1999*[133]**<br>RCT of etanercept (25 mg twice a week) and concomitant MTX (dose range 12.5–25 mg/week) vs MTX and placebo injections 2:1 allocation in favour of etanercept<br>Study duration 24 weeks | Placebo + MTX (dose range 3% of patients 12.5 mg, 60% 15–19 mg , 36% 20–25 mg/week) | 30 | 53 | 13 | 2.8 | 70% |
| | Etanercept + MTX (dose range 3% 12.5 mg, 58% 15–19 mg , 40% 20–25 mg/week) | 59 | 48 | 13 | 2.7 | 53% |
| ***The European Etanercept Investigators Group*[134,135]**<br>RCT of safety and efficacy of 4 doses of etanercept vs placebo. 12-week study and long-termobservational data | Placebo injections twice a week | 105 | 53 | 7 | 3.5 | 72% |
| | Etanercept s.c. 10 mg/week, placebo once a week | 122 | 53 | 7 | 3.2 | 79% |
| | Etanercept s.c. 10 mg twice a week | 110 | 54 | 7 | 3.0 | 72% |
| | Etanercept s.c. 25 mg/week, placebo once a week | 111 | 54 | 7 | 3.3 | 70% |
| | Etanercept s.c. 25 mg twice a week | 111 | 53 | 8 | 3.6 | 69% |
| ***Etanercept ERA trial*[122,123,136,139]**<br>RCT in 69 centres of methotrexate vs etanercept in early RA of poor prognosis. Clinical assessments blinded over 1 year, open-label year 2. Radiographic assessments blinded 2 years | Placebo s.c. + MTX increased to 20 mg/week by week 8 | 217 | 49 | 1 | 0.6 | 41% |
| | Etanercept s.c. 25 mg twice a week + placebo tabs | 207 | 51 | 1 | 0.5 | 39% |
| | Etanercept s.c. 10 mg twice a week + placebo tabs | 208 | 50 | 0.9 | 0.5 | 42% |

*Details of Moreland* et al., *1996*[107] *were not tabulated. This study is described on page 26*

* *All patients had received at least one previous DMARD but details are not reported*

*s.c., subcutaneous*

**Study duration and key outcomes**
Twenty-four weeks – primary efficacy end-point ACR20.

**Main results**
ACR20 response for placebo was 27% compared with 71% for etanercept. ACR50 and ACR70 responses are shown in *Table 10*. Swollen joint counts improved by 35% with placebo and 70% with etanercept ($p < 0.001$; figures quoted in the text of this paper are 33% and 78%, respectively; our calculations are based on data presented in a table). Other measures of disease activity also showed significant differences between placebo and etanercept (*Table 9*). Responses were observed within 4 weeks and continued to 16 weeks, when they appeared to stabilise.

Six placebo patients (20%) were withdrawn, four for lack of benefit, against two (3%) withdrawals with etanercept, none for lack of benefit (*Table 10*).

**Adverse events**
Injection-site reactions occurred in 7% of placebo patients, compared with 42% for etanercept (*Table 12*) ($p < 0.001$). All were described mild and were similar to those described above and occurred with approximately one in ten injections.

Infections, such as URTIs and sinusitis, occurred in 63% of placebo patients and 51% of etanercept patients. One patient on etanercept withdrew because of a pre-existing incisional hernia that required surgery. Post-operatively this patient developed a wound infection needing two hospital admissions. Other adverse events such as headaches, dizziness and dyspepsia occurred in similar proportions of patients in both groups. Seven per cent of etanercept patients had hypertension compared with none on placebo. Two patients in each group developed lymphopenia (< 500 cells/ml). One patient on etanercept developed pancreatitis but continued treatment. One patient on placebo developed a myocardial infarction and one patient on placebo developed a gastrointestinal bleed; both these ceased treatment. One patient (3%) treated with placebo was newly positive for anti-dsDNA antibodies compared with four (7%) treated with etanercept. SLE did not develop in any patient. Antibodies to etanercept were detected in one patient, who had a good response to treatment and did not develop injection-site reactions or other adverse events.

**Comment**
Data were reported as medians. When patients withdrew from the study the last available value was carried forward for statistical analysis. Patients were categorised as non-responders for ACR20 if they had dropped out prior to study completion.

Four patients increased oral corticosteroid and four were given intra-articular injections during the study. Injected joints were counted as tender and swollen for the remainder of the study. Two patients, of these eight, were classified as responders in the ACR20 analysis. However, reclassifying these patients as non-responders did not alter the conclusion of this study.

### *The European Etanercept Investigators Group*[134,135,140]

**Population**
Patients with at least six swollen joints and 12 tender joints, and who had failed to respond to at least one DMARD, were recruited. Patients on DMARDs at recruitment had a 4-week washout before entry. Stable doses (for at least 4 weeks before entry) of steroids (prednisolone ≤ 10 mg/day) and NSAIDs were permitted. In total, 559 patients were recruited from 60 European countries. Mean age of patients was 53 years and was comparable for placebo and etanercept. Disease duration, NSAID use, previous DMARD use, presence of RF (in 88% of patients overall) and corticosteroid use (69–79%) were comparable for placebo and etanercept groups (*Table 11*). Minor inconsistencies in the proportions of patients using corticosteroids and NSAIDs were noted in a confidential report supplied by Wyeth Laboratories.[135] Approximately 40% of patients had used four or more DMARDs previously. Disease activity was similar across groups at baseline. Patients had a mean of 22 swollen joints and 31 tender joints at study entry. Mean baseline ESR was 44 mm/hour.

**Interventions**
Subcutaneous injections were given in each case.

- Placebo injections twice weekly – 105 patients
- Etanercept 10 mg once a week, placebo once a week – 122 patients
- Etanercept 10 mg twice weekly – 110 patients
- Etanercept 25 mg once a week, placebo once a week – 111 patients
- Etanercept 25 mg twice weekly – 111 patients

**Study duration and key outcomes**
Three months – primary efficacy end-points were changes in swollen and painful joints.

**Main results**
Swollen joint counts improved by a mean of 18% with placebo after 3 months compared with 55% for etanercept 25 mg twice a week ($p < 0.0125$).

*Table 9* shows differences in group means for disease parameters rather than average change per patient as reported in this study.

ACR20 response for placebo was 12%, 47% for etanercept 10 mg once a week, 63% etanercept 10 mg twice a week, 59% etanercept 25 mg once a week, 70% etanercept 25 mg twice a week ($p < 0.05$ all active groups compared with placebo). ACR50 and ACR70 responses are shown in *Table 10*. 'Minimal disease', defined as patients with fewer than five tender or swollen joints, was noted in 2% of placebo patients, 12% etanercept 10 mg/week, 15% etanercept 10 mg twice a week, and 16% for both etanercept 25 mg groups ($p < 0.05$ all active groups versus placebo).

Details of the relationship between drug dose, concentrations and response to treatment were described in a confidential internal report.[135] A good relationship was shown between drug concentration and clinical effect. It was concluded from the analyses that achieving concentration beyond 2000 ng/ml would provide little additional benefit. The majority of patients given 25 mg twice a week achieved this concentration.

Twenty placebo patients (19%) were withdrawn, 15 patients (14%) for lack of benefit. Withdrawals for etanercept 10 mg/week were 7%, etanercept 10 mg twice a week 8%, etanercept 25 mg/week 9%, and etanercept 25 mg twice a week 5%. Five patients (5%) on placebo were hospitalised for disease exacerbation compared with three (2%) etanercept 10 mg/week, five (5%) etanercept 10 mg twice a week, and two (2%) etanercept 25 mg twice a week. One patient on placebo withdrew for an adverse event and four patients on etanercept 25 mg twice a week.

**Adverse events**

Adverse events were reported by 62% of placebo patients and between 65% and 77% of etanercept groups. No differences between groups were noted except for injection-site reactions. These occurred in 1% of placebo patients compared with 13–30% for etanercept groups. Frequency of reactions increased with increased dose.

Infections were reported by 34% of placebo patients compared with 30% or 31% for etanercept groups. Most were URTIs and no differences in other types of infection were noted between groups. One patient on etanercept 10 mg/week developed cutaneous vasculitis. Serious infections, defined as those requiring hospitalisation, those graded severe or life-threatening or needing parenteral antimicrobial agents, occurred in seven patients in total; two for placebo, one etanercept 10 mg/week, one etanercept 10 mg twice a week, two etanercept 25 mg/week, and one etanercept 25 mg twice a week. One patient on etanercept 10 mg twice a week died of 'septic shock syndrome' with negative blood cultures.

Three malignancies were reported. One patient on etanercept 10 mg twice a week developed large granular lymphocyte syndrome and died from multi-organ failure 7 weeks after study withdrawal. One patient treated with etanercept 25 mg/week was diagnosed with breast cancer. The third, a patient on placebo, had basal cell skin carcinoma noted at study entry.

One patient (1%) treated with placebo was newly positive for anti-dsDNA antibodies compared with five (4%) etanercept 10 mg/week, two (2%) etanercept 10 mg twice a week, two (2%) etanercept 25 mg/week and 11 (10%) etanercept 25 mg twice a week. In general patients had low titres of anti-dsDNA antibodies (< 1:80). SLE did not develop in any patient. Four per cent of patients developed antibodies to etanercept. No clear relationship was noted between clinical response and antibody formation to etanercept.

**Comment**

This study was planned as a 6-month double-blind study followed by an open phase but the protocol was modified to a 3-month double-blind study after inception. Reasons for this are unclear. Unblinding in etanercept studies is possible because injection-site reactions occur predominantly in etanercept-treated patients.

### *Etanercept early RA (ERA) trial*[122,123,136,139]

**Population**

Recruited patients had disease for less than 3 years, at least 10 swollen joints and 12 tender joints, and were RF-positive or had at least three bony erosions on radiographs of hands, feet and wrists. Patients on DMARDs at recruitment had a 4-week washout before entry. Stable doses (for at least 4 weeks before entry) of steroids (prednisolone ≤ 10 mg/day) and NSAIDS were permitted. In total, 632 patients from 69 North American centres were recruited.

Eighty-eight per cent of included patients had a positive RF test. Mean age of patients was 50 years. Median disease duration was 7–8 months, mean number of prior DMARDs 0.5 or 0.6. In all, 59% of patients had never received a DMARD. Mean ESR at baseline was 34 or 35 mm/hour and 39–42% of patients took corticosteroids at baseline (*Table 11*) at a mean dose between 7 mg and 9 mg.

**Interventions**
Subcutaneous injections, twice weekly, were given in each case. All patients also received folic acid 1 mg/day.

- Placebo injections and methotrexate (20 mg/week by week 8) – 217 patients
- Etanercept 10 mg injections and placebo tablets – 207 patients
- Etanercept 25 mg injections and placebo tablets – 208 patients

**Study duration and key outcomes**
Twelve months double-blind phase, further 12 months open-label phase. Primary efficacy end-points were clinical improvement of disease assessed by ACR20, ACR50, ACR70, ACR-N and ACR-N area under the curve responses, and radiographic damage assessed by modified Sharp score. Radiographic damage was also assessed at the end of 24 months without knowledge of treatment assignment.

**Main results**
ACR20 response for methotrexate was 65%, etanercept 10 mg 61%, and etanercept 25 mg 72% ($p = 0.16$ etanercept 25 mg versus methotrexate). ACR50 and ACR70 responses are shown in *Table 10*. ACR-N response was defined as the smallest degree of response from baseline in tender and swollen joints and the median of five other ACR criteria (appendix 2). This showed a 29% improvement with methotrexate, 35% with etanercept 25 mg and 29% with etanercept 10 mg ($p < 0.05$ etanercept 25 mg versus methotrexate, or versus etanercept 10 mg). Swollen joint counts improved by 58% with methotrexate and by 63% with etanercept 25 mg. Other individual measures of disease activity showed similar responses between etanercept 25 mg and methotrexate but in general a lesser response with etanercept 10 mg (*Table 9*). Responses occurred sooner with etanercept 25 mg than with methotrexate with a greater improvement by ACR-N at several time points up to 4 months ($p < 0.05$).

Quality of life as measured by the SF-36 was illustrated in an internal study report.[123] Values for physical component summary scores, estimated from illustrations, show that baseline scores improved from 29 to 40 with methotrexate (US population norm 50) and from 28 to 40 for etanercept 25 mg. Mental component summary scores improved from 47 to 52 and 46 to 51 respectively for the two groups.

Withdrawal rates for any reason were 21% methotrexate, 20% etanercept 10 mg and 15% etanercept 25 mg. Withdrawal rates for adverse events were 10%, 4% and 5% ($p = 0.016$, methotrexate versus all etanercept patients) and for lack of efficacy 4%, 7% and 5%, respectively.

**Radiographic data**
Mean baseline-modified Sharp score for patients assigned methotrexate was 13 compared with 11 for etanercept 10 mg and 12 for patients assigned etanercept 25 mg (range of total Sharp scores 0 to 398). Mean change from baseline in erosion score at 12 months was 1.03 units for methotrexate, 0.9 units etanercept 10 mg, and 0.47 units for etanercept 25 mg ($p = 0.002$ etanercept 25 mg versus methotrexate). There were no significant differences in joint space narrowing scores or total Sharp scores at 12 months. A total of 56% of patients on methotrexate had no progression on total Sharp score at 12 months compared with 62% for the two etanercept groups.

Mean progression rates in total Sharp units was 1.3 units/year (95% CI, 0.6 to 2.1) with methotrexate, 1.4 units/year (95% CI, 0.6 to 2.2) etanercept 10 mg, and 0.8 units/year (95% CI, 0.04 to 1.6) etanercept 25 mg. Progression rates measured by joint space narrowing were similar across groups. However, erosion scores progressed at 0.9 units/year (95% CI, 0.4 to 1.4) with methotrexate, 0.8 units/year (95% CI, 0.4 to 1.4) etanercept 10 mg, and 0.4 units/year (95% CI, –0.1 to 0.9) etanercept 25 mg ($p = 0.047$ etanercept 25 mg versus methotrexate).

Two-year radiographic data, which was analysed under blind conditions, is shown in *Table 8*.

**Adverse events**
Withdrawal due to adverse events was more common with methotrexate ($p = 0.016$ versus etanercept groups): in particular nausea and mouth ulcers were more common (*Table 12*). Rates for injection-site reactions were 7% methotrexate, 30% etanercept 10 mg and 37% etanercept 25 mg ($p < 0.001$ compared with methotrexate).

The number of patients experiencing infections was similar in the two groups but analysis of infection according to events per patient-year showed a rate of 1.9 for methotrexate versus 1.5 for etanercept ($p = 0.006$). No opportunistic infections occurred and there were no deaths related to infection in this study.

***TABLE 12*** *Etanercept – summary of key adverse events in clinical trials*

| Event | Study and treatment group | |
|---|---|---|
| | **Moreland *et al.*, 1999,[132] 6-month trial** | |
| | **Placebo group (*n* = 80)** | **Etanercept groups (*n* = 154)** |
| URTI (events/patient year) | 16% (0.93) | 31% (0.98) |
| Sinusitis (events/patient year) | 11% (0.42) | 12% (0.3) |
| Injection-site reaction (events/patient year) | 13% (0.79) | 46% (9.6, $p < 0.05$) |
| Diarrhoea (events/patient year) | 6% (0.28) | 8% (0.25) |
| Anti-dsDNA antibodies* | 1% | 6% |
| | **Weinblatt *et al.*, 1999,[133] 24-week trial** | |
| | **Placebo group (*n* = 30)** | **Etanercept groups (*n* = 59)** |
| Any infection | 63% | 51% |
| Injection-site reaction | 7% | 42% ($p < 0.001$) |
| Hypertension | 0 | 7% ($p = 0.3$) |
| Gastrointestinal | Diarrhoea 20%, nausea 23%, haemorrhage 1 patient | Diarrhoea 12%, nausea 12%, pancreatitis 1 patient |
| Lymphopenia | 2 patients (7%) | 2 patients (3%) |
| Anti-dsDNA antibodies* | 1 patient (3%) | 4 patients (7%) |
| | **European Etanercept Investigators Group, 2000,[134,135] 3-month trial** | |
| | **Placebo group (*n* = 105)** | **Etanercept groups (*n* = 454)** |
| Infections – any | 34% | 30% |
| Medically important† | 2 patients (2%) | 5 patients (1%) |
| URTI | 27% | 23% |
| Flu syndrome | 5% | 2% ($p = 0.192$) |
| Injection-site reactions | 1% | 23% ($p < 0.001$) |
| Injection-site haemorrhage | 10% | 11% ($p = 0.818$) |
| Hypertension | 3% | 4% |
| ANA – positive at last visit | 55% | 56% |
| Anti-dsDNA antibodies (≥ 1/10)* | 1 patient (1%) | 20 patients (4.4%) |
| Malignancy | 1 patient (1%) | 2 patients (0.4%) |
| Deaths | 0 | 1 patient |
| | **ERA trial, 2000,[122] 12-month trial** | |
| | **Methotrexate group (*n* = 217)** | **Etanercept groups (*n* = 415)** |
| Infections – any | 72% | 64% |
| Medically important† | 6 patients and episodes (2.8%) | 6 patients (1.4%), 9 episodes |
| Injection-site reactions | 7% | 34% |
| Headache | 27% | 24% |
| Gastrointestinal | Mouth ulcer 14%, nausea 29%, vomiting 8%, diarrhoea 12% | Mouth ulcer 5.5%, nausea 15%, vomiting 5%, diarrhoea 13% |
| Back pain | 6% | 8% |
| Alopecia | 12% | 6% |
| Epistaxis | 7% | 1.7% |
| Pneumonitis | 3 patients (1%) | 0 |
| ANA +ve (> 1:80) on therapy | 19% | 23.5% |
| Anti-dsDNA antibodies +ve (> 3.5 IU/mL) on therapy | 2% | 7.5% |
| Other laboratory abnormalities | Raised AST 32%, lymphopenia (< 1400 cells/μl) 79%, neutropenia (< 2000 cells/μl) 8%, thrombocytopenia (< 75 x $10^3$) 2% | Raised AST 15%, lymphopenia (< 1400 cells/μl) 62%, neutropenia (< 2000 cells/μl) 13%, thrombo-cytopenia (< 75 x $10^3$) 3% |
| Malignancy | 2 patients (1%, skin and colon) | 5 patients (1.2%, breast, lung, carcinoid, Hodgkin's, prostate) |
| Deaths | 0 | 2 (metastatic lung cancer, aortic aneurysm) |

*AST, aspartate aminotransferase*

* *Data are % of patients newly positive for anti-dsDNA antibodies by radioimmunoassay. In Moreland* et al.,[132] *only one patient was also positive by* Crithidia *assay (see text).* Crithidia *results were not reported in Weinblatt* et al.[133]

† *Defined as infections that required hospitalisation, those graded severe or life-threatening, or needing i.v. antibiotics*

Liver function abnormalities (32% against 16%) and lymphopenia (79% against 56%) were more common with methotrexate than etanercept groups ($p < 0.001$). Malignancies occurred in two patients assigned methotrexate (bladder and colon cancer), two patients assigned etanercept 10 mg (breast and lung cancer) and three patients assigned etanercept 25 mg (carcinoid lung tumour, Hodgkin's disease and prostate cancer). There were two deaths – one from disseminated lung cancer (etanercept 10 mg) and another from a dissecting aortic aneurysm.

No additional autoimmune diseases were seen. Three per cent of patients were intermittently positive for antibodies against etanercept but positive results did not influence efficacy or toxicity.

**Comment**

This trial was originally designed to show superiority of etanercept over methotrexate in preventing joint damage. However, before un-blinding, this goal was changed to that of showing equivalence of etanercept and methotrexate. This decision was made following recent data confirming that leflunomide, methotrexate and sulphasalazine could reduce joint damage.[141,142]

### Adverse events – etanercept: additional information

Post-marketing experience was described in a report supplied by Wyeth Laboratories, which indicated that around 84,000 patients had been treated with etanercept.[136] An abstract presented to the ACR meeting in Philadelphia in November 2000 by the FDA also described post-marketing experience.[120] Infection whilst on treatment with etanercept accounted for 22% of all reports. In 62% of the 149 deaths infection was thought to be a contributing factor. However, rates for mortality associated with infection are reported to be similar to the background rate in RA patients. Reports of tuberculosis were infrequent compared with infliximab. Small numbers of patients with *Pneumocystis carinii* pneumonia, herpes virus and candidiasis were reported.

Small numbers of patients developing autoimmune disorders, such as polymyositis, and multiple sclerosis, have been described. Thirteen patients taking etanercept have been suspected of having demyelinating diseases. Five of these were believed to have had symptoms before drug use, three did not have any definite evidence of demyelination and three did not experience exacerbation on repeat exposure to etanercept. No causal relationship has been established but, because studies of anti-TNF agents have suggested that these drugs exacerbate multiple sclerosis, Wyeth Laboratories has issued a warning in relation to prescribing for patients with demyelinating diseases.[143,144]

Similarly there have been three reports of aplastic anaemia, seven of pancytopenia, three of profound thrombocytopenia (platelets less than 5000, all three patients continued with treatment with recovery of platelets) and one report of agranulocytosis. Following these reports the package insert now includes a warning of the possibility of serious blood disorders.[136] However, no specific pretreatment screening procedures or requirements for monitoring of full blood count or anti-dsDNA antibody measurements whilst on treatment are indicated in the data sheet.

Rates for malignancies are reported to be within the range seen in RA patients, including lymphoma, which is known to occur at a higher rate in RA.

## Meta-analysis

Treatment with anti-TNF showed a consistent clinical benefit in all trials included in this report. Data was pooled in order to get a summary measure of treatment effect. We describe the methods and key findings below.

### Methods

As this review was completed in a limited time, we restricted meta-analyses to six important measures of treatment effect and combined treatment arms from trials where different drug doses were used. Three outcomes – HAQ, patient global assessment and swollen joint counts, which reflect physical disability, patient-centred outcomes and physician assessment of joint disease, respectively, were reported as continuous data. Three other outcomes, the ACR20, ACR50 and ACR70, which are presented as binary data and which represent an overall measure of treatment effect, were also analysed. Paulus responses were assumed to be similar to ACR responses. The primary analysis pooled results from the latest follow-up data available for the blinded, randomised, controlled period of each trial. As the periods of follow-up varied from 4 weeks to 1 year, we also pooled data, where available, at 1 month, 3 months, 6 months and 1 year.

We pooled results for trials where treatment (with or without methotrexate) was compared

to placebo. Only one trial, the Etanercept Early RA trial, compared anti-TNF to another agent. Data from this trial are shown for the latest follow-up only. Trials were analysed separately for infliximab and etanercept and then pooled to give a summary for anti-TNF as a class.

To pool outcomes that use continuous data we used the final result, not percentage change from baseline. More estimates of variability were available in this way. Where possible, the SD was taken directly from the reported results or derived from the standard error of the mean (SEM) or CIs or was estimated from reported *p*-values for a trial. Preference was given to the SD of final results but the SD from baseline data was substituted when the former was not available. Where the SD could not be estimated directly from trial data, an imputed SD was used. This was calculated from the baseline SDs from other trials recruiting a similar patient population. Imputed SDs were as follows: HAQ 0.58 (derived from five trials, $N = 1084$); swollen joint count 10.2 (derived from 11 trials, $N = 391$); patient global assessment 0.80 (derived from seven trials, $N = 264$). Where an outcome was reported on the same scale the results are presented as a weighted mean difference (WMD). Where different scales are used results are presented as a standardised mean difference (SMD).

A fixed effects model was used unless the trials demonstrated statistical heterogeneity, in which case a random effects model was also used. The most conservative result is presented.

## Anti-TNF versus placebo

### ACR improvements

Pooled analysis for ACR improvements are shown in *Figures 3, 4* and *5* as both relative risk (RR) and risk difference (RD). Clinical effectiveness, when expressed in terms of RR of achieving an improvement in ACR, increases with a higher hurdle, such that RR of achieving an ACR20 with anti-TNF was around 4, while RR of achieving ACR70 was around 8, consistent with treatment effect. However, effectiveness expressed as RD decreases, reflecting the much lower prospect of achieving an ACR50 or ACR70 with placebo. The number-needed-to-treat (NNT) to achieve an ACR20 response was 2, NNT for ACR50 was 4 and the NNT for ACR70 was 8. Both the ACR50 and ACR70 are believed to be clinically very significant, although patients who fail to achieve an ACR20 response may also have gained a clinically relevant benefit.

ACR responses with increasing treatment duration are summarised in *Table 13*. Data confirms that treatment effect is seen early, that it is sustained for 6 months or more and that data expressed as RR shows a more pronounced treatment effect with a higher hurdle.

### HAQ scores, patient global assessment and swollen joint counts

The pooled result at the end of trials for HAQ scores for combined treatment arms versus placebo gave a WMD of –0.40 (95% CI, –0.62 to –0.18) (*Figure 6*). The HAQ scale scores 0 for normal function and 3 for greatest disability, thus a reduction indicates improved function. Similar results were seen at each time interval, as shown in *Table 14*.

Patient global assessment of disease activity, which indicates the patient's view of how the arthritis is doing, was scored in most trials on a scale of 0 (best) to 10 (worst). The WMD for combined etanercept arms compared to placebo was –2.1 (95% CI, –2.7 to –1.6) at the end of the studies (*Figure 7*). Elliott (1994)[113] was not included in this meta-analysis as this study uses a scale of 1 to 5 for patient assessment of disease activity. However, the direction and effect size in this trial is consistent with the other trials. Patient global assessment was improved at all time intervals, although there was a trend suggesting a diminished effect with time.

The swollen joint count at the end of studies was reduced by 7.7 (95% CI, 4.2 to 11.4) in the combined etanercept arms compared to placebo (*Figure 8*). A similar result is seen at all time intervals except 1 year (where the data is based on the ATTRACT study only).

### Anti-TNF against other agents

The trial data clearly demonstrate that anti-TNF has a statistically significant and clinically important effect, compared to placebo, for the treatment of RA. However, only the ERA trial, a study of etanercept against methotrexate in early RA, compared anti-TNF head-to-head with a DMARD.[122] Trials in which patients continued with methotrexate but were given additional treatment with anti-TNF or placebo were not regarded as a direct comparison of DMARD against anti-TNF.

Methotrexate is held as the standard against which other DMARDs should be judged. Thus the ERA trial is important for determining the relative benefits of etanercept over a conventional

DMARD.[122] The RR of achieving an ACR20 response for the combined etanercept arms versus methotrexate was 1.03 (95% CI, 0.9 to 1.17); for etanercept 25 mg against methotrexate RR was 1.12 (95% CI, 0.96 to 1.29). Neither dose on its own achieves a statistically significant treatment effect over methotrexate.

Data on area under the curve for HAQ, swollen joint count and patient global assessment were reported in the Wyeth Laboratories clinical summary for etanercept 25 mg and methotrexate over 6 months.[136] The differences in area under the curve for these outcomes were statistically significant for all three outcomes. This reflects both an earlier response to etanercept and the fact that patients only achieved maximum methotrexate dose after 2 months. Data at 12 months, the duration of the study, were not shown. The SMDs between etanercept 25 mg (the recommended dose) and methotrexate at 1 year for these three continuous variables were not consistent in their direction of effect (*Table 15*). We conclude therefore that etanercept 25 mg cannot be regarded as superior to methotrexate on the basis of the available data. However, comparison of the ACR-N area under the curve data for methotrexate against etanercept 25 mg over 12 months shows a statistically significant advantage in favour of etanercept.[123]

**Relative risk**

| Study | Anti-TNF *n/N* | Placebo *n/N* | RR (95% CI fixed) | Weight % | RR (95% CI fixed) |
|---|---|---|---|---|---|
| ***Etanercept*** | | | | | |
| Moreland *et al.*, 1997[131] | 69/136 | 6/44 | | 11.2 | 3.72 (1.74 to 7.79) |
| Moreland *et al.*, 1999[132] | 85/154 | 9/80 | | 14.7 | 4.91 (2.61 to 9.23) |
| The European Etanercept Investigators Group, 2000[135,137] | 262/454 | 12/105 | | 24.1 | 5.05 (2.95 to 8.65) |
| Weinblatt *et al.*, 1999[133] | 42/59 | 8/30 | | 13.1 | 2.67 (1.44 to 4.94) |
| Subtotal (95% CI) | 458/803 | 35/259 | | 63.2 | 4.29 (3.12 to 5.88) |
| Test for heterogeneity $\chi^2 = 2.94$; df = 3; $p = 0.4$ | | | | | |
| Test for overall effect $z = 8.99$; $p < 0.00001$ | | | | | |
| ***Infliximab*** | | | | | |
| Elliot *et al.*, 1994[113] | 30/49 | 2/24 | | 3.3 | 7.35 (1.91 to 28.21) |
| Maini *et al.*, 1998[114] | 27/87 | 1/14 | | 2.1 | 4.34 (0.64 to 29.47) |
| ATTRACT, 2000[115,116] | 177/340 | 15/88 | | 29.5 | 3.05 (1.90 to 4.90) |
| Kavanaugh *et al.*, 2000[106] | 11/21 | 1/7 | | 1.9 | 3.67 (0.57 to 23.55) |
| Subtotal (95% CI) | 245/497 | 19/133 | | 36.8 | 3.55 (2.33 to 5.41) |
| Test for heterogeneity $\chi^2 = 1.56$; df = 3; $p = 0.64$ | | | | | |
| Test for overall effect $z = 5.88$; $p < 0.00001$ | | | | | |
| Total (95% CI) | 703/1300 | 54/392 | | 100.0 | 4.01 (3.12 to 5.17) |
| Test for heterogeneity $\chi^2 = 4.89$; df = 7; $p = 0.67$ | | | | | |
| Test for overall effect $z = 10.75$; $p < 0.00001$ | | | | | |

0.01 0.1 1 10 100

Favours control Favours treatment

**Risk difference**

| Study | Anti-TNF *n/N* | Placebo *n/N* | RD (95% CI random) | Weight % | RD (95% CI random) |
|---|---|---|---|---|---|
| ***Etanercept*** | | | | | |
| Moreland *et al.*, 1997[131] | 69/136 | 6/44 | | 12.7 | 0.37 (0.24 to 0.50) |
| Moreland *et al.*, 1999[132] | 85/154 | 9/80 | | 17.2 | 0.44 (0.33 to 0.54) |
| The European Etanercept Investigators Group, 2000[135,137] | 262/454 | 12/105 | | 24.2 | 0.46 (0.39 to 0.54) |
| Weinblatt *et al.*, 1999[133] | 42/59 | 8/30 | | 6.8 | 0.45 (0.25 to 0.64) |
| Subtotal (95% CI) | 458/803 | 35/259 | | 61.0 | 0.44 (0.39 to 0.49) |
| Test for heterogeneity $\chi^2 = 1.41$; df = 3; $p = 0.7$ | | | | | |
| Test for overall effect $z = 16.10$; $p < 0.00001$ | | | | | |
| ***Infliximab*** | | | | | |
| Elliott *et al.*, 1994[113] | 30/49 | 2/24 | | 8.2 | 0.53 (0.35 to 0.70) |
| Maini *et al.*, 1998[114] | 27/87 | 1/14 | | 8.9 | 0.24 (0.07 to 0.41) |
| ATTRACT, 2000[115,116] | 177/340 | 15/88 | | 19.3 | 0.35 (0.26 to 0.44) |
| Kavanaugh *et al.*, 2000[106] | 11/21 | 1/7 | | 2.6 | 0.38 (0.05 to 0.72) |
| Subtotal (95% CI) | 245/497 | 19/133 | | 39.0 | 0.37 (0.25 to 0.48) |
| Test for heterogeneity $\chi^2 = 5.67$; df = 3; $p = 0.13$ | | | | | |
| Test for overall effect $z = 6.24$; $p < 0.00001$ | | | | | |
| Total (95% CI) | 703/1300 | 54/392 | | 100.0 | 0.41 (0.35 to 0.46) |
| Test for heterogeneity $\chi^2 = 10.00$; df = 7; $p = 0.19$ | | | | | |
| Test for overall effect $z = 14.37$; $p < 0.00001$ | | | | | |

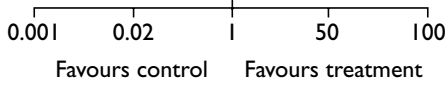
–1.0 –0.5 0 0.5 1.0

Favours control Favours treatment

***FIGURE 3*** *Combined anti-TNF arms vs placebo result at end of trial – ACR20*

**Relative risk**

| Study | Anti-TNF *n/N* | Placebo *n/N* | RR (95% CI fixed) | Weight % | RR (95% CI fixed) |
|---|---|---|---|---|---|
| ***Etanercept*** | | | | | |
| Moreland *et al.*, 1997[131] | 39/136 | 3/44 | | 12.8 | 4.21 (1.37 to 12.94) |
| Moreland *et al.*, 1999[132] | 49/154 | 4/80 | | 14.9 | 6.36 (2.38 to 17.00) |
| The European Etanercept Investigators Group, 2000[135,137] | 121/454 | 5/105 | | 22.9 | 5.60 (2.35 to 13.34) |
| Weinblatt *et al.*, 1999[133] | 23/59 | 1/30 | | 3.7 | 11.69 (1.66 to 82.47) |
| Subtotal (95% CI) | 232/803 | 13/259 | | 54.4 | 5.90 (3.44 to 10.12) |
| Test for heterogeneity $\chi^2 = 0.86$; df = 3; $p = 0.84$ | | | | | |
| Test for overall effect $z = 6.44$; $p < 0.00001$ | | | | | |
| ***Infliximab*** | | | | | |
| Elliott *et al.*, 1994[113] | 21/49 | 2/24 | | 7.6 | 5.14 (1.31 to 20.15) |
| Maini *et al.*, 1998[114] | 22/87 | 0/14 | | 2.4 | 7.67 (0.49 to 119.80) |
| ATTRACT, 2000[115,116] | 112/340 | 7/88 | | 31.4 | 4.14 (2.00 to 8.57) |
| Kavanaugh *et al.*, 2000[106] | 6/21 | 1/7 | | 4.2 | 2.00 (0.29 to 13.87) |
| Subtotal (95% CI) | 161/497 | 10/133 | | 45.6 | 4.30 (2.37 to 7.80) |
| Test for heterogeneity $\chi^2 = 0.85$; df = 3; $p = 0.84$ | | | | | |
| Test for overall effect $z = 4.79$; $p < 0.00001$ | | | | | |
| Total (95% CI) | 393/1300 | 23/392 | | 100.0 | 5.17 (3.46 to 7.71) |
| Test for heterogeneity $\chi^2 = 2.36$; df = 7; $p = 0.94$ | | | | | |
| Test for overall effect $z = 8.05$; $p < 0.00001$ | | | | | |




**Risk difference**

| Study | Anti-TNF *n/N* | Placebo *n/N* | RD (95% CI fixed) | Weight % | RD (95% CI fixed) |
|---|---|---|---|---|---|
| ***Etanercept*** | | | | | |
| Moreland *et al.*, 1997[131] | 39/136 | 3/44 | | 11.3 | 0.22 (0.11 to 0.32) |
| Moreland *et al.*, 1999[132] | 49/154 | 4/80 | | 17.9 | 0.27 (0.18 to 0.36) |
| The European Etanercept Investigators Group, 2000[135,137] | 121/454 | 5/105 | | 29.0 | 0.22 (0.16 to 0.28) |
| Weinblatt *et al.*, 1999[133] | 23/59 | 1/30 | | 6.8 | 0.36 (0.22 to 0.50) |
| Subtotal (95% CI) | 232/803 | 13/259 | | 64.9 | 0.25 (0.20 to 0.29) |
| Test for heterogeneity $\chi^2 = 3.76$; df = 3; $p = 0.29$ | | | | | |
| Test for overall effect $z = 11.40$; $p < 0.00001$ | | | | | |
| ***Infliximab*** | | | | | |
| Elliott *et al.*, 1994[113] | 21/49 | 2/24 | | 5.5 | 0.35 (0.17 to 0.52) |
| Maini *et al.*, 1998[114] | 22/87 | 0/14 | | 4.1 | 0.25 (0.12 to 0.38) |
| ATTRACT, 2000[115,116] | 112/340 | 7/88 | | 23.7 | 0.25 (0.17 to 0.33) |
| Kavanaugh *et al.*, 2000[106] | 6/21 | 1/7 | | 1.8 | 0.14 (–0.18 to 0.47) |
| Subtotal (95% CI) | 161/497 | 10/133 | | 35.1 | 0.26 (0.20 to 0.32) |
| Test for heterogeneity $\chi^2 = 1.47$; df = 3; $p = 0.69$ | | | | | |
| Test for overall effect $z = 8.16$; $p < 0.00001$ | | | | | |
| Total (95% CI) | 393/1300 | 23/392 | | 100.0 | 0.25 (0.22 to 0.29) |
| Test for heterogeneity $\chi^2 = 5.40$; df = 7; $p = 0.61$ | | | | | |
| Test for overall effect $z = 14.00$; $p < 0.00001$ | | | | | |

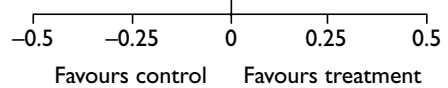



***FIGURE 4*** *Combined anti-TNF arms vs placebo result at end of trial – ACR50*

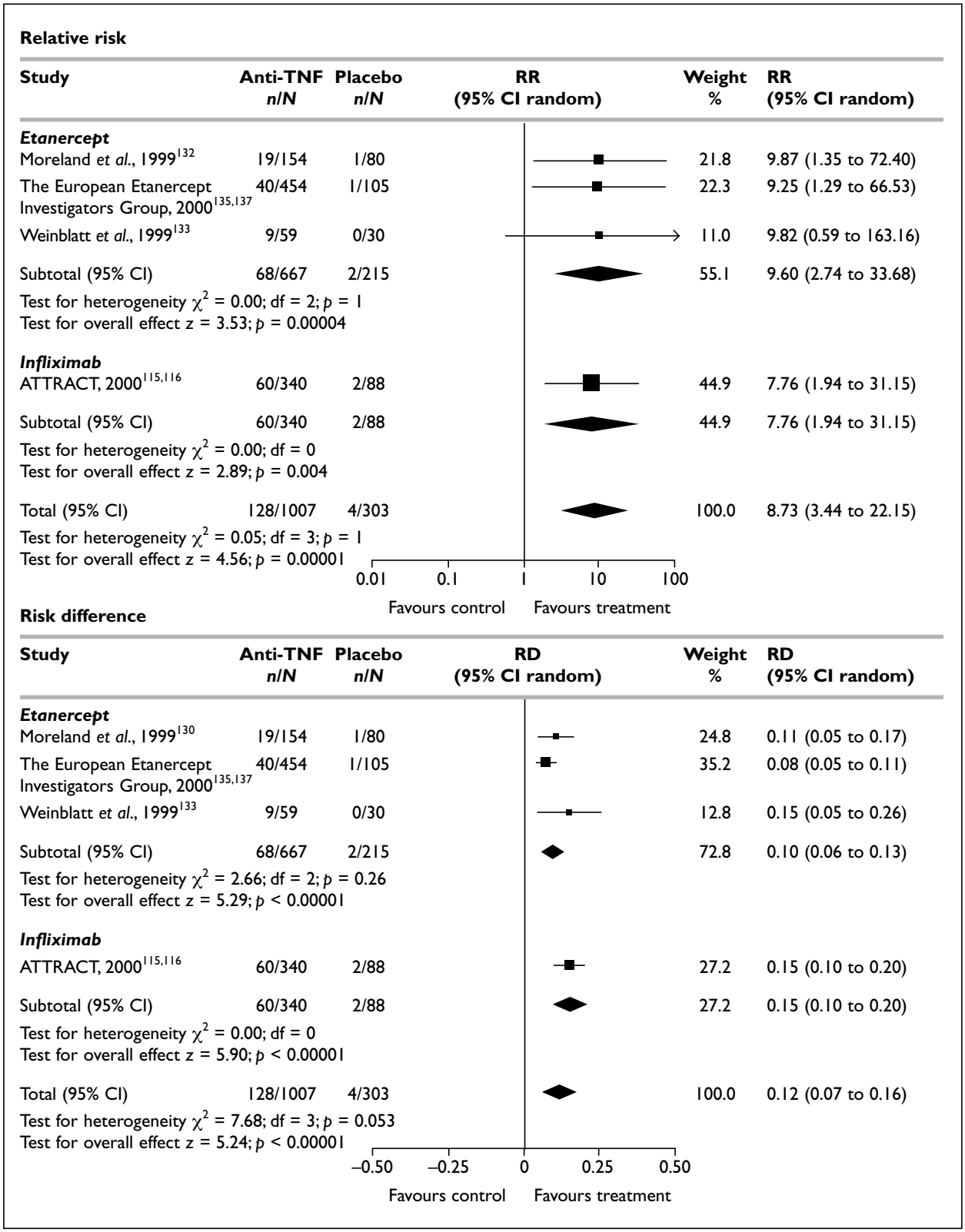



***FIGURE 5*** *Combined anti-TNF arms vs placebo result at end of trial – ACR70*

***TABLE 13*** *RR and RD (95% CI) for ACR20, ACR50 and ACR70*

| | | RR | RD |
|---|---|---|---|
| 1 month | ACR20 | 4.01 (1.65 to 9.74) | 0.44 (0.27 to 0.61) |
| | ACR50 | 6.41 (2.43 to 6.92) | 0.30 (0.15 to 0.46) |
| | ACR70 | No data | |
| 3 months | ACR20 | 2.58 (1.57 to 4.23) | 0.30 (–0.02 to 0.61) |
| | ACR50 | 4.50 (2.78 to 7.28) | 0.26 (0.19 to 0.33) |
| | ACR70 | 4.61 (1.77 to 12.02) | 0.04 (–0.01 to 0.08) |
| 6 months | ACR20 | 3.09 (2.29 to 4.18) | 0.37 (0.28 to 0.45) |
| | ACR50 | 6.72 (3.57 to 12.68) | 0.26 (0.21 to 0.30) |
| | ACR70 | 11.97 (2.94 to 48.69) | 0.12 (0.09 to 0.15) |
| 1 year* | ACR20 | 3.05 (1.90 to 4.90) | 0.35 (0.26 to 0.44) |
| | ACR50 | 4.14 (2.00 to 8.57) | 0.25 (0.17 to 0.33) |
| | ACR70 | 31.58 (1.97 to 505.75) | 0.18 (0.13 to 0.22) |

* *Data for 1 year comes from one trial only (ATTRACT)*[116]

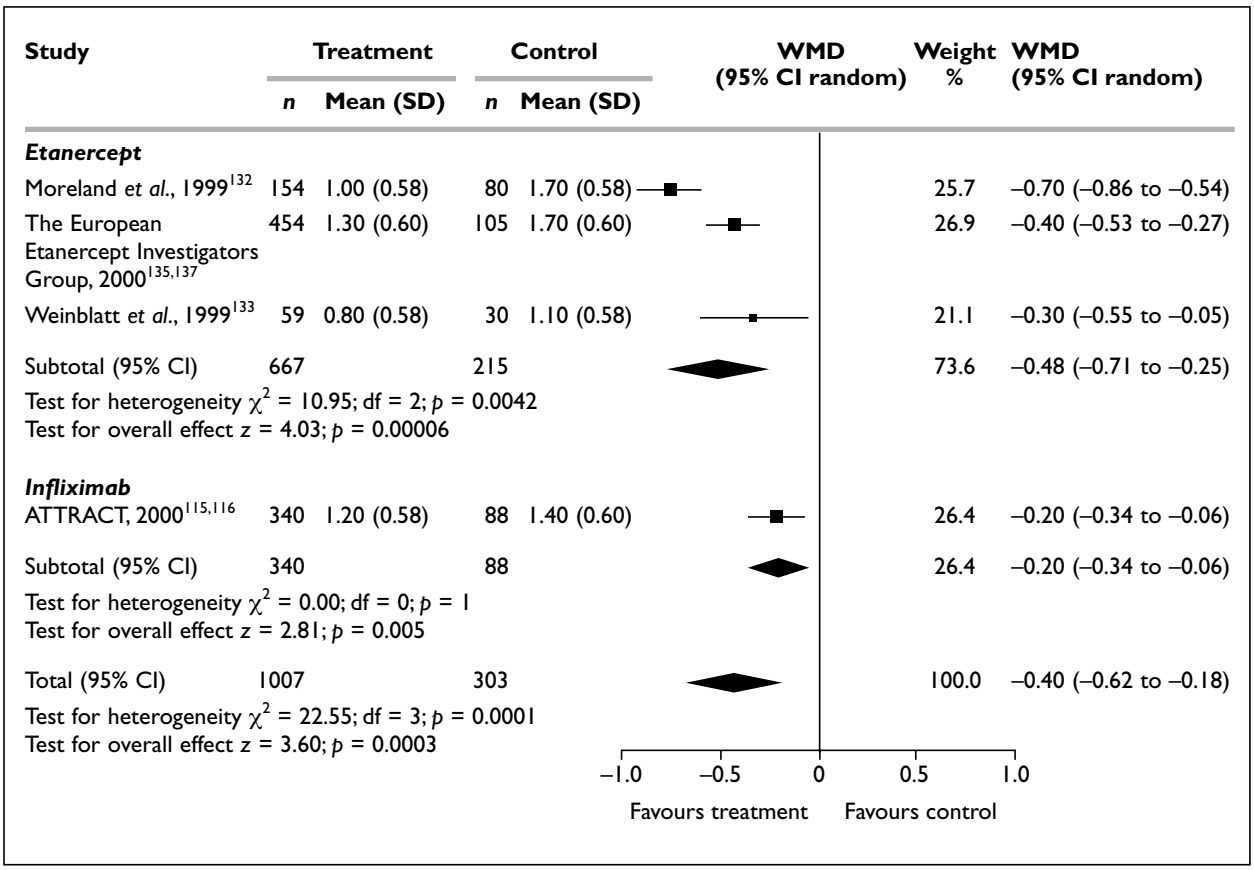



***FIGURE 6*** *HAQ: Combined anti-TNF arms vs placebo*

***TABLE 14*** *WMD (95% CI) for HAQ, patient global assessment and swollen joint count*

| | HAQ | Patient global assessment | SJC |
|---|---|---|---|
| 1 month | No data | No data | –7.7 (–12.4 to –3.0) |
| 3 months | –0.37 (–0.66 to –0.08) | –2.3 (–2.7 to –1.8) | –3.68 (–6.4 to –0.98) |
| 6 months | –0.37 (–0.77 to 0.03) | –1.9 (–2.9 to –0.9) | –8.1 (–14.5 to –1.7) |
| 1 year (1 trial only) | –0.20 (–0.34 to 0.06) | –0.6 (–0.9 to –0.4) | 1.00 (–1.81 to 3.81) |

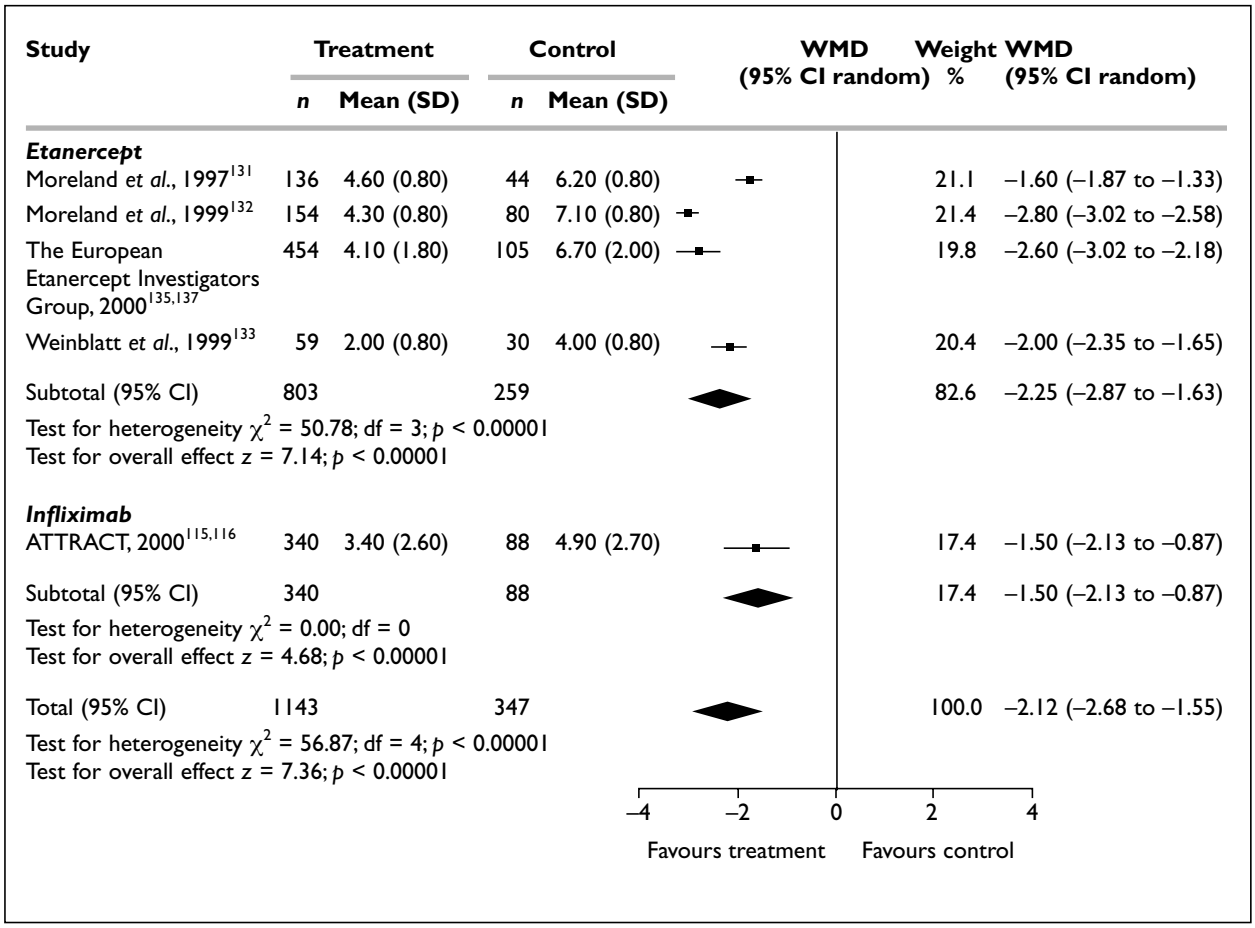



***FIGURE 7*** *Patient global assessment: Combined anti-TNF arms vs placebo*

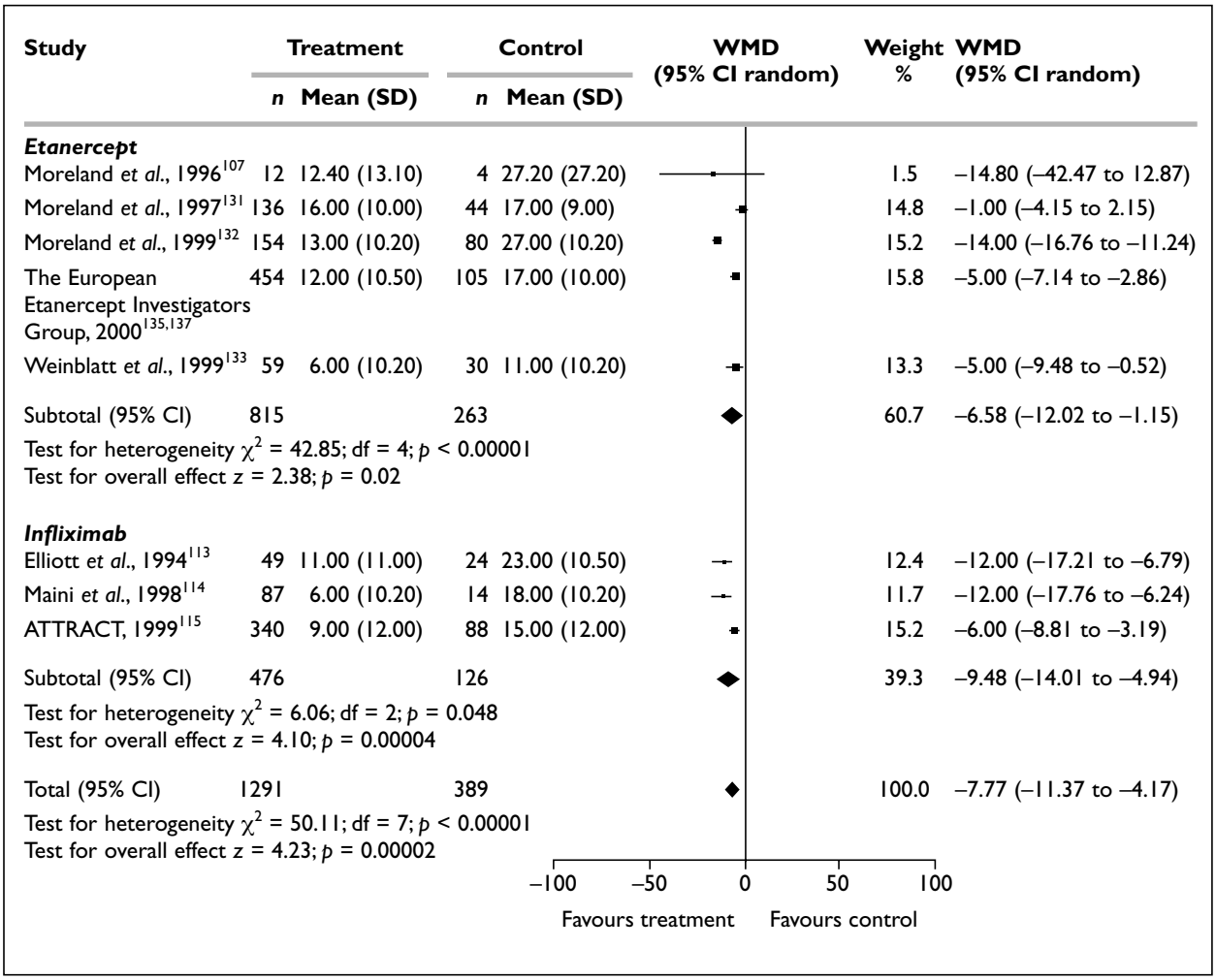



***FIGURE 8*** *Swollen joint counts: Combined anti-TNF arms versus placebo*

***TABLE 15*** *SMD (95% CI) for patient global assessment, HAQ and swollen joint count from ERA trial comparing etanercept to methotrexate*[122]

| | SMD at 1 year | | |
|---|---|---|---|
| | **10 mg twice a week** | **25 mg twice a week** | **Combined treatment arms** |
| Patient global assessment | 1.25 (1.04 to 1.46) | 0.62 (0.43 to 0.82) | 0.87 (0.70 to 1.05) |
| HAQ | 0.34 (0.15 to 0.54) | 0.00 (–0.19 to 0.19) | 0.17 (0.01 to 0.34) |
| SJC | 0.20 (0.00 to 0.39) | –0.10 (–0.29 to 0.09) | 0.00 (–0.16 to 0.16) |

# Chapter 3

# Health economics

## Summary

### Summary of existing economic evaluations

- One published health economic study of infliximab or etanercept for use in RA was found.
- This was a cost-effectiveness analysis and concluded that the incremental cost-effectiveness ratio (ICER) of etanercept plus methotrexate versus methotrexate alone was US$36,300/ACR70.

### Commentary on submitted models

***Wyeth submission (etanercept):***

- Time-slice spreadsheet model.
- Base-case ICER £18,948/quality-adjusted life-year (QALY) (as submitted).
- Sensitivity analysis range £9942 to £48,454.

***Schering-Plough submission (infliximab):***

- Markov process with 6-month cycle time.
- Base-case ICER £33,628/QALY to £36,623/QALY according to time allowed on infliximab.
- Our sensitivity analysis produced a range from £29,008 to £40,766.

### Summary of the Birmingham Preliminary Model (BPM)

- The annual drug costs of etanercept are around £9600 for infliximab and £8800 for etanercept compared with £3100 for cyclosporin, the most expensive conventional DMARD.
- A simulation model was constructed that considered improvements in quality of life but assumed no effect of either etanercept or infliximab on mortality or the need for joint replacement.
- For use as the third DMARD in a sequence of DMARDs, the BPM gave a base-case ICER of approximately £83,000/QALY for etanercept and approximately £115,000/QALY for infliximab.
- These figures reduced to £72,000/QALY for etanercept, and £95,000 for infliximab, if used last in the sequence of DMARDs.
- Sensitivity analysis in the latter case gave figures ranging from £47,000 to £128,000 for etanercept, and £62,000 to £169,000 for infliximab.
- It should be stressed that these figures do not include all potential benefits of these agents. For instance no account is taken of the possible reduction in the need for joint replacement surgery, hospitalisation or needs for aids and appliances.

## Introduction

This section of the report has three components:

- A review of existing economic evaluations of the use of anti-TNFs in RA.
- A technical commentary on the decision-analytic models used in the economic analyses reported in the manufacturers' submissions to NICE.
- A description of the new modelling and economic analyses of infliximab and etanercept used in RA patients, undertaken by the Birmingham team.

## Existing economic evaluations

### Literature search

Information on costs, cost-effectiveness and quality of life associated with RA therapies was sought from MEDLINE, HealthSTAR, NHS EED, the HTA database, DARE, EMBASE, the Health Management Information Consortium (HMIC) database and the Science Citation Index.

There is extensive literature on the burden of illness and general costs associated with RA, which provides an indication of the substantial cost burden imposed on individuals and society as a result of the condition.[87,145–153] In addition, a number of published economic analyses of drug therapies for use in RA were also identified, both relating to the use of NSAIDs,[154] and to DMARDs.[155–158] Three published economic evaluations of anti-TNF drugs for use in a population of RA patients were identified. However, two were available only in abstract form,[157,158] with insufficient detail to justify reporting at length here. Therefore, the focus of the review here is on the single published

economic evaluation by Choi and colleagues[156] and the economic analyses undertaken by (or on behalf of) the manufacturers and reported in their submissions to NICE.

*Table 16* describes some of the key study characteristics and reports results for the base-case economic analyses and results of secondary and sensitivity analyses for these studies.

Although the analysis by Choi and colleagues[156] is described in *Table 16*, it is not discussed in detail below because it uses a disease-specific measure of effect, based on ACR70 or ACR20, in estimating the cost-effectiveness ratio, which makes comparison more broadly with other studies problematic.

## Study designs

Both the Wyeth and Schering-Plough industry studies chose to use an incremental cost–utility analysis framework such that results are reported as the incremental cost per QALY gained. Incremental analysis results are clearly sensitive to the comparator chosen in order to define the increment. For their main analyses, both studies used the comparator of placebo, because data on effectiveness were drawn from placebo-controlled trials. The use of placebo as the comparator is a concern because the main policy question being addressed is whether one (or both) of the anti-TNF drugs should be added to the existing sequence of DMARDs. Thus, for some patients (who progress through the whole sequence of DMARDs), the new drugs will represent an additional therapy. For others the new drugs represent an alternative therapy. This implies that the appropriate comparison is a sequence of DMARDs including anti-TNFs against a sequence of DMARDs not including anti-TNF drugs. This comparison has been used in the Birmingham Preliminary Model (BPM) detailed later in the report.

In terms of perspective, both analyses have followed the guidance provided by NICE and considered costs being incurred by both the NHS and Personal Social Services (PSS). The study on etanercept has additionally considered productivity (or indirect costs), but the results are reported with and without such costs being included. The time horizon considered in both studies is appropriately the patient's lifetime.

## Model structures

Both economic analyses used a modelling approach to explore the costs and benefits associated with anti-TNFs over the lifetime of patients.

The submission by Schering-Plough used a Markov model to extrapolate beyond the observed data from the ATTRACT trial using data from the Arthritis, Rheumatism, and Ageing Medical Information System (ARAMIS) data-set.[2,161] Therefore, the assumption was made that patients only continue on infliximab for 1 year and so only receive the benefit brought by infliximab for 1 year. This is a conservative assumption because patients are likely to continue therapy beyond 1 year. A similar approach was adopted in the Wyeth model, such that the initial data were taken from the trial by Moreland (1999)[132] and the model extrapolated beyond the observed data.

In both models the driving parameter is the HAQ score: both costs and benefits are predicted through the estimation of relationships with HAQ scores. Positive features of the Schering-Plough model are that allowance is made for a proportion of patients continuing therapy with a DMARD and that a validation process is used whereby model predictions are compared to published estimates, in terms of such parameters as the percentage of all patients receiving DMARDs.

## Data inputs

As indicated above, the short-term effectiveness data for both analyses were taken from the main clinical trials and so represent robust estimates of the gains over placebo.

In order to calculate QALYs, data are required on health state valuations ('utilities') and the approaches taken in the two analyses are quite different. Schering-Plough used data on responses to visual analogue scale (VAS) questions from patients in the ATTRACT trial. However, such data can only be used to construct QALYs if the scale is anchored by 'full health' and 'death'. This is not made clear in their submission. In addition, values obtained from a VAS question do not represent 'utilities' because the question is not framed in terms of the sacrifice respondents might be willing to make to avoid a particular health state. For example respondents do not indicate the duration of life they would be willing to sacrifice to be returned to full health, as seen in the time trade-off approach. The use of data from VAS questions in cost–utility analysis assumes that such values represent 'utilities'. The Wyeth analysis translated HAQ scores into 'utilities' by estimating the relationship between HAQ and EuroQol-5 dimensions (EQ-5D) 'utilities' using Swedish data. Whilst this approach is

***TABLE 16*** *Summary of economic analyses reported in submissions from manufacturers*

| | **Schering-Plough NICE submission (infliximab)** | **Wyeth NICE submission (etanercept)** | **Choi *et al.*, 2000[156]** |
|---|---|---|---|
| Form of economic analysis | Cost–utility analysis | Cost–utility analysis | Cost-effectiveness analysis |
| Comparators | Infliximab (plus methotrexate) vs placebo (plus methotrexate) | Main analysis: etanercept vs placebo<br>Secondary analysis: etanercept vs infliximab (plus methotrexate) | 6 treatment options compared:<br>• Etanercept plus methotrexate<br>• Etanercept (monotherapy)<br>• Cyclosporin plus methotrexate<br>• Triple therapy (hydroxy-chloroquine, sulphasalazine, methotrexate)<br>• Methotrexate (monotherapy)<br>• No second-line agent |
| Perspective | NHS + PSS | Societal (although NHS + PSS reported separately) | Societal |
| Time horizon | Patient's lifetime | Patient's lifetime | 6 months |
| Modelling | • Markov model used to extrapolate beyond the ATTRACT trial outcomes to estimate long-term consequences of RA using ARAMIS data-set<br>• 16 health states (plus 'death') defined as combinations of 4 severity levels (defined using HAQ scores) and 4 treatment scenarios<br>• Cost and quality of life/'utilities' associated with health states in line with HAQ score and treatment scenario<br>• 6-month cycle length<br>• Model not clearly described (e.g. no diagram provided)<br>• Model validated by comparing predictions to published estimates (e.g. in terms of % of patients receiving DMARDs)<br>• UK RA life tables used | • Time-slice model used to allow extrapolation beyond the Moreland trial to estimate long-term consequences of RA<br>• HAQ scores used to predict mortality (using RA life tables adjusted for treatment effect)<br>• HAQ scores also used to predict quality of life/'utilities' (using published data)<br>• HAQ scores used to predict costs (using published data)<br>• Some assumptions:<br>– non-responders to drug therapy follow the HAQ path observed in placebo patients<br>– responders to therapy follow the 4-year path observed in the Moreland trial and progression beyond 4 years in line with placebo patients | • Decision tree |
| Effectiveness data | • Data taken from the ATTRACT trial<br>• Compared 2 strategies: placebo (plus methotrexate) vs infliximab (plus methotrexate)<br>• Trial data relating to all doses of infliximab considered as a single group because no dose relationship found<br>• Comparison in terms of the change in HAQ scores up to 54 weeks<br>• Extrapolation beyond 54 weeks using Markov model (as detailed above) | • For etanercept: data taken from the Moreland trial<br>• For infliximab: data taken from the ATTRACT trial, but only used data from patients receiving the approved dose of 3 mg/kg | • Data taken from 3 double-blind RCTs[51,71,72] and an open trial[73] |

*continued*

***TABLE 16* contd** *Summary of economic analyses reported in submissions from manufacturers*

| | Schering-Plough NICE submission (infliximab) | Wyeth NICE submission (etanercept) | Choi *et al.*, 2000[156] |
|---|---|---|---|
| Health state valuations | • VAS assessments by patients in the ATTRACT trial<br>• The anchor points on the VAS used in the study are not stated – in order to use values taken from a VAS in constructing QALYs anchors of 'full health' and 'death' are required<br>• Values obtained from a VAS are not 'utilities' | • HAQ scores converted into 'utilities' through the estimation of a regression equation<br>• Equation estimated using Swedish data on HAQ and EQ-5D published by Kobelt *et al.*, 1999[159]<br>• SF-36 data also available but a 'floor effects' problem was identified and so SF-36-based 'utilities' were only used as part of the sensitivity analysis | |
| Resource use data | • Year 1 data taken from the ATTRACT trial<br>• Data beyond year 1 taken from NOAR cohort study and linked to HAQ scores for 6-monthly intervals<br>• Some data not available from the NOAR study (e.g. use of community nurses, GPs, home helps, etc.) | • Estimates of the resource use/costs associated with HAQ scores obtained using data from published sources<br>• Direct NHS costs by HAQ estimated from Kobelt *et al.*, 1999[159] using Swedish data, and also from Yelin and Wanke, 1999[151] using US data<br>• Direct PSS costs (e.g. nursing home care) estimated from Ward *et al.*, 1998[160] using US data, and from McIntosh, 1996[153] using UK data<br>• Indirect (or 'productivity') costs by HAQ estimated from Kobelt *et al.*, 1999[159] using Swedish data | • Resource use estimates based on a combination of assumptions and published estimates of cost<br>• Inpatient and surgical costs estimated using data reported by Yelin and Wanke, 1999[151] |
| Unit cost data | • Taken from 'routinely available sources', e.g. PSSRU, McIntosh, 1996[153] | • Taken from routine sources and using currency conversion where data have been taken from other countries | • Taken from 'routinely available sources', e.g. the Red Book |
| Price year | • Not stated (although appears from sources to be 1999/2000) | • Not stated | • 1999 |
| Discounting | • Base-case: 6% costs, 1.5% benefits<br>• Sensitivity analysis considered two alternatives: 6% costs, 6% benefits; 6% costs, 0% benefits | • 6% costs, 1.5% benefits | • Not considered (because of 6-month timescale) |
| Productivity costs | • Not considered in main analysis | • Considered in main analysis but results given with and without productivity costs | • Productivity costs were considered and estimated using Swedish data but results given with and without productivity costs |

*continued*

***TABLE 16* contd** *Summary of economic analyses reported in submissions from manufacturers*

| | Schering-Plough NICE submission (infliximab) | Wyeth NICE submission (etanercept) | Choi *et al.*, 2000[156] |
|---|---|---|---|
| Sensitivity analysis | • Including estimates of resource use not available from NOAR<br>• Using UK resource utilisation reported by McIntosh, 1996[153] instead of NOAR<br>• Using the Markov model of Kobelt *et al.*, 1999[159] | • Alternative quality of life/'utility' scores (e.g. SF-36, AQoL)<br>• Cost offsets per HAQ point varied<br>• Mortality per HAQ point varied<br>• RR of RA varied<br>• HA progression varied for both placebo and active therapy<br>• Withdrawal rates varied for both placebo and active therapy | • Three-way SA was conducted on all of the main parameters in the analysis |
| Results | Infliximab (plus methotrexate) vs placebo (plus methotrexate)<br>• ICER: £33,618/QALY gained<br>• SA range: £31,014 to £42,634<br>• When the Kobelt Markov model used: £19,453 to £30,390<br>• Caution expressed: "It is not suggested that this analysis represents a comprehensive adoption of the Kobelt model to the UK" | Etanercept vs placebo<br>• ICER: £18,938/QALY gained (excluding productivity costs)<br>• SA range: £7200 to £29,700<br><br>Etanercept vs infliximab<br>• ICER: –£28,423 (etanercept dominates)<br>• SA range: dominance to £13,104 | Etanercept plus methotrexate vs methotrexate (monotherapy)<br>• ICER: US$36,300/ACR 70WR (excluding productivity costs)<br>• "The results of the extensive sensitivity analyses did not substantially affect these results" |

*AQoL, Australian quality of life; PSSRU, Personal Social Services Research Unit; SA, sensitivity analysis*

not ideal (a preferred strategy would have been to collect data on EQ-5D in the trial), it represents a reasonable compromise in the circumstances.

Resource use and cost data inputted into the Schering-Plough model were taken initially from the ATTRACT trial and subsequently estimated from NOAR. An advantage of using the NOAR data is clearly that it relates exclusively to a UK population. Cost data used in the Wyeth analysis were taken from a variety of published sources, mainly US and Swedish, with currency conversion to sterling.

Schering-Plough, in their analysis, assumed that there would be no drug wastage due to the fact that some patients require an incomplete number of vials. This was based on reports from the USA indicating that patients are being treated in groups to avoid wastage. While this is possible in the UK, such a sweeping assumption is unjustified because it requires more than one suitable patient at a specific time point with available day-case facilities and medical staff. It is unlikely that such an approach could be applied universally in the UK and so drug cost is underestimated in their analysis. The Wyeth model assumed that costs of adverse events would be similar for both infliximab and etanercept. This is unlikely to be the case because infliximab is only licensed for use with methotrexate. The assumption is justified in the report as being conservative so that, if anything, it favours infliximab.

## Analysis results

The base-case result from the Schering-Plough analysis indicates that infliximab (compared to placebo) has an ICER of £33,618/QALY gained.

The base-case result from the Wyeth analysis indicates that etanercept (compared to placebo) has an ICER of £18,938/QALY gained (excluding productivity costs). The secondary analysis, in which etanercept was compared to infliximab, found that etanercept was dominant (i.e. it was associated with a lower cost and greater effectiveness).

Both economic evaluations have undertaken sensitivity analyses, although they are limited

in the range of parameters varied and the methods employed (only single parameters and closely connected groups of parameters were changed). The main findings are not challenged by the results of the sensitivity analyses.

## Commentary on models used in manufacturers' submissions

### Report on the Wyeth model

The model was supplied in the form of an Excel spreadsheet. All calculations leading to the figures documented in the report could be checked. In each group of survivors, an average HAQ score is estimated and used to influence mortality.

We felt it appropriate to make the following amendments to the model.

**1. Calculation of death rates for normal population given age/sex mix of trial**
These calculations were based on a set of life tables. The trial data included a breakdown of the trial population by age and sex, in 5-year bands. The death rate after any number of years for the trial population was estimated by taking the death rates for each age and sex group individually after that number of years and taking a weighted average using the original fractions.

This method fails to take into account the fact that the age and sex distribution will change over time because there are disproportionately more deaths in the higher age groups.

We used the life tables provided to estimate what proportion of each age and sex group would still be alive after a given number of years. Taking an appropriate weighted average of these gives a fair estimate of the proportion of the original population still alive after that number of years; death rates could then be worked out by comparing the proportions of the original population still alive at the beginning and end of each year.

A further complication arose from the fact that the life tables provided end at age 100. The Wyeth model assumes a death rate of 100% for any age over 100. In our revision, there is a higher than usual drop in the proportion still alive every time a 5-year age group reaches the age of 100; this leads to an increased death rate for that year followed by a reduced death rate the following year. Correcting for this would require extension or extrapolation of the life tables and is unlikely to make any significant difference.

**2. Using a multiplier on annual probabilities of death**
In the Wyeth model, the probability of death in a given year for the normal population was multiplied by a fixed factor for the general RA population and a further factor dependent on HAQ scores.

Multiplying probabilities in this way is only appropriate for small probabilities; for larger probabilities it can lead to probabilities of death in 1 year that exceed 100%. The enlarged probabilities were truncated to 100% for the general RA population, but this was not done for the HAQ-score-dependent adjustment. However, in each case the numbers to which a probability of over 100% was applied were so small that including the truncation made no difference to the displayed result.

We amended the model by converting the probabilities into rates, multiplying the rates by the appropriate factor and converting back to an annual probability.

**3. Percentage of responders withdrawing between 6 months and 1 year**
The percentage of responders withdrawing between 3 months and 6 months was based directly on trial data; after that, a constant annual rate was used.

This is a reasonable method of extrapolating, but the full annual rate should not be used as a probability over a 6-month period.

We adjusted the probability of withdrawal over the period from 6 months to 1 year using the principle that the proportion not withdrawing over 6 months would be the square root of the proportion not withdrawing over 1 year. (This assumes a constant instantaneous risk of withdrawal.)

**4. Change in HAQ between 6 months and 1 year for placebo group non-responders**
For this group, a linear annual increase in HAQ score was applied until the HAQ score reached 3; the full annual increase was applied between 6 months and 1 year. We changed this to applying only half the annual increase at that point.

#### *Effect of the above changes*

*Table 17* is a copy of the table included in the Wyeth submission; *Table 18* is the amended version incorporating the above changes. *Table 19* compares the sensitivity analysis results in the Wyeth submission with those in our amended form of the model.

***TABLE 17*** *Wyeth submission base-case results*

| | Placebo | Etanercept | Incremental |
|---|---|---|---|
| Drug and monitoring costs | £0 | £21,365 | £21,365 |
| Cost offsets | £3,969 | £1,365 | –£2,605 |
| Total cost | £3,969 | £22,729 | £18,760 |
| QALY | 5.0480 | 6.0386 | 0.9906 |
| Cost per QALY | – | – | £18,938 |

***TABLE 18*** *Amended version of base-case results for Wyeth submission*

| | Placebo | Etanercept | Incremental |
|---|---|---|---|
| Drug and monitoring costs | £0 | £22,801 | £22,801 |
| Cost offsets | £4,315 | £1,663 | –£2,652 |
| Total cost | £4,315 | £24,464 | £20,149 |
| QALY | 5.5315 | 6.3687 | 0.8372 |
| Cost per QALY | – | – | £24,067 |

***TABLE 19*** *Effect of amended version on sensitivity analysis*

| Scenario | Wyeth submission | Amended version | Scenario | Wyeth submission | Amended version |
|---|---|---|---|---|---|
| Base | £18,938 | £24,067 | 12 | £19,628 | £26,857 |
| 1 | £29,737 | £48,454 | 13 | £17,607 | £21,815 |
| 2 | £17,451 | £20,916 | 14 | £20,284 | £26,468 |
| 3 | £21,943 | £28,460 | 15 | £21,665 | £27,386 |
| 4 | £17,490 | £21,234 | 16 | £16,354 | £20,428 |
| 5 | £21,567 | £27,235 | 17 | £20,060 | £25,745 |
| 6 | £17,712 | £22,590 | 18 | £18,816 | £23,871 |
| 7 | £8,439 | £11,419 | 19 | £18,083 | £25,418 |
| 8 | £7,213 | £9,942 | 20 | £18,965 | £22,331 |
| 9 | £22,133 | £29,977 | 21 | £27,275 | £37,542 |
| 10 | £17,007 | £20,826 | 22 | £16,209 | £20,067 |
| 11 | £18,556 | £22,440 | | | |

## Report on the Schering-Plough model

The model was supplied as three different versions of a Markov model, constructed using Decision-Maker software, which is entirely appropriate for this type of model. The three versions are those referred to in the Schering-Plough submission as 'primary analysis', 'radiographic progression' and 'intent-to-treat'. For convenience, the different versions are referred to as 'the model'; differences between the versions are noted as appropriate.

The model allows patients to be in one of 21 possible states at a given time; there are four possible ranges of HAQ score and five different treatment options considered (20 combinations), together with death. The five treatment options are infliximab, methotrexate alone, methotrexate with other DMARD(s), other DMARD(s), and no DMARD. The model runs in cycles of 6 months until the proportion surviving becomes negligible. As supplied, the model worked from a cohort with starting age 53 years and 77.6% female.

In each cycle, the proportion of patients in each of the 20 survival states is redistributed as follows. First, the proportion dying over the next 6 months is calculated. This depends on age and HAQ score. The age-related part of this is based on life tables

and used a weighted average of male and female death rates, according to the proportion of females in the assumed starting population. This is not strictly correct, as the proportion of females in the population will change over time because of gender-related differences in mortality. However, running the primary analysis model with an all-female population gave an ICER of £34,104/QALY compared to £32,404 for an all-male population, so the simplification used in the model is reasonable in practice.

Survivors in each cycle are then assigned an HAQ score for the end of the cycle and a treatment option for the next cycle. These generally follow fixed transition probabilities depending on the HAQ score and treatment option at the start of the cycle, with some variation in the earliest cycles of the model.

Each model gave a choice of two strategies. In the first strategy, all patients start on methotrexate, and may then progress to other treatment options, never including infliximab. In the second strategy, all patients start on infliximab. In the primary analysis and radiographic progression models, all survivors transfer to other treatments after 1 year; in the intent-to-treat model, patients may transfer to other treatments at 6 months or may remain on infliximab for up to a maximum of 2 years.

A fundamental assumption in this model is that transition probabilities at any time depend only on the current state of the patient. Subject to that assumption, the model is structurally sound, with the exception of the radiographic progression version. In that version, it is assumed that the treatment with infliximab has lasting benefit. This is modelled by increasing the probability of remaining in the same HAQ group in any cycle by a fixed value of 0.054: this applies for all treatment options following infliximab. The effect of this is that sometimes the transition probabilities can add up to more than 1. The software handles this by showing an error message and truncating the total probability to 1 where necessary. *Table 20* shows the effect of this on patients in the infliximab arm with HAQ 0 treated with no DMARD.

In fact all versions of the model contain a device to ensure that the probability of transition to state 2 is reduced if necessary. This 'error trap' does not have any effect except in the radiographic progression model.

In light of the above comments, the results from the radiographic progression model should be treated with considerable caution.

#### *Replication of the model results*

When the three versions of the model supplied were run, the results in *Table 21* were obtained. The differences between these results and those reported in the Schering-Plough submission are negligible.

#### *Further sensitivity analysis*

As stated above, the version of the model supplied ran with a cohort of age 53 with 77.6% female. *Table 22* shows the ICERs for various other starting cohorts. The results for each model appear to be quite robust to age distribution.

## Provisional Birmingham economic anti-TNF model

We constructed a simulation model to show the effect of introducing anti-TNFs into the treatment

***TABLE 20*** *Example of transition probabilities corrected by software*

| Transition to HAQ | 0 | 1 | 2 |
|---|---|---|---|
| Probability in primary analysis model | 0.7700 | 0.2050 | 0.0190 |
| Probability stated in radiographic progression model | 0.8240 | 0.2050 | 0.0190 |
| Probability corrected by software in radiographic progression model | 0.8240 | 0.1760 | 0.0000 |

*The probability of transition to HAQ 3 is not shown; this is always calculated so that the total probability adds to 1*

***TABLE 21*** *Replication of the Schering-Plough model results*

| | Incremental cost (£) | Incremental QALY (£) | ICER (£/QALY) |
|---|---|---|---|
| Primary analysis | 8,576 | 0.26 | 33,628 |
| Radiographic progression | 7,835 | 1.53 | 5,111 |
| Intent-to-treat | 14,635 | 0.40 | 36,623 |

***TABLE 22*** *Sensitivity analysis on the Schering-Plough model (figures are ICERs in £/QALY)*

| Starting cohort | Primary analysis | Radiographic progression | Intent-to-treat |
|---|---|---|---|
| Base case | 33,628 | 5,111 | 36,623 |
| Age 35 female | 39,052 | 3,626 | 40,766 |
| Age 35 male | 37,991 | 3,901 | 39,999 |
| Age 53 female | 34,104 | 4,955 | 37,006 |
| Age 53 male | 32,404 | 5,646 | 35,617 |
| Age 75 female | 29,008 | 10,358 | 32,182 |
| Age 75 male | 29,784 | 13,049 | 32,224 |

strategy for adults with RA. Limitations of time and data have meant that the model is not completely comprehensive and so accordingly we refer to it as the Birmingham Preliminary Model (BPM). After the description of the model, we discuss limitations of the model itself and the data used in this current work.

The BPM follows patients with RA from the time at which they start using DMARDs. It is assumed that DMARDs are used for the remainder of that patient's life, if possible. When the model is run, a large number of individual (virtual) patient histories are generated, both with and without anti-TNF. A cost–utility framework is adopted such that the mean costs and QALYs for the two arms of the model are compared to produce an ICER. The model was constructed using TreeAge DATA 3.5.

## Basic assumptions

Even without anti-TNFs, there are a large number of possible strategies for the use of DMARDs. A DMARD may lose effectiveness or cause problems because of toxicity. In the case of significant toxicity, the DMARD must be stopped and replaced by another, if appropriate; in the case of loss of effectiveness, a new DMARD may be used either in place of, or in addition to, the current DMARD. For simplicity it is assumed in the BPM that only one DMARD is used at a time, except for one type of combination therapy. This means that, in most cases, it is not necessary to distinguish between toxicity and loss of effectiveness as the reason for moving from one DMARD to the next.

Another issue is the order in which DMARDs are used. It is not the purpose of the BPM to assess different orders of using DMARDs other than anti-TNF, so a fixed order is used for the 'without anti-TNF' branch. The order used is as follows:

1. Sulphasalazine (SSZ)
2. Methotrexate (MTX)
3. Gold (GST)
4. Azathioprine (AZA)
5. Penicillamine (D-Pen)
6. Hydroxychloroquine (HCQ)
7. Leflunomide (LEF)
8. Cyclosporin (CyA)

Any patient who lives long enough to complete all of the above is then given combination therapy consisting of cyclosporin plus methotrexate, provided that neither of these has proved toxic. After combination therapy, or if combination therapy cannot be given, patients are given palliative treatment consisting of analgesia and steroids. We recognise however that other agents such as chlorambucil and cyclophosphamide may also be used in severe disease that has failed conventional strategies.

*Figure 9* shows the possible pathways for any individual patient in the two arms of the model. The dashed lines indicate the pathways when anti-TNF is included in the model; the dotted curve applies when anti-TNF is not included.

## Individual patient pathways

For any individual patient, the total lifetime remaining from entry into the model and the maximum time on each of the DMARDs are sampled from appropriate distributions. Each cycle of the model is not a fixed time period, as would be the case in a standard Markov analysis, but rather represents the time spent on a particular DMARD, and so varies between patients and across DMARDs. The following calculations are made for each cycle of the model:

1. The maximum time on a DMARD is compared with the patient's remaining lifetime; the actual time on a DMARD is the smaller of the two. (In the case of palliative treatment, the actual time is the remaining lifetime.)
2. Costs are accrued and QALYs are updated for the actual time on a DMARD.
3. A logic node is used to determine the next state of the patient: if the DMARD lasts the remaining

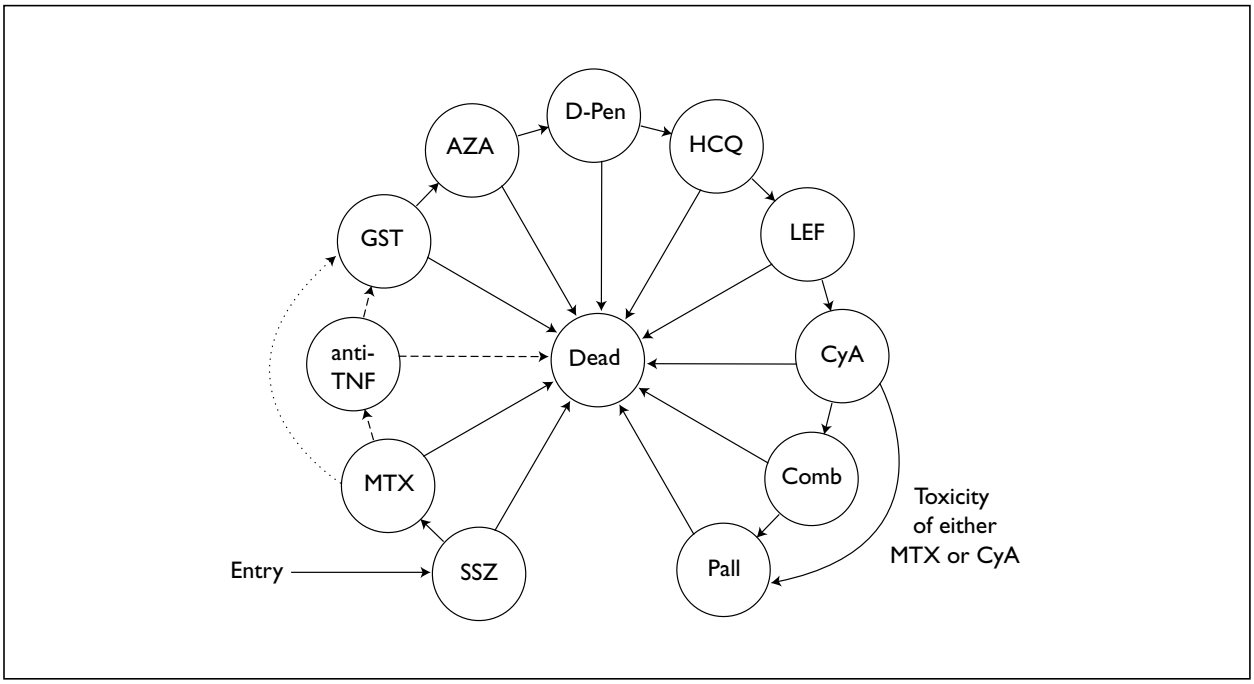



***FIGURE 9*** *Pathways for the BPM (SSZ, sulphasalazine; MTX, methotrexate; GST, gold; AZA, azathioprine; D-Pen, penicillamine; HCQ, hydroxychloroquine; LEF, leflunomide; CyA, cyclosporin; Comb = combination of MTX plus CyA; Pall = palliative treatment)*

lifetime, then transfer is to death, otherwise to the next DMARD. (In the case of palliative treatment, transfer is to death.)

4. In the case of patients moving on from methotrexate or cyclosporin, it is determined whether the cause of quitting the drug is toxicity. Transfer from cyclosporin is to palliative treatment if either of these drugs was significantly toxic.

For example, if the patient is given a remaining life span of 6 years, and maximum times of 2 years on sulphasalazine and 5 years on methotrexate, then that patient actually spends 2 years on sulphasalazine and 4 years on methotrexate. The sampled times for other DMARDs are not then used for this patient.

## Costs

The costs of any DMARD include monitoring costs. Each DMARD has its own pattern of monitoring; these generally involve more intensive monitoring in the early stages. The assumptions made concerning the nature of the pretreatment monitoring of patients and the monitoring whilst on treatment are presented in *Table 23* for all DMARDs. Where possible these were based on information available in BSR guidelines. To avoid unnecessary complication, it is assumed that there is a fixed start-up cost for any DMARD, followed by a constant cost per unit time. These were estimated by applying the resource use data detailed in *Table 23* to the unit costs reported in *Table 24*. Costs are discounted at 6% per year, in line with current UK Treasury guidance, using a continuous discounting function; the start-up cost is taken to apply at the time of starting the DMARD. Discounting was applied patient-by-patient both to the starting point of the model and to the point of divergence between strategies. Both sets of results are given.

## QALY calculations

It is characteristic of RA that patients experience considerable fluctuations in quality of life, particularly in the early stages of the condition.[73] It is assumed that these fluctuations can be adequately represented by a smoothed curve showing a decline over time. The basic curve is taken to be that which a patient would follow without DMARD use. It is assumed that patients start a DMARD at a point below this curve, but improve over a short time to an improved quality of life. The improvement is taken to remain constant relative to the basic curve until the DMARD loses effectiveness or becomes toxic, at which time it declines to a point below the basic curve. QALYs are discounted in the same way as costs, but using a discount rate of 1.5% per year, in line with current UK Treasury guidance. *Figure 10* shows the assumed pattern for a single DMARD.

### *Simplifying QALY calculations*

As described above, the QALY calculations require data on the typical pattern of quality of life without DMARD use under palliative treatment. As it is

***TABLE 23*** *Assumptions concerning patient monitoring*

| DMARD | Pretreatment | On treatment |
|---|---|---|
| Infliximab | FBC, ESR, CRP, LFTs, ANA, anti-dsDNA antibodies, CXR | FBC, ESR, CRP, U&E, LFTs at weeks 2, 6 and every 8 weeks (at times of infusions). ANA and anti-dsDNA antibodies may be done twice a year |
| Etanercept | FBC, U&E, ESR and/or CRP, LFTs, CXR | FBC, ESR, CRP, U&E, LFTs at weeks 2, 4, 8 and 12, then every 8–12 weeks thereafter |
| Sulphasalazine | FBC, ESR and/or CRP, LFTs | FBC every 2 weeks for first 12 weeks. LFTs every 4 weeks for first 12 weeks. FBC and LFTs every 3 months thereafter |
| Methotrexate | FBC, U&E, ESR and/or CRP, LFTs and CXR | FBC, LFTs (± U&E) every 2 weeks while dose changes being made (i.e. for between 4 and 6 months). Once stable FBC, LFTs (± U&E) monthly |
| Gold (myocrisin) | FBC, U&E, ESR and/or CRP, LFTs, urinalysis | FBC, U&E, LFTs, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, and then monthly. Treatment given by i.m. injections |
| Hydroxy-chloroquine | No specific monitoring requirements. Assumption: routine blood checks to monitor disease state (i.e. FBC, ESR or CRP, U&E and LFTs) | |
| Penicillamine | FBC, U&E, ESR and/or CRP, LFTs, urinalysis | FBC, U&E, ESR or CRP, urinalysis every 2 weeks until stable dose (assumed to be 4 months). Every month thereafter |
| Leflunomide* | FBC, U&E, ESR and/or CRP, LFTs, BP, urinalysis | FBC every 2 weeks for 6 months, every 8 weeks thereafter. BP every 2 weeks for 3 months. LFTs monthly for 6 months, every 8 weeks thereafter |
| Leflunomide* | FBC, U&E, ESR and/or CRP, LFTs, BP, urinalysis | FBC every 2 weeks for 6 months, every 8 weeks thereafter. BP every 2 weeks for 3 months. LFTs monthly for 6 months, every 8 weeks thereafter |
| Cyclosporin | FBC, U&E (x 2), blood lipids, ESR and/or CRP, LFTs, urinalysis. Normal BP (x 2) | FBC, U&E, BP every 2 weeks until stable dose for 3 months. The latter guidance is unlikely to be adhered to in practice so we assumed that checks would be done every 2 weeks for 4 months. LFTs monthly and serum lipids every 6 months |
| Azathioprine | FBC, U&E, ESR and/or CRP, LFTs | FBC and LFTs weekly for 6 weeks, then every 2 weeks for 3 visits. Monthly thereafter |

*FBC, full blood count; U&E, urea, electrolytes and creatinine; LFTs, liver function tests; urinalysis, urine dipstick test for blood, protein and glucose; BP, blood pressure; CXR, chest X-ray*

*ESR not strictly required for monitoring drugs but will usually be done to monitor disease activity – we have assumed it is done on each occasion*

* *BSR guidelines not available, monitoring requirements estimated*

assumed that the effect of DMARDs is additive to the general pattern of quality of life, it can be shown that such data are not in fact necessary. The two parts of *Figure 11* compare the quality of life patterns for an individual in a (hypothetical) simplified version of the model, in which an anti-TNF agent is introduced between two other DMARDs. The two parts of *Figure 12* show the quality of life patterns relative to the basic curve. It can be seen that the difference between quality of life estimates in *Figure 12* is the same as in *Figure 11*. This remains true regardless of discount rate, shape of assumed basic curve and lifetime of patient.

The basic effect of each DMARD can then be modelled as a constant increase in quality of life per unit time. The 'end effects' can conveniently be simplified to a fixed reduction in total QALYs for starting each new DMARD and a fixed reduction in total QALYs for finishing any DMARD. The reduction does not apply if the patient remains on the DMARD for the remaining lifetime. For discounting purposes, the end effects are taken at the time of starting and finishing the DMARD in question. Note that this method has the advantage of being workable when the DMARD is only used for a very short time.

## Summary of costs and QALY calculations

*Table 25* summarises the cost and QALY calculations for each DMARD. Palliative treatment follows a similar pattern, but there is of course no ending to be included.

***TABLE 24*** *Unit costs*

| Resource item | Unit cost (£) | Assumptions | Source for unit costs |
|---|---|---|---|
| ***Visits*** | | | |
| General practitioner (per visit) | 18.00 | | Netten *et al.*, 2000[162] |
| Hospital outpatient (per visit) | 78.00 | | |
| Hospital inpatient (per day) | 202.00 | | |
| ***DMARDs**** | | | |
| Sulphasalazine | 48.65 | 2.5 g/day | *British National Formulary* |
| Methotrexate | 10.21 | 15 mg/week taken orally | |
| Gold | 82.08 | | |
| Hydroxychloroquine | 45.51 | 300 mg/day | |
| Penicillamine | 29.88 | 500 mg/day | |
| Leflunomide | 139.50 | 20 mg/day | |
| Cyclosporin | 520.06 | 3.25 mg/kg/day, 70 kg patient | |
| Azathioprine | 47.11 | 150 mg/day | |
| Infliximab | 2216.40 | 70 kg patient, drug wastage if full vials not used, cost per administration of £124 | |
| Etanercept | 2072.00 | 102 doses per annum | |
| ***Tests*** | | | |
| FBC | 11.15 | | Trust Finance department |
| ESR | 11.15 | | |
| LFT | 6.19 | | |
| U&E | 6.19 | | |
| CXR | 20.00 | | |
| Urinanalysis | 0.08 | | |

* *Drug costs for 3 months, including administration costs*

*Price year: 2000*

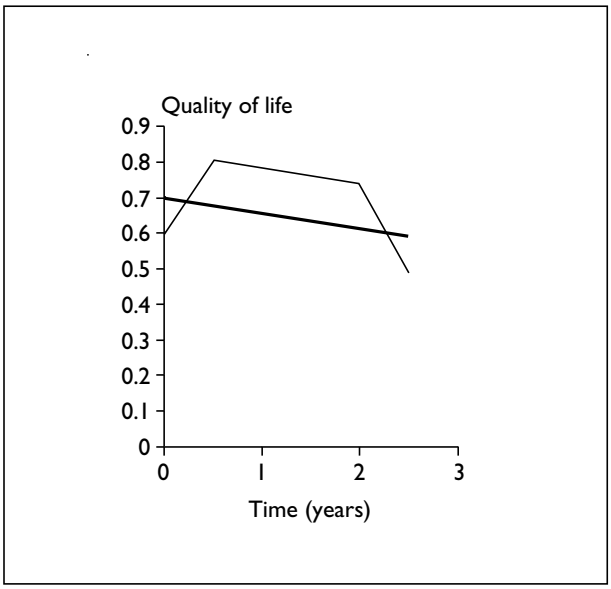



***FIGURE 10*** *Example of assumed pattern of quality of life (——, basic; ——, DMARDs)*

## Data used in the BPM

### *Lifetime distribution*

We used the age and sex distribution given by Symmons and colleagues[163] to represent an incident cohort. For each age and sex group we generated probabilities of survival to a given number of years by applying the SMR of 1.5 to a set of life tables for the general population.[85] These were then weighted by the age and sex distribution of the assumed incident cohort to produce an estimated survival distribution. For simplicity, the survival distribution was grouped into bands of 5 years, as shown in *Table 26,* and assumed to be spread uniformly within each 5-year band.

### *Time on each DMARD*

A Weibull distribution was fitted to the available data points. A variable $X$ has a Weibull distribution with shape parameter $a$ and scale parameter $b$ if


***FIGURE 11*** *Assumed quality of life patterns with and without DMARDs for an individual (——, basic; ——, DMARDs)*

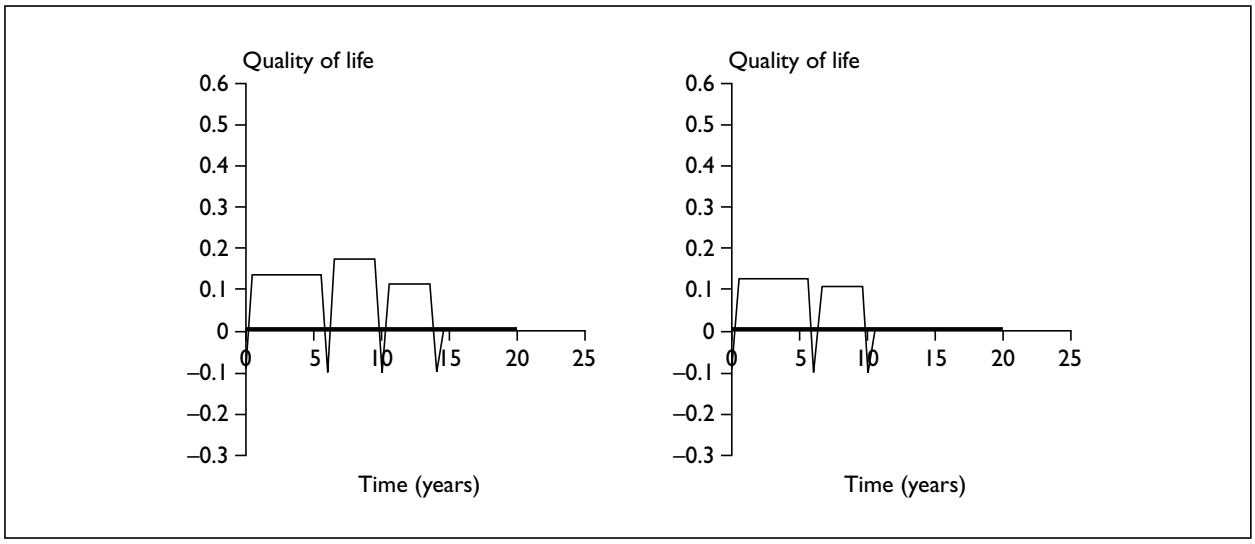



***FIGURE 12*** *Quality of life patterns relative to the basic curve (——, basic; ——, DMARDs)*

***TABLE 25*** *Summary of costs and QALY calculations*

| Time | Cost | QALYs |
|---|---|---|
| At start of DMARD | Fixed cost per DMARD | Fixed deduction from QALY total |
| While on DMARD | Constant per unit time | Constant per unit time (assumed relative to basic curve) |
| At end of DMARD (only applies if DMARD finished during lifetime of patient) | | Fixed deduction from QALY total |

***TABLE 26*** *Survival pattern assumed in the BPM*

| **Survival (years)** | **0–5** | **5–10** | **10–15** | **15–20** | **20–25** | **25–30** | **30–35** | **35–40** |
|---|---|---|---|---|---|---|---|---|
| Probability | 0.117 | 0.118 | 0.114 | 0.108 | 0.099 | 0.089 | 0.079 | 0.070 |
| **Survival (years)** | **40–45** | **45–50** | **50–55** | **55–60** | **60–65** | **65–70** | **70–75** | |
| Probability | 0.059 | 0.048 | 0.037 | 0.027 | 0.018 | 0.011 | 0.006 | |

$\left(\frac{X}{b}\right)^a$ has a negative exponential distribution with unit mean. A shape parameter $a < 1$ indicates that the hazard rate decreases with time; if $a > 1$ the hazard rate increases with time. The scale parameter is approximately equal to the mean of the distribution. In some cases, only two data points were available, in which case the scale parameter was set to 1, effectively using a negative exponential distribution. *Table 27* shows the values used.

### *Toxicity of DMARDs*

This was only relevant in our model for methotrexate and cyclosporin. For cyclosporin it was assumed drug cessation was due to toxicity, with a probability of 0.8 regardless of time spent on drug.[166] For methotrexate, the probability $p$ was set to depend on the time $t$ years on the drug, by the formula

$$p = 0.362 + 0.115e^{-0.457t}$$

which was derived from a comparison between the survival curves given in Maetzel and colleagues.[45]

### *Cost of DMARDs*

As indicated above, this consists of a one-off cost for starting a DMARD together with an annual cost of using the drug. Costs include administration and monitoring costs. *Table 28* shows the costs used.

### *QALY calculations*

Where possible, we estimated the change in HAQ score associated with any DMARD by averaging the results from the sources shown in *Table 29*. To convert this to an annual change in QALYs in

***TABLE 28*** *Costs associated with each DMARD*

| DMARD | Start-up (£) | Use (£) |
|---|---|---|
| Sulphasalazine | 564.62 | 575.96 |
| Methotrexate | 514.04 | 1184.92 |
| Gold | 2644.92 | 1547.64 |
| Hydroxychloroquine | 112.68 | 632.76 |
| Penicillamine | 453.33 | 1397.4 |
| Leflunomide | 952.28 | 1130.04 |
| Cyclosporin | 413.67 | 3090.52 |
| Azathioprine | 684.72 | 1332.52 |
| Infliximab | 1703.92 | 9608.58 |
| Etanercept | 558.17 | 8783.32 |
| Combination | 413.67 | 3131.36 |
| Symptom control | 0 | 312 |

***TABLE 29*** *Reduction in HAQ scores and QALY gains (per year) with each DMARD*

| DMARD | HAQ | QALY | Source |
|---|---|---|---|
| Sulphasalazine | 0.25 | 0.050 | Smolen *et al.*, 1999[141] |
| Methotrexate | 0.33 | 0.066 | Strand *et al.*, 1999[142] |
| Leflunomide | 0.49 | 0.098 | Smolen *et al.*, 1999[141]<br>Strand *et al.*, 1999[142] |
| Infliximab | 0.60 | 0.120 | Quartey (personal communication) |
| Etanercept | 0.60 | 0.120 | Moreland *et al.*, 1999[132]<br>Weinblatt *et al.*, 1999[131]<br>The European Etanercept Investigators Group, 2000[137] |
| All other DMARDs | 0.25 | 0.050 | Assumed as for sulphasalazine (Smolen *et al.*, 1999[141]) |

***TABLE 27*** *Distribution of time on each DMARD*

| DMARD | Shape | Scale | Source |
|---|---|---|---|
| Sulphasalazine | 0.71 | 2.76 | Maetzel *et al.*, 2000[45] |
| Methotrexate | 0.77 | 4.62 | Maetzel *et al.*, 2000[45] |
| Etanercept | 1.52 | 4.72 | Crnkic *et al.*, 2001[164] |
| Infliximab | 1.29 | 2.66 | Crnkic *et al.*, 2001[164] |
| Gold | 0.71 | 3.08 | Maetzel *et al.*, 2000[45] |
| Azathioprine | 0.73 | 1.60 | Hawley and Wolfe, 1991[165] |
| Penicillamine | 0.62 | 1.86 | Pincus *et al.*, 1992[56] |
| Hydroxychloroquine | 1.00 | 3.62 | Maetzel *et al.*, 2000[45] |
| Leflunomide | 0.67 | 3.10 | Crnkic *et al.*, 2001[164] |
| Cyclosporin | 1.00 | 1.70 | Lynch and Robinson, 2000[166] |
| Combination | 1.00 | 1.74 | Tugwell *et al.*, 1995[167]<br>Gerards *et al.*, 2000[168] |

***TABLE 30*** *Base-case results for the BPM*

| | Discounted to start of programme | | | | | |
|---|---|---|---|---|---|---|
| | Costs (£) | | Benefits (QALYs) | | | |
| | Mean | SE | Mean | SE | ICER (£/QALY) | Approx. 95% CI |
| Etanercept | 28,431 | 173 | 0.947 | 0.0055 | | |
| Infliximab | 24,975 | 144 | 0.849 | 0.0051 | | |
| No anti-TNF | 14,546 | 62 | 0.733 | 0.0047 | | |
| Etan–base | 13,885 | 131 | 0.214 | 0.002 | 64,881 | (63,059 to 66,812) |
| Infl–base | 10,430 | 103 | 0.116 | 0.002 | 89,973 | (87,082 to 93,063) |
| Etan–infl | 3,456 | 34 | 0.098 | 0.001 | 35,229 | (34,314 to 36,193) |
| | **Discounted to point of divergence** | | | | | |
| | Costs (£) | | Benefits (QALYs) | | | |
| | Mean | SE | Mean | SE | ICER (£/QALY) | Approx. 95% CI |
| Etan–base | 19,573 | 168 | 0.236 | 0.003 | 83,095 | (80,863 to 85,454) |
| Infl–base | 14,725 | 133 | 0.128 | 0.002 | 115,937 | (111,822 to 119,209) |
| Etan–infl | 4,848 | 44 | 0.108 | 0.001 | 44,912 | (43,797 to 46,084) |

our base-case analysis we multiplied by a conversion rate of 0.2, based on the EQ-5D scores from Australian data used in the Wyeth submission. We also considered a range from 0.168 (the study by Kobelt and colleagues[159]) to 0.230 (Australian quality of life index scores from the Australian data). The figure for sulphasalazine was used for all other DMARDs; a figure of zero was used for palliation in line with the explanation given above. The QALY losses at start and at end were set to 0.2 times the appropriate QALY gain figure.

## Results of the BPM

The BPM was run using etanercept and infliximab in turn as the anti-TNF, and without either anti-TNF. In each of the three runs, the same 10,000 virtual patients were used. The results are shown in *Table 30*. The standard errors shown result from the essentially stochastic nature of the model, and could have been reduced by increasing the (virtual) sample size. Standard errors are shown merely to give an indication that a sufficient sample size has been used: population means are the statistic of interest. The analysis here shows discounting both to the start of the programme and to the point of divergence between options. Elsewhere in this report only the latter figures (which relate more directly to the decision point) are quoted.

The analysis reported in *Table 30* assumed that the anti-TNF is used in third place in the sequence of DMARDs, as shown in *Figure 9*. This means that for some patients (those for whom DMARDs last their remaining lifetime) the anti-TNF replaces other, less expensive, DMARDs, while for others the anti-TNF extends the total time that patients have on DMARDs. An alternative comparison may be made by moving anti-TNFs to the end of the sequence of DMARDs (after combination therapy). The results of this analysis are shown in *Table 31*.

### *Sensitivity analysis*

There is uncertainty in all the data included in the BPM. In particular, there is uncertainty about the overall mortality, time spent on each DMARD, and effect of DMARDs on quality of life. Because of the way the model was structured, both costs and QALYs gained on sulphasalazine and methotrexate will be identical in all arms of the model, and thus cancel out in the incremental analysis. The same applies to all DMARDs other than the anti-TNFs themselves in the case where anti-TNFs are moved to last place in the sequence. Thus the results in *Table 31* are considerably more robust than those in *Table 30*.

To test the effect of mortality assumptions, we replaced the survival pattern from *Table 26* with similar patterns, assuming SMRs of 1.1 and 2.1. These made virtually no difference to the ICERs shown in *Table 31* – the point estimate for the ICER for etanercept over base changed from

***TABLE 31*** *Effect of using anti-TNFs after other DMARDs*

| | Discounted to start of programme | | | | | |
|---|---|---|---|---|---|---|
| | Costs (£) | | Benefits (QALYs) | | | |
| | Mean | SE | Mean | SE | ICER (£/QALY) | Approx. 95% CI |
| Etanercept | 18,777 | 109 | 0.862 | 0.0053 | | |
| Infliximab | 17,690 | 95 | 0.806 | 0.0050 | | |
| No anti-TNF | 14,546 | 62 | 0.733 | 0.0047 | | |
| Etan–base | 4,232 | 70 | 0.128 | 0.002 | 33,011 | (31,547 to 34,618) |
| Infl–base | 3,145 | 54 | 0.072 | 0.001 | 43,584 | (41,498 to 45,892) |
| Etan–infl | 1,087 | 19 | 0.056 | 0.001 | 19,398 | (18,559 to 20,317) |
| | **Discounted to point of divergence** | | | | | |
| | Costs (£) | | Benefits (QALYs) | | | |
| | Mean | SE | Mean | SE | ICER (£/QALY) | Approx. 95% CI |
| Etan–base | 12,320 | 177 | 0.172 | 0.003 | 71,659 | (68,716 to 74,866) |
| Infl–base | 9,183 | 137 | 0.097 | 0.002 | 94,798 | (90,566 to 99,444) |
| Etan–infl | 3,137 | 47 | 0.075 | 0.001 | 41,796 | (40,112 to 43,628) |

£71,659/QALY to £71,471 with SMR 1.1 and £71,838 with SMR 2.1.

We also varied the quality of life gain for anti-TNFs from a base-case value of 0.6 reduction in HAQ score to a range from 0.4 to 0.8. As in the base case, we maintained the assumption of equal effectiveness between etanercept and infliximab in this regard.

Finally we varied the conversion rate from decrease in HAQ score to QALYs gained per year from its base-case value of 0.2 to a range from 0.168 to 0.23.

We considered a 'best case' using 0.8 for reduction in HAQ score, 0.23 conversion rate to QALYs and 1.1 for SMR, and a 'worst case' using 0.4 for reduction in HAQ score, 0.168 conversion to QALYs and 2.1 for SMR; for anti-TNFs being used either third or last in the sequence of DMARDs. The results of this sensitivity analysis are shown in *Table 32*.

## Limitations of the BPM and further research needs

The BPM is limited in scope, mainly as a result of data limitations. It does not consider the effect of DMARDs on joint replacement, hospitalisation or mortality. The structure of the model is perfectly capable of accommodating all of these issues. For example, it would be possible to adjust a patient's remaining lifetime to take account of the effect of a DMARD. However, the simplification of QALY calculations described above could not then be used.

The most pressing need is reliable data on quality of life issues. In particular, further data are required on:

- the quality of life pattern of a typical RA patient
- how this is altered by each DMARD
- the pattern of variation among individuals.

***TABLE 32*** *Sensitivity analysis in the BPM*

| Position of anti-TNF | SMR | H | U | Discounted to start of programme: ICER (£/QALY) | | |
|---|---|---|---|---|---|---|
| | | | | Etan–base | Infl–base | Etan–infl |
| Third | 1.5 | 0.6 | 0.2 | 64,881 | 89,973 | 35,229 |
| Third | 1.1 | 0.8 | 0.23 | 38,480 | 52,840 | 21,330 |
| Third | 2.1 | 0.4 | 0.168 | 144,770 | 206,663 | 75,060 |
| Last | 1.5 | 0.6 | 0.2 | 34,618 | 45,892 | 20,317 |
| Last | 1.1 | 0.8 | 0.23 | 21,229 | 28,007 | 12,573 |
| Last | 2.1 | 0.4 | 0.168 | 60,027 | 79,351 | 34,945 |
| **Position of anti-TNF** | **SMR** | **H** | **U** | **Discounted to point of divergence: ICER (£/QALY)** | | |
| | | | | **Etan–base** | **Infl–base** | **Etan–infl** |
| Third | 1.5 | 0.6 | 0.2 | 83,095 | 115,397 | 44,912 |
| Third | 1.1 | 0.8 | 0.23 | 49,530 | 68,135 | 27,290 |
| Third | 2.1 | 0.4 | 0.168 | 184,455 | 263,791 | 95,121 |
| Last | 1.5 | 0.6 | 0.2 | 74,866 | 99,444 | 43,628 |
| Last | 1.1 | 0.8 | 0.23 | 46,612 | 61,603 | 27,433 |
| Last | 2.1 | 0.4 | 0.168 | 128,283 | 169,953 | 74,076 |

*H, reduction in HAQ score for anti-TNF, U, conversion rate from HAQ to QALY*

# Chapter 4

# Comments and conclusions

## Implications for other parties

The substantial economic impact of RA in terms of direct and indirect costs has been highlighted elsewhere in this report. Studies indicate a wide range of potential costs that cannot readily be explained by socioeconomic or clinical factors. However, it is apparent that a minority of patients may account for a high proportion of the direct medical costs. Costs incurred by individuals, in a cohort of early arthritis patients, are similar to costs incurred by healthcare services. Costs incurred by family and friends in terms of foregone paid work, foregone leisure time and other factors greatly exceed costs incurred by individuals and healthcare services. Clearly this could have an impact on the quality of life of patients and carers. Also physical disability, resulting in difficulties in self-care, and work disability, both have implications for PSS.

## Factors relevant to the NHS

The use of anti-TNF agents to treat RA has implications for current practices in rheumatology. For instance widespread use of infliximab would lead to a greater demand for day-case facilities by rheumatology departments because it is given intravenously. Currently there is great variation in the use of day-case facilities by rheumatologists, determined in part by local resources of inpatient and outpatient facilities. Widespread use of etanercept to treat RA, on the other hand, would place a greater demand on outpatient facilities. This would necessitate, for example, greater involvement of outpatient nurses in order that patients and carers may be taught to self-administer injections, for nurses to provide back-up in case of difficulties and provide disease and drug monitoring services. Again there are great variations in the use of nurse specialists in rheumatology and relatively few training opportunities for nurses wishing to specialise in this area. However, increasing use of DMARDs has led to a greater requirement for specialised nurses.

The long-term impact of anti-TNF agents on joint damage cannot be determined with certainty at present. A reduced risk of joint damage and destruction has the potential to reduce the need for surgery for patients with RA. This may lead to a reduced demand on orthopaedic services.

Some trials of anti-TNF agents used to treat other types of arthritis such as psoriatic arthritis and ankylosing spondylitis have been published.[169,170] These have shown favourable outcomes. Patients with psoriatic arthritis suffer, in some cases, similar difficulties to patients with severe RA. Indeed many with disease involving many joints fulfil diagnostic criteria for RA. Therapeutic choices for patients with severe psoriatic arthritis are similar to those available for patients with RA with a more limited evidence base.[171] It seems likely that there will be a demand to treat patients with other severe rheumatic diseases with anti-TNF agents.

Finally, issues of equity have been highlighted by the wide variation in availability of anti-TNF therapies across the UK. Clinicians have spent considerable effort and time attempting to secure treatments, in many cases without success. The review process being undertaken by NICE has been cited as one reason for limiting access.

## Discussion

### Principal findings

The key findings of this review of infliximab and etanercept for RA were as follows:

- Etanercept and infliximab are effective treatments for RA, compared with placebo, both in terms of improving symptoms of the disease and in preventing radiographic damage because of disease.
- The effect was consistent across trials for both agents with a relative 'risk' of achieving an ACR20 with active treatment of 4, rising to 8.7 for ACR70.
- NNTs for one patient to achieve an ACR20, an ACR50 and an ACR70 response were 2, 4 and 8, respectively. This compares with NNTs of 4 for ACR20 with leflunomide and sulphasalazine and NNTs of 5 or 6 for ACR50 with these agents in recent trials.[139,140] These are favourable NNTs for medical interventions but emphasise the

importance of direct comparisons between DMARDs in estimating the ICER of new treatments for RA.
- Etanercept was as effective as methotrexate for RA patients who had recent onset disease, judged to be of poor prognosis, in the one trial that compared a conventional DMARD directly with anti-TNF.
- Optimum efficacy was seen with infliximab at a dose of 10 mg/kg, but the recommended dose is 3 mg/kg. The recommended and optimum dose of etanercept was 25 mg twice weekly. A comparison of etanercept 25 mg versus 50 mg, in a study that did not meet our inclusion criteria, showed comparable benefits of these doses.
- Minor adverse events were common with both active agents and placebo. Side-effects attributable to active treatment included injection-site reactions consisting of a localised rash, irritation and bruising with etanercept and infusion-related events such as fever, chills, urticaria and dyspnoea with infliximab.
- Serious events directly attributable to anti-TNF were uncommon, but post-marketing surveillance suggests vigilance for tuberculosis and SLE with infliximab and for blood dyscrasias with etanercept.
- The annual drug costs are around £9600 for infliximab and £8800 for etanercept compared with £3100 for cyclosporin, the most expensive conventional DMARD.
- A simulation model was constructed that considered improvements in quality of life but assumed no effect of either etanercept or infliximab on mortality or the need for joint replacement.
- For use as the third DMARD in a sequence of DMARDs, the BPM gave a base-case ICER of approximately £83,000/QALY for etanercept and approximately £115,000/QALY for infliximab.
- These figures reduced to £72,000/QALY for etanercept, and £95,000 for infliximab, if used last in the sequence of DMARDs.
- Sensitivity analysis in the latter case gave figures ranging from £47,000 to £128,000 for etanercept, and £62,000 to £169,000 for infliximab.
- It should be stressed that these figures do not include all potential benefits of these agents. For instance no account is taken of the possible reduction in the need for joint replacement surgery, hospitalisation or needs for aids and appliances.

## Assumptions, limitations and uncertainties

- A strength of this review was the comprehensive search strategy that was facilitated by industry and lead researchers who provided unrestricted access to unpublished material at an early stage of the review process. In addition, expert input at an early stage ensured that a clinically relevant perspective was maintained throughout.
- Included studies were of high quality, as judged by the Jadad scale. Failure to complete a course of allocated treatment was more common for groups treated with placebo. In these cases the last available observation was carried forward and used as the value at study end. It is not known whether this method of analysis could have introduced unforeseen biases, however some sensitivity analyses assuming a worst-case scenario were reported.
- There is a potential for bias through unblinding in anti-TNF studies. For instance because infusion and injection-related adverse events, usually of a minor nature, are more frequent with active therapy, there is a potential for both physicians and patients becoming aware of treatment allocation.
- As this review was undertaken in a limited time, meta-analyses were restricted to selected outcomes judged to be of greater clinical significance. In addition, analysis was compared for all active treatment arms against placebo. This may underestimate efficacy, as a number of included studies were preliminary dose-finding studies. Further analyses are required taking into account dose effect.
- Assumptions in relation to the economic analyses were described in detail in the relevant section. The preliminary nature of our model, mandated by time and data constraints, indicates that the data should be interpreted with caution. Further analyses examining the potential impact of effective DMARDs on joint replacement surgery, hospitalisation and mortality need to be explored in detail and could be examined in due course.
- Our model assumes that continued therapy with a DMARD implies sustained effectiveness. We used data from observational cohorts studying drug survival with particular DMARDs. Patients and clinicians are aware of the limitations and flaws of such an assumption.[46]
- By assuming an NHS and PSS perspective only, as required by NICE, we may have significantly underestimated the potential economic advantages of effective control of disease because costs incurred by families and carers are substantial.
- Strategies for treating RA are potentially very complex and could include alternative approaches such as early use of combination therapy whereby drugs are withdrawn if the approach works (step-down) or other strategies

described earlier in this report (page 6). Our model is based on the saw-tooth strategy in which there is continued or serial use of one or multiple DMARDs. This approach appears to be effective in clinical practice.[172] However, there are limited long-term data on optimum strategies for treating RA.

### Implications for research

Only one study included in this review compared anti-TNF directly with another DMARD, a study comparing etanercept with methotrexate. This showed equivalent efficacy. Other studies in which patients continued methotrexate while receiving placebo or active anti-TNF cannot be regarded as true comparative studies of anti-TNF and a DMARD. Such direct comparisons have a potential for further informing practice in rheumatology, especially where difficult therapeutic choices that take cost into account are being made. Our economic analysis also emphasised the need for longitudinal data on quality of life of RA patients and the impact of DMARDs and other interventions commonly used in RA on quality of life. Further research is also needed to assess the impact of DMARDs on joint replacement, mortality and quality of life. Finally, as indicated above, further research and development of models is necessary, especially to allow consideration of other facets of RA in order to improve current models and inform decision-making.

## Conclusions

Infliximab and etanercept are clearly beneficial to patients with RA. This benefit for drug costs alone comes at a price that is currently three times the cost of the most expensive conventional DMARD. Whether these costs can be recouped through more effective control of disease, and prevention of disease-related complications, is unknown.

# Acknowledgements

The authors wish to thank the following individuals for their help and advice during the writing of this report:

Dr Carole Cummins, Institute of Child Health, Children's Hospital, Birmingham, UK.

Deborah Hartland, Department of Public Health and Epidemiology, The University of Birmingham, UK.

Professor R Maini, The Kennedy Institute of Rheumatology Division, Imperial College School of Medicine, London, UK.

Nigel Morgan, FCA, MA, Oxford.

Dr Paul Quartey, Medical Director, Schering-Plough Ltd, Welwyn Garden City, Hertfordshire, UK.

Dr Alan Reynolds, Manager Scientific Affairs, Wyeth Laboratories, Taplow, Middlesex, UK.

## Contributions of the authors

Dr Paresh Jobanputra (Consultant Rheumatologist) carried out the searches and data extraction and wrote the introduction, background, narrative on key studies and discussion, and edited the report.

Dr Pelham Barton (Lecturer in Mathematical Modelling) constructed and analysed the BPM, appraised the industry models and edited the report.

Dr Stirling Bryan (Professor in Health Economics) reviewed the industry submissions and, with Dr Paresh Jobanputra, developed the cost and utility inputs into the BPM and edited the report.

Dr Amanda Burls (Senior Clinical Lecturer in Public Health and Epidemiology) carried out data extraction, undertook the meta-analyses and edited the report.

Anne Fry-Smith assisted with the searches.

This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors and Dr Paresh Jobanputra is guarantor.

# References


1. Harrison B, Symmons D. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. *Rheumatology (Oxford)* 2000;**39**:939–49.
2. Wolfe F, Zwillich S. The long-term outcome of rheumatoid arthritis. A 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1072–82.
3. Jacoby R, Jayson M, Cosh J. Onset, early stages, and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11-year follow-up. *BMJ* 1973;**2**:96–100.
4. Smedstad L, Vaglum P, Moum T, Kvien T. The relationship between psychological distress and traditional clinical variables: a 2-year prospective study of 216 patients with early rheumatoid arthritis. *Br J Rheumatol* 1997;**36**:1304–11.
5. Harris E. Clinical features of rheumatoid arthritis. In: Kelley W, Harris E, Ruddy S, Sledge C, editors. Textbook of rheumatology. Philadelphia: WB Saunders & Co.; 1993. p. 874–911.
6. Arnett F, Edworthy S, Bloch D. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
7. Harrison B, Symmons D, Barrett E, Silman A. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. *J Rheumatol* 1998;**25**:2324–30.
8. Wiles N, Symmons D, Harrison B, Barrett E, Barrett J, Scott D, *et al.* Estimating the incidence of rheumatoid arthritis. Trying to hit a moving target? *Arthritis Rheum* 1999;**42**:1339–46.
9. Emery P, Symmons D. What is early rheumatoid arthritis? Definition and diagnosis. *Bailliere's Clin Rheumatol* 1997;**11**:13–26.
10. Silman A. Epidemiology and rheumatic diseases. In: Maddison P, Isenberg D, Woo P, Glass D, editors. Oxford textbook of rheumatology. Oxford: Oxford University Press; 1998. p. 811–28.
11. UK National Statistics. URL: http://www.statistics.gov.uk
12. MacGregor A, Snieder H, Rigby A, Koskenvuo M, Kapiro J, Aho K. Characterising the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000;**43**:30–7.
13. Barton A, John S, Ollier W, Silman A, Worthington J. Association between rheumatoid arthritis and polymorphisms of tumor necrosis factor receptor II, but not tumor necrosis factor receptor I in Caucasians. *Arthritis Rheum* 2001;**44**:61–5.
14. Harris E. Etiology and pathogenesis of rheumatoid arthritis. In: Kelley W, Harris E, Ruddy S, Sledge C, editors. Textbook of rheumatology. Philadelphia: WB Saunders & Co.; 1993. p. 833–73.
15. Jobanputra P, Davidson F, Graham S, O'Neill H, Simmonds P, Yap L. High frequency of parvovirus B19 in patients tested for rheumatoid factor. *BMJ* 1995;**311**:1542.
16. Maini R, Feldmann M. Immunopathogenesis of rheumatoid arthritis. In: Maddison P, Isenberg D, Woo P, Glass D, editors. Oxford textbook of rheumatology. Oxford: Oxford University Press; 1998. p. 983–1004.
17. Jobanputra P. Immunology of articular cartilage: Investigations into the pathogenesis of inflammatory arthritis [MD thesis]. University of Southampton; 1993.
18. Jobanputra P, Corrigall V, Kingsley G, Panayi G. Cellular responses to human chondrocytes: absence of allogeneic responses in the presence of HLA-DR and ICAM-1. *Clin Exp Immunol* 1992;**90**:336–44.
19. Fell J, Jubb R. The effect of synovial tissue on the breakdown of articular cartilage in organ culture. *Arthritis Rheum* 1977;**20**:1359–71.
20. Pettipher E, Higgs G, Henderson B. Interleukin-1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint. *Proc Natl Acad Sci U S A* 1986;**83**:8749–53.
21. Brennan F, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNFα antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 1989;**2**:244–7.
22. Lotz M. Cytokines and their receptors. In: Koopman W, editor. Arthritis and allied conditions. A textbook of rheumatology. Philadelphia: Lippincott, Williams & Wilkins; 1996. p. 439–78.
23. Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. *N Engl J Med* 1996;**334**:1717–25.
24. Beutler B, Cerami A. The biology of cachetin/TNF – a primary mediator of the host response. *Annu Rev Immunol* 1989;**7**:625–55.

25. Moreland L. Inhibitor of tumor necrosis factor for rheumatoid arthritis. *J Rheumatol* 1999; **26** Suppl 1:7–15.

26. Kollias G, Douni E, Kassiotis G, Kontoyiannis D. The function of tumour necrosis factor and receptors in models of multi-organ inflammation, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. *Ann Rheum Dis* 1999;**58** Suppl 1:132–9.

27. Chikanza I, Roux-Lombard P, Dayer J-M, Panayi G. Tumor necrosis factor soluble receptors behave as acute phase reactants following surgery in patients with rheumatoid arthritis, chronic osteomyelitis, and osteoarthritis. *Clin Exp Immunol* 1993;**92**:485–9.

28. Herbein G, O'Brien W. Tumor necrosis factor (TNF)-alpha and TNF receptor in viral pathogenesis. *Proc Soc Exp Biol Med* 2000;**223**:241–57.

29. Taylor P, Peters A, Paleolog E, Chapman P, Elliott M, McCloskey R, *et al.* Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor alpha blockade in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:38–47.

30. Scott D, Shipley M, Dawson A, Edwards S, Symmons D, Woolf A. The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness. *Br J Rheumatol* 1998;**37**:546–54.

31. Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis. URL: http://www.sign.ac.uk

32. Scott D. Clinical guidelines for management. *Bailliere's Clin Rheumatol* 1997;**11**:157–79.

33. American College of Rheumatology. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum* 1996;**39**:713–22.

34. Jobanputra P. Rheumatic disease. A guide for general practitioners. URL: http://rheuma.bham.ac.uk/NewSite/education/site.htm

35. Kroot E, van Gestel A, Swinkels H, Albers M, van de Putte LBA, van Riel PL. Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. *J Rheumatol* 2001;**28**:1511–17.

36. Wolfe M, Lichtenstein D, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999;**340**:1888–99.

37. Boers M, Verhoeven A, Markusse H, Van der Laar M, Westhovens R, Van Denderen J. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;**350**:309–18.

38. Kirwan J, The Arthritis Rheumatism Council Low-Dose Corticosteroid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;**333**:142–6.

39. Hickling P, Jacoby R, Kirwan J, The Arthritis Rheumatism Council Low-Dose Corticosteroid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. *Br J Rheumatol* 1998;**37**:930–6.

40. De Broe S, Hewitson P, McBride A. Leflunomide: a new disease modifying drug for rheumatoid arthritis. URL: http://www.hta.nhsweb.nhs.uk/rapidhta

41. Cronstein BN. The mechanism of action of methotrexate. *Rheum Dis Clin North Am* 1997;**23**:739–55.

42. Van der Heide A, Jacobs J, Bijlsma W, Heurkens A, van Booma-Frankfort C, van der Veen MJ. The effectiveness of early treatment with 'second-line' antirheumatic drugs. *Ann Intern Med* 1996;**124**:699–707.

43. Munro R, Hampson R, McEntegart A, Thompson E, Madhok R, Capell H. Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study. *Ann Rheum Dis* 1998;**57**:88–93.

44. Jeurissen M, Boerbooms A, van de Putte A, Doesburg W, Mulder J, Rasker J. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight week randomised double-blind study. *Arthritis Rheum* 1991;**34**:961–72.

45. Maetzel A, Wong W, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* 2000;**39**:975–81.

46. Jobanputra P, Hunter M, Clark D, Lambert C, Hurst N. An audit of methotrexate and folic acid for rheumatoid arthritis. Experience from a teaching centre. *Br J Rheumatol* 1995;**34**:971–5.

47. Felson D, Anderson J, Meenan R. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A meta-analysis of published clinical trials. *Arthritis Rheum* 1992;**35**:1117–25.

48. Verhoeven A, Boers M, Tugwell P. Combination therapy in rheumatoid arthritis: updated systematic review. *Br J Rheumatol* 1998;**37**:612–19.

49. Mottonen T, Hannonen P, Leirsalo-Repo M, Nissila M, Kautiainen H, Korpela M. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999;**353**:1568–73.

50. Proudman S, Conaghan P, Richardson C, Griffiths B, Green M, McGonagle D, *et al.* Treatment of poor prognosis early rheumatoid arthritis. A randomised study of treatment with methotrexate, cyclosporin A, and intraarticular corticosteroids compared with sulphasalazine alone. *Arthritis Rheum* 2000;**43**:1809–19.

51. Farr M, Bacon P. How and when should combination therapy be used? The role of an anchor drug. *Br J Rheumatol* 1995;**34**:100–3.

52. Tugwell P. Combination therapy in rheumatoid arthritis: meta-analysis. *J Rheumatol* 1996; **23** Suppl 44:43–6.

53. Wang B, Balise R, Fries J. Frequency of two-DMARD combinations in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1998;**41**(Suppl):S59.

54. Scott D, Paulus H, Marubini E, Laasonen L, Priolo F, Yocum D, *et al.* Pooled 12-month DC-ART results of six prospective, randomised, controlled studies on cyclosporine or MTX, MTX+CsA and pGold salts in patients with early severe RA. *Arthritis Rheum* 2000;**43**(Suppl):S345.

55. Kroot E, van Gestel A, de Boo T, van Riel P. Methotrexate withdrawal or early first DMARD discontinuation do not predict consecutive DMARD survival in patients with rheumatoid arthritis: results of a 15 year observational study. *Arthritis Rheum* 2000;**43**(Suppl):S343.

56. Pincus T, Marcum S, Callahan L. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices. II. Second line drugs and prednisolone. *J Rheumatol* 1992;**19**:1885–94.

57. ten Wolde S, Breedveld F, Hermans J, Vandenbroucke J. Randomised placebo controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* 1996;**347**:347–52.

58. Gøtzche P, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang K. Randomised placebo controlled trial of withdrawal of slow-acting drugs and of observer bias in rheumatoid arthritis. *Scand J Rheumatol* 1996;**25**:194–9.

59. Viller F, Guillemin F, Briancon S, Moum T, Suurmeijer T, van den Heuvel W. Compliance to drug treatment of patients with rheumatoid arthritis: a 3 year longitudinal study. *J Rheumatol* 1999;**26**:2114–22.

60. Kroot E, van de Putte L, van Riel PL. Management of therapy resistant rheumatoid arthritis. *Bailliere's Clin Rheumatol* 1999;**13**:737–52.

61. Denman A. Antirheumatic drugs. In: Maddison P, Isenberg D, Woo P, Glass D, editors. Oxford textbook of rheumatology. Oxford: Oxford University Press; 1998. p. 581–608.

62. Felson D, Anderson J, Boers M, Bombardier C, Furst D, Goldsmith C, *et al.* American College of Rheumatology preliminary definitions of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.

63. Felson D, Anderson J, Lange M, Wells G, LaValley M. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998;**41**:1564–70.

64. Quinn M, Conaghan P, Astin P, Green M, Karim Z, Emery P. Using improvement criteria may lead to over treatment in early RA. *Rheumatology* 2001;**40**(Suppl):S81.

65. Food and Drug Administration. Guidance to Industry. Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). URL: http://www.fda.gov/cber/gdlns/rheumcln.htm

66. Pinals R, Masi A, Larsen R. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981;**24**:1308–15.

67. Group for the Respect of Ethics and Excellence in Science (GREES). Recommendations for the registration of drugs used in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1998;**37**:211–15.

68. The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP). Points to consider on clinical investigation of slow-acting anti-rheumatic medicinal products in rheumatoid arthritis. July 2002. URL: http://www.emea.eu.int/pdfs/human/ewp/055695en.pdf

69. Vliet Vlieland T, Hazes J. Efficacy of multidisciplinary team care programs in rheumatoid arthritis. *Semin Arthritis Rheum* 1997;**27**:110–22.

70. Verhagen A, de Vet HC, de Bie RA, Kessels A, Boers M, Knipschild P. Taking baths: the efficacy of balneotherapy in patients with arthritis. A systematic review. *J Rheumatol* 1997;**24**:1964–71.

71. Lorig K, Lubeck D, Kraines R, Scleznick M, Holman H. Outcomes of self-help education for patients with arthritis. *Arthritis Rheum* 1985;**28**:680–5.

72. Vliet Vlieland T, Breedveld F, Hazes J. The two-year follow-up of a randomised comparison of inpatient multidisciplinary team care and routine outpatient care for active rheumatoid arthritis. *Br J Rheumatol* 1997;**36**:82–5.

73. Wiles N, Barrett J, Barrett E, Silman A, Symmons D. Disability in patients with early inflammatory polyarthritis cannot be 'tracked' from year to year: An examination of the hypothesis underlying percentile reference charts. *J Rheumatol* 1999;**26**:800–4.

74. Wiles N, Dunn J, Barrett E, Harrison B, Silman A, Symmons D. One year follow-up variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. *J Rheumatol* 2000;**27**:2360–6.

75. Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, *et al.* How does disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years follow-up in 732 patients from the early RA Study (ERAS). *Rheumatology* 2000;**39**:603–11.

76. Uhlig T, Smedstad L, Vaglum P, Moum T, Gerard N, Kvien T. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. *Rheumatology* 2000;**39**:732–41.

77. Wolfe F. The prognosis of rheumatoid arthritis: Assessment of disease activity and disease severity in the clinic. *Am J Med* 1997;**103**:S12–18.

78. Barrett E, Scott D, Wiles N, Symmons D. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. *Rheumatology* 2000;**39**:1403–9.

79. Chorus A, Miedema H, Wevers C, van der Linden S. Labour force participation among patients with rheumatoid arthritis. *Ann Rheum Dis* 2000;**59**:549–54.

80. Young A, van der Heijde D. Can we predict aggressive disease? *Bailliere's Clin Rheumatol* 1997;**11**:27–48.

81. Valenzuela-Castano A, Garcia-Lopez A, Perez-Vilches D, Rodriguez-Perez R, Gonzalez-Escribano M, Nunez-Roldan A. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10 year observational study. *J Rheumatol* 2000;**27**:571–4.

82. Drossaers-Bakker K, Kroon H, Zwinderman A, Breedveld F, Hazes J. Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. *Rheumatology* 2000;**39**:998–1003.

83. Scott D, Pugner K, Kaarela K, Doyle D, Woolf A, Holmes J. The links between joint damage and disability in rheumatoid arthritis. *Rheumatology* 2000;**39**:122–32.

84. Guedes C, Dumont-Fischer D, Leichter-Nakache S, Boisser M. Mortality in rheumatoid arthritis. *Rev Rheumatisme, English Edn* 1999;**66**:492–8.

85. Goodson N, Wiles N, Lunt M, Dunn G, Barrett E, Scott D, *et al.* Increased mortality in seropositive patients during the early years of inflammatory polyarthritis. *Rheumatology* 2001;**40**(Suppl):S71.

86. Cooper N, Mugford M, Barrett B, Scott D, Symmons D. Economic impact of early inflammatory polyarthritis to the individual, health care service and society: preliminary results. *Arthritis Rheum* 2000;**43**(Suppl):S143.

87. Cooper N. Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology* 2000;**39**:28–33.

88. Liang M. Psychosocial management of rheumatic diseases. In: Kelley W, Harris E, Ruddy S, Sledge C, editors. Textbook of rheumatology. Philadelphia: WB Saunders & Co.; 1993. p. 535–43.

89. Coulter A. Managing demand at the interface between primary and secondary care. *BMJ* 1998;**316**:1974–6.

90. The British Society for Rheumatology. Musculoskeletal disorders: Providing for the patient's needs. No. 3. A basis for planning rheumatology services. London: The Society. URL: https://www.msecportal.org/portal/editorial/PublicPages/bsr/536883012/10.doc

91. The British Society for Rheumatology. Musculoskeletal disorders: providing for the patient's needs. No. 2. Epidemiologically based estimates of manpower requirements. London: The Society; 1994.

92. Hicks N, Baker I. General practitioner's opinions of health services available to their patients. *BMJ* 2000;**302**:991–3.

93. Ashcroft J. Arthritis: Understanding people's everyday needs. London: Arthritis Care, 1997.

94. Cohen M. Accentuate the positive: we are better than guidelines. *Arthritis Rheum* 1997;**40**:2–4.

95. Tannenbaum S. What physicians know. *N Engl J Med* 1993;**329**:1268–71.

96. The British Society for Rheumatology. New treatments in arthritis: The use of TNF-α blockers in adults with rheumatoid arthritis. Report of a working party of the British Society for Rheumatology. London: The Society; 2000. URL: https://www.msecportal.org/portal/editorial/PublicPages/bsr/536883013/1.doc

97. BSR/ARC Biologics registry. URL: http://www.arc.man.ac.uk/webbiologicsreg.htm

98. American College of Rheumatology. Report of the American College of Rheumatology Blue Ribbon Committee on New Therapies. Atlanta, GA: ACR; 2000.

99. Wyeth Laboratories. Immunex. Enbrel product information. URL: http://www.enbrel.com/gen/gen05.jsp

100. Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, *et al.* Regulation of cytokine, cytokine inhibitors and acute-phase proteins following anti-TNF alpha therapy in rheumatoid arthritis. *J Immunol* 1999;**163**:1521–8.

101. Centocor. Remicade. Full prescribing information. URL: http://www.remicade-com

102. Douglas K, Bowman SJ. How many patients are eligible for anti-TNF therapy in the UK. *Rheumatology* 2001;**40**:1416.

103. Kvein T, Uhlig T, Kristiansen S. Which proportion of RA patients are candidates for TNF-targeted therapy – cost-implications for the society. *Arthritis Rheum* 1999;**42**(Suppl):S78.

104. Jadad A, Moore R, Carroll D, Jenkinson C, Reynolds J, Gavaghan D, *et al.* Assessing the quality of reports on randomised clinical trials: Is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.

105. Choy E, Kingsley G, Panayi G. Monoclonal antibody therapy in rheumatoid arthritis. *Br J Rheumatol* 1998;**37**:484–90.

106. Kavanaugh A, St Clair E, McCune W, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor – a monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000;**27**:841–50.

107. Moreland L, Margolies G, Heck L, Saway A, Blosch C, Hanna R. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein. Toxicity and dose finding trial in refractory rheumatoid arthritis. *J Rheumatol* 1996;**23**:1849–55.

108. Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7. *Ann Rheum Dis* 1999;**58**:170–2.

109. Edwards C. PEGylated recombinant human soluble tumor necrosis factor receptor type I (r-Hu-sTNF-R1): novel high affinity TNF receptor designed for chronic inflammatory diseases. *Ann Rheum Dis* 1999;**58** Suppl 1:173–81.

110. Rankin E, Choy E, Kassimos D, Kingsley G, Sopwith A, Isenberg D. The therapeutic effects of an engineered human anti-tumour necrosis factor alpha antibody (CDP571) in rheumatoid arthritis. *Br J Rheumatol* 1995;**34**:334–42.

111. Lukina G, Sigidin Y, Skurkovich S, Skurkovich B. New approaches to biological immunomodulation therapy of rheumatoid arthritis: neutralisation of basic cytokines. *Terapevitcheskii Arkhiv* 1998;**5**:32–7.

112. Sander O, Rau R. Treatment of refractory rheumatoid arthritis with a tumor necrosis factor α receptor fusion protein (TNFR55-1gG1) – a monocentric observation in 80 patients. *J Rheumatol* 1998;**57**:307–11.

113. Elliott M, Maini R, Feldmann M, Kalden J, Antoni C, Smolen J. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994;**334**:1105–10.

114. Maini R, Breedveld F, Kalden J, Smolen J, Davis D, MacFarlane J. Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.

115. Maini R, St Clair E, Breedveld F, Furst D, Kalden J, Weisman M. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999;**359**:1932–9.

116. Lipsky P, van der Heijde D, St Clair E, Furst D, Breedveld F, Kalden J. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;**343**:1594–602.

117. Centocor. Confidential. Clinical Study Report (102-week). Protocol C0168T22. A placebo-controlled, double-blinded, randomised clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment. February 2001.

118. Antoni C, Kavanagh A, Manger B, Kalden J, Keenan G, Schaible T. Responses to infliximab therapy in the ATTRACT trial assessed with the disease activity score (DAS); clinical response measured by DAS correlated with arrest of radiologic progression and shows higher response rates than ACR20 criteria. *Arthritis Rheum* 2000;**43**(Suppl):S147.

119. Kavanaugh A, Lipsky P, Furst D, Weisman M, St Clair W, Smolen J, *et al.* Infliximab improves long-term quality of life and functional status in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S147.

120. Maini R, Breedveld F, Kalden J, Smolen J, Davis D, MacFarlane J, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.

121. Centocor. Confidential. Clinical Study Report (54-week). Protocol C0168T22. A placebo-controlled, double-blinded, randomised clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment. February 2001.

Centocor markets Remicade® (infliximab) in the USA.

122. Bathon J, Martin R, Fleischmann R, Tesser J, Schiff M, Keystone E. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.

123. Wyeth Laboratories. Multicenter double-blind, randomised phase III study comparing recombinant human tumor necrosis factor receptor (p75) fusion protein (TNFR:Fc or etanercept) to methotrexate in patients with early rheumatoid arthritis: Final report. Confidential internal report, December 2000.

124. van der Heijde D, van Leeuwen M, van Riel P, Koster A, Van't Hof M, van Rijswijk MH. Biannual radiographic assessments of hands and feet in a three-year prospective follow up of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992;**35**:26–34.

125. Sharp J, Young D, Bluhm G, Brook A, Brower A, Corbett M. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum* 1985;**28**:1326–35.

126. Keenan G, Schaible T, Boscia J. Invasive pulmonary aspergillosis associated with infliximab therapy. *N Engl J Med* 2001;**344**:1100.

127. Gershon S, Wise R, Niu M, Siegel J. Postlicensure reports of infection during use of etanercept and infliximab. *Arthritis Rheum* 2000;**43**:2857.

128. Medicines Control Agency. Infliximab (Remicade) and tuberculosis. URL: http://www.mca.gov.uk/mca/csm/remicade.htm

129. Charles P, Smeenk R, de Jong J, Feldmann M, Maini R. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor α. *Arthritis Rheum* 2000;**43**:2383–90.

130. Smolen J, Steiner G, Breedveld F, Kalden J, Lipsky P, Maini R. Anti-TNFα therapy and drug induced lupus-like syndrome. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:217.

131. Moreland L, Baumgartner S, Schiff M, Tindall E, Fleischmann R, Weaver A. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;**337**:141–7.

132. Moreland L, Schiff M, Baumgartner S, Tindall E, Fleischmann R, Bulpitt K. Etanercept therapy in rheumatoid arthritis: a randomised, controlled trial. *Ann Intern Med* 1999;**130**:478–86.

133. Weinblatt M, Kremer J, Bankhurst A, Bulpitt K, Fleischmann R, Fox R. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;**340**:253–9.

134. Wajdula J. A double-blind, placebo-controlled study of the efficacy and safety of four different doses of etanercept in patients with rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:163.

135. Wyeth Laboratories. A double-blind, placebo-controlled study of the efficacy and safety of four different doses of etanercept in patients with rheumatoid arthritis: Final report. Confidential internal report, May 2000.

136. Wyeth Laboratories. Enbrel (Etanercept) clinical written summary. Confidential internal report received from Dr Alan Reynolds, 27 February 2001.

137. Ericson M, Wajdula J, on behalf of the European Etanercept Investigators Group. A double-blind, placebo controlled study of the efficacy and safety of four different doses of etanercept in patients with rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:S82.

138. Mathias S, Colwell H, Miller D, Moreland L, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. *Clin Ther* 2000;**22**:128–9.

139. den Broeder A, van Gestel A, van Riel P. Evaluation of the disease activity in patients with RA during longterm treatment with anti-TNFα. *Ann Rheum Dis* 2000;**59** Suppl 1:165.

140. Genovese M, Martin R, Fleischmann R, Keystone E, Bathon J, Spencer-Green G, *et al.* Enbrel® (Etanercept) versus methotrexate in early rheumatoid arthritis (ERA trial): 2 year follow-up. *Arthritis Rheum* 2000;**43**(Suppl):S269.

141. Smolen J, Kalden J, Scott D, Rozman B, Kvein T, Larsen A, *et al.* Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet* 1999;**353**:259–66.

142. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, *et al.* Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999;**159**:2542–50.

143. The Lenercept Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. TNF neutralisation in MS – results of a randomised, placebo-controlled multicentre study. *Neurology* 1999;**53**:457–65.

144. Van Oosten B, Barkhof F, Truyen L, Boringa J, Bertelsmann F, von Blomberg B, *et al.* Increased MRI activity and immune activation in two multiple sclerosis patients treated with monoclonal anti-tumor necrosis factor antibody cA2. *Neurology* 1996;**47**:1531–4.

145. Clarke A, Levinton C, Joseph L, Penrod J, Zowall H, Sibley J, *et al.* Predicting the short term direct medical costs incurred by patients with rheumatoid arthritis. *J Rheumatol* 1999;**26**:1068–75.

146. Gabriel S, Crowson C, Luthra H, Wagner J, O'Fallon W. Modelling the lifetime costs of rheumatoid arthritis. *J Rheumatol* 1999;**26**:1269–74.

147. Allaire S, Prashker M, Meenan R. The costs of rheumatoid arthritis. *Pharmacoeconomics* 1994;**6**:513–22.

148. Merkesdal S, Ruof J, Huelsemann J, Schoeffski O, Maetzel A, Mau W, *et al.* Development of a matrix of cost domains in economic evaluation of rheumatoid arthritis. *J Rheumatol* 2001;**28**:657–61.

149. Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. *J Rheumatol* 1996;**23**:47–51.

150. Clarke A, Zowall H, Levinton C, Assimakopoulos H, Sibley J, Haga M, *et al.* Direct and indirect medical costs incurred by Canadian patients with rheumatoid arthritis: a 12 year study. *J Rheumatol* 1997;**24**:1051–60.

151. Yelin E, Wanke L. An assessment of the annual and long-term direct costs of rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:1209–18.

152. van Jaarsveld C, Jacobs J, Schrijvers A, Heurkens A, Haanen H, Bijlsma J. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. *Br J Rheumatol* 1998;**37**:837–47.

153. McIntosh E. The cost of rheumatoid arthritis. *Br J Rheumatol* 1996;**35**:781–90.

154. Gabriel S, Campion M, O'Fallon W. A cost-utility analysis of misoprostol prophylaxis for rheumatoid arthritis patients receiving nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 1994;**37**:333–41.

155. Anis A, Tugwell P, Wells G, Stewart D. A cost effectiveness analysis of cyclosporine in rheumatoid arthritis. *J Rheumatol* 1996;**23**(Pt 4):609–16.

156. Choi H, Seeger J, Kuntz K. A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:2316–27.

157. Choi H, Seeger J, Kuntz K. A cost-effectiveness analysis of treatment options for patients with methotrexate (MTX)-naive rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S389.

158. Kavanaugh A, Patel K, Bala M, San Diego L, Malvern C. Cost effectiveness of infliximab in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S144.

159. Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. *Arthritis Rheum* 1999;**42**:347–56.

160. Ward MW, Lubeck D, Leigh JP. Longterm health outcomes of patients with rheumatoid arthritis treated in managed care and fee-for-service practice settings. *J Rheumatol* 1998;**25**:641–9.

161. Fries J. The ARAMIS (American Rheumatism Association Medical Information System) post-marketing surveillance program. *Drug Inf J* 1985;**19**:257–62.

162. Netten A, Curtis L, compilers. Unit costs of health and social care 2000. Canterbury: University of Kent, Personal Social Services Unit (PSSRU), 2000.

163. Symmons D, Barrett E, Bankhead C, Scott D, Silman A. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk arthritis register. *Br J Rheumatol* 1994;**33**:735–9.

164. Crnkic M, Teleman A, Saxne T, Geborek P. Survival on drug as a tool for evaluation of drug tolerability. Initial experience in southern Sweden of infliximab, etanercept and leflunomide in rheumatoid arthritis. *Rheumatology* 2001; **40** Suppl 1:82–3.

165. Hawley D, Wolfe F. Are the results of controlled clinical trials and observational studies of second line therapy in rheumatoid arthritis valid and generalisable as measures of rheumatoid arthritis outcome. *J Rheumatol* 1991;**18**:1008–14.

166. Lynch N, Robinson E. Cyclosporin use in inflammatory arthritis: a 2-year prospective national audit. *Arthritis Rheum* 2000;**43**(Suppl):S344.

167. Tugwell P, Pinculs T, Yocum D, Stein M, Gluck O, Kraag G, *et al.* Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995;**333**:137–41.

168. Gerards A, Landewe R, Prins A, Bruijn G, Goei T, Dijkmans B. Combination therapy with cyclosporin A and methotrexate in patients with early aggressive rheumatoid arthritis, a randomised double blind placebo controlled trial. *Arthritis Rheum* 2000;**43**(Suppl):S382.

169. Mease P, Goffe B, Metz J, Vanderstoep A, Finck B, Burge D. Etanercept in the treatment of psoriatic arthritis and psoriasis. *Lancet* 2000;**356**:385–90.

170. Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor α monoclonal antibody infliximab. *Arthritis Rheum* 2000;**43**:1346–52.

171. Jones G, Crotty M, Brooks P. Interventions for psoriatic arthritis (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.

172. Sokka T, Möttönen T, Hannonen P. Disease modifying anti-rheumatic drug use according to the 'saw tooth' treatment strategy improves the functional outcome in rheumatoid arthritis: results of a long-term follow-up study with review of the literature. *Rheumatology* 2000;**39**:34–42.

173. Fries J, Spitz P, Kraines R, Holman H. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45.

174. van Gestel A, Prevoo M, Van't Hof M, Rijswijk M, van Riel P. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. *Arthritis Rheum* 1995;**39**:34–40.

175. van Gestel A, Haagsma C, van Riel P. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998;**41**:1845–50.

176. Paulus H, Egger M, Ward J, Williams H. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs, based on findings in patients treated with placebo. *Arthritis Rheum* 1990;**33**:477–84.

177. Hochberg M, Chang R, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992;**35**:498–502.

178. Antoni C, Maini R, Breedveld F, Smolen J, Lipsky P, Furst D. Subgroup analyses show consistent clinical benefit in a 30-week double blind trial (ATTRACT) with an anti-TNFα monoclonal antibody, infliximab, in rheumatoid arthritis patients on methotrexate. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:217.

179. Barrera P, den Broederm A, van der Mass A, van Ede A, Kimeney B, Laan R. Drug survival, efficacy and toxicity of monotherapy with a fully human anti-TNFα monoclonal antibody versus MTX in RA. *Ann Rheum Dis* 2000;**59**(Suppl 1):164.

180. Barrera P, Joosten L, den Broeder A, van de Putte LBA, van Riel PL, van den Berg W. Effect of a fully human anti-TNFα monoclonal antibody on the local and systemic expression of TNF and IL-1. *Ann Rheum Dis* 2000;**59**(Suppl 1):164.

181. Barrera P, Joosten L, den Broeder A, van de Putte LBA, van den Berg W. Effect of a fully human anti-TNFα monoclonal antibody on the local and systemic expression of TNFα and IL-Iβ. *Arthritis Rheum* 1999;**42**(Suppl):S75.

182. Baumgartner S, Fleischmann R, Moreland L, Schiff M, Markenson J, Spencer-Green G. Improvements in disability in rheumatoid arthritis patients with early versus established disease treated with Enbrel. *Arthritis Rheum* 2000;**43**(Suppl):S230.

183. Breedveld F, Lipsky P, St Clair W, Smolen J, Furst D, Kalden J. A phase III randomised, double-blind, placebo-controlled study of infliximab (Remicade) in active RA despite methotrexate therapy: safety of the ATTRACT trial. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:216.

184. Buch M, Jarrett S, Bingham S, Marzo-Ortega H, Fairclough A, Emery P. Incidence of adverse events in patients with rheumatoid arthritis receiving infliximab. *Rheumatology* 2001;**40**:32–3.

185. Caldwell J, Davis M, Jelaca-Maxwell K, Wang A, Wason S, Chase W. A phase I study of PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-R1 [p55]) in subjects with rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:157.

186. Conaghan P, Quinn M, O'Connor P, Wakefield R, Karim Z, Astin P, *et al.* Can high-dose infliximab achieve remission in early rheumatoid arthritis. *Rheumatology* 2001;**40**:31–2.

187. Cope A, Maini R. Soluble tumor necrosis factor receptor in arthritis. *J Rheumatol* 1995;**22**:382–4.

188. Crnkic M, Mansson B, Saxne T, Geborek P. Infliximab and etanercept treatment in rheumatoid arthritis. A Swedish experience. *Arthritis Rheum* 2000;**43**(Suppl):S227.

189. Crnkic M, Teleman A, Saxne T, Geborek P. Infliximab, etanercept and leflunomide in rheumatoid arthritis. Clinical experience in southern Sweden. *Rheumatology* 2001;**40**:82.

190. Davis M, Frazier J, Martin S, Edwards C. Non-immunogenicity of a PEGylated soluble tumor necrosis factor receptor type I (PEG sTNF-R1[p55]). *Ann Rheum Dis* 2000;**59** Suppl 1:157.

191. den Broeder A, Joosten L, Saxne T, Fenner H, van Riel P, van de Putte LBA, *et al.* Effect of long-term anti-TNF monotherapy on radiologic course and on markers of cartilage breakdown and endothelial activation in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S227.

192. den Broeder A, Joosten L, Saxne T, Heinegard D, Fenner H, van de Putte LBA, *et al.* Radiographic progression, pro-MMP, COMP and adhesion molecule levels. Correlations with disease activity in RA patients treated with human anti-TNF antibody. *Ann Rheum Dis* 2000;**59**:190–1.

193. den Broeder A, van Gestel A, van Riel P. Evaluation of the disease activity in patients with RA during long-term treatment with anti-TNF. *Arthritis Rheum* 1999;**42**(Suppl):S135.

194. Eijsbouts A, den Broeder A, van den Hoogen F, Laan R, Hermus A, Sweep F. The effect of anti-TNF-treatment is not mediated through the HPA-axis. *Ann Rheum Dis* 2000;**59** Suppl 1:165.

195. Elliott M, Maini R, Feldmann M, Long-Fox A, Charles P, Katsikis P. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α. *Arthritis Rheum* 1993;**36**:1681–90.

196. Elliott M, Maini R, Feldmann M, Long-Fox A, Charles P, Bijl H, *et al.* Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis. *Lancet* 1994;**344**:1125–7.

197. El-Rafie A, Kirwan P, Corcoran O, Osman H, Foley-Nolan D. Infliximab is an effective treatment in refractory RA and improvements measured in hand grip strength parallel improvements in disease parameters. An open label single centre study. *Rheumatology* 2001;**40**(Suppl):S32.

198. Emery P, Maini R, Lipsky P, Breedveld F, Smolen J. Infliximab plus methotrexate prevents structural damage, reduces signs and symptoms and improves disability in patients with active early rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:48.

199. Fantini F, Sinigaglia L, Zeni S, Cagnoli M, Favalli E, Colombelli P. Short-term treatment with monoclonal anti-tumor necrosis factor-α antibody in refractory long-standing rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S227.

200. Finck B, Martin R, Fleischmann R, Moreland L, Schiff M, Bathon J. A phase III trial of etanercept vs methotrexate in early rheumatoid arthritis. *Arthritis Rheum* 1999;**42**(Suppl):S117.

201. Fleischmann R, Moreland L, Baumgartner S, Schiff M, Tindall E, Weaver A. Response to etanercept in rheumatoid arthritis patients over 65 years. A retrospective analysis of clinical trial results. *Arthritis Rheum* 1999;**42**(Suppl):S347.

202. Furst D, Weisman M, Paulus H, Bulpitt K, Weinblatt M, Polisson R. Neutralisation of TNF by lenercept (TNFr55-IgG1, Ro45-2081) in patients with rheumatoid arthritis treated for three months: results of an US phase II trial. *Arthritis Rheum* 1996;**39**(Suppl):S243.

203. Galaria N, Werth V, Schumacher H. Leucocytoclastic vasculitis due to etanercept. *J Rheumatol* 2000;**27**:2041–4.

204. Garrison L, McDonnell N. Etanercept: therapeutic use in patients with RA. *Ann Rheum Dis* 1999; **58** Suppl 1:165–9.

205. Geborek P, Saxne T. Clinical protocol for monitoring of targeted therapies in rheumatoid arthritis. *Rheumatology* 2000;**39**:1159–61.

206. Hammond A, Jeganathan N. Experience of anti-TNF treatment with infliximab (Remicade) and methotrexate in routine clinical practice over 40 weeks. *Rheumatology* 2001;**40**(Suppl):S51.

207. Hodgson R, Hayes J, Scott G, Storrs P, Smiley D, McKenna F. Predictors of early response to infliximab in resistant rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:166.

208. Hodgson R, Scott G, Storrs P, Hayes J, McKenna F. Insensitivity of ACR response criteria to detect clinical response with infliximab in resistant rheumatoid arthritis. *Ann Rheum Dis* 2000; **59** Suppl 1:166.

209. Kavanaugh A, Schaible T, DeWoody K, Marsters P, Dittrich K, Harriman G. Long-term follow-up of patients treated with infliximab (antiTNFα antibody) in clinical trials. *Arthritis Rheum* 1999;**42**(Suppl):S401.

210. Keystone E. The role of tumor necrosis factor antagonism in clinical practice. *J Rheumatol* 1999;**57**:22–8.

211. Kremer J, Weinblatt M, Fleischmann R, Bankhurst A, Burge D. Etanercept in addition to methotrexate in rheumatoid arthritis: long-term observations. *Arthritis Rheum* 2000;**43**(Suppl):S270.

212. Kremer J, Spencer-Green G, Hanna R, Korth-Bradley J. Enbrel (etanercept) pharmacokinetics in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S229.

213. Kuhne C, Zielinski S, Kekow M, Kekow J. Superior efficacy of etanercept therapy in rheumatoid arthritis when combined with methotrexate. *Arthritis Rheum* 2000;**43**(Suppl):S230.

214. Lampa J, Berg L, Harju A, Klareskog L, Padyukov L. Association of cytokine promoter polymorphisms with the clinical effect of soluble TNF receptor therapy in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S230.

215. Lipsky P, St Clair E, Furst D, Breedveld F, Smolen J, Kalden J. 54-week clinical and radiographic results from the ATTRACT trial: a phase III study of infliximab (Remicade™) in patients with active RA despite methotrexate. *Arthritis Rheum* 1999;**42**(Suppl):S401.

216. Lipsky P, van der Heijde D, St Clair E, Smolen J, Furst D, Kalden J. 102-week clinical and radiologic results from the ATTRACT trial: a 2-year, randomised, controlled, phase 3, trial of infliximab (Remicade) in patients with active RA despite methotrexate. *Arthritis Rheum* 2000;**43**(Suppl):S401.

217. Maini R, Smolen J, Breedveld F, Kalden J, St Clair E, Furst D. Anti-TNFα monoclonal antibody, infliximab (cA2,Remicade) in active rheumatoid arthritis combined with methotrexate therapy: Results of a phase III trial at 30 weeks. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:5.

218. Maini R, Smolen J, Breedveld F, Kalden J, St Clair E, Furst D. Long term (1 year) results of a placebo-controlled, randomised phase III, clinical trial of infliximab (cA2, Remicade™) combined with methotrexate in rheumatoid arthritis. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:216.

219. Maini R, van der Heijde D, Emery P, Breedveld F, Smolen J, Kalden J. Sustained clinical benefit and arrest of radiographic joint damage in patients with active rheumatoid arthritis treated with infliximab along with methotrexate (ATTRACT trial). *Ann Rheum Dis* 2000;**59** Suppl 1:36.

220. Maini R, van der Heijde D, St Clair W, Smolen J, Furst D, Kalden J, *et al.* Clinical and radiographic responses in a 2-year, randomised, controlled, phase 3 trial of infliximab (Remicade) in active RA despite MTX therapy. *Rheumatology* 2001;**40**(Suppl):S82.

221. Martin R, Weaver A, Keystone E, Moreland L, Finck B, Spencer-Green G. Comparison of area under the curve (AUC) of disease activity score (DAS) and numeric CR response (ACR-N) as measures of clinical improvement in clinical trials. *Ann Rheum Dis* 2000;**59** Suppl 1:43.

222. Martin R, Ruderman E, Fleischmann R, Moreland L, Schiff M, Bathon J. A phase III trial of etanercept vs methotrexate in early rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:47.

223. Marzo-Ortega H, Bingham S, Burns S, Buch M, Brown C, Ahmed K, *et al.* Analysis of the length of time taken to flare following discontinuation of infliximab therapy. *Rheumatology* 2001;**40**(Suppl):S33.

224. Miller M, Morton G, Anderson L, Keroach B, Radis C. One year community-based experience with etanercept in the treatment of rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S229.

225. Mohan N, Edwards E, Cupps T, Oliverio P, Siegel J. Demyelination diagnosed during etanercept (TNF receptor fusion protein) therapy. *Arthritis Rheum* 2000;**43**(Suppl):S228.

226. Moreland L, Baumgartner S, Tindall E, Schiff M, Fleischmann R, Weaver A. Long-term safety and efficacy of etanercept (Embrel® in DMARD refractory rheumatoid arthritis. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:216.

227. Moreland L, Cohen S, Baumgartner S, Schiff M, Tindall E, Burge D. Long-term use of etanercept in patients with DMARD-refractory rheumatoid arthritis. *Arthritis Rheum* 1999;**42**(Suppl):S401.

228. Moreland L, Cohen S, Baumgartner S, Schiff M, Tindall E, Burge D. Long-term use of etanercept in patients with rheumatoid arthritis: North American experience. *Ann Rheum Dis* 2000;**59** Suppl 1:157.

229. Moreland L, McCabe D, Caldwell J, Sack M, Weisman M, Henry G. Phase I/II trial of recombinant methionyl human tumor necrosis factor binding protein PEGylated dimer in patients with active refractory rheumatoid arthritis. *J Rheumatol* 2000;**27**:601–9.

230. Moreland L, Cohen S, Baumgartner S, Schiff M, Tindall E, Bulpitt K. Long-term use of Enbrel in patients with DMARD-refractory rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S270.

231. Murphy F, Enzenauer R, Battafarano D, David-Bajar K. Etanercept associated injection-site reactions. *Arch Dermatol* 2000;**136**:556–7.

232. Ostrov B. Beneficial effect of etanercept on rheumatoid lymphedema. *Arthritis Rheum* 2001;**44**:240–1.

233. Padyukov L, Lampa J, Hermansson Y, Harju A, Klareskog L. Implication of cytokine gene polymorphisms in prediction of Enbrel treatment in rheumatoid arthritis patients. *Rheumatology* 2001;**40**(Suppl):S85.

234. Pedersen R, Wajdula J. A long-term, open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis: interim analysis of European experience. *Ann Rheum Dis* 2000;**59** Suppl 1:158.

235. Petefy C, Palmer W, Schweizer M, White D, Finck B. Comparison of etanercept vs methotrexate in early rheumatoid arthritis using gadolinium-enhanced magnetic resonance imaging. *Arthritis Rheum* 1999;**42**(Suppl):S241.

236. Qvistgaard E, Rogind H, Graff L, Bliddal H, Danneskiold-Samsoe B. Muscle function during treatment of rheumatoid arthritis with Enbrel. *Ann Rheum Dis* 2000;**59** Suppl 1:162.

237. Rau R, Simianer S, Weier R, Kroot E, van Riel P, den Broeder A, *et al.* Effective combination of the fully human anti-TNF body D2E7 and methotrexate in active rheumatoid arthritis. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:217.

238. Rau R, Herborn G, Sander O, van de Putte LBA, van Riel P, den Broeder A, *et al.* Long-term treatment with the fully human anti-TNF antibody D2E7 slows radiographic disease progression in rheumatoid arthritis. *Arthritis Rheum* 1999; **42**(Suppl):S400.

239. Richter C, Wanke L, Steinmetz J, Reinhold-Keller E, Gross W. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. *Rheumatology* 2000;**39**:1437–9.

240. Rogind H, Qvistgaard E, Graff L, Torp-Pedersen S, Bliddal H, Danneskiold B. Ultrasonographic changes in relation to clinical observations after treatment of rheumatoid arthritis with Enbrel (TNF-α receptor,TNR). XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:106.

241. Sandqvist G, Saxne T, Geborek P. Treatment with etanercept or infliximab improves hand function in patients with long-standing rheumatoid arthritis. *Rheumatology* 2001;**40**(Suppl):S32.

242. Schattenkirchner M, Wastlhuber J, Rau R, Herborn G, Kroot E, van Riel P. Long-term use of the fully human anti-TNF antibody D2E7 in combination with methotrexate in active rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S228.

243. Schiff M, Mease P, Weinblatt M, Moreland L, Burge D. Randomised controlled trial of 25 mg versus 50 mg Embrel (etanercept) twice weekly in rheumatoid arthritis (RA). *Arthritis Rheum* 2000;**43**(Suppl):S391.

244. Shergy W, Isern R, Cooley D, Harshbarger J, Huffstutter J, Smith D. Infliximab (Remicade™) ameliorates clinical signs and symptoms of rheumatoid arthritis within 48 hours: results of the PROMPT study. *Arthritis Rheum* 2000;**43**(Suppl):S227.

245. Sigidin Y, Loukina G, Skurkovich B. Double-blind placebo-controlled study of antibodies to interferon-γ versus antibodies to tumor necrosis factor α in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S290.

246. Sigidin Y, Loukina G, Skurkovich S, Skurkovich B. Randomised double-blind comparison of antibodies to interferon gamma (anti-IFN-gamma) versus antibodies to tumor necrosis factor alfa (anti-TNF) and placebo in rheumatoid arthritis. *Ann Rheum Dis* 2000;**59** Suppl 1:170.

247. Sigidin Y, Loukina G, Skurkovich S, Skurkovich B. Anti-interferon therapy of the rheumatic diseases. XIV European League Against Rheumatism (EULAR) Congress, Abstracts book. *Ann Rheum Dis* 1999:219.

248. Smolen J, Schaible T, DeWoody K, Marsters P, Dittrich K, Papandrikopoulou N. Long-term follow-up of patients treated with infliximab in clinical trials. *Ann Rheum Dis* 2000;**59** Suppl 1:164.

249. Somerville M, Price-Forbes A, Brooksby A, Leeder J, Merry P, Scott D, *et al.* TNFa therapy initiation audit: rationing on an equitable basis – The Norfolk and Norwich (N/N) experience. *Rheumatology* 2001;**40**(Suppl):S52.

250. Terslev L, Rogina H, Qvistgaard W, Torp-Pedersen S, Danneskiold-Samsoe B, Biddal H. Effects of long term treatment with Enbrel (TNF alpha receptor, TNR) on rheumatoid arthritis evaluated by ultrasonographic changes in relation to clinical observations. *Ann Rheum Dis* 2000;**59**(Suppl):S162.

251. Ulfgren A, Andersson U, Engstrom M, Klareskog L, Maini R, Taylor P. Systematic anti-TNFα therapy in rheumatoid arthritis down-regulates synovial TNFα formation. *Ann Rheum Dis* 2000;**59** Suppl 1:162–3.

252. van der Heijde D, Emery P, Lipsky P, Breedveld F, Smolen J, Kalden J. Consistent improvement in radiographic joint damage in patients with active rheumatoid arthritis treated with infliximab along with methotrexate. *Ann Rheum Dis* 2000; **59** Suppl 1:161.

253. van de Putte LBA, Rau R, Breedveld F, Kalden J, Malaise M, Schattenkirchner M. One year efficacy results of the fully human anti-TNF antibody D2E7 in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**(Suppl):S269.

254. van de Putte LBA, Rau R, Breedveld F, Kalden J, Malaise M, Schattenkirchner M. Efficacy of the fully human anti-TNF antibody D2E7 in rheumatoid arthritis. *Arthritis Rheum* 1999;**42**(Suppl):S400.

255. van de Putte LBA, van Riel PL, den Broeder A, Schattenkirchner M, Wastlhuber J, Rihl M. Long-term treatment with the fully human anti-TNF-antibody D2E7 slows radiographic disease progression in rheumatoid arthritis. *Arthritis Rheum* 1999;**42**(Suppl):S400.

256. Wagner C, Schantz A, LaSorda J, DiNoto D, Wang H, Marsters P. Human anti-chimeric antibody (HACA) responses to infliximab (Remicade™) in the ATTRACT clinical study of patients with active rheumatoid arthritis. *Arthritis Rheum* 1999;**42**(Suppl):S83.

257. Wajdula J, Pedersen R, Sanda M. A long-term open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis (interim analysis). *Arthritis Rheum* 2000;**43**(Suppl):S229.

258. Warris A, Bjorneklett A, Gaustad P. Invasive pulmonary aspergillosis associated with infliximab therapy. *N Engl J Med* 2001;**344**:1099–100.

259. Weisman M, Keystone E, Paulus H, Weinblatt M, Furst D, Moreland L. A dose escalation study designed to demonstrate the safety, tolerability, and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with methotrexate in patients with active RA. *Arthritis Rheum* 2000;**43**(Suppl):S391.

260. Yazici Y, Belostocki K, Erkan D, Mashenskya L, Harrison M. Increased disease activity in rheumatoid arthritis patients before and during one year of treatment with etanercept. *Arthritis Rheum* 2000;**43**(Suppl):S229.

261. Yelin E, Roepke L, Katz P. Long term impact of Enbrel on functional status of persons with RA. *Arthritis Rheum* 2001;**43**(Suppl):S147.

# Appendix 1

## Health Assessment Questionnaire[173]

| Patient label: | | | | Date: |
|---|---|---|---|---|
| We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form. | | | | |
| PLEASE TICK THE ONE RESPONSE THAT BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK | | | | |
| | Without ANY difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
| | Score = 0 | Score = 1 | Score = 2 | Score = 3 |
| **1. DRESSING & GROOMING – Are you able to:** | | | | |
| Dress yourself including tying shoelaces and doing buttons? | | | | |
| Shampoo your hair? | | | | |
| **2. RISING – Are you able to:** | | | | |
| Stand up from an armless straight chair? | | | | |
| Get in and out of bed? | | | | |
| **3. EATING – Are you able to:** | | | | |
| Cut your meat? | | | | |
| Lift a cup or glass to your mouth? | | | | |
| Open a new carton of milk (or soap powder)? | | | | |
| **4. WALKING – Are you able to:** | | | | |
| Walk outdoors on flat ground? | | | | |
| Climb up five steps? | | | | |

| PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES | | | |
|---|---|---|---|
| Cane | | Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.) | |
| Walking frame | | Built-up or special utensils | |
| Crutches | | Special or built-up chair | |
| Wheelchair | | Other (specify) | |

| PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON | | | |
|---|---|---|---|
| Dressing and grooming | | Eating | |
| Rising | | Walking | |

| | Without ANY difficulty | With SOME difficulty | With MUCH difficulty | Unable to do |
|---|---|---|---|---|
| | Score = 0 | Score = 1 | Score = 2 | Score = 3 |
| **5. HYGIENE – Are you able to:** | | | | |
| Wash and dry your entire body? | | | | |
| Take a bath? | | | | |
| Get on and off the toilet? | | | | |
| **6. REACH – Are you able to:** | | | | |
| Reach and get a 5 lb object (e.g. a bag of potatoes) from above your head? | | | | |
| Bend down to pick up clothing from the floor? | | | | |
| **7. GRIP – Are you able to:** | | | | |
| Open car doors? | | | | |
| Open jars which have been previously opened? | | | | |
| Turn taps on and off? | | | | |
| **8. ACTIVITIES – Are you able to:** | | | | |
| Run errands and shop? | | | | |
| Get in and out of a car? | | | | |
| Do chores such as vacuuming, housework or light gardening? | | | | |

| PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES: | | | |
|---|---|---|---|
| Raised toilet seat | | Jar opener (for jars previously opened) | |
| Bath seat | | Long-handled appliances for reach | |
| Bath rail | | Other (specify) | |

| PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON | | | |
|---|---|---|---|
| Hygiene | | Gripping and opening things | |
| Reach | | Errands and housework | |

## Scoring of HAQ

Add the maximum score for each of the 8 sections and divide by 8 to give a score between 0 and 3. If aid/device or help is needed the score for that activity automatically = 2 (unless 3 has already been ticked). Normal function = 0, most severely affected = 3.

# Appendix 2

# Assessment of response to DMARDs

## American College of Rheumatology (ACR) response criteria[61]

- Tender joint count
- Swollen joint count
- At least three of:
  - global disease activity assessed by observer
  - global disease activity assessed by patient
  - patient assessment of pain
  - physical disability score (e.g. HAQ)
  - acute phase response (e.g. ESR or CRP)

Response is defined as ACR20, ACR50 or ACR70, where the figures refer to percentage improvement in the clinical measures shown above.

## European League Against Rheumatism (EULAR) response criteria[174,175]

This measure is referred to as the DAS. Currently the DAS28, based on a simplified method, is favoured for use. The DAS28 is calculated from the following formula:

DAS28 = (0.555 × square root of tender joint count using 28 defined joints)
+ (0.284 × square root of swollen joint count using 28 defined joints)
+ [0.7 ln (ESR)]
+ (0.0142 × patient global assessment of disease activity on 0–10 VAS)

A working party for the BSR proposed that patients would require a score > 5.1, indicating highly active disease, to be eligible for anti-TNF therapies. In addition they defined a lack of response as being failure of DAS28 score to improve by > 1.2 or failure to achieve a DAS28 < 3.2.[97]

## Paulus response criteria[176]

Responses in four of six selected measures are required for improvement. Improvement by 20% or more in the following measures is required (the threshold for percentage improvement may be increased, e.g. to 50%, 70%, as for ACR responses):

- early morning stiffness
- ESR
- joint pain or tenderness score
- joint swelling score
- patient overall assessment of current disease severity improved by ≥ 2 grades on 5-point scale, or from grade 2 to 1
- physician overall assessment of current disease severity improved by ≥ 2 grades on 5-point scale, or from grade 2 to 1.

# Appendix 3

## ACR revised criteria for classification of functional status in RA[177]

| Class | Description |
|---|---|
| Class I | Completely able to perform usual activities of daily living (self-care, vocational and avocational) |
| Class II | Able to perform usual self-care and vocational activities, but limited in avocational activities |
| Class III | Able to perform usual self-care activities, but limited in vocational and avocational activities |
| Class IV | Limited ability to perform usual self-care, vocational and avocational activities |
| Usual self-care activities include dressing, feeding, bathing, grooming and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific | |

# Appendix 4

## Yield from MEDLINE and EMBASE searches

Date: 21-Mar-2001
Database: MEDLINE <1966 to present>

| Set | Search | Results |
|---|---|---|
| 1 | exp *Arthritis, rheumatoid/pc,dt, ec,th [Prevention & Control, Drug Therapy, Economics, Therapy] | 10,370 |
| 2 | exp *tumor necrosis factor/or "tumor necrosis factor".mp. | 38,112 |
| 3 | exp *receptors, tumor necrosis factor/or "receptor, tumor necrosis factor".mp. | 3,749 |
| 4 | "ANTI-TNF".mp. | 1,516 |
| 5 | "ANTI-TNF-ALPHA".mp. | 894 |
| 6 | "ANTI TUMOR NECROSIS FACTOR".mp. | 275 |
| 7 | "INFLIXIMAB".mp. | 70 |
| 8 | "REMICADE".mp. | 8 |
| 9 | "ENBREL".mp. | 7 |
| 10 | "ETANERCEPT".mp. | 49 |
| 11 | or/2-10 | 39,970 |
| 12 | 1 and 11 | 239 |
| 13 | Limit 12 to human | 229 |

Date: 21-Mar-2001
Database: EMBASE <1988 to present>

| Set | Search | Results |
|---|---|---|
| 1 | exp *Rheumatoid arthritis/ dm,dt,th [Disease Management, Drug Therapy, Therapy] | 7,822 |
| 2 | exp *tumor necrosis factor/or "tumor necrosis factor".mp. | 44,546 |
| 3 | exp *tumor necrosis factor alpha/or exp *tumor necrosis factor receptor/ | 13,629 |
| 4 | exp *tumor necrosis factor alpha antibody/or exp *tumor necrosis factor antibody/ or exp infliximab/ or "anti-tumor necrosis factor".mp. | 1,024 |
| 5 | exp Etanercept/ | 270 |
| 6 | "REMICADE".mp. | 147 |
| 7 | "ENBREL".mp. | 126 |
| 8 | "ANTI-TNF$".mp. | 1,577 |
| 9 | "ANTI-TNF-ALPHA".mp. | 697 |
| 10 | or/2-9 | 44,847 |
| 11 | 1 and 10 | 538 |
| 12 | limit 11 to human | 502 |

# Appendix 5

## Notes on radiographic scoring methods

### Modified Sharp method[125]

Radiographs of hands, wrists and feet are scored. In all, 46 joints are scored for erosions. Erosions are scored on a 6-point scale. A score of 0 indicates no new erosion and no worsening of an existing erosion. Each point increase indicates occurrence of a new erosion or 20% worsening of an existing erosion. In all, 42 joints are scored for narrowing on a 5-point scale. A score of 0 indicates no narrowing, 1 indicates minimal narrowing, 2 loss of 50% of the joint space, 3 loss of 75% of the joint space and 4 complete loss of the joint space. Scores for joint space narrowing and erosions are summed to give a total Sharp score.

### van der Heijde modification of Sharp method[124]

As above, radiographs of hands, wrists and feet are scored. In this case 44 joints are scored for erosions, 32 in the hands and wrists, and 12 in the feet. Each hand or wrist joint is scored on a 5-point scale according to the surface area involved – 0 indicates no erosion, 5 extensive loss of bone from more than one-half of the articulating bone. Each foot joint is scored a maximum of 10. Maximum erosion score for hands is 160 and for feet 120.

Joint space narrowing is scored in 30 hand and wrist joints, and 10 joints in the feet. A 4-point scoring system is used. A score of 0 indicates no narrowing, a score of 1 is focal or doubtful narrowing, 2 is general narrowing of < 50%, 3 is general narrowing of > 50% of the original joint space and 4 is bony ankylosis or complete luxation. Maximum score for joint space narrowing of hands is 120 and for feet 48.

# Appendix 6

## List of included and excluded studies

| | Citation | Inclusion? | Reason for exclusion/comment |
|---|---|---|---|
| 1 | Antoni *et al.*, 2000[118] | Yes | Abstract. ATTRACT study. DAS data |
| 2 | Antoni *et al.*, 1999[178] | No | Abstract. ATTRACT study. Subgroup analysis |
| 3 | Barrera *et al.*, 2000[179] | No | Abstract. Drug survival on D2E7 |
| 4 | Barrera *et al.*, 2000[180] | No | Abstract. Observational study (D2E7) |
| 5 | Barrera *et al.*, 1999[181] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 6 | Bathon *et al.*, 2000[122] | Yes | ERA trial. Etanercept vs methotrexate (1 year) |
| 7 | Baumgartner *et al.*, 2000[182] | No | Abstract. *Post hoc* comparison of responses to etanercept in early vs late RA |
| 8 | Breedveld *et al.*, 1999[183] | No | Abstract. ATTRACT study. Superseded |
| 9 | Buch *et al.*, 2001[184] | No | Abstract. Report of adverse events from a single centre |
| 10 | Caldwell *et al.*, 2000[185] | No | Abstract. Did not meet inclusion criteria (anti-TNF agent PEG sTNFR1 [p55]) |
| 11 | Centocor, 2001[117] | No | Confidential: Clinical Study Report. Did not meet inclusion criteria |
| 12 | Charles *et al.*, 2000[129] | No | Observations of anti-dsDNA antibodies after infliximab |
| 13 | Conaghan *et al.*, 2001[186] | No | Abstract. Observational study of infliximab |
| 14 | Cope and Maini, 1995[187] | No | Review article |
| 15 | Crnkic *et al.*, 2000[188] | No | Abstract. Observational study (etanercept and infliximab) |
| 16 | Crnkic *et al.*, 2001[189] | No | Abstract. Observational study (etanercept, infliximab and leflunomide) |
| 17 | Crnkic *et al.*, 2001[164] | No | Abstract. Observational study (etanercept, infliximab and leflunomide) |
| 18 | Davis *et al.*, 2000[190] | No | Abstract. Did not meet inclusion criteria (anti-TNF agent PEG sTNFR1 [p55]) |
| 19 | den Broeder *et al.*, 2000[191] | No | Abstract. Observational study (D2E7) |
| 20 | den Broeder *et al.*, 2000[192] | No | Abstract. Observational study (D2E7) |
| 21 | den Broeder *et al.*, 1999[193] | No | Abstract. Observational study (D2E7) |
| 22 | den Broeder *et al.*, 2000[139] | No | Abstract. Duplicated observational study (D2E7) |
| 23 | Edwards, 1999[109] | No | Review article |
| 24 | Eijsbouts *et al.*, 2000[194] | No | Abstract. Did not meet inclusion criteria (D2E7 & TNFR:Fc fusion protein Ro 45-2081 study) |
| 25 | Elliott *et al.*, 1994[113] | Yes | RCT (total 73 patients) of infliximab (cA2) |
| 26 | Elliott *et al.*, 1993[195] | No | Observational study (infliximab, cA2) |
| 27 | Elliott *et al.*, 1994[196] | No | Observational study (infliximab, cA2) |
| 28 | El-Rafie *et al.*, 2001[197] | No | Abstract. Observational study (infliximab) |
| 29 | Emery *et al.*, 2000[198] | No | Abstract. ATTRACT study. Superseded |
| 30 | Ericson *et al.*, 1999[137] | No | Abstract. See Wyeth Laboratories[135,136] |
| 31 | Fantini *et al.*, 2000[199] | No | Abstract. Observational study (infliximab) |
| 32 | Finck *et al.*, 1999[200] | No | Abstract. Enbrel ERA trial. Superseded |
| 33 | Fleischmann *et al.*, 1999[201] | No | Abstract. *Post hoc* analysis (etanercept) |
| 34 | Furst *et al.*, 1996[202] | No | Abstract. Did not meet inclusion criteria (lenercept study) |
| 35 | Galaria *et al.*, 2000[203] | No | Case report |
| 36 | Garrison and McDonnell, 1999[204] | No | Review article (etanercept) |
| 37 | Geborek and Saxne, 2000[205] | No | Observational study (infliximab, etanercept) |
| 38 | Genovese *et al.*, 2000[140] | No | Abstract. Open-label extension of 1-year RCT (see Bathon *et al.*, above). Observations at 2 years |

*continued*

| | Citation | Inclusion? | Reason for exclusion/comment |
|---|---|---|---|
| 39 | Gershon *et al.*, 2000[127] | No | Abstract. Post-licensing reports of infections (etanercept and infliximab) |
| 40 | Hammond and Jeganathan, 2001[206] | No | Abstract. Observational study (infliximab) |
| 41 | Hodgson *et al.*, 2000[207] | No | Abstract. Observational study (infliximab) |
| 42 | Hodgson *et al.*, 2000[208] | No | Abstract. Observational study (infliximab) |
| 43 | Kavanaugh *et al.*, 2000[119] | Yes | ATTRACT study. Data combined with other data |
| 44 | Kavanaugh *et al.*, 2000[106] | Yes | Placebo-controlled study of 28 patients (infliximab) |
| 45 | Kavanaugh *et al.*, 1999[209] | No | Observational study (infliximab) |
| 46 | Keenan *et al.*, 2001[126] | No | Post-marketing reports of fungal infections with infliximab |
| 47 | Kempeni, 1999[108] | No | Review article |
| 48 | Keystone, 1999[210] | No | Review article |
| 49 | Kremer *et al.*, 2000[211] | No | Abstract. Observational study (etanercept) |
| 50 | Kremer *et al.*, 2000[212] | No | Abstract. Observational study (etanercept) |
| 51 | Kuhne *et al.*, 2000[213] | No | Abstract. Observational study (etanercept) |
| 52 | Kvein *et al.*, 1999[103] | No | Abstract. Cost estimates for anti-TNF therapies |
| 53 | Lampa *et al.*, 2000[214] | No | Abstract. Observational study (etanercept) |
| 54 | Lipsky *et al.*, 1999[215] | No | Abstract. Data superseded |
| 55 | Lipsky *et al.*, 2000[116] | Yes | ATTRACT study. 1-year data |
| 56 | Lipsky *et al.*, 2000[216] | No | Abstract. ATTRACT study (2-year data). Did not meet inclusion criteria |
| 57 | Lukina *et al.*, 1998[111] | No | Did not meet inclusion criteria (novel polyclonal anti-TNF agent) |
| 58 | Maini *et al.*, 1998[114] | Yes | Phase II study of infliximab |
| 59 | Maini *et al.*, 1999[217] | No | Abstract. ATTRACT study. Data superseded |
| 60 | Maini *et al.*, 1999[218] | No | Abstract. ATTRACT study. Superseded |
| 61 | Maini *et al.*, 1999[115] | Yes | ATTRACT study. Data combined with other data |
| 62 | Maini *et al.*, 2000[219] | No | Abstract. ATTRACT study. Data superseded |
| 63 | Maini *et al.*, 2001[220] | No | Abstract. ATTRACT study (2-year data). Did not meet inclusion criteria |
| 64 | Martin *et al.*, 2000[221] | No | Abstract. Etanercept studies. Data duplication |
| 65 | Martin *et al.*, 2000[222] | No | Abstract. Etanercept vs methotrexate. Data superseded |
| 66 | Marzo-Ortega *et al.*, 2001[223] | No | Abstract. Observational study (infliximab) |
| 67 | Mathias *et al.*, 2000[138] | Yes | Data combined with Moreland *et al.* |
| 68 | Miller *et al.*, 2000[224] | No | Abstract. Observational study (etanercept) |
| 69 | Mohan *et al.*, 2000[225] | No | Abstract. Case reports |
| 70 | Moreland *et al.*, 1996[107] | Yes | Preliminary toxicity and dose-finding study |
| 71 | Moreland *et al.*, 1997[131] | Yes | Placebo vs etanercept at 3 different doses (12-week) |
| 72 | Moreland *et al.*, 1999[132] | Yes | Placebo vs etanercept 10 or 25 mg (26-week) |
| 73 | Moreland *et al.*, 1999[226] | No | Abstract. Observational data (etanercept) |
| 74 | Moreland *et al.*, 1999[227] | No | Abstract. Observational data (etanercept). Superseded |
| 75 | Moreland, 1999[25] | No | Review article |
| 76 | Moreland *et al.*, 2000[228] | No | Abstract. Observational data (etanercept) |
| 77 | Moreland *et al.*, 2000[229] | No | Did not meet inclusion criteria (TNF binding protein, PEGylated dimer) |
| 78 | Moreland *et al.*, 2000[230] | No | Abstract. Observational data over 2 years (etanercept) |
| 79 | Murphy *et al.*, 2000[231] | No | Case report |
| 80 | Ostrov, 2001[232] | No | Case report |
| 81 | Padyukov *et al.*, 2001[233] | No | Abstract. Observational study (etanercept) |
| 82 | Pedersen and Wajdula, 2000[234] | No | Abstract. Observational data (etanercept) |
| 83 | Petefy *et al.*, 1999[235] | No | Abstract. Preliminary data on magnetic resonance imaging, clinical data superseded |
| 84 | Qvistgaard *et al.*, 2000[236] | No | Abstract. Observational study of muscle function (etanercept) |
| 85 | Rankin *et al.*, 1995[110] | No | Did not meet inclusion criteria (anti-TNF agent CDP571) |

*continued*

| Citation | Inclusion? | Reason for exclusion/comment |
|---|---|---|
| 86 Rau *et al*., 1999[237] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 87 Rau *et al*., 1999[238] | No | Abstract. Observational study (D2E7) |
| 88 Richter *et al*., 2000[239] | No | Case report |
| 89 Røgind *et al*., 1999[240] | No | Abstract. Data duplication. Ultrasound observations in a subgroup |
| 90 Sander and Rau, 1998[112] | No | Did not meet inclusion criteria (anti-TNF agent TNFR55-IgG1) |
| 91 Sandqvist *et al*., 2001[241] | No | Abstract. Observational study (infliximab and etanercept) |
| 92 Schattenkirchner *et al*., 2000[242] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 93 Schiff *et al*., 2000[243] | No | Abstract. Comparison of 2 doses of etanercept |
| 94 Shergy *et al*., 2000[244] | No | Abstract. Observational study of rapidity of response to infliximab |
| 95 Sigidin *et al*., 2000[245] | No | Abstract. Did not meet inclusion criteria (polyclonal anti-TNF agent, see Lukina *et al*. above) |
| 96 Sigidin *et al*., 2000[246] | No | Abstract. Did not meet inclusion criteria, as above |
| 97 Sigidin *et al*., 1999[247] | No | Abstract. Did not meet inclusion criteria (polyclonal anti-TNF agent, see Lukina *et al*. above) |
| 98 Smolen *et al*., 1999[130] | No | Abstract. Case reports. Infliximab |
| 99 Smolen *et al*., 2000[248] | No | Abstract. Observational data of infliximab trials |
| 100 Somerville *et al*., 2001[249] | No | Abstract. Priority setting for anti-TNF therapies |
| 101 Terslev *et al*., 2000[250] | No | Abstract. Observational study of ultrasound changes (etanercept) |
| 102 Ulfgren *et al*., 2000[251] | No | Abstract. Observational study (infliximab) |
| 103 van der Heijde *et al*., 2000[252] | No | Abstract. ATTRACT study. Data superseded |
| 104 van de Putte *et al*., 2000[253] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 105 van de Putte *et al*., 1999[254] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 106 van de Putte *et al*., 1999[255] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 107 Wagner *et al*., 1999[256] | No | Abstract. ATTRACT study. Preliminary report of anti-chimeric antibody responses to infliximab |
| 108 Wajdula, 2000[134] | Yes | The Etanercept European Investigators Network study. See Ericson *et al*., and Wyeth Laboratories Clinical Study Report[136] |
| 109 Wajdula *et al*., 2000[257] | No | Abstract. Observational study (etanercept) |
| 110 Warris *et al*., 2001[258] | No | Case report of aspergillosis (infliximab) |
| 111 Weinblatt *et al*., 1999[133] | Yes | Etanercept and concomitant methotrexate 24-week study |
| 112 Weisman *et al*., 2000[259] | No | Abstract. Did not meet inclusion criteria (D2E7) |
| 113 Wyeth Laboratories Research, 2000[123] | Yes | Confidential: Internal study report. Protocol 16.0012, see Bathon *et al*.[122] |
| 114 Wyeth Laboratories Research, 2001[136] | Yes | Confidential: Internal clinical written summary of key etanercept trials. Data combined with other included sources |
| 115 Wyeth Laboratories Research, 2000[135] | Yes | Confidential: Internal clinical written summary. Protocol 0881A1-300-EU |
| 116 Yazici *et al*., 2000[260] | No | Abstract. Observational study (etanercept) |
| 117 Yelin *et al*., 2001[261] | No | Abstract. Observational study (etanercept) |

# Appendix 7

## Etanercept clinical trials planned or in progress

| Protocol no. | Study title | Duration of treatment | No. of patients | Start date | Location |
|---|---|---|---|---|---|
| ***Rheumatoid arthritis studies*** | | | | | |
| 0881A-100502 | Rheumatoid Arthritis Pharmacoeconomics and Outcomes Longitudinal Observational Study (RAPALO) | 5 years | 1000 | Jan 1999 | USA |
| 0881A-100715 | Swiss clinical quality control management project | 2 years | 1000 | TBD | Switzerland |
| 0881A-100748 | Single joint intra-articular injection of Enbrel for RA | 3 months | 60 | Oct 2000 | Taiwan |
| 0881A-100093 | A double-blind, randomised, comparative, placebo-controlled study on the efficacy and safety of methotrexate + etanercept vs methotrexate plus placebo in patients with active RA | 1 month | 25 | TBD | Denmark |
| 0881A-100790 | International Outcomes Registry for Enbrel | 5 years | 2500 | TBD | |
| 0881A-100149 | Open-label evaluation of the efficacy and safety of Etanercept in Common Rheumatology Usage (ECRU) | 4 months | 2000 | Dec 1999 | Multinational |
| 0881A-100795 | The role of anti-TNF therapy with etanercept in the prevention of rheumatoid cachexia | 12 months | 50 | Jun 2001 | UK |
| 0881A-100844 | A naturalistic study to determine the clinical efficacy, safety and effects on quality of life of etanercept in normal clinical practice in the UK | 12 months | 100 | Sep 2000 | UK |
| 881A-100930 | The role of self-efficacy in the administration of Enbrel | 3 months | 30 | TBD | UK |
| 881A-100931 | The role of TNF$\alpha$ and anti-TNF$\alpha$ therapy on neutrophil function in RA | 6 months | 20 | Jun 2001 | UK |
| 881A-100906 | Study to assess the efficacy of etanercept with synovial analysis in patients with rheumatoid arthritis who have failed treatment with infliximab | 4 months | 35 | Jun 2001 | UK |

# Studies in other rheumatic diseases

## Etanercept clinical trials

| Protocol no. | Study title | Duration of treatment | No. of patients | Start date | Location |
|---|---|---|---|---|---|
| ***Rheumatoid arthritis studies*** | | | | | |
| 0881A1-301-EU | Open-label safety study of etanercept in patients with rheumatoid arthritis | 4 years | 549 | Apr 1998 | Europe |
| 0881A1-308-AU/EU | A double-blind study evaluating the efficacy and safety of the combination of etanercept and methotrexate in comparison to etanercept alone or methotrexate alone in rheumatoid arthritis patients | up to 19 months | 615* | Oct 2000 | Australia, Europe, Israel |
| 0881A1-309-AU/EU | A 6-month, double-blind comparison of etanercept, sulphasalazine and the combination of etanercept and sulphasalazine in rheumatoid arthritis patients with an inadequate response to sulphasalazine | Up to 15 months | 250* | Oct 2000 | Australia, Europe |
| 16.0018 | Open-label extension treatment with TNFR:Fc for participating patients in TNFR:Fc clinical trials | 5 years | 638 | Jul 1997 | North America |
| 16.0023 | Open-label extension treatment with TNFR:Fc for participating patients in TNFR:Fc clinical trial 16.0012 | 1 year or more (TBD†) | 466 | Mar 1999 | North America |
| 16.0029 | Double-blind, randomised, placebo-controlled study of ENBREL (etanercept) in the treatment of rheumatoid arthritis subjects with comorbid disorders | 16 weeks | 1000* | Apr 2000 | North America |
| 0881A1-202-JA | Phase II, double-blind, dose–response comparative study of TNR-001 in rheumatoid arthritis | 12 weeks | 150* | Feb 2001 | Japan |
| 0881A1-310-JA | Open-label extension treatment for patients participating in study 0881A1-202-JA | TBD | 150* | May 2001 (expected) | Japan |

*TBD, to be determined*

* *For those studies currently enrolling, number of patients is the number planned*

One other trial of anti-TNF identified from National Research register:
Lead researcher – Professor Paul Emery, Rheumatology & Rehabilitation Unit, The General Infirmary Leeds, Great George Street, Leeds LS1 3EX, UK

A randomised study using magnetic resonance imaging to evaluate the effectiveness of infliximab in combination with methotrexate in early, poor prognosis rheumatoid arthritis patients. NRR project N0436061552

End date 01/10/2001

Schering-Plough were not able to give any specific information in correspondence

# Appendix 8

## Infliximab study outcomes. Individual measures of disease activity

| Study | SJC (0–66)* | | TJC (0–68)* | | Pain score patient (0–10) | | GS patient (0–10) | | GS physician (0–10) | | CRP (mg/dL) | | ESR (mm/h) | | HAQ (0–3) | | EMS (minutes) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| ***ATTRACT study, 2000,[116] 54-week data***† | | | | | | | | | | | | | | | | | | |
| Placebo ($n$ = 88 at baseline, $n \approx$ 69 week 54) | 21 | 15 | 31 | 17 | 6.3 | 4.9 | 6.0 | 4.9 | 6.2 | 4.0 | 4.0 | 2.8 | 49 | 41 | 1.7 | 1.4 | 199 | 96 |
| Infliximab 3 mg/kg every 8 weeks ($n$ = 86 at baseline, $n \approx$ 77 week 54) | 22 | 10 | 32 | 13 | 6.8 | 3.9 | 6.4 | 3.7 | 6.0 | 2.8 | 3.9 | 1.6 | 49 | 27 | 1.8 | 1.3 | 164 | 51 |
| Infliximab 3 mg/kg every 4 weeks ($n$ = 86 at baseline, $n \approx$ 80 week 54) | 21 | 9 | 31 | 13 | 6.2 | 3.5 | 5.9 | 3.4 | 6.0 | 2.3 | 3.5 | 1.5 | 52 | 31 | 1.7 | 1.2 | 186 | 51 |
| Infliximab 10 mg/kg every 8 weeks ($n$ = 87 at baseline, $n \approx$ 82 week 54) | 23 | 8 | 32 | 11 | 6.6 | 3.1 | 6.3 | 3.1 | 6.1 | 2.5 | 3.3 | 1.2 | 50 | 28 | 1.7 | 1.1 | 226 | 58 |
| Infliximab 10 mg/kg every 4 weeks ($n$ = 81 at baseline, $n \approx$ 74 week 54) | 24 | 8 | 34 | 12 | 6.2 | 3.6 | 5.9 | 3.6 | 5.9 | 2.5 | 4.2 | 1.1 | 49 | 29 | 1.7 | 1.2 | 181 | 49 |
| ***Elliott* et al., *1994,[113] 4-week data*** | | | | | | | (0–5) | (0–5) | (0–5) | (0–5) | | | | | | | | |
| Placebo x 1 | 23 | 23 | 28 | 26 | 6.8 | 6.9 | 3.8 | 3.8 | 3.7 | 3.6 | 6.2 | 6.0 | 63 | 65 | | | 182 | 172 |
| Infliximab 1 mg/kg x 1 | 21 | 13 | 29 | 17 | 6.6 | 4.2 | 3.7 | 3.0 | 3.7 | 3.0 | 6.7 | 5.8 | 58 | 52 | NR | NR | 142 | 100 |
| Infliximab 10 mg/kg x 1 | 22 | 9 | 28 | 11 | 6.7 | 2.5 | 3.6 | 2.6 | 3.6 | 2.2 | 6.4 | 3.5 | 63 | 43 | | | 143 | 8 |
| ***Maini* et al., *1998,[114] 6-week data***‡ | | | | | | | | | | | | | | | | | | |
| Placebo + MTX 7.5 mg | 17 | 18 | 28 | 25 | 6.7 | – | 6.9 | – | 7.6 | – | 5.1 | 6.8 | 50 | – | 2.0 | – | | |
| Infliximab 1 mg/kg + MTX 7.5 mg | 16 | 4 | 17 | 5 | 6.5 | – | 4.9 | – | 7.1 | – | 3.2 | 1.4 | 44 | – | 1.4 | – | | |
| Infliximab 1 mg/kg, no MTX | 20 | 9.5 | 33 | 11 | 5.7 | – | 5.2 | – | 7.3 | – | 5.3 | 4.4 | 46 | – | 1.4 | – | | |
| Infliximab 3 mg/kg + MTX 7.5 mg | 16 | 6 | 21 | 9 | 6.0 | – | 6.5 | – | 6.3 | – | 4.2 | 1.2 | 60 | – | 2.0 | – | | |
| Infliximab 3 mg/kg, no MTX | 17 | 7 | 31 | 9 | 5.9 | – | 5.8 | – | 7.3 | – | 1.8 | 1.6 | 31 | – | 1.8 | – | | |
| Infliximab 10 mg/kg + MTX 7.5 mg | 20 | 66 | 26 | 4 | 6.2 | – | 5.8 | – | 7.2 | – | 3.5 | 1.0 | 55 | – | 1.9 | – | | |
| Infliximab 10 mg/kg, no MTX | 19 | | 23 | 10 | 7.1 | – | 6.9 | – | 7.1 | – | 4.5 | 2.8 | 44 | – | 1.9 | – | | |

*GS, global score*

* *Number of joints assessed for swelling (SJC) or tenderness (TJC) except where indicated otherwise. Scores are in the range 0 to 58 for SJC and 0 to 60 for TJC in Elliott* et al.[113]

† *All patients also received MTX. Data shown are mean values obtained from copies of tables included in a confidential internal report.[121] Numbers of patients evaluated at week 54 shows that loss of data occurred for up to 26% of patients (e.g. ESR assessed post-treatment)*

‡ *The 6-week time point was chosen because figure 2 in this study shows placebo data terminating at 6 weeks. Data at 6 weeks were estimated from figure 2. Median duration of response for the groups shown were: placebo (with MTX) 0 weeks, infliximab 1 mg/kg (no MTX) 2.6 weeks, infliximab 1 mg/kg (with MTX) 16.5 weeks, infliximab 3 mg/kg (no MTX) 17.2 weeks, infliximab 3 mg/kg (with MTX) 16.5 weeks, infliximab 10 mg/kg (no MTX) 10 weeks, infliximab 10 mg/kg (with MTX) > 18 weeks*

# Appendix 9

## Etanercept study outcomes. Individual measures of disease activity

| Study | SJC (0–68)* | | TJC (0–71)* | | Pain score patient (0–10) | | Global score (0–10) | | | | CRP (mg/dL) | | ESR (mm/h) | | HAQ (0–3)† | | EMS (minutes) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Patient | | Physcian | | | | | | | | | |
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| ***Moreland* et al., *1997*[129†]** | | | | | | | | | | | | | | | | | | |
| Placebo twice a week, *n* = 44 | 22 | 17 | 29 | 22 | 6.4 | 6.1 | 6.7 | 6.2 | 7.0 | 5.9 | 3.9 | 2.6 | 40 | 40 | 146 | 141 | 294 | 246 |
| Etanercept 0.25 mg/m$^2$ twice a week, *n* = 46 | 24 | 19 | 32 | 24 | 6.9 | 5.6 | 7.1 | 5.8 | 7.4 | 5.6 | 4.1 | 2.4 | 44 | 39 | 153 | 137 | 258 | 318 |
| Etanercept 2 mg/m$^2$ twice a week, *n* = 46 | 24 | 17 | 32 | 17 | 6.7 | 4.6 | 6.9 | 4.6 | 7.2 | 4.3 | 3.6 | 2.0 | 36 | 27 | 138 | 123 | 312 | 156 |
| Etanercept 16 mg/m$^2$ twice a week, *n* = 44 | 24 | 11 | 30 | 13 | 6.3 | 3.1 | 6.5 | 3.2 | 6.5 | 2.7 | 3.6 | 0.9 | 35 | 21 | 135 | 104 | 294 | 66 |
| ***Moreland* et al., *1999*[130]** | | | | | | | | | | | | | | | | | | |
| Placebo twice a week, *n* = 80 | 25 | 27 | 35 | 33 | 6.5 | 7.9 | 6.9 | 7.1 | 6.9 | 6.8 | 4.1 | 12.6 | 39 | 46 | 1.7 | 1.6 | 288 | 366 |
| Etanercept 10 mg twice a week, *n* = 76 | 25 | 14 | 34 | 19 | 6.6 | 4.0 | 6.9 | 4.8 | 6.9 | 4.6 | 5.3 | 6.3 | 44 | 40 | 1.8 | 1.2 | 264 | 174 |
| Etanercept 25 mg twice a week, *n* = 78 | 25 | 13 | 33 | 15 | 6.7 | 3.1 | 7.0 | 3.8 | 6.9 | 3.9 | 4.7 | 3.2 | 35 | 29 | 1.6 | 1.1 | 300 | 261 |
| ***Weinblatt* et al., *1999*, [131] *24-week study*** | | | | | | | | | | | | | | | | | | |
| Placebo + MTX, *n* = 30 | 17 | 11 | 28 | 17 | 5.6 | 4.4 | 6.0 | 4.0 | 6.5 | 4.0 | 2.6 | 1.6 | 36 | 30 | 1.5 | 1.1 | 102 | 75 |
| Etanercept 25 mg twice a week + MTX, *n* = 59 | 20 | 6 | 28 | 7 | 5.0 | 1.8 | 6.0 | 2.0 | 6.0 | 2.0 | 2.2 | 0.5 | 25 | 15 | 1.5 | 0.8 | 90 | 10 |
| ***ERA trial, 2000*, [134–136] *52-week data*** | | | | | | | | | | | | | | | | | | |
| MTX (20 mg/week by week 8), *n* = 217 | 24 | 10 | 30 | 12 | 5.6 | 2.4 | 6.1 | 2.9 | 6.0 | 2.5 | 2.4 | 0.6 | 35 | 18 | 1.4 | 0.7 | 222 | 36 |
| Etanercept 10 mg twice a week, *n* = 208 | 24 | 11 | 31 | 13 | 5.6 | 3.2 | 6.1 | 3.8 | 6.3 | 3.0 | 2.5 | 0.6 | 35 | 24 | 1.4 | 0.9 | 222 | 60 |
| Etanercept 25 mg twice a week, *n* = 207 | 24 | 9 | 31 | 11 | 5.9 | 2.7 | 6.1 | 3.3 | 6.2 | 2.3 | 2.0 | 0.5 | 34 | 20 | 1.5 | 0.7 | 228 | 60 |
| ***The European Etanercept Investigators Group, 2000*[132,133,137]** | | | | | | | | | | | | | | | | | | |
| Placebo, *n* = 105 | 22 | 18 | 31 | 26 | 6.6 | 6.5 | 6.9 | 6.7 | 6.8 | 6.3 | 4.6 | 6.1 | 46 | 55 | 1.8 | 1.9 | 256 | 247 |
| Etanercept 10 mg/week, *n* = 122 | 23 | 14 | 31 | 18 | 6.5 | 4.3 | 6.8 | 4.6 | 6.7 | 4.4 | 4.9 | 3.5 | 44 | 37 | 1.8 | 1.4 | 217 | 162 |
| Etanercept 10 mg twice a week, *n* = 110 | 22 | 11 | 31 | 16 | 6.4 | 3.6 | 6.6 | 3.8 | 6.3 | 3.5 | 3.9 | 2.6 | 42 | 34 | 1.8 | 1.2 | 227 | 164 |
| Etanercept 25 mg/week, *n* = 111 | 22 | 10 | 31 | 15 | 6.5 | 3.7 | 6.8 | 4.1 | 6.7 | 3.6 | 4.5 | 2.7 | 43 | 33 | 1.8 | 1.2 | 223 | 189 |
| Etanercept 25 mg twice a week, *n* = 111 | 22 | 10 | 31 | 13 | 6.6 | 3.4 | 6.9 | 3.8 | 6.7 | 3.3 | 4.9 | 3.2 | 48 | 34 | 1.9 | 1.3 | 203 | 136 |

*All values are mean except for all shown data in Weinblatt* et al.*, and ESR and CRP in the ERA trial*

* *Figures shown in brackets are the number of joints assessed. For SJC The European Etanercept Investigators Study counted 0 to 66 and for TJC 0 to 68*

† *Values in Moreland* et al.*, 12-week study are from a modified version of HAQ with additional questions assessing physical function and psychological status.*[261] *Score range quoted is 45–245 however a communication from Wyeth Laboratories indicates that this is an error. The score range should be 53–249*[269]

# Health Technology Assessment Programme

## Prioritisation Strategy Group

**Members**

**Chair,**
**Professor Kent Woods**,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Professor Bruce Campbell,
Consultant Vascular
& General Surgeon,
Royal Devon & Exeter Hospital

Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing,
University of Bristol

Dr John Reynolds,
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Dr Ron Zimmern,
Director, Public Health
Genetics Unit,
Strangeways Research
Laboratories, Cambridge

## HTA Commissioning Board

**Members**

**Programme Director,**
**Professor Kent Woods**,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

**Chair,**
**Professor Shah Ebrahim,**
Professor in Epidemiology
of Ageing,
University of Bristol

**Deputy Chair,**
**Professor Jon Nicholl,**
Director, Medical Care
Research Unit,
University of Sheffield

Professor Douglas Altman,
Director, ICRF Medical
Statistics Group,
University of Oxford

Professor John Bond,
Director, Centre for Health
Services Research, University
of Newcastle-upon-Tyne

Professor John Brazier,
Director of Health Economics,
University of Sheffield

Dr Andrew Briggs,
Research Fellow,
Institute of Health Sciences,
University of Oxford

Ms Christine Clark,
Freelance Medical Writer,
Bury, Lancs

Professor Martin Eccles,
Professor of
Clinical Effectiveness,
University of Newcastle-
upon-Tyne

Dr Andrew Farmer,
General Practitioner &
NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Adrian Grant,
Director, Health Services
Research Unit,
University of Aberdeen

Dr Alastair Gray,
Director, Health Economics
Research Centre,
Institute of Health Sciences,
University of Oxford

Professor Mark Haggard,
Director, MRC Institute
of Hearing Research,
University of Nottingham

Professor Jenny Hewison,
Academic Unit of Psychiatry
& Behavioural Sciences,
University of Leeds

Professor Peter Jones,
University Department
of Psychiatry,
University of Cambridge

Professor Alison Kitson,
Director, Royal College of
Nursing Institute, London

Professor Sarah Lamb,
Research Professor
in Physiotherapy,
University of Coventry

Dr Donna Lamping,
Head, Health Services
Research Unit,
London School of Hygiene
& Tropical Medicine

Professor David Neal,
Department of Surgery,
University of Newcastle-
upon-Tyne

Professor Tim Peters,
Social Medicine,
University of Bristol

Professor Martin Severs,
Professor in Elderly
Health Care,
University of Portsmouth

Dr Jonathan Shapiro,
Senior Fellow, Health Services
Management Centre,
Birmingham

Dr Sarah Stewart-Brown,
Director, Health Services
Research Unit,
University of Oxford

Dr Gillian Vivian, Consultant
in Nuclear Medicine &
Radiology, Royal Cornwall
Hospitals Trust, Truro

*continued*

## Diagnostic Technologies & Screening Panel

**Members**

**Chair,**
**Dr Ron Zimmern,**
Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Mrs Stella Burnside,
Chief Executive,
Altnagelvin Hospitals Health & Social Services Trust,
Londonderry

Dr Paul O Collinson,
Consultant Chemical Pathologist &
Senior Lecturer,
St George's Hospital,
London

Dr Barry Cookson,
Director, Laboratory of Hospital Infection, Public Health Laboratory Service,
London

Professor Howard Cuckle,
Professor of Reproductive Epidemiology,
University of Leeds

Professor Adrian K Dixon,
Professor of Radiology,
Addenbrooke's Hospital,
Cambridge

Dr David Elliman,
Consultant in Community Child Health,
St. George's Hospital, London

Dr Tom Fahey,
Senior Lecturer in General Practice,
University of Bristol

Dr Andrew Farmer,
General Practitioner & NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Jane Franklyn,
Professor of Medicine,
University of Birmingham

Dr Antony J Franks,
Deputy Medical Director,
The Leeds Teaching Hospitals NHS Trust

Dr J A Muir Gray,
Programmes Director,
National Screening Committee,
NHS Executive, Oxford

Dr Peter Howlett,
Executive Director – Planning,
Portsmouth Hospitals NHS Trust

Dr S M Ludgate,
Medical Director,
Medical Devices Agency,
London

Professor Jennie Popay,
Professor of Sociology & Public Health,
Institute for Health Research,
University of Lancaster

Dr Susan Schonfield,
CPHM Specialist Commissioning,
Public Health Directorate,
Croydon Primary Care Trust

Mrs Kathlyn Slack,
Professional Support,
Diagnostic Imaging & Radiation Protection Team,
Department of Health,
London

Mr Tony Tester,
Chief Officer,
South Bedfordshire Community Health Council,
Luton

Dr Andrew Walker,
Senior Lecturer in Health Economics,
University of Glasgow

Professor Martin J Whittle,
Head of Division of Reproductive & Child Health,
University of Birmingham

## Pharmaceuticals Panel

**Members**

**Chair,**
**Dr John Reynolds,**
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Professor Tony Avery,
Professor of Primary Health Care,
University of Nottingham

Professor Iain T Cameron,
Professor of Obstetrics & Gynaecology,
University of Southampton

Mr Peter Cardy,
Chief Executive,
Macmillan Cancer Relief,
London

Dr Christopher Cates,
GP & Cochrane Editor,
Bushey Health Centre,
Bushey, Herts

Dr Karen A Fitzgerald,
Pharmaceutical Adviser,
Bro Taf Health Authority,
Cardiff

Dr Felicity J Gabbay,
Managing Director,
Transcrip Ltd,
Milford-on-Sea, Hants

Mr Peter Golightly,
Director, Trent Medicines Information Services,
Leicester Royal Infirmary

Dr Alastair Gray,
Director, Health Economics Research Centre,
Institute of Health Sciences,
University of Oxford

Mrs Sharon Hart,
Managing Editor, *Drug & Therapeutics Bulletin*,
London

Dr Christine Hine,
Consultant in Public Health Medicine,
Bristol South & West Primary Care Trust

Mrs Jeannette Howe,
Deputy Chief Pharmacist,
Department of Health,
London

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Dr Frances Rotblat,
CPMP Delegate,
Medicines Control Agency,
London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St James's University Hospital, Leeds

Mrs Katrina Simister,
New Products Manager,
National Prescribing Centre,
Liverpool

Professor Terence Stephenson,
Professor of Child Health,
University of Nottingham

Dr Richard Tiner,
Medical Director,
Association of the British Pharmaceutical Industry,
London

Professor Jenifer Wilson-Barnett, Head of Florence Nightingale School of Nursing & Midwifery, King's College,
London

# Therapeutic Procedures Panel

**Members**

**Chair,**
**Professor Bruce Campbell,**
Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor John Bond,
Professor of Health Services Research, Centre for Health Services Research, University of Newcastle-upon-Tyne

Ms Judith Brodie,
Head of Cancer Support Service, Cancer BACUP, London

Ms Tracy Bury,
Head of Research & Development, Chartered Society of Physiotherapy, London

Mr Michael Clancy,
Consultant in A & E Medicine, Southampton General Hospital

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham

Dr Carl E Counsell,
Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd,
Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Gene Feder,
Professor of Primary Care R&D, St Bartholomew's & the London, Queen Mary's School of Medicine & Dentistry, University of London

Professor Richard Johanson,
Consultant & Senior Lecturer, North Staffordshire Infirmary NHS Trust, Stoke-on-Trent (deceased Feb 2002)

Dr Duncan Keeley,
General Practitioner, Thame, Oxon

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester

Professor Rajan Madhok,
Medical Director & Director of Public Health, North & East Yorkshire & Northern Lincolnshire Strategic Health Authority, York

Dr Mike McGovern,
Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford,
Consultant Physician, Frenchay Healthcare Trust, Bristol

Professor Mark Sculpher,
Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr Ken Stein,
Senior Lecturer in Public Health, Peninsular Technology Assessment Group, University of Exeter

*continued*

# Expert Advisory Network

**Members**

Mr Gordon Aylward,
Chief Executive,
Association of British
Health-Care Industries,
London

Mr Shaun Brogan,
Chief Executive,
Ridgeway Primary Care Group,
Aylesbury, Bucks

Mr John A Cairns,
Reader in Health Economics,
Health Economics
Research Unit,
University of Aberdeen

Professor Nicky Cullum,
Director of Centre for
Evidence-Based Nursing,
University of York

Dr Katherine Darton,
Information Unit,
MIND – The Mental
Health Charity, London

Professor Carol Dezateux,
Professor of
Paediatric Epidemiology,
Institute of Child Health,
London

Professor Pam Enderby,
Dean of Faculty of Medicine
Institute of General Practice
& Primary Care,
University of Sheffield

Mr Leonard R Fenwick,
Chief Executive,
Freeman Hospital,
Newcastle-upon-Tyne

Professor David Field,
Professor of
Neonatal Medicine,
The Leicester Royal
Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher &
Tutor & President,
National Childbirth
Trust, Henfield,
West Sussex

Ms Grace Gibbs,
Deputy Chief Executive
Director for Nursing,
Midwifery & Clinical
Support Services,
West Middlesex
University Hospital,
Isleworth, Middlesex

Dr Neville Goodman,
Consultant Anaesthetist,
Southmead Hospital, Bristol

Professor Robert E Hawkins,
CRC Professor & Director
of Medical Oncology,
Christie Hospital NHS Trust,
Manchester

Professor F D Richard Hobbs,
Professor of Primary Care
& General Practice,
University of Birmingham

Professor Allen Hutchinson,
Director of Public Health &
Deputy Dean of ScHARR,
University of Sheffield

Professor David Mant,
Professor of General Practice,
Institute of Health Sciences,
University of Oxford

Professor Alexander Markham,
Director,
Molecular Medicine Unit,
St James's University Hospital,
Leeds

Dr Chris McCall,
General Practitioner,
The Hadleigh Practice,
Corfe Mullen, Dorset

Professor Alistair McGuire,
Professor of Health Economics,
London School of Economics,
University of London

Dr Peter Moore,
Freelance Science Writer,
Ashtead, Surrey

Dr Andrew Mortimore,
Consultant in Public
Health Medicine,
Southampton City Primary
Care Trust

Dr Sue Moss,
Associate Director,
Cancer Screening
Evaluation Unit,
Institute of Cancer Research,
Sutton, Surrey

Mrs Julietta Patnick,
National Coordinator,
NHS Cancer
Screening Programmes,
Sheffield

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe,
Stoke Poges, Berks

Ms Marianne Rigge,
Director, College of Health,
London

Dr William Rosenberg,
Senior Lecturer &
Consultant in Medicine,
University of Southampton

Professor Ala Szczepura,
Director, Centre for
Health Services Studies,
University of Warwick

Dr Ross Taylor,
Senior Lecturer,
Department of General
Practice & Primary Care,
University of Aberdeen

Mrs Joan Webster,
Consumer member,
HTA – Expert
Advisory Network

## Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278