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The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis

W Clark, P Jobanputra, P Barton and A Burls

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The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis

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Note: a small amount of information was submitted to the National Institute for Clinical Excellence in confidence and has been removed from this version of the report. However, it should be noted that the Institute's Appraisal Committee had access to the full report to draw up their guidance.

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Abstract

The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis

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Objectives: To review the evidence of the clinical and cost-effectiveness of anakinra, an interleukin-1 receptor antagonist (IL-1Ra), for the treatment of rheumatoid arthritis (RA) in adults.
Data sources: Electronic bibliographic databases. *Scrip*, Food and Drug Administration (FDA) submissions for new drug applications, European Agency for the Evaluation of Medicinal Products (EMEA) reports and the pharmaceutical company submission to the National Institute for Clinical Excellence.
Review methods: Studies were identified that included randomised controlled trials (RCTs) or economic evaluations of anakinra in adult patients with RA. Existing health economic reviews were also assessed. Data were extracted and quality assessed using a structured approach. The Birmingham Rheumatoid Arthritis Model (BRAM) was used to compare disease-modifying antirheumatic drug (DMARD) sequences, chosen to reflect current clinical practice, with and without anakinra, at different points in the DMARD sequence.
Results: Five high-quality RCTs of anakinra in adult patients with RA, involving a total of 2905 patients, of whom 2146 received anakinra, were identified. The results of the clinical trials were consistent with clinical benefit (compared with placebo) as measured by American College of Rheumatology (ACR) composite response rate at 6 months. Variation in response rate was seen across the trials, which is likely to be a reflection of the size of the trials and the wide range of doses evaluated. Consistent benefit was seen at the higher dose evaluated. Benefit was evident both with monotherapy and when used in combination with methotrexate. Data on the efficacy end-points evaluated in a large pragmatic safety study have not been made available, which is of concern. Anakinra treatment was associated with a high incidence of injection-site reactions. Serious adverse events were infrequent, but longer term follow-up is required. No fully published economic evaluations of anakinra in patients with RA were identified. The BRAM gives a base-case estimate of the incremental cost-effectiveness ratio (ICER) of anakinra of £106,000 to £604,000/quality-adjusted life-year (QALY). In the sensitivity analyses substantial variations were made in key parameters and ICERs were shown to be responsive. However, ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.
Conclusions: Anakinra can be considered modestly effective in the treatment of RA based on ACR response, although no conclusion can currently be made on the effect of treatment on disease progression. Adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than tumour necrosis factor (TNF) inhibitors all used in combination with methotrexate, although these results should be interpreted with caution. The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other TNF inhibitors, as these agents have a different mechanism of action. Thus, anakinra

may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved. Further research would be valuable in the following areas: RCTs to evaluate the efficacy, safety and cost of anakinra over the longer term; comparative trials of anakinra with other DMARDs and biological modifiers; assessment of the role of anakinra in the treatment of patients who have failed to achieve a benefit while taking infliximab or etanercept; assessment on the impact of DMARDs and anakinra on joint replacement, mortality and quality of life; controlled clinical trials of combination therapy with two anticytokines; investigations into newer biological therapies; and the utility of radiographic outcomes in clinical trials of RA.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Severe adverse event An event suggesting significant hazard including fatal or life-threatening events; those requiring or prolonging hospitalisation; or resulting in persistent or significant disability/incapacity, congenital abnormality or birth defect.

List of abbreviations

ACR	American College of Rheumatology
ADR	adverse drug reaction
ANC	absolute neutrophil count
ARA	American Rheumatism Association
BCP	biochemical profile
BRAM	Birmingham Rheumatoid Arthritis Model
BSR	British Society for Rheumatology
CI	confidence interval
CRP	C-reactive protein
CXR	chest X-ray
CyA	ciclosporin A
DARE	Database of Abstracts of Reviews of Effectiveness
DAS	disease activity score
DMARD	disease-modifying antirheumatic drug
EJC	erosive joint count
EMEA	European Agency for the Evaluation of Medicinal Products
EMS	early morning stiffness
EPAR	European Public Assessment Report
ERAS	Early Rheumatoid Arthritis Study
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HEED	Health Economic Evaluation Database
HLA	human leucocyte antigen
ICER	incremental cost-effectiveness ratio
Ig	immunoglobulin
IL	interleukin
IL-1Ra	interleukin-1 receptor antagonist
i.m.	intramuscular
ISR	injection site reaction
ISTP	Index to Scientific and Technical Proceedings
ITT	intention to treat
i.v.	intravenous
LFTs	liver function tests

continued

List of abbreviations *continued*

LOCF	last observation carried forward
LOE	lack of efficacy
MCP	metacarpophalangeal joint
MCV	mean red blood cell volume
MTP	metatarsophalangeal joint
MTX	methotrexate
NA	not applicable
NDA	new drug application
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
NR	not reported
NRR	National Research Register
NSAID	non-steroidal anti-inflammatory drug
Pall	patients receiving palliation
PIP	proximal interphalangeal joint
QALY	quality-adjusted life-year
QoL	quality of life
QSE	quasi-standard error
RA	rheumatoid arthritis
RCT	randomised controlled trial
RD	risk difference
RF	rheumatoid factor
RR	relative risk
SAE	severe adverse event
s.c.	subcutaneous
SCI	Science Citation Index
SD	standard deviation
SEM	standard error of the mean
SJC	swollen joint count
SMR	standardised mortality ratio
TJC	tender joint count
TNF	tumour necrosis factor
URTI	upper respiratory tract infection
UTI	urinary tract infection
WBC	white blood cell
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Description of technology

This report reviews the evidence of the clinical and cost-effectiveness of anakinra, an interleukin-1 receptor antagonist (IL-1Ra), for the treatment of rheumatoid arthritis (RA) in adults. Anakinra is licensed in Europe for use in combination with methotrexate, for patients with an inadequate response to methotrexate alone. Anakinra acts in the same way as naturally occurring IL-1Ra, transiently binding to the IL-1 receptor, augmenting the natural regulation of the proinflammatory effects of IL-1.

Epidemiology and background

RA is a chronic illness characterised by inflammation of the synovial tissues in joints, which can lead to joint destruction. Key aims of treatment include:

- 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.

RA affects around 0.5–1% of the population, with approximately 421,330 patients affected in England and Wales. Prevalence increases with age, so that prevalence at the age of 65 is six times that at 25 years. Peak age of onset is in the sixth decade and RA is more common in women than in men, by a ratio of 2.5:1.

Corticosteroids, non-steroidal anti-inflammatory drugs and analgesics are used to control symptoms, but early use of disease-modifying antirheumatic drugs (DMARDs) is key, with the aim of slowing disease progression. There are approximately eight DMARDs currently in common use in the UK. Variable effectiveness or loss of effectiveness over time and toxicity hamper their use, with low continuation rates seen over time. New DMARDs are therefore of great importance. Several new agents have appeared in recent years, including the tumour necrosis factor (TNF) inhibitors, infliximab and etanercept.

Number and quality of studies, and direction of evidence

Five randomised controlled trials (RCTs) of anakinra in adult patients with RA, involving a total of 2905 patients, of whom 2146 received anakinra, were identified. All compared anakinra with placebo and all but one presented outcome data at 24 weeks. In three trials anakinra was administered in combination with methotrexate/other DMARDs and in two as monotherapy. Only two trials evaluated the licensed dose of 100 mg daily. All five trials were identified as high quality.

Summary of benefits

The results of the clinical trials are consistent with clinical benefit (compared with placebo) as measured by American College of Rheumatology (ACR) composite response rate at 6 months. Variation in response rate was seen across the trials, which is likely to be a reflection of the size of the trials and the wide range of doses evaluated. Consistent benefit was seen at the higher dose evaluated [number needed to treat (NNT) to achieve an ACR20 response of 7, 95% confidence interval (CI) 5 to 11, at licensed dose]. Benefit was evident both with monotherapy and when used in combination with methotrexate.

Data on the efficacy end-points evaluated in a large pragmatic safety study (0757) have not been made available. This is of concern. Given the nature and scale of this study such data have the potential to alter the overall findings of this review. In the absence of data the reviewers made an educated guess about the result of trial 0757. Assuming that this trial failed to reach conventional levels of statistical significance with a p-value of treatment difference in the order of $p < 0.1$ to < 0.2, an estimate of effectiveness was derived for trial 0757. The derived estimate has been combined with the data from the earlier trials, using a random effects model, to give a best estimate about anakinra's effectiveness for ACR20 response: relative risk 1.43

(95% CI 1.16 to 1.76), risk difference 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25).

Anakinra can be considered modestly effective in the treatment of RA based on ACR response. Reduction in Health Assessment Questionnaire scores, a measure of disability, was small. Robust data on radiologically assessed joint damage are not currently available. No conclusion can therefore be made on the effect of treatment on disease progression.

Direct comparisons with other biological modifiers are not available. Adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. Such indirect results should be interpreted with caution, but can be useful in guiding clinical practice in the absence of direct comparisons between agents.

Anakinra treatment was associated with a high incidence of injection-site reactions. Serious adverse events were infrequent, but longer term follow-up is required.

Economic evaluation

Existing economic evaluations

- No fully published economic evaluations of anakinra in patients with RA were identified. Two abstract reports presented limited data.

Commentary on submitted model

- This is a Markov model with a 6 month cycle time.
- Problems associated with the structure of this model make its conclusion, that the ICER for anakinra is £16,545/quality-adjusted life-year (QALY), unreliable.

Summary of the economic analysis

The Birmingham Rheumatoid Arthritis Model (BRAM) was used to compare DMARD sequences of drugs, chosen to reflect current clinical practice, with and without the addition of anakinra at different points in the DMARD sequence. The BRAM gives a base-case estimate of the incremental cost-effectiveness ratio (ICER) of anakinra of £106,000 to £604,000/QALY. This model uses data from public domain trial results only. These recruited a highly selective patient population and may well give a more favourable estimate of cost-effectiveness than would be achieved in an average clinic population.

In the sensitivity analyses substantial variations were made in key parameters and ICERs were shown to be responsive. However, ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other TNF inhibitors, as these agents have a different mechanism of action. Thus, anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Recommendations for research

- Current clinical trials with anakinra are of limited duration. RCTs are required to evaluate the efficacy, safety and cost of anakinra over the longer term in patients with such a chronic disease.
- Comparative trials of anakinra with other DMARDs and biological modifiers are needed to identify the comparative efficacy of these drugs and to guide clinical practice to optimise patient care.
- Trials are required to assess the role of anakinra in the treatment of patients who have failed to achieve a benefit while taking infliximab or etanercept.
- Further research is needed to assess the impact of DMARDs and anakinra on joint replacement, mortality and quality of life. Continued pharmacovigilance and analysis of potential adverse effects of new and old DMARDs are essential.
- Optimal treatment of RA may require combinations of therapeutic compounds that inhibit different mediators. Controlled clinical trials of combination therapy with two anticytokines are required to inform clinical practice, before such an approach is widely adopted.
- Suggestions that newer biological therapies reduce radiographic damage without necessarily improving clinical outcomes need to be confirmed if treatments in the absence of a clinical response are to be justified.
- Further research is needed to improve the utility of radiographic outcomes in clinical trials of RA, either by building on existing efforts with plain radiographs or through the use of newer imaging methods.

Chapter 1

Aim 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 anakinra in RA.
- To review the economic evidence about the cost-effectiveness of anakinra compared with other treatment options.
- To describe other agents being developed for the treatment of RA, and outline areas for research.

Chapter 2
Background

Description of underlying health problem

Clinical features of RA

RA is a systemic inflammatory disorder that mainly affects synovial joints. The pathological hallmarks of RA are an inflammatory reaction, increased cellularity of synovial tissue and joint damage. RA is characterised by pain, swelling and stiffness of synovial joints. These symptoms are often worse in the morning and after periods of inactivity. RA may also affect other organ systems, with a potential for severe disability and life-threatening complications. 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 commonly also experience lethargy and occasionally experience weight loss and fever.

The severity of disease can be very variable. In a community cohort 18% of RA patients 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 have a joint replaced within 22 years of disease onset.[1,2] (For details of the HAQ see Appendix 1.) Symptoms of RA may have a rapid onset (overnight in some cases) or evolve over weeks, months or years.[3] Common patterns of disease are:

- disease of small or medium joints, particularly the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands, metatarsophalangeal (MTP) 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: pain and stiffness affecting the shoulder and hip girdles (polymyalgic presentation); systemic symptoms such as weight loss and joint pain without a true arthritis; 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. The pain and disability of early RA are linked to disease severity and to measures of psychological distress.[4] The course of 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 to aid research. 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 disease. They have limited utility in routine practice. Most clinicians diagnose RA without formal reference to such criteria, with many patients not meeting formal criteria, at least early in their disease.[7,8] Criteria were also developed as an algorithm. These are more readily met in clinical practice.[9]

Radiographic features of 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. 'Erosion' refers to focal loss of bone and cartilage that occurs near the joint margin. More diffuse loss of cartilage results in a reduced joint space. As joint damage progresses joint deformity or instability may occur and at a late stage bony ankylosis or fusion may occur. With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. At an earlier stage other surgery such as

TABLE 1 *The 1987 revised ARA criteria for classification of RA*

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints lasting for 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 joint
4. Symmetrical arthritis	Simultaneous involvement of the same joint areas 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 posteroanterior 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 1–4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.	

Adapted from Arnett *et al*. (1988).[6]

removal of synovial tissues (synovectomy) or soft-tissue procedures such as tendon release or repair may be necessary.

Epidemiology

RA is the most common form of inflammatory arthritis. It affects around 0.5–1% of the population. Recent estimates from England and Wales show an annual incidence of 31 per 100,000 women and 13 per 100,000 men, and a prevalence of 1.2% in women and 0.4% in men.[10] Therefore, there are approximately 476,170 patients with RA in the UK, and 421,330 (309,890 women and 111,440 men) in England and Wales (population 52,041,916).[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.[12] Prevalence increases with age, so that prevalence at the age of 65 is six times that at 25 years. Peak age of onset is in the sixth decade and RA is more common in women than in men, by a ratio of 2.5 to 1.[13]

Aetiology

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

- Genetic influence is estimated at 50–60%.[14] 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 antigens. The occurrence of RA in both monozygotic twins is 12–15%.[12,13] A family history of RA gives an individual a risk ratio of 1.6 compared with the expected population rate.[15]
- Infectious agents have been suspected as causal agents, but without any conclusive or convincing evidence.[16,17]
- Lifestyle factors such as diet, occupation or smoking are not causally linked to RA.
- Sex hormones are implicated since there is an increased incidence in women and, in general, improvement during pregnancy.[12]
- Rheumatoid factor (RF), an autoimmune response to immunoglobulin G (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.

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 polymorphonuclear cells, with lesser numbers of T cells and macrophages. In disease, the synovial lining layer is increased to 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.

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 cytokines in RA

Almost all biological processes involve cytokines. These include normal development, immunity and inflammation. Cytokines are multifunctional and are highly expressed in RA tissues.[18–20] They function in a network of overlapping, synergistic, antagonistic and inhibitory activities. The net biological response appears to depend on the balance of counteracting factors.[21] Tumour necrosis factor (TNF) and interleukin-1 (IL-1) are two of the key proinflammatory cytokines in RA. In early disease (< 6 months) both cytokines are expressed in abundance.[22]

IL-1 and TNF-α have both local and systemic effects in RA. Locally they enhance the migration of leucocytes from the circulation into the inflamed joint. They also contribute to the growth of new blood vessels, which characterises rheumatoid synovitis. Most importantly, IL-1 and TNF-α are key mediators of the tissue destruction and osteopenia seen in a rheumatoid joint.

The relationship between cytokines is complex. TNF-α appears to regulate production of a variety of proinflammatory agents, including IL-1.[20] IL-1 itself can induce expression of TNF-α and also uniquely up-regulate its own expression.[22] IL-1 and TNF-α have overlapping effects, but IL-1 is recognised as a primary inducer of acute-phase proteins,[23] and appears to have a more important role in promoting cartilage and bone destruction.

Role of IL-1 and IL-1 receptor antagonist in RA

There are three members of the IL-1 family: IL-1α, IL-1β and interleukin-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β are secreted by immune cells in response to infectious or inflammatory challenge. IL-1Ra (IL-1 receptor antagonist) regulates IL-1α and IL-1β activity by blocking their actions.

Each member of this family binds to two receptors, designated type 1 (IL-1RI) and type 2 (IL-1RII), that are present on a variety of cells. The binding of IL-1α and IL-1β to type 1 receptors leads to cellular signalling and biological effects. By contrast, binding of IL-1α and IL-1β to the type 2 receptor (IL-1RII) does not cause cellular signalling. IL-1RII is a decoy receptor that functions by scavenging IL-1α and IL-1β. IL-1Ra competes with IL-1α and IL-1β for binding to type 1 receptors. Binding of IL-1Ra to IL-1R1 does not lead to cellular signalling.

Both receptors (IL-1RI and IL-1RII) may be cleaved from cell surfaces and circulate as soluble proteins (sIL-1RI and sIL-1RII). Soluble receptors may also bind to all members of the IL-1 family. However, sIL-1RII preferentially binds to IL-1α and IL-1β, further inhibiting the activity of these cytokines. Binding of sIL-1RI to IL-1Ra reduces the amount of IL-1Ra that is available to inhibit the actions of IL-1α and IL-1β.[23–27]

Mice in which the gene for IL-1Ra has been knocked out develop either an inflammatory arthritis resembling RA or a lethal arterial inflammation.[28,29] These data support the concept that an imbalance in IL-1 regulation can lead to destructive tissue inflammation.

IL-1Ra is found in large amounts in the synovial fluid and tissues of patients with RA, but local production appears to be insufficient to inhibit IL-1 effectively. Fewer than 5% of type 1 receptors need to be occupied by IL-1 to induce biological responses.[25] High local tissue concentrations of IL-1Ra must therefore be achieved to be physiologically inhibitory, a 10–1000-fold excess of IL-1Ra being required to block the effects of IL-1 *in vivo*.[25]

Goals of management

The goals of treating RA are:[30,31]

- to control symptoms of joint pain and inflammation
- to minimise loss of function and to maintain or improve quality of life (QoL)
- 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.

As with any chronic incurable disease a long-term treatment plan is required that is repeatedly re-examined in the light of clinical parameters and patient preferences.[32] Clinicians recognise that many factors need to be considered during this interaction with patients.[33] These include:

- discussion of drug and non-drug therapeutic options: an open discussion about the benefits and risks of these options including an awareness of the hazards of untreated disease and also of rare potentially life-threatening adverse events with some drugs
- 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
- 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 antirheumatic drugs (DMARDs), including sulfasalazine, methotrexate, gold preparations, penicillamine, azathioprine, hydroxychloroquine, leflunomide, ciclosporin A and cytokine inhibitors (e.g. TNF inhibitors).

Daily pain control and stiffness are managed by NSAIDs, low-dose prednisolone (e.g. 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 elsewhere.[31,34] Corticosteroids may be given in varying doses by mouth, or as intra-articular, intramuscular or intravenous injections. They are often used as short-term treatment for acute relapses, as bridge therapy or step-down therapy to allow rapid control of disease while awaiting the effects of DMARDs.[35] 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.[35,36] Long-term therapy may also be justified on the grounds that low-dose prednisolone prevents joint damage.[37]

DMARDs are slow-acting drugs that provide symptomatic relief and reduce the risk of progressive joint damage. Most DMARDs take several weeks or months to work. The mode of action of many DMARDs is not fully understood, but many appear to act by immune suppression. For example, methotrexate (MTX) and leflunomide, a newly available DMARD, are antimetabolites,[38] whereas etanercept and infliximab are inhibitors of TNF-α.[39]

It is generally accepted that patients with RA should be treated with DMARDs soon after diagnosis. Delayed use of DMARDs leads to worse outcomes.[31,40,41] 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.[31,38,42] The remaining drugs appear to have comparable efficacy. A meta-analysis of treatment termination rates showed that continued drug use 5 years after starting a DMARD was 36% for methotrexate, 23% for intramuscular gold and 22% for sulfasalazine. Median time for drug use for these agents was 41, 24 and 18 months, respectively, underlining a key limitation of DMARDs:[43] that is, relatively short-term use, or drug survival, of a DMARD for a disease with a lifelong course.

DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preference, complicating co-morbidity or a combination of these.[44] DMARD toxicity varies from relatively minor adverse reactions to life-threatening events such as bone-marrow suppression. Hydroxychloroquine and methotrexate appear to have the most favourable risk–benefit profile.[45] Methotrexate is widely regarded as the standard against which other drugs should be judged, especially because of its lower propensity for treatment termination. Effective disease control may also lead to other benefits such as reduced cardiovascular mortality.[46]

DMARDs are used in a variety of ways. Some use several agents at once in patients with severe disease (combination therapy), whereas others use DMARDs in sequence and either add one DMARD

to another or replace one DMARD with another in an effort to attain disease control.[47] Increasingly, combinations of DMARDs are used, although evidence in favour of combining DMARDs is limited.[48–50] Preferred DMARD combinations include methotrexate combined with hydroxychloroquine or ciclosporin A.[47] Of the TNF inhibitors, infliximab is only currently licensed for use in combination with methotrexate. An analysis of sequential use of DMARDs suggests that there may be reduced likelihood of sustained therapy with each successive DMARD.[51] It appears that the prospect of prolonged therapy for a DMARD is greatest if that DMARD is the drug first used in a sequence of DMARDs.[52] 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.[51]

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.[53,54] 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.[55]

Disease in some patients appears to be resistant to conventional approaches, but there is no clear definition of 'resistant RA'. Criteria for 'refractory' RA have been proposed recently.[56] The following demands must be met, according to the criteria described:

- That patients have used at least three DMARDs, including methotrexate (≥ 15 mg/week) and sulfasalazine (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).
- That patients have persistently active disease (DAS > 3.7) despite therapy.

Toxicity of DMARDs

The high rate for discontinuation of DMARDs is a key concern 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.[52] Treatment cessation because of toxicity is more likely with intramuscular gold than with sulfasalazine or methotrexate.[43] 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 not usually achieved, using current criteria for remission, but very effective disease control is possible in many patients. Modern clinical trials assess the response of a patient to therapy by using a composite measure that combines several measures of disease activity (Appendix 2). The American College of Rheumatology (ACR) definition of improvement and the disease activity score (DAS) are two of the most commonly used measures. The ACR response, for example, requires an improvement in:[57]

- 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 rata (ESR) or C-reactive protein (CRP)].

Response is defined as ACR20, ACR50 or ACR70, where 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 achieve this hurdle may still gain a worthwhile clinical response, especially in early RA.[58,59] The perspective of regulatory agencies in approving new drugs for RA was summarised in a review of anti-TNF therapies.[39]

Radiographic outcomes are believed by many to be the most important outcome measure in RA. A variety of schemes have been developed to assess joint damage in RA using radiographs. The most commonly used measures are the Sharp and Larsen methods and modifications of these methods (Appendix 3). Plain radiographs are insensitive to change, but are cheap and widely available. A majority of patients show only mild or no progression on plain radiographs over periods of 1–2 years.[60] In addition, there are significant problems of measurement error between two independent observers viewing the same set of radiographs. For example, the smallest detectable deterioration in the hands and feet radiographs of an individual over 12 months is estimated to be 15 Sharp units and 8 Larsen units, if 95% agreement between observers is required.[61] The group mean change in the Sharp score for anti-TNF agents

TABLE 2 *Toxicity of commonly used DMARDs*

Drug	Common reactions	Uncommon reactions	Rare or very rare reactions
Azathioprine	Nausea, rash, hypersensitivity, mouth ulcers	Leucopenia, infection	Lymphoma (long-term use)
Ciclosporin A	Headaches, hypertension, renal impairment, depression, nausea, paraesthesia, tremor, hypertrichosis, gingival hyperplasia, depression	Incipient renal failure, gout	Malignancy
Etanercept	Injection-site reactions, pruritus, fever, infections, allergic reactions, autoantibody formation	Serious infections, thrombocytopenia, angioedema, urticaria	Anaemia, leucopenia, pancytopenia, aplastic anaemia, serious allergic/anaphylactic reactions, seizures, CNS demyelinating disorders, malignancy
Gold	Rash and pruritus, diarrhoea (especially oral gold), mouth ulcers, thrombocytopenia, proteinuria	IgA deficiency, reduced Igs, neutropenia, cholestatic jaundice	Marrow aplasia, pneumonitis, exfoliative dermatitis
Hydroxychloroquine	Nausea, diarrhoea, rash, headache, dizziness, blurred vision	Muscle weakness	Retinal toxicity
Infliximab	Infusion-related reactions (dyspnoea, urticartia, headache), rash, pruritus, increased sweating, dry skin, fatigue, chest pain, viral infection, respiratory tract infections, sinusitis, flushing, vertigo/dizziness, nausea, diarrhoea, abdominal pain, dyspepsia, abnormal hepatic function	Fungal and bacterial infections, autoantibodies, anaphylactic reactions, anaemia, leucopenia, neutropenia, thrombocytopenia, lymphadenopathy, conjunctivitis, cardiovascular symptoms/disease, gastrointestinal symptoms, abnormal skin pigmentation, alopecia, myalgia, arthralgia, injection-site reactions	CNS demyelinating disorders, pancytopenia, anaphylactic shock, opportunistic infections, malignancy
Leflunomide	Hypertension, nausea, diarrhoea, mouth ulcers, abnormal LFTs, headache, dizziness, hair loss, rash	Hypokalaemia, taste disturbance, tendon rupture, anxiety	Severe abnormality of LFTs, Stevens–Johnson syndrome, leucopenia (< 2.0), pancytopenia, 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 pruritus, proteinuria, thrombocytopenia (dose related)	Glomerulonephritis	Myasthenia, polymyositis, systemic lupus erythematosus, red cell aplasia, neutropenia
Sulfasalazine	Nausea, rash, discoloured urine, leucopenia, fever, mouth ulcers, dizziness, oligospermia, raised MCV	Neutropenia, agranulocytosis, abnormal LFTs, reduced Igs	Pneumonitis

Adapted from and reproduced with permission from NCCHTA.[39]
Data are collated from a variety of sources, primarily Denman.[63]
Common: occurrence in approximately 1–10% of patients; uncommon: 0.1–1%; rare: 0.01–0.1%; very rare: 0.01% or less.
LFTs, liver function tests; MCV, mean red blood cell volume; Igs, immunoglobulins.

over 1 or 2 years was in the range of 0–7 Sharp units.[39] Others have reported that the median annual change in Larsen units was 6.5 units in patients with high levels of clinical disease.[62] Therefore, although radiographic outcomes are important in RA there are obvious challenges in improving the reliability and utility of radiological outcomes for clinical trials.

Non-drug therapy

Management of severe RA often requires input from a multidisciplinary team of health professionals.[31,64] This includes assessment, education and advice from an occupational therapist, physiotherapist, podiatrists, specialist nurses and many others. Hospitalisation occurs less often than it used to, but is still sometimes needed for those with severe disease or life-threatening complications.[65]

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, and medical complications such as radiographic damage or the need for surgery. 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-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.[66] At 5 years disability (HAQ > 1) is predicted by age at symptom onset, a high disability score at presentation (i.e. disability at presentation predicts itself), rheumatoid nodules, female gender, psychological status and joint tenderness.[67–69] Accuracy of 76% is reported for a combination of these factors (excluding female gender).[67] Physical function of patients followed soon after disease onset, and defined by ACR classification for function (Appendix 4), is normal in up to 40% of patients at 5 years. Moderate or severe disability occurs in 15.4%.[68]
- **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.[70,71] 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.[72] Manual workers, not surprisingly, suffer most limitations.[68]
- **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.[73] 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.[74] 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.[75,76]
- **Major joint replacement surgery** (including hip, knee, shoulder, and elbow replacements) was required in 8% of RA patients 5 years after diagnosis.[68] 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 owing to the availability of inpatient facilities.[68] However, medical treatment of severe RA in hospital can lead to better outcomes up to 2 years after hospitalisation, compared with routine outpatient care.[77]
- **Mortality**, especially due to cardiovascular disease, may be increased in RA. Studies of inception cohorts (defined as those with disease duration of less than 2 years) show a standardised mortality ratio (SMR) of between 0.87 and 1.38 (mean 1.22). Skin nodules, greater physical disability RF and treatment with steroids were associated with increased mortality.[70,78] Deaths from infection, lymphoma or leukaemia, and deaths related to the digestive system appear to occur 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.[68,79]

Burden of illness

RA 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, but patients and families, rather than healthcare services, incur a majority of the economic costs early in disease.[80] Mean annual direct and indirect costs, for the year 1996, are reported at £3575 and £3638 per patient, respectively.[81] 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.

Current service provision

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] Joint pain is the leading reason for referral to hospital outpatient services, with an annual rate of referral exceeding 40 per 1000 population.[82] The British Society for Rheumatology (BSR) and other organisations recognise a significant shortfall in rheumatology service provision (estimated at approximately 300 whole-time consultant rheumatologists in the UK).[83,84] Prolonged waiting times for patients to be seen in hospitals, and opinions of GPs and patient groups, provide support for the view that rheumatology provision is insufficient.[85,86]

The majority of patients followed up in a hospital rheumatology department have RA or another type of inflammatory arthritis or connective tissue disease. A proportion of such patients may also require inpatient treatment. There are considerable variations in inpatient facilities for patients with rheumatic disease. This may account for variations in hospitalisation rates seen for RA.[83]

Description of the 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 use of any specific treatment in any one individual are inappropriate.[87,88] This is especially true for RA where, in addition to considering a patient's perspective, significant co-morbidity is likely to influence therapeutic choices.

Anakinra is only licensed in Europe for use in combination with methotrexate in those patients who have not responded sufficiently to methotrexate alone. A BSR committee has issued guidelines on the appropriate use of anakinra in RA.[89] The guidance is similar to that issued on the use of etanercept and infliximab in RA.[90] It is recommended that anakinra should only be used if the following criteria are 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 intramuscular gold, hydroxychloroquine, sulfasalazine, 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 6-monthly basis.[91]

The BSR biologics registry is a prospective cohort study designed to compare the risk, over 5 years, of developing malignancy, lymphoproliferative malignancy, infection requiring hospitalisation, serious co-morbidity and death in two cohorts. The first cohort is a group of patients with rheumatic disorders newly exposed to a biological drug. The comparison cohort is a group of patients with similar disease characteristics newly exposed to other non-biological drugs. 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 and anakinra. All UK hospitals are obliged to collect data on patients treated with anti-TNF agents[92] and seven centres across the UK are recruiting the comparison cohort. The BSR and the manufacturers of etanercept, infliximab and anakinra have funded the study. Physicians contributing patient data do not receive support or reimbursement for data gathering. It seems likely that smaller units and

those with less support from professions allied to medicine will have difficulty meeting the demands of the patient registry. It is unclear how complete participation can be ensured by the National Institute for Clinical Excellence (NICE) and BSR, nor is it apparent how standards for data recording are maintained and audited. All data collected in the registry are owned by the BSR[93] (Watson K, BSRBR Study Co-ordinator: personal communication, October 2002).

Description of the technology

Anakinra (TN Kineret®) is a recombinant, non-glycosylated form of human IL-1Ra with a single methionine residue added at the amino-terminus.[94,95] It is the first biological agent of this type designed specifically to modify the biological response of IL-1. Amgen launched it in the UK in April 2002. It has been available in the USA since November 2001.

Anakinra is administered by the patient, or carer, as a single daily subcutaneous injection. It should be administered at approximately the same time each day, with rotation of the injection site. It is supplied in prefilled syringes containing the recommended fixed daily dose of 100 mg. Prefilled syringes of anakinra need to be stored in a refrigerator (2–8°C) and protected from light. Each syringe should be allowed to reach room temperature before it is administered. Anakinra prefilled syringes should not be removed from a refrigerator for more than a single period of 12 hours (at temperatures up to 25°C).

Training may be needed for administration of injections and in some cases injections may have to be administered by a healthcare professional. Patients need access to a refrigerator for storage of syringes and a sharps bin for disposal of used syringes. No other equipment is required.

The bioavailability of anakinra was 95% after a 70 mg subcutaneous injection in healthy volunteers.[96] Peak plasma concentrations are seen within 3–7 hours in patients with RA. Anakinra is excreted in the urine, less than 10% unchanged, with a terminal half-life of about 6 hours. The site of metabolism is not known. Absorption of anakinra is the rate-limiting factor for clearance of the drug from plasma following subcutaneous injection.[97] Accumulation of anakinra does not occur after daily subcutaneous injections (of up to 2 mg/kg per day) for 24 weeks in patients with RA. Plasma clearance of the drug is reduced by 70–75% in patients with severe or end-stage renal disease.[94] Use in such patients is contraindicated.[96]

Anakinra acts in the same way as naturally occurring IL-1Ra, transiently binding to the IL-1 receptor, augmenting the natural regulation of IL-1.

Anakinra is licensed in Europe "for the treatment of the signs and symptoms of RA in combination with methotrexate, in patients with an inadequate response to methotrexate alone".[96] The summary of product characteristics further recommends that "treatment should be initiated and supervised by specialist physicians experienced in the treatment and diagnosis of RA".[96] Anakinra is not recommended for use in children and adolescents under 18 years of age.

The European licence is more restrictive than the US licence, which allows use "for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age and older who have failed 1 or more disease modifying antirheumatic drug". Prescribers are advised not to use anakinra in combination with TNF inhibitors.[98]

Anakinra is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/minute) and in those with hypersensitivity to the active substance, any of the excipients or to *Escherichia coli*-derived proteins. Anakinra is not recommended for use in patients with neutropenia, those with pre-existing malignancies, or pregnant or breast-feeding women.[96] Women of childbearing potential are advised to use effective contraception during treatment. Caution is advised in moderate renal impairment and in those with a history of recurring infections or with underlying conditions that may predispose them to infections.[96] It is recommended that neutrophil counts are assessed before initiating anakinra treatment, monthly during the first 6 months of treatment and quarterly thereafter. If neutropenia develops anakinra should be discontinued and neutrophil counts monitored closely.[96]

Degree of diffusion

Currently, data on the usage of anakinra in the NHS are limited. Amgen was unwilling to provide data on the use of anakinra in the UK since it viewed these as commercially sensitive. [**Confidential information removed**.]

Anticipated costs

The acquisition cost of 1 year's treatment with anakinra (100 mg daily by subcutaneous injection) is £7471.[99] Anakinra is currently being supplied by

one of two routes, both of which incur additional expense: directly by Hospital Trusts, which incurs an additional cost of 17.5%, or by a home care company at an additional cost of 8% of the drug acquisition cost.

Additional costs associated with supervision, training, safety and efficacy monitoring, and collection of data for the BSR registry also need to be taken into account.

It is not possible to give any reliable estimate of how many RA patients are likely to be eligible for anakinra, since anti-TNF agents are only now being widely used in the UK. If we assume that 30% of patients do not respond to anti-TNF agents (based on clinical trials of anti-TNF agents), and if we assume that 10% of RA patients known to hospital departments are eligible for anti-TNF, then 3% of RA patients might be eligible for anakinra (9480 patients in England and Wales currently).[39]

Chapter 3
Effectiveness

Methods for reviewing effectiveness

Search strategy

The following electronic bibliographic databases were searched, with a stop date of 1 November 2002: Cochrane Library, MEDLINE, EMBASE, Science Citation Index (SCI), National Research Register (NRR), NHS Database of Reviews of Effectiveness (DARE), Index to Scientific and Technical Proceedings (ISTP), NHS Economic Evaluation Database (NHS EED), Health Economic Evaluation Database (HEED).

Search terms included the text words: anakinra; kineret; interleukin-1 receptor antagonist; IL-1ra; rhu-IL-1Ra; and the index terms: arthritis, rheumatoid; receptors; interleukin-1.

Studies were limited to humans. No language, date or age restrictions were applied. A meta-search engine was used to search the Internet, and links were followed up. Proceedings from the ACR and European Congress of Rheumatology meetings were searched electronically for the years 2001 and 2002.

Scrip, Food and Drug Administration (FDA) submissions for new drug applications, European Agency for the Evaluation of Medicinal Products (EMEA) reports and the pharmaceutical company submission to NICE were hand searched. The reference lists of identified publications were reviewed to identify any additional studies and/or citations.

Inclusion and exclusion criteria

Two reviewers independently applied the following inclusion/exclusion criteria to all potential studies. Disagreements were resolved by discussion, referring to a third party when necessary. Reviewers were not blinded to any features of the report, including authorship; however, inclusion/exclusion decisions were made before detailed scrutiny of the results.

Inclusion criteria

Those criteria for inclusion related to the population, intervention and comparator considered and the publication status of the report were applicable to both the clinical effectiveness and cost-effectiveness parts of the review.

- **population**: adults aged 18 years and above with rheumatoid arthritis
- **intervention**: anakinra (Kineret®) alone or in combination with other drugs
- **comparator**: Placebo, or other drug treatments for RA
- **publication**: all data to be included irrespective of publication status.

Studies were included in the final analysis of the review if they met the above criteria and the additional criteria for study design and outcomes as specified below for the clinical and cost-effectiveness parts of the review.

Clinical effectiveness review

- **Study design**: randomised or quasi-randomised controlled trials
- **outcomes**: to include mortality, morbidity (e.g. disability/mobility, disease progression, joint damage, pain, adverse events), response rates and QoL.

Cost-effectiveness review

- **Study design**: economic evaluation studies: cost analysis, cost-effectiveness, cost–utility and cost–benefit studies. Existing health economic reviews were also assessed
- **outcomes**: to include QoL, costs and incremental cost-effectiveness ratio (ICER).

Exclusion criteria

- Trials only recruiting children with juvenile idiopathic arthritis
- trials with no comparator arm
- trials that were not randomised (clinical effectiveness part of review only)
- articles reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms.

Data extraction strategy

Two reviewers independently extracted data using predesigned data extraction forms. Disagreements were resolved by discussion. Data from studies with multiple publications were extracted and reported as a single study.

Clinical effectiveness review
The following data were extracted:

- details of the study population and baseline characteristics of the intervention and control groups, with particular reference to disease characteristics and previous treatment history
- details of the intervention, such as dose, mode of administration, frequency of administration and duration of treatment
- details of completion rates across the groups, reasons for withdrawal, loss to follow-up
- details of individual outcomes measured, such as:
  - changes in disease activity, e.g. ACR improvement criteria, swollen joint count, pain, joint space narrowing and erosion
  - changes in QoL
  - adverse events reported.

Results were extracted, where possible for the intention-to-treat (ITT) population, as raw numbers, plus any summary measures with standard deviations, confidence intervals and *p*-values where given.

Cost-effectiveness review
The following data were extracted:

- details of the study characteristics, including type of economic analysis, intervention and comparator, perspective, time-frame and modelling used
- details of the data used to populate the evaluation and the key assumptions made, such as effectiveness data, cost data, health state valuations and discounting rate
- details of the results and sensitivity analysis.

Quality assessment strategy

Two reviewers undertook quality assessments independently, using a structured approach. Disagreements were resolved by discussion, with reference to a third party where necessary.

Clinical effectiveness review
The validity of included studies was assessed by looking at the method of randomisation, the concealment of allocation, the comparability of baseline characteristics between the different arms, blinding, withdrawals and losses to follow-up for each patient group. Based on these criteria a Jadad score was calculated (*Table 3*). (The Jadad score ranges from 0 to 5, with a score of 5 representing trials of highest quality.)

Cost-effectiveness review
The criteria of Drummond and co-workers served as an a priori standard for the assessment of economic evaluations.[100] These evaluate the study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results.

Results

Quantity and quality of research available

Sensitive rather than specific search strategies were used. The considerable interest in the potential role of biological therapies in the management of RA, particularly following the positive research data on anti-TNF therapy, has generated a large number of publications. Identified reports included many reviews, news articles, observational studies and studies investigating IL-1-related disease mechanisms, as well as a small number of clinical trials of IL-1Ra therapy. Results of MEDLINE and EMBASE searches are shown in Appendix 5.

Identified studies, inclusions and exclusions

Fifty-eight publications that potentially reported relevant trials were identified, comprising 13

TABLE 3 *Summary of Jadad scores for included studies*

Study	Truly random allocation	Was concealment adequate?	Was treatment allocation masked from:			Significant difference in completion rates between groups	Jadad score
			Participants	Investigators	Assessors		
560[101,102,103,107]	Yes	Yes	Yes	Yes	Yes	No	5
0182[103,108]	Yes	Yes	Yes	Yes	Yes	No	5
0180[101,103,104,109]	Yes	Yes	Yes	Yes	Yes	No	5
0145[101,105,110]	Yes	Yes	Yes	Yes	Yes	No	5
0757[101,103,106,111]	Yes	Yes	Yes	Yes	Yes	No	5

published reports, and 45 abstracts. All were identified from searches of electronic databases.

A number of duplicate publications were identified, which included abstracts for trials subsequently published in full, abstracts on the same data presented at more than one meeting, and full reports of the same trial published in more than one journal. Where identical data were presented in different publications then, if available, the fully published report was included. Where there were duplicate abstracts the most recent report was included. In the case of duplicates of fully reported trials the original report was included.

In other cases several abstracts and full papers presented subsets of data or details of a specific outcome. These were included if pertinent outcome data, not found in other sources, were presented.

Efficacy data from the open-label extension phase of blinded studies, or studies that were unblinded for safety or ethical reasons, were excluded.

The FDA new drug application (NDA) and EMEA European Public Assessment Report (EPAR) were available from the Internet and provided detailed information on the trials considered in the licensing application for anakinra in the USA and Europe, respectively.[101] Clinical trial reports on four trials were provided in Amgen's submission to NICE. These were considered in conjunction with the randomised controlled trial (RCT) reports.

Five RCTs of anakinra were included in the review, two evaluated monotherapy and three anakinra in combination with other DMARDs, one of which was principally a safety study. Only one efficacy trial and the safety study specifically evaluated anakinra at a dose of 100 mg/day (licensed dose). **Confidential information removed**.

A flow diagram illustrating the volume of literature identified and the selection of relevant reports is shown in *Figure 1*. A list of included and excluded reports, with a brief comment and reasons for exclusion, is shown in Appendix 6. Additional trials of anakinra in RA are currently in progress.

In evaluating adverse events with anakinra data from the included studies, postmarketing surveillance and other experiences are evaluated and discussed.

Quality and efficacy

Five trials that met the inclusion criteria were identified: four efficacy trials [two monotherapy (0560,[102] 0182[103]), two in combination with MTX (0180,[104] 0145[105])] and one safety study [combined therapy (0757)[106]]. Four were identified from electronic searches and one from the FDA and EMEA licensing submissions. A description of the included studies is given in *Table 4*.

The four efficacy trials have all been completed, but fully published data are only available for two. The low-dose ranging trial (2.5–30 mg/day), 0182, has never been published and the largest efficacy trial, 0145, has just been completed. Currently, only interim and preliminary end-point data are available. The safety study (0757) is still ongoing; interim data are currently available. The large efficacy trial (0145) and the safety study (0757) both evaluated anakinra at a dose of 100 mg/day, while the other studies considered ranges of doses.

All included trials were of high quality (*Table 3*).

All trials were described as double-blind, with active and control medication having similar appearance. There is, however, the potential that unblinding occurred owing to differences in adverse event profiles of the treatments, particularly injection site reactions (ISRs). This is discussed in more detail later in the report.

A description of the study characteristics and key data are given below for each trial. Results from all trials are shown in *Tables 5*–*7*.

Anakinra monotherapy

Two short-term dose-ranging placebo-controlled trials have evaluated the efficacy of anakinra monotherapy in the treatment of RA. The study by Bresnihan and colleagues is published in full.[102] Data on the smaller dose ranging study are only available in the FDA NDA submission and European centralised marketing authorisation application.[101,103,112]

Study 0560: Bresnihan and colleagues (1998)[101,102,103,107]

Population This Phase 2 dose ranging study enrolled adult patients with active RA as defined by ACR criteria. Patients did not have to have failed, or been intolerant of, prior DMARD treatment. For those who were on DMARD treatment before enrolment, this treatment had to be withdrawn at least 6 weeks before entry.

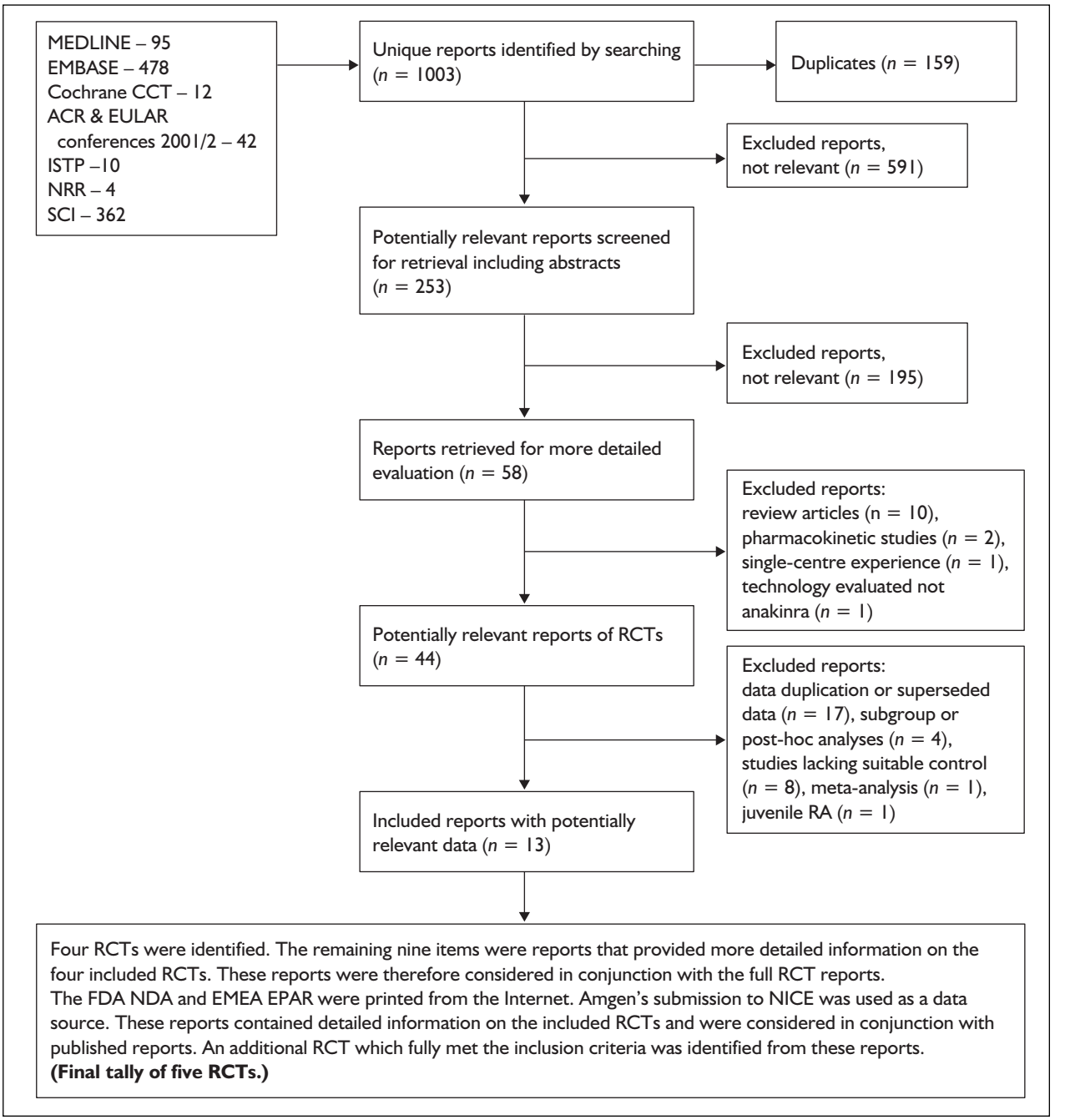


FIGURE 1 *Flow diagram for identified reports*

In total, 473 patients from 41 centres across 11 European countries were enrolled. Patients were aged between 18 and 75 years (mean 53.1 years), were almost exclusively white (99%) and were predominantly women (75%). Patients had active disease, with a median of 32–35 tender and 25–26 swollen joints, median HAQ of 1.5 or 1.6, median CRP of 2.7–3.2 mg/dl and a mean ESR above 45 mm/hour at baseline. Median disease duration was 3.3 years for placebo and 3.9 years for anakinra. Patients had received a median of 1 previous DMARD, and 36% had previously received methotrexate. Nearly a quarter of all patients had not received any previous DMARD (116 of the 473 patients; 19–34% across the treatment groups). Patients were permitted to continue treatment with NSAIDs and low-dose oral corticosteroids (taken by 83.5 % and 42.6%, respectively) provided that drug doses remained constant during the trial. Approximately 70% of patients were RF positive and 73% had erosions on baseline radiographs.

TABLE 4 *Description of included studies*

Study and description	Intervention and patient characteristics						
	Interventions ***Anakinra and placebo were administered as once-daily subcutaneous injections***	**Patient nos**	**Mean age (years)**	**Mean disease duration (years)**	**Mean no. of previous DMARDs**	**% On steroids**	**% On NSAIDs**
Monotherapy: DMARDs not permitted							
Bresnihan *et al*., 1998[101,102,103,107] (0560)							
Study duration: 24 weeks	Placebo	121	52	3.7	1.3	40.5	89.3
Placebo-controlled RCT in 31 European centres of a range of doses of anakinra	Anakinra 30 mg/day	119	53	4.3	1.3	48.7	82.4
	Anakinra 75 mg/day	116	53	4.2	1.3	40.5	87.9
	Anakinra 150 mg/day	116	54	3.9	1.2	41.4	85.3
Study 960182[103,108]							
Study duration: 12 weeks	Placebo	30	51.7	4.9	2.1	50.0	93.3
Placebo-controlled RCT in multiple centres in Europe to evaluate the efficacy of lower doses of anakinra	Anakinra 2.5 mg/day	42	54.2	2.8	1.4	38.1	78.6
	Anakinra 10 mg/day	40	52.3	3.7	1.6	47.5	90.0
	Anakinra 30 mg/day	29	49.8	2.7	1.4	41.4	82.8
Combination therapy with DMARDs							
Cohen *et al*., 2002[101,103,104,109] (0180)		(12 weeks)			(Excl. MTX)		
Study duration: 24 weeks	Placebo + MTX	74	53.0	7.8	2.1	66.2	67.6
Methotrexate controlled RCT in 36 centres across the USA, Canada and Australia to evaluate the efficacy of anakinra in combination with methotrexate	Anakinra 0.04 mg/kg per day + MTX	63	52.6	6.3	2.0	68.5	79.4
	Anakinra 0.1 mg/kg per day + MTX	74	53.0	8.8	1.9	64.9	70.3
	Anakinra 0.4 mg/kg per day + MTX	77	52.8	7.0	1.4	58.4	67.5
	Anakinra 1.0 mg/kg per day + MTX	59	49.0	6.5	1.8	62.7	64.4
	Anakinra 2.0 mg/kg per day + MTX	72	54.1	8.0	1.9	65.3	65.3
Cohen *et al*., 2001[101,103,105,110,112] (0145)		(interim analysis)					
Study duration: 12 months (interim data to 6 months)							
Methotrexate controlled RCT in 106 centres across the USA, Canada and Australia to evaluate the effect of anakinra in combination with methotrexate on disease progression	Placebo + MTX	251[a]	57.0	10.4	NR	52.2	77.3
	Anakinra 100 mg/day + MTX	250[a]	55.7	11.1		53.2	75.6

continued

TABLE 4 *Description of included studies (cont'd)*

Study and description	Intervention and patient characteristics						
	Interventions ***Anakinra and placebo were administered as once-daily subcutaneous injections***	**Patient nos**	**Mean age (years)**	**Mean disease duration (years)**	**Mean no. of previous DMARDs**	**% On steroids**	**% On NSAIDs**
Fleischman *et al*., 2001[101,103,106,111] (0757) Study duration: 3 years (6 months double blind + remainder open label) International placebo-controlled RCT in 169 centres to evaluate the safety of anakinra in clinical practice. Patients were permitted to continue with their current stable DMARD treatment	Placebo + current DMARD regimen Anakinra 100 mg/day + current DMARD treatment	283[b] 1116[b]	56 55	11 10	NR	61 57	86 87

[a] 253 patients were randomised into each treatment arm; baseline characteristics are only provided for the 501 patients who were randomised and received at least one dose of study drug.
[b] 284 patients were randomised to control and 1130 to anakinra treatment; baseline characteristics are only provided for patients who received at least one dose of study drug.
NR, not reported.

TABLE 5 *Disease activity at baseline across the treatment groups*

Study	SJC (0–66)	TJC (0–68)	Pain score patient	Global score		CRP (mg/dl)	ESR (mm/hour)	HAQ (0–3)	EMS (minutes)
				Patient	Physician				
Bresnihan *et al*., 1998[102,107] (0560)			(0–1)	(0–4)	(0–4)				
24 week data[a] *(unadjusted)*									
Placebo	25.6 ± 10.3	32.8 ± 14.1	0.62 ± 0.2	3.0 ± 0.5	3.0 ± 0.4	4.2 ± 4.2	47 ± 30	1.5 ± 0.6	127 ± 92
Anakinra 30 mg/day	26.2 ± 9.9	33.4± 13.5	0.62 ± 0.2	3.1 ± 0.5	3.1 ± 0.4	4.1 ± 3.7	49 ± 27	1.5 ± 0.6	138 ± 102
Anakinra 75 mg/day	26.2 ± 10.2	35.7± 14.4	0.65 ± 0.2	3.1 ± 0.5	3.1 ± 0.5	4.2 ± 3.8	53 ± 31	1.6 ± 0.7	138 ± 109
Anakinra 150 mg/day	26.6 ± 9.5	35.2± 13.5	0.63 ± 0.2	3.1 ± 0.5	3.1 ± 0.4	4.0 ± 4.0	49 ± 30	1.6 ± 0.7	133 ± 101
Study 960182[103,108]			(0–100)	(0–4)	(0–4)				
12 week data									
Placebo	25.1 ± 10.2	35.8 ± 13.0	65.6 ± 16.0	3.2 ± 0.5	3.3 ± 0.5	4.2 ± 3.9	47 ± 27	1.6 ± 0.7	136 ± 84
Anakinra 2.5 mg/day	22.6 ± 10.1	32.4 ± 13.4	62.5 ± 18.5	3.1 ± 0.5	3.0 ± 0.4	3.1 ± 3.3	45 ± 26	1.7 ± 0.5	124 ± 92
Anakinra 10 mg/day	24.0 ± 10.2	32.1 ± 11.6	56.3 ± 18.5	3.0 ± 0.5	3.1 ± 0.4	2.7 ± 2.9	40 ± 21	1.6 ± 0.6	132 ± 94
Anakinra 30 mg/day	23.7 ± 9.6	32.4 ± 12.7	55.4 ± 18.8	3.1 ± 0.4	3.1 ± 0.4	2.8 ± 4.3	41 ± 27	1.5 ± 0.7	117 ± 83
Cohen *et al*., 2002[104,109] (0180)			(0–100)	(0–100)	(0–100)				
24 week data									
Placebo + MTX	18.4 ± 9.8	28.1 ± 13.9	52.5 ± 22.2	52.6 ± 21.5	56.7 ± 18.5	2.0 ± 2.6	36 ± 28	1.4 ± 0.6	140 ± 113
Anakinra 0.0 4mg/kg per day + MTX	18.8 ± 8.7	23.9 ± 11.4	46.4 ± 20.9	47.6 ± 21.2	55.7 ± 19.2	2.2 ± 3.46	37 ± 23	1.4 ± 0.6	129 ± 90
Anakinra 0.1 mg/kg per day + MTX	18.3 ± 9.2	25.9 ± 14.8	51.6 ± 22.4	51.1 ± 21.5	61.2 ± 17.6	1.6 ± 1.6	38 ± 25	1.5 ± 0.7	117 ± 91
Anakinra 0.4 mg/kg per day + MTX	19.1 ± 9.2	27.1 ± 13.0	51.2 ± 21.3	50.4 ± 19.3	60.1 ± 18.5	2.1 ± 2.5	37 ± 26	1.5 ± 0.6	120 ± 91
Anakinra 1.0 mg/kg per day + MTX	17.6 ± 8.8	22.0 ± 12.9	47.5 ± 22.8	47.5 ± 21.5	53.6 ± 17.0	1.6 ± 2.3	37 ± 25	1.3 ± 0.6	134 ± 99
Anakinra 2.0 mg/kg per day + MTX	17.4 ± 8.1	24.6 ± 12.8	54.6 ± 21.4	51.2 ± 21.7	55.8 ± 18.5	2.0 ± 2.6	35 ± 21	1.3 ± 0.6	143 ± 98
Cohen *et al*., 2001[105,110] (0145)			(0–100)	(0–100)	(0–100)				
24 week data									
Placebo + MTX	20 ± 10.2	24.5 ± 13.1	55.7 ± 20.4	52.3 ± 19.8	57.0 ± 18.4	2.6 ± 2.6	43 ± 22	1.32 ± 0.6	111 ± 99
Anakinra 100 mg/day + MTX	20.1 ± 11.7	26.8 ± 15.7	59.2 ± 21.6	53.2 ± 22.1	57.4 ± 18.7	2.7 ± 2.6	42 ± 22	1.36 ± 0.6	102 ± 84
Fleischman *et al*., 2001[106,111] (0757)									
24 week data									
Placebo + current DMARD regimen	18.3 ± 11.7	22.6 ± 14.5	NR	NR	NR	2.7± 3.3	NR	NR	NR
Anakinra 100 mg/day + current DMARD treatment	18.8 ± 11.9	22.6 ± 14.7				2.7± 3.3			

Data are shown as mean ± SD.

[a] Based on modified ITT population (n = 468). Four patients (two placebo, one anakinra 75 mg/day, one anakinra 150 mg/day) had no postbaseline assessment and were excluded from the analysis.

SJC, swollen joint count; TJC, tender joint count.

TABLE 6 *Mean change in measures of disease activity from baseline*

Study	SJC (0–66)	TJC (0–68)	Pain score patient	Global score		CRP (mg/dl)	ESR (mm/hour)	HAQ (0–3)	EMS
				Patient	Physician				
Bresnihan *et al*., 1998[102,107] (0560)			(0–1)	(0–4)	(0–4)				
24 week data[a] *(unadjusted)*									
Placebo	–5.7 (0.9)	–5.2 (1.4)	–0.05 (0.03)	–0.5 (0.09)	–0.6 (0.08)	–0.4 (0.28)	+1 (2)	0.0 (0.04)	–14 (10)
Anakinra 30 mg/day	–7.9 (1.2)	–8.6 (1.3)	–0.13 (0.03)*	–0.7 (0.09)	–0.9 (0.08)*	–1.3 (0.25)**	–9 (2)***	–0.2 (0.05)*	–36 (10)
Anakinra 75 mg/day	–6.8 (1.0)	–9.3 (1.3)	–0.12 (0.03)	–0.8 (0.09)	–0.9 (0.09)*	–1.0 (0.31)**	–8 (2)***	–0.2 (0.04)*	–55 (11)**
Anakinra 150 mg/day	–9.5 (0.9)**	–11.9 (1.2)***	–0.17 (0.03)***	–0.9 (0.09)*	–1.0 (0.08)***	–1.0 (0.49)**	–10 (3)***	–0.3 (0.06)***	–48 (10)
Study 960182[103,108]									
12 week data[b]									
Placebo	–6.8 (1.7)	–11.4 (2.4)	–21.5 (4.3)	–1.0 (0.15)	–1.20 (0.13)	0.02 (0.19)	–2 (3)	–0.33 (0.09)	–55 (14)
Anakinra 2.5 mg/day	–3.0 (1.5)	–7.2 (2.1)	–14.7 (3.8)	–0.8 (0.14)	–0.72 (0.12)	–0.01 (0.17)	1 (3)	–0.30 (0.08)	–26 (13)
Anakinra 10 mg/day	–6.3 (1.5)	–9.7 (2.1)	–11.9 (3.8)	–0.9 (0.14)	–0.92 (0.12)	–0.06 (0.17)	–5 (3)	–0.09 (0.08)	–25 (13)
Anakinra 30 mg/day	–6.4 (1.7)	–12.0 (2.4)	–12.9 (4.4)	–0.9 (0.16)	–0.82 (0.14)	0.01 (0.19)	–2 (3)	–0.21 (0.09)	–32 (15)
Cohen *et al*., 2002[104,109] (0180)			(0–100)	(0–100)	(0–100)				
24 week data[c]									
Placebo + MTX	–4.2 (1.0)	–8.3 (1.5)	–2.6 (3.1)	–3.6 (3.0)	–14.1 (2.9)	–0.19 (0.34)	–4 (2)	–0.15 (0.07)	–50 (12)
Anakinra 0.04 mg/kg per day + MTX	–5.0 (0.9)	–6.9 (1.4)	–3.8 (2.9)	–5.3 (2.8)	–11.5 (2.6)	0.15 (0.30)	–4 (2)	–0.25 (0.07)	–45 (11)
Anakinra 0.1 mg/kg per day + MTX	–5.7 (1.0)	–7.9 (1.5)	–12.3 (3.1)	–12.4 (3.0)	–20.3 (2.9)	–0.06 (0.35)	–10 (2)	–0.33 (0.07)	–63 (12)
Anakinra 0.4 mg/kg per day + MTX	–6.7 (0.9)	–9.7 (1.4)	–8.9 (3.0)*	–8.1 (2.9)*	–20.4 (2.8)	–0.74 (0.33)	–12 (2)**	–0.24 (0.07)	–41 (11)
Anakinra 1.0 mg/kg per day + MTX	–6.3 (0.9)	–8.3 (1.4)	–12.9 (3.0)*	–13.8 (2.9)*	–22.3 (2.8)*	–0.77 (0.32)	–12 (2)**	–0.37 (0.07)*	–74 (11)
Anakinra 2.0 mg/kg per day + MTX	–7.6 (1.0)*	–11.2 (1.6)	–22.8 (3.3)***	–20.4 (3.2)***	–24.5 (3.1)*	–0.77 (0.38)	–15 (3)**	–0.51 (0.07)***	–82 (13)
Cohen *et al*., 2001[105,110] (0145)			(0–100)	(0–100)	(0–100)				
24 week data[d]									
Placebo + MTX	–6.5 (0.6)	–8.7 (0.9)	–11.7 (1.8)	–8.9 (1.7)	–20.1 (1.5)	–0.10 (0.04)	–6 (1)	–0.18 (0.03)	–36 (6)
Anakinra 100 mg/day + MTX	–6.8 (0.6)	–12.0 (0.9)**	–19.0 (1.7)**	–17.7 (1.6)***	–25.2 (1.5)*	–0.51 (0.03)***	–16 (1)***	–0.29 (0.03)*	–48 (6)
Fleischman *et al*., 2001[106,111] (0757)									
24 week data	NR	NR	NR	NR	NR	NR	NR	NR	NR
Placebo + DMARD									
Anakinra 100 mg/day + DMARD									

Data are shown as mean (SEM).

[a] Based on modified ITT population (n = 468). Four patients (two placebo, one anakinra 75 mg/day, one anakinra 150 mg/day) had no postbaseline assessment and were excluded from the analysis.

[b] ITT analysis using least squares mean obtained from repeated measures mixed model adjusted for centre and baseline value, with the exception of HAQ outcome data which are provided for the completer subset only.

[c] Least squares mean obtained from repeated measures mixed model adjusted for study centre and baseline variable.

[d] Adjusted mean and SE estimated by EMEA based on repeated measures mixed model adjusted for study week, treatment by study week interaction, centre and baseline value.

* $p < 0.05$ vs placebo. ** $p \leq 0.01$. *** $p \leq 0.001$.

TABLE 7 *Percentage of patients showing ACR response and percentage discontinuing therapy*

Study and intervention	ACR20	ACR50	ACR70	Drug cessation		
				Any reason	Lack of efficacy	Toxicity
Bresnihan *et al.*, 1998[102,107] (0560) *24 week data*[a]						
Placebo	27	7	1	26	20	4
Anakinra 30 mg/day	39*	17*	4	20	13	4
Anakinra 75 mg/day	34	11	1	19	12	6
Anakinra 150 mg/day	43*	17*	1	24	9	9
Study 960182[103,108] *12 week data*						
Placebo	43	13	6.7	10	0	7
Anakinra 2.5 mg/day	26	2.4	0	19	7	7
Anakinra 10 mg/day	28	7.5	0	7.5	2.5	2.5
Anakinra 30 mg/day	34	6.9	0	10	3	7
Cohen *et al.*, 2002[104,109] (0180) *24 week data*						
Placebo + MTX	23	4	0	19	7	4
Anakinra 0.04 mg/kg per day + MTX	19	13	5	21	14	3
Anakinra 0.1 mg/kg per day + MTX	30	20	7	16	10	1
Anakinra 0.4 mg/kg per day + MTX	36	11	2	22	8	7
Anakinra 1.0 mg/kg per day + MTX	42*	24	10	22	7	14
Anakinra 2.0 mg/kg per day + MTX	35	17	7	26	6	15
Cohen *et al.*, 2001[105,110] (0145) *24 week data*						
Placebo + MTX	22	8	2	27	NR	9
Anakinra 100 mg/day + MTX	38***	17***	6*	22		13
Fleischman *et al.*, 2001[106,111] (0757) *24 week data*						
Placebo + current DMARD regimen	NR	NR	NR	19	NR	6
Anakinra 100 mg/day + current DMARD treatment				23		12

[a]

* $p < 0.05$. *** $p \leq 0.001$.

At baseline notable differences across the treatment groups were fewer men, lower previous DMARD use and fewer erosions in the highest anakinra dose group.

Interventions All interventions were given as a single daily subcutaneous injection administered by the patient or caregiver. Patients were randomised to one of four treatment groups:

- placebo (n = 121)
- anakinra 30 mg/day (n = 119)
- anakinra 75 mg/day (n = 116)
- anakinra 150 mg/day (n = 116).

One patient withdrew before receiving study medication.

Study duration and key outcomes Study duration was 24 weeks. The primary outcome measure was ACR composite score and Paulus criteria. Nine secondary efficacy outcome measures were prespecified. The Larsen score and erosive joint count were also evaluated.

Main efficacy results With modified ITT analysis 27%, 39%, 34% and 43% patients met the ACR20 response criteria at week 24 when treated with placebo and anakinra 30 mg, 75 mg and 150 mg, respectively (p = 0.047, 0.276, 0.014 for each dose versus placebo). Similar responses were documented using Paulus criteria with 20% response in 21%, 39%, 37% and 44% of patients, respectively.

Sustained ACR20 response, defined as ACR20 response for 4 of the 6 study months, one of which must be observed at week 12 or 24, was achieved by 11% patients treated with placebo, and 28%, 28% and 24% of patients treated with anakinra 30 mg, 75 mg and 150 mg, respectively (p = 0.0009, 0.0005, 0.0083 vs placebo). ACR50 responses occurred in 8% of placebo patients, 13%, 10% and 18% with increasing doses of anakinra [last observation carried forward (LOCF) method]. ACR70 responses occurred in less than 1% of cases, except for the group treated with anakinra 30 mg (4%).

The mean changes from baseline in the components of the ACR were all significantly reduced with the highest dose of anakinra. Consistent changes across all these criteria were not evident for the other two doses of anakinra evaluated (*Table 6*).

The duration of early morning stiffness (EMS) was only significantly reduced with 75 mg anakinra versus placebo (p = 0.006). Hand radiographs were available for 74% of the patients at baseline and 24 weeks. The mean Larsen score increased by 6.4 (from a baseline of 15.4) with placebo compared with increases of 3.8, 3.9 and 4.0, respectively, with increasing doses of anakinra (p = 0.04, p = 0.09 and p = 0.11 comparing anakinra with placebo). The number of joints with erosions increased by 2.6 with placebo (5.0 at baseline) compared with increases of 1.5, 1.0 and 1.7, respectively, with increasing doses of anakinra (p = 0.02, p = 0.004 and p = 0.074 comparing anakinra with placebo).

Twenty-seven per cent of patients dropped out of this trial before the 6 month primary end-point, with the highest dropout occurring in the placebo group (26% placebo vs 20%, 19% and 24% anakinra 30 mg, 75 mg and 150 mg, respectively). Of the completers, 37% of placebo patients achieved ACR20 response at 24 weeks compared with 49.5%, 42% and 52% with increasing doses of anakinra (p = 0.12, 0.56 and 0.04, respectively). One patient allocated to anakinra withdrew before receiving study medication. Of the remaining withdrawals 20% patients on placebo and 12% on anakinra (all doses) withdrew owing to lack of efficacy, and 4% and 9%, respectively, for adverse effects.

Adverse events These were reported in detail in an internal company report. Severe adverse events, as defined by the FDA (refer to glossary), occurred in 12% of placebo-treated patients compared with 8%, 15% and 16% with increasing doses of anakinra.

The most frequent adverse event was ISRs (25% placebo, 50%, 73% and 81%, respectively, with increasing doses of anakinra). Most ISRs were graded 'mild' or 'moderate', but some took 2–3 weeks to resolve. Symptoms of ISRs included local irritation, pain and urticaria. Patients experiencing ISRs usually reported them within 28 days of starting treatment. No ISR was recorded as a serious adverse event, but ISRs led to study withdrawal in 2% of placebo-treated patients, and 1%, 3% and 5% of anakinra patients (30 mg/day, 75 mg/day, 150 mg/day, respectively). Worsening of joint pain was reported by 50% of placebo-treated patients and 48%, 42% and 38%, respectively, for anakinra 30 mg, 75 mg and 150 mg doses. Headaches were reported in 6% patients on anakinra 150 mg compared with 1% with placebo (no further details given).

Infections occurred in 38% patients treated with placebo and 37% treated with anakinra (all doses).

The most common infections were upper respiratory tract infections (URTIs), influenza-like symptoms and urinary tract infections (UTIs). Infections resulting in antibiotic therapy occurred in 12% placebo-treated and 15–17% anakinra-treated patients. Six patients were hospitalised for infections, 4 in the 150 mg anakinra group. Serious infections were reported in seven patients: placebo (one: URTI), 75 mg (two: one URTI and one bursitis), 150 mg (four: one UTI/URTI, one herpes zoster and two bursitis) anakinra.

Three patients given anakinra were withdrawn owing to neutropenia ($< 2.0 \times 10^3/\mu l$; as required by study protocol). Clinical symptoms were not seen and neutrophils recovered on drug withdrawal. In three patients, one in each anakinra arm, anti-IL1-Ra antibodies were detected at two or more follow-up visits (titres of between 1:50 and 1:800).

Four patients on anakinra (two 30 mg, two 150 mg, none receiving placebo or 75 mg) developed a malignancy during treatment (lung cancer, oral squamous cell cancer, basal cell carcinoma, thyroid cancer). A further patient who received 30 mg anakinra was diagnosed with small cell lung cancer 3 weeks after completing the study. These were all considered unrelated to the study drug.

Comments Patients were enrolled if they had had RA for longer than 6 months but less than 8 years. Thus, patients were at an early stage of disease and 59% of patients had received fewer than two DMARDs at inclusion. Patients who had failed to respond to three or more previous DMARDs were excluded; however four patients were reported as having received four previous DMARDs at baseline. Differences between groups at baseline in terms of DMARD use did not predict response to anakinra.

It seems likely that unmasking to treatment allocation occurred during the study, owing to the high rate of ISRs in patients receiving anakinra, particularly the 150 mg dose.

The modified ITT analysis included all patients who had taken at least one dose of study drug and had at least one postbaseline evaluation. No adjustment for multiple comparisons was undertaken in the reporting of the trial results. *p*-Values quoted in the papers are thus nominal values. If Bonferroni adjustment for multiple comparisons were applied, *p*-values would have to be less than 0.017 for significance at the 0.05 level to be retained.

Sensitivity analyses were reported, in an internal company report, by assuming that subjects with missing data or unusable data at week 24 had not responded. Reported *p*-values for ACR20 comparing anakinra with placebo were 0.033, 0.186 and 0.033 for anakinra 30, 75 and 150 mg, respectively.

The trial protocol specified that radiological progression of the disease would be assessed by the Larsen score and erosive joint count (EJC) following defined methodology. A post-hoc analysis rereading the data using different methodology was undertaken to calculate a modified Sharp score. The results from this reanalysis suggested that anakinra may have activity in inhibiting radiological progression. However, data from 133 patients were not included in this reanalysis. Caution is therefore advised in the interpretation of this post-hoc analysis. The FDA state that "the lack of statistical significance of the primary analysis and large amount of missing data (26%) limit the conclusions that can be based on this data". The reanalysis using Sharp score is not therefore considered in this evaluation.

Study 0182: unpublished[103,108]

This European RCT was a Phase 1 pilot study, conducted in 15 centres across six European countries in 1997. It was undertaken to evaluate the efficacy of lower doses of anakinra.

Population Adult patients (≥ 18 years of age) with active RA for at least 6 months but less than 8 years were enrolled into this trial. Patients had to have at least ten swollen joints and were not permitted to use DMARDs during the study. DMARDs were discontinued at least 6 weeks before study entry, with the exception of ciclosporin, which had to be stopped 6 months before the trial commenced. Treatment with NSAIDs and/or low doses of oral corticosteroids could be continued provided doses were stable for at least 4 weeks before entry.

In total, 141 patients were randomised to treatment for 12 weeks. Of 141 patients 108 (77%) were female. Patients had a mean age of 52 years (range 25–80 years) and all were white. The majority (79–93%) of patients were using NSAIDs at baseline and 38–50% were receiving corticosteroids. Patients had active disease, with an average of 32–36 tender/painful joints and 23–25 swollen joints, mean HAQ of 1.5–1.7 and mean ESR of 40–47 mm/hour. Mean CRP concentrations were higher in the placebo group (4.2 mg/dl) than

in the anakinra groups (2.7–3.1 mg/dl). Mean disease duration was also higher in the placebo group (4.9 years) than in the anakinra treatment groups (2.7–3.7 years), as was the median number of previous DMARDs (2.0 vs 1.0). Of placebo-treated patients, 53% had previously used methotrexate compared with 29–40% of anakinra-treated patients. At baseline 59–76% of patients across the treatment groups were positive for RF.

At baseline notable differences in baseline characteristics of the placebo group were longer mean duration of RA, higher proportion of methotrexate use, lower proportion of DMARD-naive subjects, higher mean CRP concentration and higher RF titres.

Interventions All treatments were given by subcutaneous injection, once daily. Patients were randomised to:

- placebo (n = 30)
- anakinra 2.5 mg/day (n = 42)
- anakinra 10 mg/day (n = 40)
- anakinra 30 mg/day (n = 29).

Study duration and key outcomes Study duration was 12 weeks. The primary end-point was ACR20 response at week 12.

Secondary end-points included change from baseline in ACR components at week 12, ACR50 ACR70, duration of morning stiffness and ESR.

Main efficacy results No statistically significant effects of anakinra on primary or secondary end-points were documented.

ACR20 response was seen in 43% of placebo-treated patients and 26%, 28% and 34% of patients treated with anakinra 2.5 mg, 10 mg and 30 mg, respectively.

Twelve per cent of patients withdrew prematurely: 10% placebo, 19%, 7.5% and 10% anakinra 2.5 mg, 10 mg and 30 mg, respectively.

Adverse events Anakinra was well tolerated, with 5.4% of patients withdrawing from treatment owing to an adverse reaction. Adverse events occurred at comparable rates across the treatment groups (including infections). The most frequent event was RA flare; 17% on placebo and 14% on anakinra. ISRs were reported in 3% of placebo and 12%, 18% and 35% of patients treated with anakinra 2.5 mg, 10 mg and 30 mg/day.

No changes in white blood cell (WBC) counts were documented. Antibodies to anakinra were seen in 5% of anakinra-treated patients.

Comments ITT analysis was undertaken for all randomised patients who received at least one dose of study drug with non-responder imputation.

Despite the placebo response rate in this trial being higher than that seen in the other efficacy trials with anakinra, the ACR response seen with the low doses of anakinra was low and cannot be considered different to that achieved with placebo.

Anakinra in combination with DMARDs/MTX

Two trials have evaluated use in combination with MTX, only one of which has been completed and published in full.[104] The second trial is a 1 year study which focuses on the effect of treatment on disease progression. Although this trial has now been completed, full data on the 1 year end-point are not yet available. Data to 6 months (for a subset of patients) on the effect of treatment on ACR responses are reported in an abstract,[105] the FDA and EMEA submission documents and the clinical study report provided by Amgen in confidence. A third trial, a pragmatic safety study, evaluated use in combination with DMARDs.[106]

Study 0180: Cohen and colleagues (2002)[101,103,104,109]

Population Patients enrolled in this trial had active RA despite treatment with methotrexate for at least 6 months (15–25 mg/week). The dose of methotrexate had to have remained stable for at least 3 months before study entry and was maintained at this level throughout the trial. Patients received folic acid to reduce methotrexate toxicity.

Concomitant treatment with other DMARDs was not permitted. These were discontinued at least 12 weeks before study entry, with the exception of hydroxychloroquine and sulfasalazine, which were discontinued at least 8 weeks before entry. Treatment with NSAIDs and low-dose oral corticosteroids (≤ 10 mg/day of prednisolone or equivalent) was permitted provided doses were stabilised for 4 weeks before study entry and for the duration of the trial.

Active disease was defined as at least six swollen joints and the presence of at least two of the following:

- at least nine tender and painful joints
- morning stiffness lasting for at least 45 minutes
- CRP of greater than 1.5 mg/dl.

A total of 419 patients participated in this study across 36 centres in the USA, Canada and Australia. The design was complicated by a change to the original trial protocol (see comments below). The 419 patients were evaluated at the 12 week end-point, of whom 317 were also evaluated at the 24 week end-point.

The mean age of patients enrolled in the trial was 52.5 years and mean disease duration 7.5 years. Over 80% of patients were white and 66.5% were female. Excluding methotrexate, the median number of previous DMARDs was 2.0 for all groups except for patients treated with 0.4 and 2.0 mg/kg per day of anakinra who had received a median of 1.0 previous DMARD. Twenty per cent of placebo patients and 14%, 19%, 31%, 27% and 23% of anakinra patients (in increasing doses) had not received any other DMARD previously. NSAID use (68.9%) and oral corticosteroid use (64.1%) varied across the groups, but was generally comparable between control and the higher anakinra doses evaluated (1.0 and 2.0 mg/kg per day). Seventy to eighty per cent of patients were RF positive at baseline.

The median dose of methotrexate at baseline was 15 mg/week for all groups, except for patients on 0.04 and 0.1 mg/kg per day of anakinra, who received 17.5 mg and 15.6 mg per week, respectively. Patients had a mean of 18 swollen and 25 tender joints at baseline. The mean tender joint count varied across the treatment groups, with the highest level seen in the control group (28 joints) and the lowest in patients treated with anakinra 1.0 mg/kg per day (22 joints). Mean baseline ESR ranged from 35.1 to 37.9 mm/hour across treatment groups (*Table 5*). Median HAQ scores for all groups were either 1.4 or 1.5 at baseline.

Intervention Study drugs were all administered by subcutaneous injection once daily by the patient or caregiver. Rotation of the injection site was advised. Patients were randomised to:

- control (MTX alone) (n = 74, 12 weeks; n = 48, 24 weeks)
- anakinra 0.04 mg/kg per day (n = 63, 12 and 24 weeks)
- anakinra 0.1 mg/kg per day (n = 74, 12 weeks; n = 46, 24 weeks)
- anakinra 0.4 mg/kg per day (n = 77, 12 weeks; n = 55, 24 weeks)
- anakinra 1.0 mg/kg per day (n = 59, 12 and 24 weeks)
- anakinra 2.0 mg/kg per day (n = 72, 12 weeks; n = 46, 24 weeks).

Study duration and key outcomes Study duration was 12 weeks, subsequently amended to 24 weeks. The primary efficacy end-point was ACR20 at week 12.

In addition to ACR20 response at week 24, 11 secondary efficacy end-points were specified, including ACR50 and ACR70. All but one (sustained ACR20 response) were assessed at both 12 and 24 weeks. A sustained ACR20 response was defined as an ACR20 response for at least 4 out of the 6 months of therapy (not necessarily consecutive), one of which was at week 12 or 24.

Main results ACR20 response at week 12 was 19% with control and 25%, 35%, 25%, 46% and 38% with anakinra 0.04–2.0 mg/kg per day, respectively. A significant dose response was seen (p = 0.001) across the anakinra groups. The proportions of patients showing ACR20 responses were significantly greater for 0.1, 1.0 and 2.0 mg/kg per day of anakinra compared with control (p = 0.014, 0.001 and 0.007, respectively). Similar results were apparent for ACR20 at 24 weeks, but a significantly improved response was only apparent with the 1.0 mg/kg per day dosage group (p = 0.018 vs control). ACR20 responses were evident from week 2, but statistically significant differences between active and control treatment did not appear before week 4.

A sustained ACR20 response (see above for definition) was seen more frequently for anakinra 0.1, 1.0 and 2.0 mg/kg per day compared with control (30%, 31% and 35%, respectively, vs 15% with control; $p < 0.05$ for all).

The proportion of patients achieving ACR50 and ACR70 was higher at all doses of anakinra evaluated (with a significant dose response) compared with control at both time-points. ACR50 responses at week 24 were 4% for control and 8%, 13%, 9%, 14% and 11% for anakinra groups with increasing dose. ACR70 responses at 24 weeks were 0% for control and 5%, 6.5%, 2%, 10% and 6.5% for anakinra groups with increasing dose. Statistical tests to assess the significance of these improvements compared with control were not reported, but only 16 patients of 345 treated with anakinra showed ACR70 responses at week 12 or 24.

The adjusted mean change from baseline in the components of the ACR criteria are presented for control versus anakinra (*Table 6*). At week 24 statistically significant changes from baseline compared with control were apparent for swollen

joint count (2.0 mg/kg per day only), pain (0.1, 1.0 and 2.0 mg/kg per day only), physicians' global assessment (1.0 and 2.0 mg/kg per day), patients' global assessment (0.1, 1.0 and 2.0 mg/kg per day), HAQ (1.0 and 2.0 mg/kg per day) and ESR (0.4, 1.0 and 2,0 mg/kg per day). The improvements in tender joint count, CRP and duration of morning stiffness did not reach statistical significance.

Eighty-eight patients (21%) withdrew from the study: 19% control and 21%, 16%, 22%, 22% and 26% across the anakinra dose groups. Withdrawals were due to lack of efficacy in 7%, 14%, 10%, 8%, 7% and 6% of patients, respectively.

Adverse events Across the dosage groups 4% patients on control, and 3%, 1%, 7%, 14% and 15% patients on anakinra 0.04–2.0 mg/kg per day withdrew from the study as a result of adverse events. ISRs were the most common adverse reaction encountered and increased in frequency with increasing anakinra dose: 28% control, and 19%, 38%, 56%, 64% and 63% anakinra 0.04–2.0 mg/kg per day. These were generally mild to moderate and diminished with time. ISRs led to withdrawal from treatment in 3%, 0%, 0%, 1%, 7% and 10%, respectively, across the groups.

The second most frequently reported side-effect, potentially related to anakinra, was headache, seen in 15% placebo, and 24%, 20%, 17%, 34% and 14% of patients in the 0.04, 0.1, 0.4, 1.0 and 2.0 mg/kg per day anakinra groups, respectively.

Severe adverse events were reported in 19% patients treated with placebo compared with 8–18% treated with any dose of anakinra studied. No deaths were reported during the study. Two patients (one control, one anakinra 2.0 mg/kg per day) were diagnosed with a new malignancy during the study (lung cancer, breast cancer), but neither was considered related to the study drug.

Other adverse drug reactions (ADRs) were not reported in detail. URTI was documented in 22% of patients treated with control compared with 14–24% treated with anakinra; other ADRs included sinusitis (15% vs 5–14%), abdominal pain (1% vs 6%), arthralgia (7% vs 6%) and worsening of RA (11% vs 6%). Serious infections occurred in seven patients in total: one control, two anakinra 0.04, one anakinra 0.1, one anakinra 0.4 and two anakinra 1.0 mg/kg per day.

Five cases of neutropenia (one in each anakinra dose group) occurred during the course of the study. In all cases patients were withdrawn from treatment and WBC levels returned to normal.

Antibodies to IL-1Ra were detected in nine of the 354 patients screened: one control and eight anakinra. Seven of the eight patients on anakinra who developed these antibodies suffered with ISRs.

Comments This trial represents the first study to explore anakinra in combination with methotrexate.

The design of this study was complicated by a change to the initial protocol. The study was originally designed to evaluate the 12 week efficacy of anakinra across three doses (0.1, 0.4 and 2.0 mg/kg per day). It was subsequently amended to a 24 week study and included two additional doses of anakinra (0.04 and 1.0 mg/kg per day). Of the 105 patients originally enrolled in the 12 week trial only three reconsented and remained in the trial to 24 weeks. The impact of this self-selection is unlikely to undermine significantly the results of this study owing to the small numbers of patients involved.

Results were analysed by ITT with non-responder imputation. Adjusted mean changes were reported adjusted for study centre and baseline value.

Again, there is the potential for unblinding owing to the high frequency of ISRs with anakinra.

Study 0145: Cohen and colleagues (2001)[101,103,105,110,112]

Population Patients enrolled in this trial had active RA despite treatment with methotrexate for at least 24 weeks (10–25 mg/week) at a stable dose for at least 8 weeks before study entry. Patients also took folic acid at a dose of approximately 1 mg/day. At baseline evidence of at least one bony erosion was required.

Active disease was defined as at least six swollen and nine tender joints and a CRP level ≥ 1.5 mg/dl or ESR ≥ 28 mm/hour.

Concomitant treatment with DMARDs other than MTX had to be discontinued at least 60 days before study entry. Treatment with NSAIDs and low-dose oral corticosteroids (≤ 10 mg/day of prednisolone or equivalent) was permitted provided patients were on a stable dose for at least 4 weeks before study entry. Rescue analgesics were allowed up to 12 hours before a scheduled study evaluation and intra-articular corticosteroids could be administered to two joints on two separate

occasions (doses not specified) provided that injections were at least 2 weeks before the next assessment visit. The treated joint was thereafter classified as a 'failed' joint in the joint assessment. The protocol permitted use of NSAIDs or oral steroids (or increases in dose), temporarily, for flare of RA symptoms. However, written permission was required for changes in steroid doses.

In total, 906 patients were recruited into this trial across 106 centres in the USA, Canada and Australia; 506 were included in the interim analysis.

The mean age of patients enrolled in the trial was 56.3 years. Mean disease duration was 10.8 years. Eighty seven per cent of patients were white and 77% were female. Patients had a mean of 20 swollen and 26 tender joints at baseline. The number of previous DMARDs used was not stated. NSAID use (76.4%) and oral corticosteroid use (52.7%) were comparable in both groups. In total, 76.8% of patients were RF positive at baseline. The median dose of methotrexate at baseline was 15 mg/week and median HAQ score 1.38 in both groups. Mean baseline ESR was 42 mm/hour and CRP 2.6 mg/dl.

Intervention Study drugs were all administered by subcutaneous injection once daily by the patient. Patients were randomised to:

- control (MTX alone) (n = 253, 24 weeks; 453, 52 weeks)
- anakinra 100 mg (n = 253, 24 weeks; 453, 52 weeks).

Study duration and key outcomes The primary end-point was radiographic progression measured by modified Sharp score at 1 year. However, a 6 month interim analysis was undertaken on the 506 patients enrolled in the trial as of 18 May 2000 with ACR20 as a primary end-point. Sustained ACR20 response, ACR50, ACR70 and other ACR components of disease activity were secondary end-points. Sustained ACR20 response was defined as an ACR20 response for at least 4 out of the 6 months of therapy (not necessarily consecutive), and one of which was at week 12 or 24.

The study blind, for the primary outcome of radiographic progression, was maintained during the interim analysis.

Main results ACR20 response at 24 weeks was 22% with MTX and placebo (control) versus 38% for anakinra 100 mg with MTX ($p < 0.001$). It was assumed that where ACR responses could not be calculated because of missing data, ACR response did not occur ('non-responder imputation'). Similarly, patients who increased their baseline dose of methotrexate or corticosteroids were classified as non-responders from the time of dose increase. A significant difference in ACR20 response between the groups was apparent from week 4. The ACR response increased to week 12 in patients on control and then plateaued. For patients on anakinra plus MTX, ACR20 response continued to increase to at least week 20.

Sustained ACR20 response was reported in 12% of patients treated with control and 27% treated with anakinra plus MTX ($p < 0.001$).

The proportion of patients who achieved ACR50 and ACR70 was 17% and 5.6%, respectively, with anakinra plus MTX, compared with 8% and 2% with control ($p = 0.001$ and $p = 0.024$).

The mean reduction in swollen joints for patients treated with control was 6.5 joints (total assessed 66) compared with 6.8 for anakinra plus MTX ($p = 0.686$) at 24 weeks. This result is surprising since an ACR20 response requires a 20% improvement in swollen and tender joints as well as three other disease components (from physician and patient global, patient's assessment of pain, disability score and ESR or CRP). These other disease parameters showed significant differences when comparing anakinra plus MTX and control (*Table 6*).

Over 6 months, 67 (26.5%) patients on control and 56 (22.1%) on anakinra withdrew from the study. Two patients randomised to control and three to anakinra did not receive study drug and were excluded from the ITT analysis. Of the other withdrawals 29 (12%) patients on control and 12 (5%) on anakinra withdrew at the subject's request and 10 (4%) versus 3 (1%) because of disease progression. Lack of efficacy per se was not specified as a reason.

Preliminary data reported in an abstract indicate that the anakinra group had less joint damage over 52 weeks ($p = 0.002$). It is also stated that those who failed to achieve an ACR20 response at 24 weeks also had less joint damage.[112]

Adverse events Withdrawals due to adverse events are reported to have occurred in 9% of patients on control and 13% on anakinra. ISRs were the most common adverse event and occurred in 24% control and 65% anakinra-treated patients,

leading to withdrawal from the study in 0.8% and 8.4%, respectively. These reactions were generally mild to moderate and transient.

Infectious episodes occurred in 26% of control patients compared with 33% for anakinra, but there were similar numbers of serious infections (0.8%). Serious adverse events, affecting a variety of body systems, occurred in eight (3.2%) control patients and 11 (4.4%) anakinra patients. No patients died while receiving study drug, although one patient died of congestive heart failure 37 days after discontinuing the study drug (anakinra).

Comments This trial was complicated by allowing an LOE designation after 16 weeks. LOE designation was defined as a failure to achieve ACR20 response on three consecutive visits spanning 8 weeks. These patients continued with study drug and had their regimen optimised by changing their methotrexate, corticosteroid and/or NSAID doses. If patients continued to meet the LOE criteria after these dosage changes then hydroxychloroquine, sulfasalazine, gold, minocycline, leflunomide or ciclosporin could be added. Nineteen patients (7.6%) in each arm increased corticosteroid or DMARD usage (eight patients on control because of failure to meet efficacy criteria and five patients on anakinra). Subjects who required a change in their baseline medication owing to LOE were classified as non-responders for the ACR20.

To prevent assessors becoming aware of treatment allocation due to ISRs, independent assessors were used to evaluate swollen and tender joint counts.

Results, for the interim analysis, were analysed by ITT for all randomised subjects who received at least one dose of study drug (n = 251 control, n = 250 anakinra plus MTX), with non-responder imputation. Sensitivity analysis around the primary end-point conducted by the FDA identified that the difference in ACR20 response rates between control and anakinra remained statistically significant when the analysis was adjusted to:

- a completer analysis
- consider only patients with no injection site reaction
- count patients who responded after a change to their treatment regimen as responders, not failures.

Subset analysis by the FDA found no evidence that the benefit from anakinra was limited to any identifiable subset of RA patients in terms of age, gender, ethnicity, disease duration, RF status and acute-phase reactants at baseline, and baseline level of disease activity.

This 1 year trial, with a planned recruitment of 990 patients, was designed to evaluate radiographic outcome using the modified Sharp total score at 12 months. Only limited data are currently available. Preliminary analysis suggests that anakinra plus MTX inhibits joint destruction compared with MTX alone (change from baseline to week 52 in total modified Sharp score, p = 0.002). This effect on disease progression was also apparent in patients who failed to achieve an ACR20 response at week 24.

Study 0757: Fleischman and colleagues (2001)[106]
This large randomised placebo-controlled international study was undertaken to evaluate the safety of anakinra in the "usual RA patient seen in clinical practice".

Population Adult patients (age ≥ 18 years) with RA for at least 3 months were enrolled. Those on DMARDs as either monotherapy or combination therapy had to be on stable doses for at least 2 months. Concomitant treatment with NSAIDs and/or low-dose oral corticosteroids (doses stabilised for at least 1 month) was also permitted. A minimum of three swollen and three tender/painful joints or morning stiffness of at least 45 minutes were required for entry.

Changes in NSAIDs, corticosteroids or DMARDs were permitted during the study as clinically needed. The following drugs, however, were not permitted: etanercept, infliximab, mycophenolate mofetil, cyclophosphamide, ciclosporin and prosorba column.

In total, 1414 patients in Australia, Belgium, Canada, Germany, Ireland, Sweden, the UK and the USA were enrolled. Over 80% of patients were enrolled in the USA. Concomitant diseases were present in 5–10% patients: chronic obstructive pulmonary disease 5%, history of pneumonia (9%), asthma 9%, coronary artery disease 10%, diabetes mellitus 6%. The trial was double blinded and controlled for the first 6 months with an open-label extension to 3 years (still ongoing).

The mean age of patients enrolled in this trial was 55 years, with 23.0% patients aged 65 or over. Mean disease duration was 10.2 years (median 7.5 years); 88% patients were white and 75% were female. Patients had a mean of 19 swollen and

23 tender joints at baseline. Mean baseline CRP was 2.7 mg/dl (median 1.7 mg/dl).

DMARDs were taken by 82% of patients on control and 78% of patients randomised to anakinra. Figures for MTX were 59% and 52%, respectively, with a mean (and median) dose of MTX of 15 mg/week in both groups. After MTX the most common DMARDs were hydroxychloroquine (22% patients) sulfasalazine (14%) and leflunomide (10%). Combinations of DMARDs were being given to 30% on control and 28% on anakinra.

At baseline a high proportion of patients were on NSAIDs (87%) and corticosteroids (58%), with similar usage in both groups.

Intervention Study drugs were administered by subcutaneous injection once daily. Patients were randomised to treatment in a 1:4 ratio:

- control (placebo plus current DMARD regimen) (n = 284)
- anakinra 100 mg/day (n = 1130).

Study duration and key outcomes Study duration was 3 years. The primary end-point for this ongoing study is safety, evaluated by death, serious and severe adverse events and discontinuation from the study owing to adverse events.

This study was controlled and blinded to 6 months with open-label anakinra planned for 3 years. Safety data for the 6 month controlled trial are available. The open-label phase completed at the end of 2002. No efficacy end-points have been reported and none is currently available from Amgen.

Results were analysed by ITT for all randomised subjects who received at least one dose of study drug (n = 283 control, n = 1116 anakinra).

The study had 63% probability of observing at least one case of an adverse event occurring with an incidence of ≥ 0.1% over 2.5 years. At the 6 month end-point there was a > 99% chance of detecting an adverse event occurring at a rate of 1%.

Main results By 6 months 54 of 284 (19%) of the patients allocated to control and 255 of the 1130 (23%) patients allocated to anakinra had withdrawn prematurely. Withdrawal because of an adverse event occurred in 6% and 11.5%, respectively. Consent was withdrawn by approximately 6% of patients in each group before completing 6 months.

ISRs in particular were more common with anakinra and occurred in 73% versus 33% of control patients. ISRs led to withdrawal in 7% versus 1% of patients, respectively. Anakinra caused ISRs that were described as erythema, pruritus or rash, whereas control caused ISRs reported as pain or ecchymoses. Most ISRs occurred within 1 month, but the duration of each ISR was not determined.

Respiratory events were experienced by 34.6% of control-treated and 35.0% of anakinra-treated patients, and consisted primarily of URTI and sinusitis. Pneumonia or bronchopneumonia occurred in two control (0.7%) patients and 15 (1.4%) anakinra patients, leading to withdrawal in five of these 15. Musculoskeletal pain and worsening of RA occurred more commonly in control-treated patients and led to withdrawal in 3.5% of patients compared with 2.1% for anakinra-treated patients.

Five patients died during the 6 month study: one on control (0.4%) and four on anakinra (0.4%). Causes of death were myocardial infarction (control), pulmonary fibrosis, suicide, melanoma and upper gastrointestinal bleeding (anakinra).

Serious adverse events (SAEs) were reported in 7.8% control-treated and 7.7% anakinra-treated patients. By body system a higher proportion of serious adverse events was seen with anakinra for the gastrointestinal (2% vs 0.4%) and respiratory (2% vs 0.4%) systems. Severe adverse events were reported in 13.1% of control and 15.5% of anakinra-treated patients.

The overall incidence of infections was similar for control and anakinra: 43.5% vs 41.2%. However, severe infections were more common with anakinra: 2.1% vs 0.4%. None was fatal. The most common severe infections seen with anakinra were pneumonia (ten patients), cellulitis (three patients) and osteomyelitis (three patients). Patients who developed infections tended to be male and older.

In total, nine malignancies were reported during the 6 month study: four (0.4%) anakinra and five (2%) control.

Comments This large pragmatic trial was concerned with safety, but it also provides effectiveness data for anakinra, in a typical clinical population of patients with RA. The first 6 months of the trial when efficacy data were collected, was blinded. ACR assessments were undertaken at screening and at month 6. All data collection for

the 6 month end-points was completed by 26 July 2000. The effectiveness data from this trial were requested from Amgen, but the pharmaceutical company declined to make it available. They issued the following statement:

> "Study 990757 was designed to evaluate the overall safety of anakinra in 1,414 patients with rheumatoid arthritis (RA) in the average clinical practice to contrast against the more controlled patient populations enrolled in previous studies. The primary safety endpoints assessed the incidence of: adverse events, deaths, serious adverse events, and adverse events leading to withdrawal, and infections. No efficacy endpoints were planned for the study. This study included patients receiving a variety of concurrent RA medications including multiple DMARD therapies, as well as patients who were DMARD-free. Concurrent DMARDs included MTX, sulfasalazine, hydroxychloroquine, gold, penicillamine, leflunomide, and azathioprine. The study population also included patients predisposed to infection due to a history of underlying disease such as pneumonia, asthma, controlled diabetes, and chronic obstructive pulmonary disease. Patients with co-morbidities such as hypertension, coronary artery disease and congestive heart failure were also included.
>
> Given the study was not designed to assess efficacy, and the varied patient population defined above, it would be inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study. Confounding factors such as disease duration, concomitant medications and co-morbid conditions make it difficult to define discrete patient populations in whom efficacy could be assessed and even where this is possible, the low numbers of patients in such analyses renders any clinical or statistical assessment invalid."

It is not true that no efficacy end-points were planned for the study. Table 7-1 of the study report shows that ACR scores (at the screening assessment and at 6 months) were collected prospectively. That this was planned from the start of the trial is confirmed in Table 7-2 of the study report, Summary of Protocol Amendments, which shows that making an ACR score assessment was not a later amendment.

Although the primary end-point of this study was safety, the non-disclosure of efficacy data is of concern, owing to both the large size of this trial and its 'real-life' design.

Meta-analysis

Treatment with anakinra at doses in line with the licensed dose of 100 mg/day showed a consistent clinical benefit in the trials included in this report. Data were pooled to obtain a summary measure of treatment effect. The methods and key findings are described below.

Methods

As this is a rapid review meta-analyses were restricted to six important measures of treatment. 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 represent an overall measure of treatment effect, were also analysed. The primary analysis pooled results from the latest follow-up data available for the blinded, randomised, controlled period of each trial (24 weeks for all studies, with the exception of 0182 where data are presented at week 12).

Results were pooled for trials where anakinra (with or without methotrexate) was compared with placebo. Pooled results for use in combination with methotrexate (licensed indication) are also presented. For the dose-ranging trials (0560, 0180) a chi-squared test for trend was undertaken for the ACR end-point based on the aggregated data. Since individual patient data were not available for the disease activity end-points a test for trend could not be undertaken since group data may be subject to the ecological fallacy. [The ecological fallacy is the attribution of group-level associations (e.g. from aggregated trial data or countries) to the individuals that constitute the group.] Given that the test for trend on the ACR 20, 50 and 70 end-points suggested that there may be a dose response, the doses closest to the licensed dose were pooled (75 mg and 150 mg for study 0560, 1.0 and 2.0 mg/kg per day for study 0180). However, all data should be considered relevant. A sensitivity analysis including all data is therefore also reported.

Where possible, the standard deviation (SD) was taken directly from the reported results or derived from the standard error of the mean (SEM) where used. Where an outcome was reported on the same scale the results are presented as a weighted mean difference (WMD).

A fixed effects model was used since statistical heterogeneity was not demonstrated across the trials.

To pool outcomes that use continuous data, the final result was used, not percentage change from baseline. More estimates of variability were available in this way.

ACR improvements

Licensed dose analysis

Pooled analyses for ACR improvements (at or around the licensed dose of anakinra, based on $n = 1007$) are shown in *Figures 2–4* as both relative risk (RR) and risk difference (RD). A clear treatment effect is evident for ACR20, but the effect on the more rigorous end-points of ACR50 and ACR70 is much smaller.

Clinical effectiveness, when expressed in terms of RR of achieving an improvement in ACR, increases

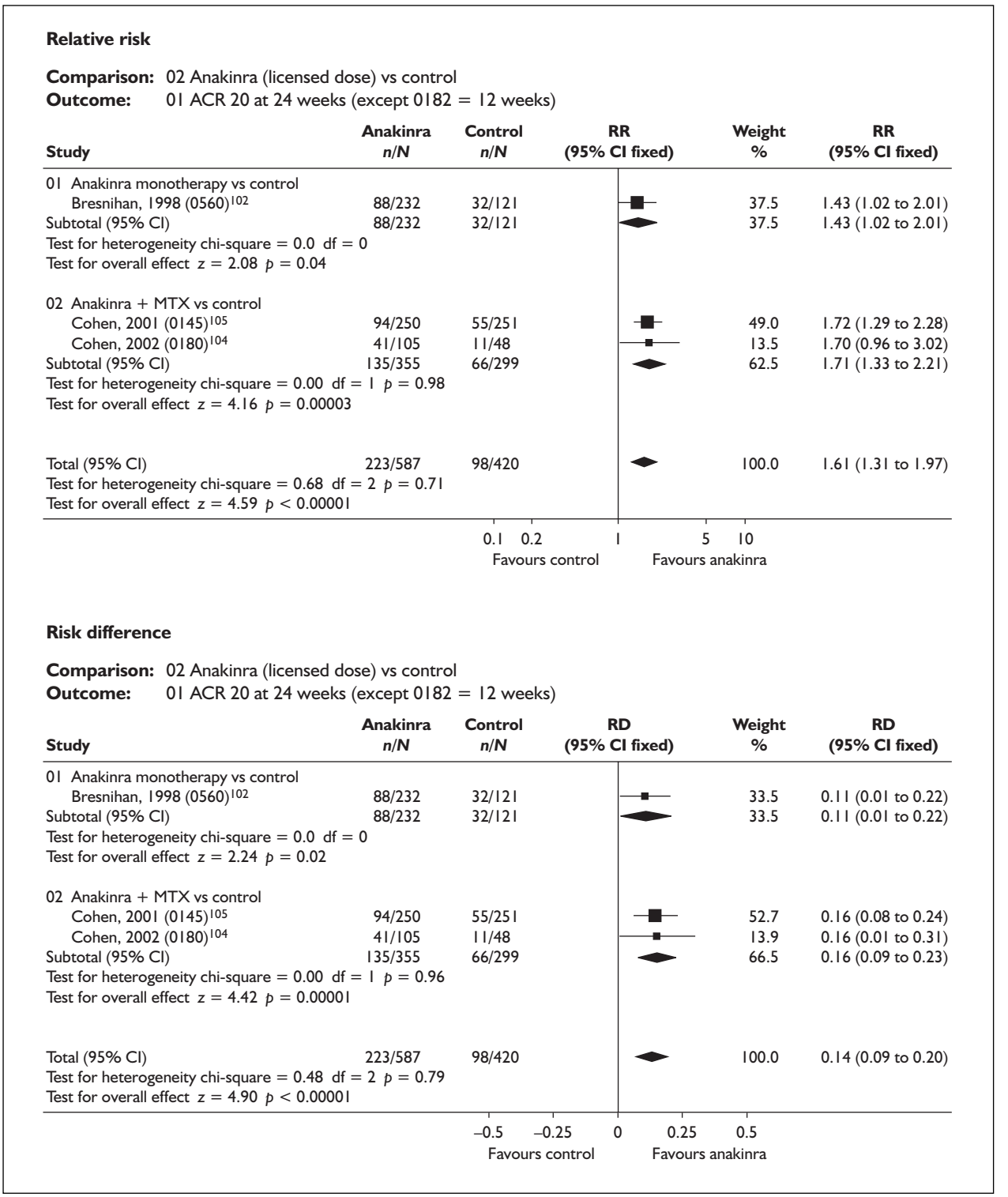


FIGURE 2 *Anakinra (licensed dose) versus placebo, result at end of trial: ACR20*

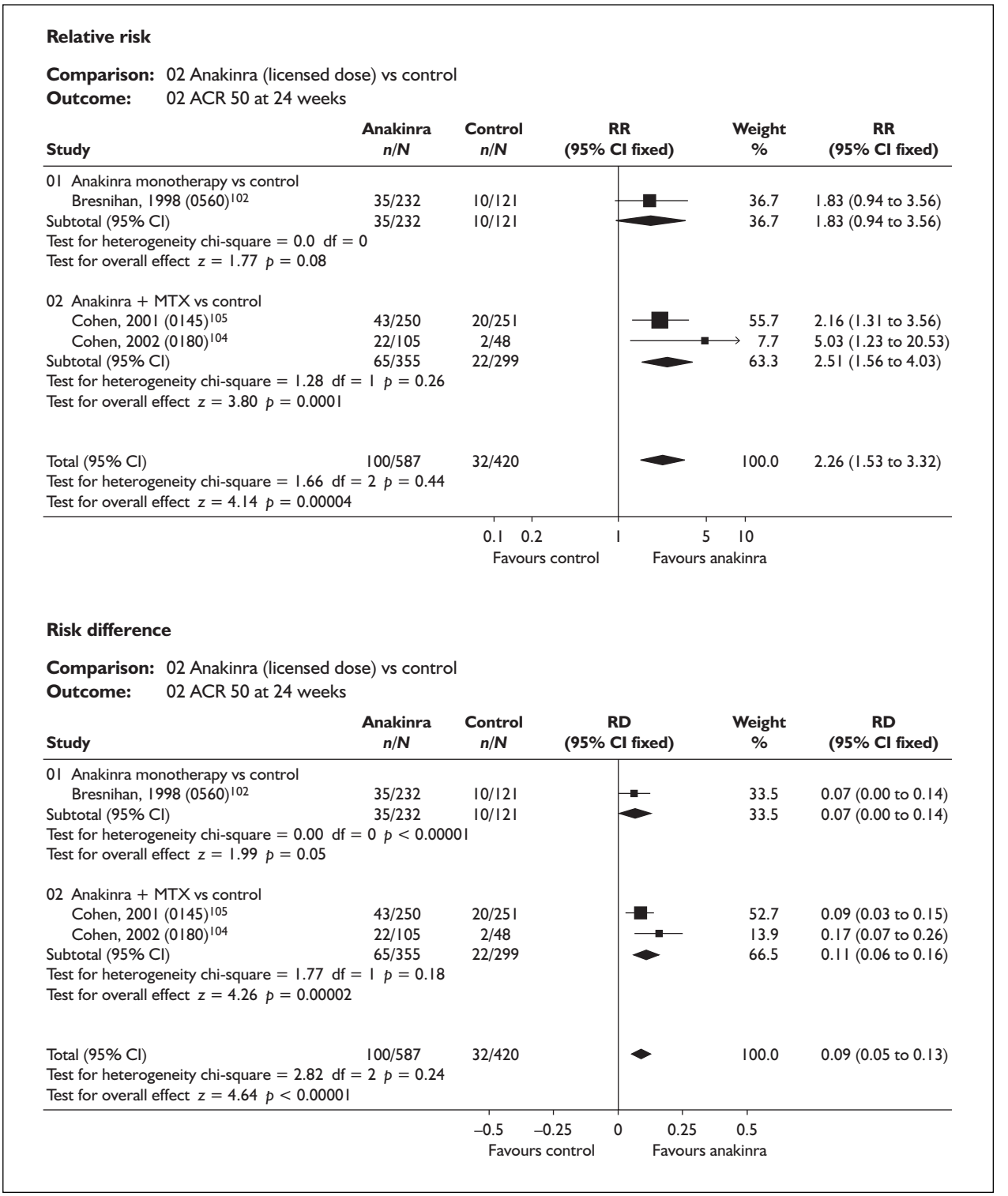


FIGURE 3 *Anakinra (licensed dose) versus placebo, result at end of trial: ACR50*

with a higher hurdle, such that the RR of achieving an ACR20 with anakinra was 1.6, while the RR of achieving ACR70 was around 3, consistent with treatment effect. However, effectiveness expressed as an 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 7 [95% confidence interval (CI) 5 to 11], the NNT for ACR50 was 11 (95% CI 8 to 20) and the NNT for ACR70 was 33 (95% CI 20 to 100). Both the ACR50 and ACR70 are believed to be clinically very significant.

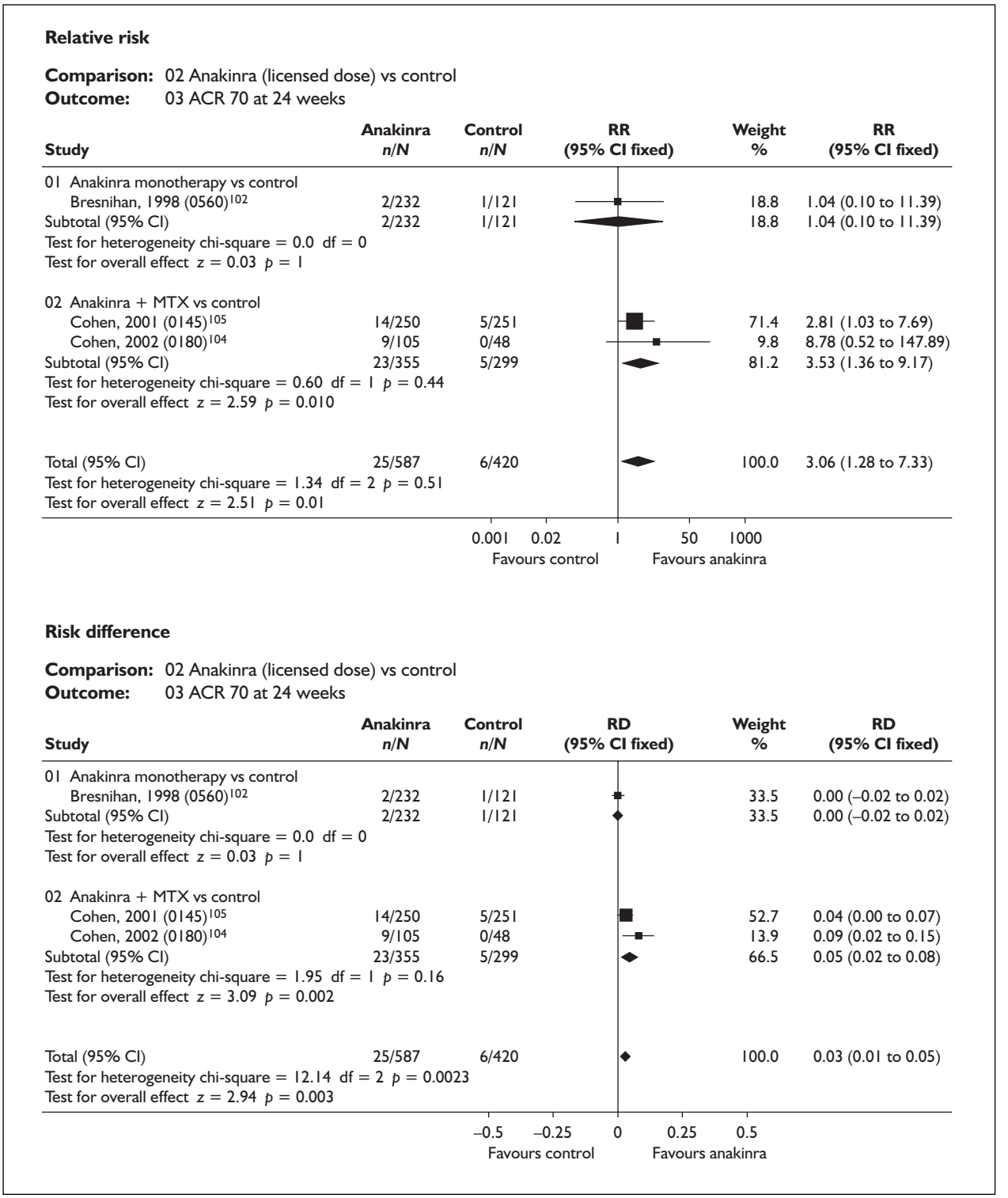


FIGURE 4 *Anakinra (licensed dose) versus placebo, result at end of trial: ACR70*

For the subset of patients enrolled in trials who received anakinra (at or around the licensed dose) in combination with methotrexate (based on $n = 654$), the NNT to achieve an ACR20 response was 6, ACR50 was 9 and ACR70 was 20.

All dose analysis

When ACR end-point data for all doses of anakinra evaluated in clinical trials are pooled (based on $n = 1429$), the NNT to achieve an ACR20 response increases to 9 (95% CI 6 to 17)

and for ACR50 increases to 13 (95% CI 9 to 25). A statistical benefit in terms of ACR 70 response is no longer apparent.

Sensitivity analysis considering study 0757
For any decision made there will always remain some uncertainty and variability in the data that inform the decision. A key role of decision analytic modelling is not only to obtain the best estimate based on current knowledge but, importantly, to investigate the consequences of plausible estimates concerning the uncertainties.

Trial 0757 had less restrictive inclusion criteria, to reflect the characteristics of people with RA, than the other trials (which use a more controlled patient population not representative of average clinical practice) and is therefore probably the most generalisable of all the trials to real-life practice. Thus, the findings of study 0757 are highly relevant to the health technology assessment. Moreover, over half the people who have received anakinra (1116 out of the 2146) were in this trial (of whom 77.4% completed the first 6 months), so a significant amount of trial data are missing. For these reasons trial 0757 should not be ignored.

The fact that the pharmaceutical company has declined to allow the effectiveness data for this trial into the public domain and their assertion that any statistical assessment of efficacy would be invalid suggest to the authors of this report that the effectiveness in this pragmatic trial may have been less than in the earlier trials and probably did not reach conventional levels of statistical significance.

If the assumption were made that the withheld data showed no difference in effectiveness between the anakinra and placebo recipients, this would give the following combined estimate of effect for ACR 20 response: RR 1.39 (95% CI 1.03 to 1.87), RD 0.10 (95% CI 0.01 to 0.19). However, this figure almost certainly underestimates the effectiveness of anakinra seen in this trial as it is unlikely that, given the positive results from earlier trials, the result from 0757 would be completely null or negative.

However, the authors think that the result was probably suggestive of benefit but failed to reach conventional levels of statistical significance. Based on the assumption that the results from this trial favour anakinra over placebo but the p-value of treatment difference was possibly of the order of $p < 0.1$ to $p < 0.2$, the authors worked backwards to derive a plausible estimate of effectiveness for trial 0757. Of the 283 placebo patients, 66 were assumed to have an ACR20 response (paralleling the 23% response rate seen in the combined results for the placebo groups in earlier trials). Working backwards, a response rate of 303/1116 in the anakinra group would have given a two-sided $p < 0.2$ or one-sided $p < 0.1$.

This figure for trial 0757 was combined with the data from the earlier trials to give the best summary estimate about anakinra's effectiveness (*Figure 5*). Given the fact that there is clinical heterogeneity in terms of different population characteristics, co-morbidities and co-medications in trial 0757 compared with earlier trials, 0757 was combined with previous trials using a random effects model. This gives the following as the best summary estimate of effectiveness for the ACR20 response: RR 1.43 (95% CI 1.16 to 1.76), RD 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25).

HAQ scores, patient global assessment and swollen joint counts
The pooled result at the end of trials for HAQ scores for anakinra versus placebo gave a weighted mean difference of –0.18 (95% CI –0.12 to –0.24) with licensed doses (*Figure 6*) and –0.16 (95% CI –0.11 to –0.22) for all doses. The HAQ scale scores 0 for normal function and 3 for greatest disability, thus a reduction indicates improved function. Improvement in function was slightly less in the pooled analysis of trials which evaluated anakinra (licensed dose) in combination with methotrexate (WMD –0.14, 95% CI –0.07 to –0.22).

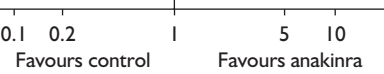
Patient global assessment of disease activity, which indicates the patient's view of how the arthritis is doing, was scored in most trials on a scale of 0 (best) to 100 (worst). The WMD for anakinra at licensed dose compared with placebo was –10.4 (95% CI –6.3 to –14.4) at the end of the studies (*Figure 7*). This also represents the improvement seen with use in combination with methotrexate. The monotherapy trials 0560 and 0182 used a scale of 0–4 for patient assessment of disease activity and were not included in this meta-analysis. No effect was evident in the low-dose study 0182, but in study 0560 the direction of effect on patients' global assessment of disease activity was consistent with the other trials, although the size of benefit is much smaller.

The swollen joint count at the end of studies was reduced by 1.5 (95% CI –0.38 to –2.68) in the anakinra (licensed dose) arms compared with

Relative risk

Comparison: 03 Anakinra (licensed dose) vs control including 0757
Outcome: 01 ACR 20 at 24 weeks (except 0182 = 12 weeks)

Study	Anakinra *n/N*	Control *n/N*	RR (95% CI random)	Weight %	RR (95% CI random)
01 Anakinra monotherapy vs control					
Bresnihan, 1998 (0560)[102]	88/232	32/121		23.7	1.43 (1.02 to 2.01)
Subtotal (95% CI)	88/232	32/121		23.7	1.43 (1.02 to 2.01)
Test for heterogeneity chi-square = 0.0 df = 0					
Test for overall effect $z = 2.08$ $p = 0.04$					
02 Anakinra + MTX vs control					
Cohen, 2001 (0145)[105]	94/250	55/251		29.5	1.72 (1.29 to 2.28)
Cohen, 2002 (0180)[104]	41/105	11/48		10.9	1.70 (0.96 to 3.02)
Subtotal (95% CI)	135/355	66/299		40.4	1.71 (1.33 to 2.21)
Test for heterogeneity chi-square = 0.00 df = 1 $p = 0.98$					
Test for overall effect $z = 4.16$ $p = 0.00003$					
03 Anakinra + DMARD vs control					
Fleishmann, 2001[106]	303/1116	66/283		36.0	1.16 (0.92 to 1.47)
Subtotal (95% CI)	303/1116	66/283		36.0	1.16 (0.92 to 1.47)
Test for heterogeneity chi-square = 0.0 df = 0					
Test for overall effect $z = 1.28$ $p = 0.2$					
Total (95% CI)	526/1703	164/703		100.0	1.43 (1.61 to 1.76)
Test for heterogeneity chi-square = 4.89 df = 3 $p = 0.18$					
Test for overall effect $z = 3.39$ $p = 0.0007$					



Risk difference

Comparison: 03 Anakinra (licensed dose) vs control including 0757
Outcome: 01 ACR 20 at 24 weeks (except 0182 = 12 weeks)

Study	Anakinra *n/N*	Control *n/N*	RD (95% CI random)	Weight %	RD (95% CI random)
01 Anakinra monotherapy vs control					
Bresnihan, 1998 (0560)[102]	88/232	32/121		22.9	0.11 (0.01 to 0.22)
Subtotal (95% CI)	88/232	32/121		22.9	0.11 (0.01 to 0.22)
Test for heterogeneity chi-square = 0.0 df = 0					
Test for overall effect $z = 2.24$ $p = 0.02$					
02 Anakinra + MTX vs control					
Cohen, 2001 (0145)[105]	94/250	55/251		28.2	0.16 (0.08 to 0.24)
Cohen, 2002 (0180)[104]	41/105	11/48		14.1	0.16 (0.01 to 0.31)
Subtotal (95% CI)	135/355	66/299		42.4	0.16 (0.09 to 0.23)
Test for heterogeneity chi-square = 0.00 df = 1 $p = 0.96$					
Test for overall effect $z = 4.42$ $p = 0.00001$					
03 Anakinra + DMARD vs control					
Fleishmann, 2001[106]	303/1116	66/283		34.7	0.04 (–0.02 to 0.09)
Subtotal (95% CI)	303/1116	66/283		34.7	0.04 (–0.02 to 0.09)
Test for heterogeneity chi-square = 0.00 df = 0 $p < 0.00001$					
Test for overall effect $z = 1.35$ $p = 0.18$					
Total (95% CI)	526/1703	164/703		100.0	0.11 (0.04 to 0.18)
Test for heterogeneity chi-square = 7.17 df = 3 $p = 0.067$					
Test for overall effect $z = 3.05$ $p = 0.002$					

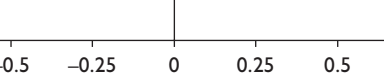


FIGURE 5 *Anakinra (licensed dose including study 0757) versus placebo, result at end of trial: ACR20*

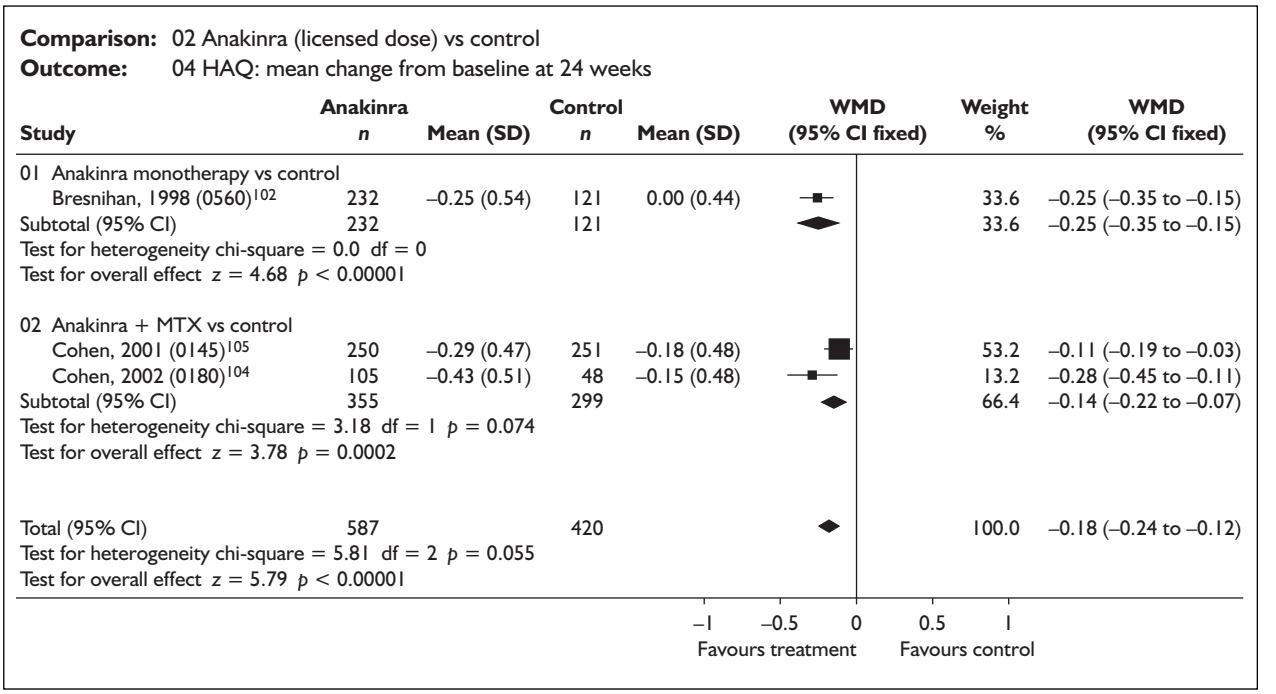


FIGURE 6 *HAQ: anakinra (licensed dose) versus placebo*

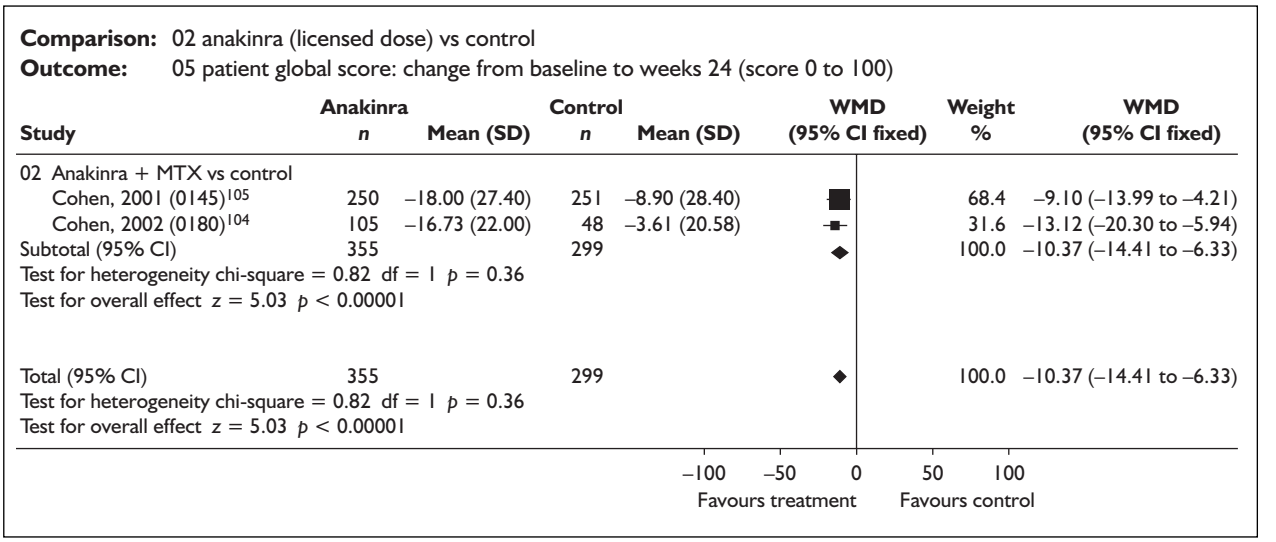


FIGURE 7 *Patient global assessment: anakinra (licensed dose) versus placebo*

placebo (*Figure 8*) and by 1.2 (95% CI –0.11 to –2.2) for all doses. Similar but slightly smaller benefit which was not statistically significant was evident with use in combination with methotrexate, with a reduction of 1.2 (95% CI 0.15 to –2.54).

Anakinra compared with other agents

The trial data clearly demonstrate that anakinra at the higher doses evaluated has a statistically significant effect, compared with placebo, on ACR 20% response rates in patients with RA. However, no trials have directly compared anakinra head-to-head with another DMARD, or more specifically another biological modifier. In trials where patients continued with methotrexate but were given additional treatment with anakinra or placebo, these were not regarded as a direct comparison of DMARD against anakinra.

In Europe anakinra is only licensed for use in combination with methotrexate. A number of trials with TNF inhibitors have evaluated use in combination with methotrexate. Direct comparisons

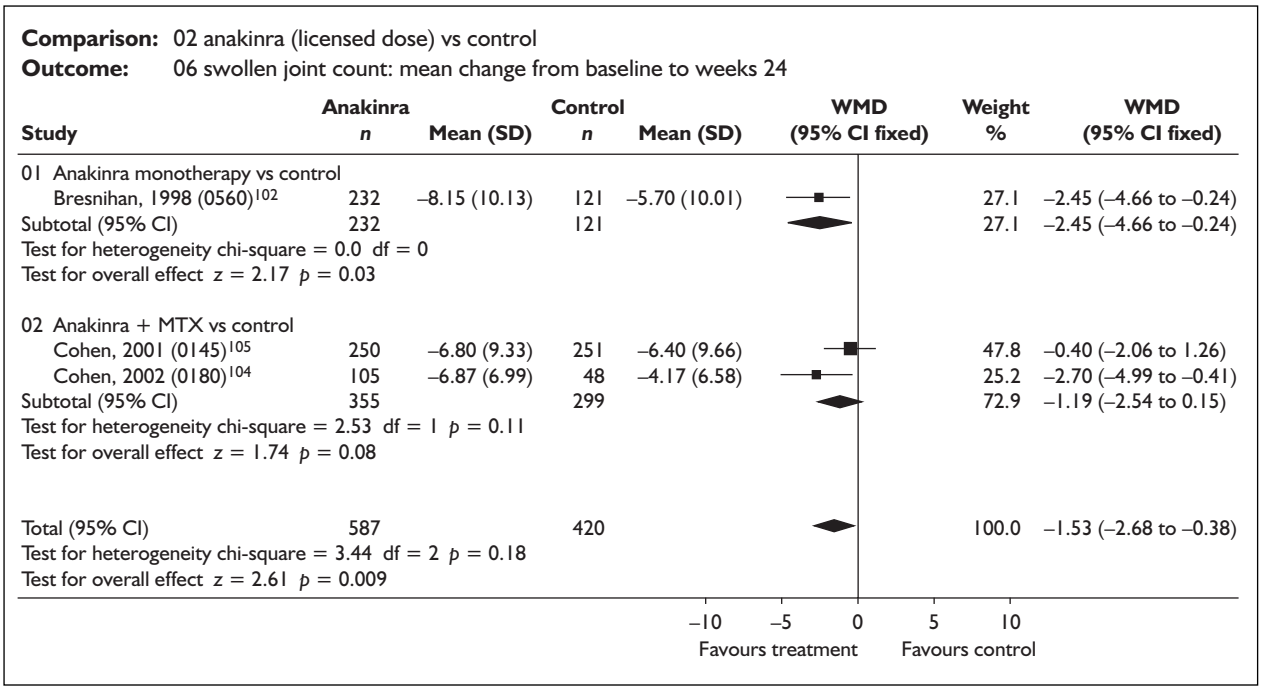


FIGURE 8 *Swollen joint counts: anakinra (licensed dose) versus placebo*

TABLE 8 *Adjusted indirect comparison of anakinra with TNF inhibitors*

Intervention	RD (95% CI) for ACR20 response
TNF inhibitor + MTX vs MTX alone[39]	0.37 (0.28 to 0.45)
Anakinra + MTX vs MTX alone[103]	0.16 (0.09 to 0.23)
Anakinra + MTX vs TNF inhibitor + MTX	–0.21 (–0.32 to –0.10)

between these classes of drugs have not been undertaken. When there is no direct comparison it has been demonstrated that the adjusted indirect method (which makes some adjustment for variability in prognostic factors at baseline across trials) may be used to obtain some evidence about the relative efficacy of competing interventions. Such indirect results should be interpreted with caution, since the estimate provided may differ from that obtained by direct comparison within RCTs. Nevertheless the adjusted indirect method can be useful in guiding clinical practice in the absence of direct comparisons between agents.[113]

Results from four clinical trials that evaluated different cytokine inhibitors in combination with effective doses of methotrexate have now been published: two with anakinra,[104,105] one with etanercept[114] and one with infliximab.[115]

Table 8 compares the clinical responses in terms of ACR across these trials, for all treatment doses combined for the etanercept and infliximab studies and the licensed dose for anakinra. This differentiation was made since for anakinra a dose response appeared to be evident across the doses evaluated. The response was measured at end-point, 24 weeks for anakinra and etanercept and 54 weeks for infliximab.

This indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate.

For the adjusted indirect comparison to be valid, the key underlying assumption is that the relative efficacy of an intervention is consistent in patients included in different trials; that is, that the estimated relative efficacy is generalisable. For both TNF inhibitors and anakinra consistent benefit was seen across clinical trials, trials were of similar design, conducted in similar settings with similar sorts of patients and were of high quality. Diagnostic criteria are standard in most

TABLE 9 *Summary of adverse events reported in clinical trials with anakinra (all doses)*

Adverse event		Clinical trial				
	Treatment	**0560**	**0182**	**0180**	**0145**	**0757**
% withdrawing due to AE	Control	4.1%	7%	4.1%	9%	6%
	Anakinra	6.6%	5%	7.8%	13%	11.5%
Individual events						
Deaths	Control	0%	0%	0%	0%	0.4%
	Anakinra	0%	0%	0%	0%	0.4%
Serious adverse events	Control	11.6%	6.7%	4.1%	3.2%	7.8%
	Anakinra	12.8%	6.3%	6.7%	4.4%	7.7%
Malignancy	Control	0%	0%	1.4%	NR	1.8%
	Anakinra	1.1%	0%	0.3%	NR	0.4%
ISRs	Control	25%	3%	28%	24%	33%
	Anakinra	54.5%	19.8%	48%	65%	73%
Any infection	Control	38%	13.3%	50%	25.9%	43.5%
	Anakinra	37%	13.5	48.4%	33.3%	41.2%
Serious infection	Control	0.8%	NR	1.4%	0.8%	0.4%
	Anakinra	1.7%	NR	1.7%	0.8%	2.1%
Neutropenia	Control	4%	0%	0%	NR	NR
	Anakinra	9%	0%	1.4%	NR	NR
Antibodies to IL-1Ra	Control	0%	0%	1.8%	NR	NR
	Anakinra	0.9%	5%	2.7%	NR	NR

Trial 0145 – interim data whilst the trial was ongoing. AE data are limited to avoid breaking the blinding of the trial.

contemporary trials and inclusion and exclusion criteria can also be considered sufficiently similar. The authors therefore believe that such an indirect comparison is valid. Overall, if results from RCTs are generalisable to clinical practice then they should also be generalisable to other trials in which similar patients were included.

Adverse effects: summary and additional data

The safety data for anakinra are derived from 2606 subjects with RA who have been exposed to anakinra in clinical trials, including 1812 (1379 ≥ 100 mg/day) exposed for at least 6 months and 570 (237 ≥ 100 mg/day) exposed for at least 1 year.[96] Safety for up to 4.5 years has been evaluated in 67 patients in the open-label extension study of 0560. No new safety concerns arose over this time.

Published data on adverse effects are available from the American prescribing information, the SPC, the four clinical efficacy studies and the 6 month, double-blind safety study. Amgen also have safety data from over 12,000 patients in the postmarketing setting. Adverse events reported in the trial programme are summarised in *Table 9*.

Across the five RCTs, adverse events led to withdrawal from treatment in 6.7% of control and 10.1% of anakinra-treated patients. The differences in withdrawal rates between control and anakinra were primarily the result of ISRs.

Deaths

Eighteen patients died while taking study medication (five during double-blind treatment and 13 during open-label extension studies): four cancer, three infections, five cardiovascular events and six other. All but one of these deaths occurred in patients taking anakinra. A further patient died 37 days after discontinuing study drug (anakinra) from a condition which developed while on study medication.[103]

Serious adverse events

SAEs were essentially defined as any events that represented a significant hazard to health. These encompassed events that were life threatening, permanently disabling, required or prolonged hospitalisation, resulted in death, or constituted cancer, congenital abnormality or overdose. The incidence of serious adverse events in each of the four trials presenting results was similar with control and active treatment: 6.5% and 8%, respectively, across all four trials.

For trials 0560, 0182, 0180 and 0145 the number of SAEs was small and no meaningful conclusions can be drawn. No treatment specific trends were noted.

TABLE 10 *Reports of and withdrawals due to ISRs across clinical trials*

Trial		Control	Anakinra								
			30 mg	75 mg	150 mg	0.04 mg/kg	0.1 mg/kg	0.4 mg/kg	1.0 mg/kg	2.0 mg/kg	100 mg
0560	ISR	25%	50%	73%	81%						
	Withdrawals	2%	0.8%	3%	5%						
0182	ISR	3%	35%								
	Withdrawals	0%	0%								
0180	ISR	28%				19%	38%	56%	64%	63%	
	Withdrawals	2.7%				0%	0%	1.3%	6.8%	9.7%	
0145	ISR	24%									65%
	Withdrawals	0.8%									8.4%
0757	ISR	33%									73%
	Withdrawals	1.4%									7.1%

In trial 0757, although the incidence of SAEs was similar between the study groups, when analysed by body systems compared with control a higher proportion of anakinra-treated patients suffered gastrointestinal (< 0.4% vs 1.8%) and respiratory (0.4% vs 1.6%) events. No predominant gastrointestinal event was evident; however, the higher incidence of respiratory events could in part be accounted for by a higher incidence of pneumonia. In contrast, more patients on control suffered a serious musculoskeletal event (2.8% vs 2.5%) with anakinra, predominantly RA.

Malignancies

Twenty-two malignancies were reported across studies 0560, 0180 (and their open-label extensions) and 0757: 16 with anakinra treatment and six with control. No predominant type of malignancy was observed. A single malignancy, prostate cancer, was reported during the 6 month interim analysis of study 0145. Owing to maintenance of the blind it is not known which medication this patient was receiving.

The incidence of malignancies within clinical trials was within the expected range. Follow-up over the longer term is, however, required to evaluate fully the effects of anakinra on malignancy.

Injection site reactions

These represent the most common and consistently reported treatment-related adverse event associated with anakinra in clinical trials, being seen in over 60% of patients who received therapeutic doses compared with < 34% with control. Such ISRs resulted in withdrawal from treatment in up to 10% of patients treated with anakinra and up to 3% treated with control (*Table 10*).

These reactions were characterised by erythema, ecchymosis, inflammation and pain. Such reactions were usually reported as mild to moderate, occurred within the first 4 weeks of treatment and typically lasted for 14–28 days. The frequency of ISRs was seen to increase with increasing doses of anakinra across the trials.

Infections

The overall incidence of infections in each trial was comparable across the control and active treatment groups, ranging from 26 to 50% (*Table 9*).

URTIs, bronchitis, influenza-like symptoms and UTIs were the most commonly reported infections in trials 0560, 0180 and 0757 (*Table 11*). Sinusitis was also documented as a common event in all but trial 0560. These data are not available for studies 0182 and 0145. For the interim analysis of 0145 it is stated in the trial report that respiratory infections were most common (15.5% with control vs 21.2% with anakinra, no further details given).

In the large safety study (0757), although the incidence of infections was similar across the two groups, when analysed by body system, the gastrointestinal system showed a higher proportion of subjects with infections in the anakinra arm compared with control (5.0% vs 2.8%).[103] No individual type of infection or group of infections accounted for this difference.

Considering the subset of infections defined as serious, the incidence in study 0757 was increased with anakinra compared with control (2% vs 0.4%). The most common infections were pneumonia, cellulitis and osteomyelitis. None of the 23 infections in patients on anakinra was fatal. All resolved, with the exception of one case of

TABLE 11 *Incidence of commonly occurring infections for studies 0560, 0180 and 0757*

Infection	Clinical trial					
	0560		0180		0757	
	Control	Anakinra	Control	Anakinra	Control	Anakinra
URTI	6.6%	7.1%	21.6%	17.1%	18.4%	13.3%
Sinusitis	1.7%	0.9%	14.9%	8.4%	6.0%	6.7%
Bronchitis	4.1%	2.6%	0%	3.2%	4.6%	3.4%
Influenza-like symptoms	5.8%	5.7%	5.4%	6.1%	6.4%	5.8%
UTI	5.8%	3.4%	5.4%	5.2%	5.3%	4.6%

osteomyelitis. The potential risk factors identified for the higher incidence of serious infections were corticosteroid use and possibly asthma.[103]

In studies 0560, 0180, 0182 and 0145 only small numbers of patients developed serious infections.

Neutropenia

Treatment with anakinra is associated with small reductions in the mean values for WBC count and absolute neutrophil count (ANC). The incidence of neutropenia, surprisingly, is not reported for all trials. Trial protocols, however, required treatment to be withdrawn when WBC or ANC levels fell below predefined values.[116]

Across studies 0560 and 0180, 85 out of 696 patients treated with anakinra (12%) developed neutropenia, compared with ten out of 195 treated with control (4%). For these figures neutropenia is defined as an increase of at least one grade of the neutropenia. Most of this neutropenia was mild.[103]

Withdrawal due to neutropenia was reported for eight patients (1.1%) receiving anakinra and none receiving control in these trials. Time since initiation of anakinra treatment varied, with about one-third developing in the first 100 days and one-third after 200 days of treatment. In all cases the ANC recovered on withdrawal of the drug. Only one case was associated with an infection.[103]

No data on neutropenia are provided for the large pragmatic safety study.

Antibodies to IL-1Ra

Limited data are available. In study 0560, of 454 patients who had baseline and follow-up serum samples available, three patients on anakinra developed positive reactions for anti-IL-1Ra antibody reactivity, at two or more follow-up visits. None was observed in the control group. In study 0180 one out of 57 screened patients administered control and eight out of 297 administered anakinra were seropositive for antibodies to IL-1Ra at some time during the study. Injection site reaction occurred in seven out of eight seropositive patients given anakinra. No evidence of neutralising antibodies was detected.

Chapter 4
Economic analysis

Summary

Summary of existing economic evaluations

- No fully published economic evaluations of anakinra in patients with RA were identified. Two abstract reports presented limited data.

Commentary on submitted model

- Markov model with 6-month cycle time.
- There are problems associated with the structure of this model which make its conclusion, that the ICER for anakinra is £16,545 per quality-adjusted life-year (QALY), unreliable.

Summary of the Birmingham economic model

The Birmingham Rheumatoid Arthritis Model (BRAM) compares DMARD sequences of drugs, chosen to reflect current clinical practice, with and without anakinra, at different points in the DMARD sequence.

The BRAM gives a base-case estimate of the ICER of anakinra of between £106,000 and £604,000/QALY.

This model uses data from public domain trial results only. These trials recruited a highly selective patient population and may well overestimate the cost-effectiveness that anakinra would achieve in an average clinic population.

In the sensitivity analyses quite substantial variations were made in key parameters and ICERs were shown to be responsive. ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other TNF inhibitors, as these agents have a different mechanism of action. Thus, anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Introduction

This section of the report has three components:

- a review of existing economic evaluations of the use of anakinra in RA
- a technical commentary on the decision-analytic models used in the economic analyses reported in Amgen's submissions to NICE
- a description of the modelling and economic analyses of anakinra use in RA patients, undertaken by the authors.

Existing economic evaluations

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.[81,117–125] Several published economic analyses of drug therapies for use in RA were also identified, relating to the use of NSAIDs, for example, see Gabriel and colleagues[126] and DMARDs.[127–130]

No fully published economic evaluations of anakinra treatment for patients with RA were identified from the literature. Two abstract reports of economic evaluations, which considered the use of anakinra in patients with RA, were identified.[131,132] These abstracts contained insufficient detail to justify reporting here at length. Hochberg and colleagues present a cost-minimisation analysis. This is based on ACR response from placebo-controlled RCTs conducted with etanercept, infliximab and anakinra, all in combination with MTX. Indirect comparison suggests that anakinra is associated with higher cost to achieve an ACR response than the TNF inhibitors. As discussed previously, caution is advised when interpreting data from indirect comparisons.[131]

Brennan and colleagues developed a conceptual model of clinical pathways to compare therapeutic strategies: use of anakinra blind versus use in patients testing positive for IL-1A allele 2 (using outcome data from a preliminary study). The analysis suggested that there is the potential for a pharmacogenetic test to be cost-effective in RA.[132]

Report on the Amgen model

Within their submission to NICE Amgen present an economic evaluation using a Markov model (see Appendix 7 for how this economic evaluation was scored using the checklist). The Amgen Markov model was based on the modelling structure used by Kobelt and colleagues.[133,134] The Kobelt model classifies patients into six disease states by HAQ score. By allowing a separate set of transition probabilities for each time cycle within the model, the Kobelt model is able to fit any set of patient-level data to describe the progression over the period of follow-up of a study. This non-parametric approach has the advantage that it does not impose any structural assumptions on the data. However, it means that it is not obvious how to extrapolate time forward using the model. More importantly, the transition probabilities so fitted may be averages across heterogeneous groups of patients, in which case they would not have any meaning for particular patients. This would certainly be the case if the model were applied to a group of patients receiving a variety of different treatments.

It is a fundamental assumption in a Markov model that health states relate to homogeneous groups of patients. This assumption cannot be maintained if patients are receiving different treatments with varying effectiveness. A Markov model for a condition with varying severity which is treated by a sequence of drugs must therefore have at least a full range of states for each drug and each health state. For example, if there are to be six levels of severity and ten drugs, then a minimum of $6 \times 10 = 60$ Markov states is required. In the case of RA, more states than this are needed, to allow for effects of starting and finishing on DMARDs.

The published form of the Kobelt model, with only six states for live patients, is not suitable for assessing the impact of a strategy of using drugs sequentially, either singly or in combination. The Amgen model overcomes this limitation to some extent by incorporating two sets of six 'live' states, one set for patients on anakinra and one set for patients not on anakinra.

It is not at all clear what population is being modelled. The statements on pages 39–40 of the Amgen submission appear to contradict one another. First, the report states that the model is used to estimate the cost-effectiveness:

> "… in the treatment of patients with RA in whom conventional DMARDs are no longer effective."

However, then it talks about patients who fail anakinra being

> "… maintained with conventional DMARDs. In addition, if treatment resulted in any adverse event that led to withdrawal from the treatment, the patient would be classified as a failure, and would be treated from then on with conventional DMARDs."

If anakinra is to be used as anything other than a 'last resort' treatment, the patients not on anakinra will consist of a mixture of those still able to benefit from DMARDs and those not taking them. In this case it would not be appropriate to regard these as homogeneous groups, applying costs and transition probabilities to the groups as a whole.

The Amgen model is thus totally inappropriate structurally to answer any question relating to the possible inclusion of anakinra anywhere other than last in a sequence of possible treatments. Questions of cost-effectiveness of anakinra anywhere else in the sequence simply cannot be answered by any set of data inputs to such a model.

Thus, if it is to be coherent, the model should be interpreted as applying only to the choice of anakinra as therapy when all others have failed. Even considering the model as applying to the question of whether anakinra should be used ahead of palliation when all other treatments have failed, there are several problems with the model, which are addressed below.

Technical aspects of the model

The model was supplied in two forms, one based on study 960180 (anakinra in combination with MTX) and one based on study 0560 (anakinra as monotherapy). The two forms have the same basic structure, but differ in the data used to populate the model. The model runs to a cycle length of 6 months.

Model structure

Each version of the model compares two strategies, one involving anakinra and the other not. For the branch not involving anakinra, there are seven states: six live states and one representing death. Time-dependent transition probability matrices are used to determine the proportions of patients in each state at the end of each cycle. The first cycle uses the results of the appropriate study (960180 or 0560), but subsequent cycles use instead probabilities calculated from the Early Rheumatoid Arthritis Study (ERAS) data set.

For the branch involving anakinra, there are 13 states: six live states for remaining on anakinra, six live states for anakinra failures, and death. Transition probabilities from the failure states are as for the non-anakinra arm. For patients on anakinra, a probability of death is first applied; survivors may then remain on anakinra or not, and may change health state. The same transition matrices for health states are used for those who remain on anakinra and those who do not. The transition matrices for the first cycle are taken from study 960180 or 0560 as appropriate. The second cycle probabilities are taken from 0564, and are the same in the two versions of the model (except for a difference in rounding in one case). For later cycles, the transition probabilities used are the mean of the probabilities in the previous two cycles.

There are several problems associated with this structure. These are detailed below. State numbers referred to here are for the six health states determined by HAQ score, ranging from state 1 (best; HAQ < 0.6) to state 6 (worst; HAQ 2.6–3.0). Many of the problems are inherent in the structure of the model as supplied; where it is possible to test an alternative by changing the values of variables used in the model, the effect of such changes is quoted below.

Different handling of death according to treatment

For patients still on anakinra, the probability of death is derived from UK death rates. However, for patients not on anakinra, death rates are included in the transition matrices derived from the ERAS data set. In all cases, there are zero probabilities for death recorded for many cycles. A common pattern is for non-zero probabilities to appear in alternate cycles only. This suggests that survival data were only available on an annual basis, but all deaths have been put into the same half of successive years. This structure is clearly inappropriate. The effect of changing it cannot readily be assessed without major structural alteration to the model.

Independence of transition with response status

For patients who are on anakinra at the start of a cycle, the transition probabilities for health states are exactly the same for those remaining on anakinra as for those quitting. It would be more reasonable to assume that those staying on anakinra would in general be in a better health state than those quitting the drug. The effect of this assumption is to give a lasting benefit to anakinra, after patients have stopped taking it. There is no reversion to previous state when anakinra is discontinued. Again the structure of the model is such that it is not possible to correct for this without major structural alteration.

Calculation of transition probabilities after the first two cycles for anakinra patients

Transition probabilities for anakinra patients after the first two cycles are calculated as the mean of the probabilities for the previous two cycles. Applying this process repeatedly has the effect that the probability for a given transition converges towards a figure $\frac{1}{3}p + \frac{2}{3}q$, where p is the probability for the first cycle and q for the second cycle. This does not seem to be a sensible way of calculating these. The sensitivity analysis provided includes the effect of fixing the probabilities for later cycles to remain at the value for the second cycle. This is done separately for the probability of remaining on anakinra, and for the transition probabilities between health states for those remaining on anakinra. The effect of each of these changes is to increase the ICER slightly. In the model based on trial 960180, the ICER increases from £16,545 to £17,561 if the probability of remaining on anakinra is fixed after the second cycle. It increases from £16,545 to £17,399 if the transition probabilities between health states are similarly fixed. The combined effect of the two changes is not stated. The method used, calculating each row as the mean of the previous two rows, is obviously inappropriate. In the model based on 960180, ICER increases from £16,545 to £18,597 if both sets of probabilities are fixed from the second cycle.

Overfitting

Tables of transition probabilities for the first 6 months were supplied, based on trial 960180 (see page 46 of Amgen submission). These were given to three decimal places. The first table relates to the 131 patients on 1.0 mg/kg anakinra or 2.0 mg/kg anakinra; the second table to the 74 patients on placebo. (Total numbers taken from the clinical study report.) Each column relates to the patients in a given health state at the start of the study, and gives the proportions in each health state after 6 months. There is a minimum number of patients in each column for whom actual outcomes can be rounded to give the proportions shown in the Amgen tables. These are shown in *Tables 12* and *13*.

In each case, the minimum numbers in each column add up to the declared total numbers in

TABLE 12 *Patients on anakinra: health states at start of study and after 6 months*

	From					
To	**State 1**	**State 2**	**State 3**	**State 4**	**State 5**	**State 6**
State 1	17	17	7	5	0	0
State 2	2	5	16	4	0	0
State 3	0	1	10	15	1	1
State 4	0	0	5	13	6	0
State 5	0	0	0	4	2	0
State 6	0	0	0	0	0	0
Total	19	23	38	41	9	1

Actual numbers of patients inferred from *Table 13* in the Amgen submission (anakinra, trial 960180).

TABLE 13 *Patients on placebo: health states at start of study and after 6 months*

	From					
To	**State 1**	**State 2**	**State 3**	**State 4**	**State 5**	**State 6**
State 1	5	5	5	0	0	0
State 2	1	6	3	5	0	0
State 3	0	2	7	7	0	0
State 4	0	0	5	10	2	0
State 5	0	0	1	5	5	0
State 6	0	0	0	0	0	0
Total	6	13	21	27	7	0

Actual numbers of patients inferred from *Table 14* in the Amgen submission (placebo, trial 960180).

the trials. It can thus be inferred that these tables reflect the exact numbers in the study.

The probabilities used have been applied exactly, with no attempt at smoothing or checking for consistency between anakinra and placebo. For example, consider the transitions for the improvement from state 3 to state 1. The trial results are consistent ($\chi^2 = 0.024$, $p = 0.877$) with a null hypothesis that the proportions are the same, and so it is entirely plausible that the 'correct' transition probability should be higher for anakinra than for placebo. In this case, the model uses a probability of 0.184 for anakinra and 0.238 for placebo. Here, the overfitting appears to favour placebo. However, for the question of overall improvement from state 3, the model uses probabilities of 0.605 for anakinra against 0.381 for placebo. Again, the trial result is not statistically significant ($\chi^2 = 1.904$, $p = 0.168$).

A more serious problem with the overfitting is that there are large numbers of zeros in the transition matrices. Where these zeros occur also in trial 0564, the given transition becomes impossible at any point in the model. In particular, it is not possible to reach state 6 from any other health state while on anakinra.

The base-case run of the model has 8.5% of patients starting in state 6. For these patients on anakinra they must be non-responders but move to state 3 in the first 6 months. Since there is no transition probability available on placebo, the model assumes that all such patients die in the first 6 months. If patients starting in state 6 are excluded from the model, the ICER increases from £16,545 to £29,101 in the base case, or from £18,597 to £34,159 if the anakinra probabilities are fixed after the second cycle.

Because of the small numbers starting in state 5 in the trial, the difference between the proportions improving (0.778 against 0.286) is still not statistically significant ($\chi^2 = 2.133$, $p = 0.144$). If patients starting in states 5 and 6 are excluded from the model, the ICER increases from £16,545 to £33,409 in the base case, or from £18,597 to £40,100 if the anakinra probabilities are fixed after the second cycle.

It should be stressed that all alternative ICER calculations shown here are to indicate the magnitude of the effects of some of the faults in the Amgen model. Because of the major structural errors, these calculations should not be regarded as plausible estimates for the cost-effectiveness of anakinra, even as a 'last resort' therapy.

Costing

Apart from the cost of anakinra, the costs for the model are based on costs for each health state. These costs include costs of DMARDs and associated monitoring for a substantial proportion of the patients in the data set from which they were derived. Such costs cannot be regarded as representative of costs for patients who are not taking DMARDs. If these costs are removed completely, the ICER for the model based on study 960180 decreases from £16,545 to £16,314. It can thus be seen that the effect of these costs on the model is not substantial.

Utilities

The model is based on utilities for each of the health states. The base-case utilities used are taken from applying the EQ-5D questionnaire to a group of patients. The numbers in each state ranged from approximately 25 to 40. The mean values for each group are used, and appear to be reasonable. No half-cycle correction has been applied in assessing the utilities; instead, the utility for each cycle is based on the state at the end of the cycle. Effectively, this means that the time horizon for the model is increased by 3 months.

Sensitivity analysis

Several one-way sensitivity analyses have been carried out. These include fixing transition probabilities for anakinra responders as described above. In addition, a probabilistic sensitivity analysis was performed which varied the cost and utility estimates for the various health states in the model, but no other parameters. There are some minor problems with the way the distributions for utility scores were determined. However, the purpose of probabilistic sensitivity analysis is to represent all the uncertainty together. A probabilistic sensitivity analysis on a limited set of variables does not meet this purpose.

Crucial uncertainties which have not been tested include the following two. First, there is uncertainty in transition probabilities resulting from the very small numbers in certain states in the trials. Second, the model uses the same transition probabilities between health states for patients starting a cycle on anakinra, regardless of whether anakinra remains effective. The structure of the model does not allow this issue to be tested.

Conclusion

The results of the Amgen model must be treated with considerable caution.

Methods for economic analysis

The aim of this analysis is to assess the cost-effectiveness of adding anakinra to an existing treatment pathway for rheumatoid arthritis compared with the same pathway without anakinra. The costs are from an NHS perspective.

The economic analysis was conducted using the BRAM. This model is a revised version of a previous model used in the assessment of etanercept and infliximab.[39] The BRAM is an individual sampling model. A large number of virtual patient histories is simulated, costs and QALYs being accumulated as required. Full details of the means used to implement the model are to be found in a parallel report.[135] A complete description of the model structure is given below. The basic model structure is as in *Figure 9*.

Patients are assumed to follow a sequence of DMARDs, involving starting treatment, some time on the treatment, quitting the DMARD and selecting the next treatment. The pattern is then repeated for the next DMARD. Any patient surviving all the DMARDs moves on to palliation. Patients' HAQ scores are assumed to improve (decrease) on starting a DMARD; this improvement is lost on quitting the DMARD, which may be for reasons of either toxicity or loss of effectiveness. While on any treatment, patients' condition is assumed to decline slowly over time; this is modelled as increases of 0.125 in HAQ score occurring from time to time. HAQ scores are calculated so that a unit change in disability detected by this questionnaire is 0.125; a patient may have a minimum score of 0 and a maximum of 3.0 (see Appendix 1 for details of the HAQ). All patients are followed through to death, which necessarily occurs while on some form of treatment (DMARD or palliation). Mortality risk is assumed to be dependent on current HAQ score, as well as age and gender.

Strategies compared using the BRAM

Table 14 shows the two strategies for using DMARDs considered in this report. These treatment pathways were based on a systematic review of the literature on treatment of RA patients

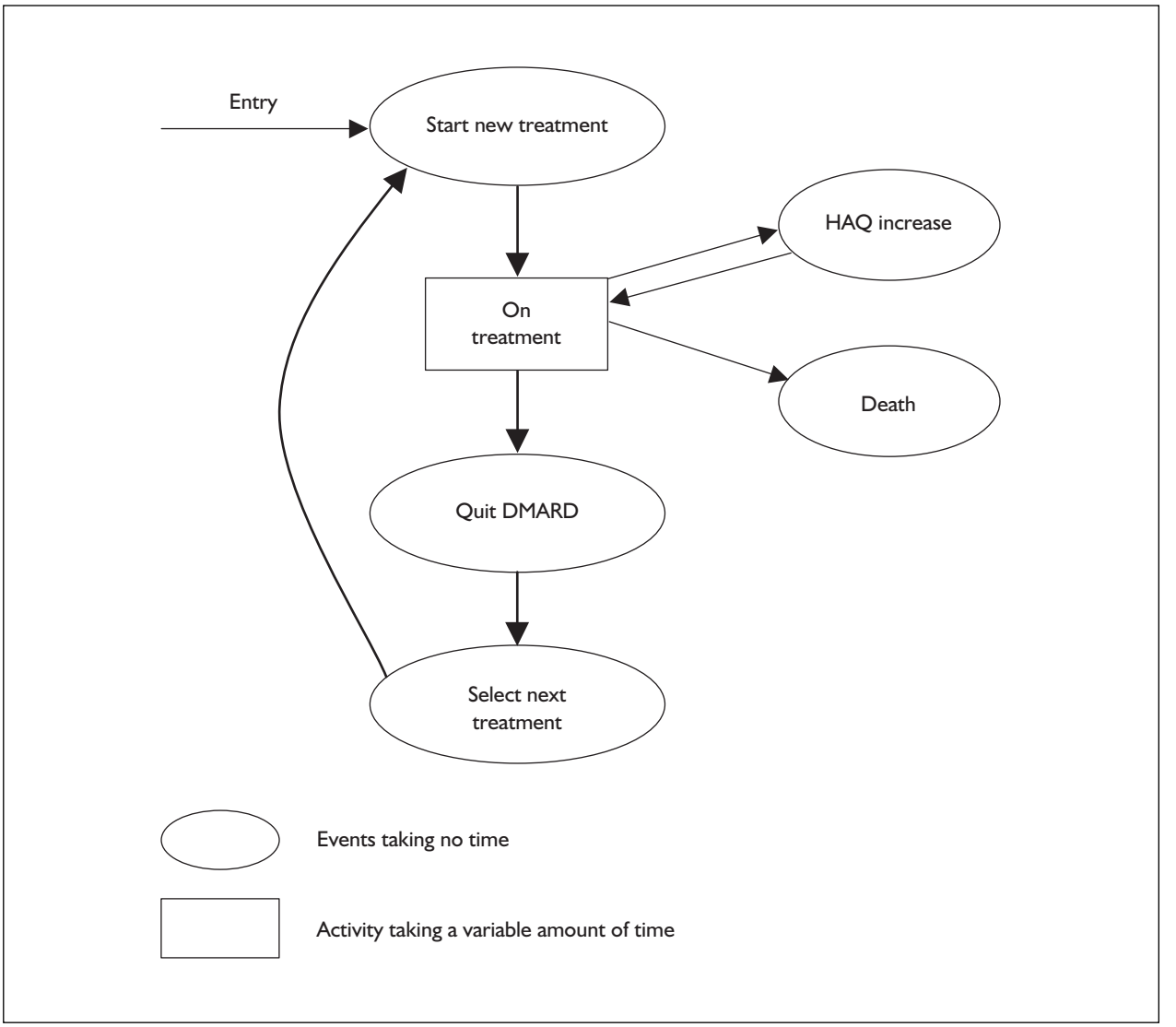


FIGURE 9 *Basic structure of the model*

TABLE 14 *Strategies used in the BRAM for assessment of anakinra*

	Strategy 1	**Strategy 2**
Sequence of DMARDs used	Sulfasalazine MTX Leflunomide (Etanercept) Infliximab[a] **Anakinra**[a] Injectable gold Azathioprine Ciclosporin (CyA) Combination MTX + CyA	Sulfasalazine MTX Hydroxychloroquine Injectable gold Leflunomide (Etanercept) Infliximab[a] **Anakinra**[a] Azathioprine Ciclosporin (CyA) Combination MTX + CyA

[a] These drugs are used with MTX in the model, in accordance with the licensed indication, unless the patient simulated has had toxicity to MTX, in which case they are used alone as this reflects what occurs in current clinical practice.

TABLE 15 *Initial age and gender distribution*

Age (years)	15–24	25–34	35–44	45–54	55–64	65–74	75–84	Total
Male	0.6	1.2	2.3	5.8	6.4	9.3	5.2	30.8
Female	2.9	5.8	9.9	16.9	14.0	15.1	4.6	69.2

with DMARDs and a survey of rheumatologists in the UK in 2002.[47] (Note that neither of these strategies uses penicillamine, because the survey revealed that this treatment was not widely used.)

The combination of methotrexate and ciclosporin was not used if either of its components had been quitted on the grounds of toxicity. In each case, the comparison is made between the strategy as shown (with anakinra in the middle) and without anakinra. Because of current supply problems with etanercept (Wyeth Medical Information: personal communication, 22 January 2003), each strategy was subdivided according to the use or non-use of etanercept; versions using etanercept are referred to as strategies 1A and 2A; without etanercept, strategies 1B and 2B. Further comparisons were made moving anakinra to the end of the list, after combination therapy; again, the comparison in each case was between the strategy with anakinra last, and without anakinra. Thus, a total of eight pairwise comparisons could be made for any set of parameter values.

Starting point for comparisons

Since both treatment arms in any comparison start with the same initial drug sequence, early costs and QALYs are the same. Therefore, in each case, the starting point for comparison was the point of divergence between the two options compared. All patients in the model were started at the beginning of the sequence; patients who did not reach the point of divergence were not included in the analysis. Costs and QALYs were accumulated only from the point of divergence, and discounted (at 6% and 1.5%, respectively) to that point. In principle, it would be possible to start the model at the divergence point. This would, however, require knowledge of the distribution of patients by age, gender and HAQ score at the divergence point, and thus separate starting populations for each comparison. The method used requires only a single data set for its starting population.

The model assumes a constant risk of increase of HAQ score while on treatment and that an individual's HAQ score increases gradually and in steps of 0.125, apart from the effects of starting and ending treatment. While HAQ can change at any stage of disease, and is known to be more labile in early disease, the assumption of a gradual increase in HAQ is reasonable for the parts of the model where comparisons are being made, as the model applies to the later stages of the disease. The rate of increase in HAQ was chosen to reflect the empirically observed increase reported by Scott and Strand.[136]

TABLE 16 *Starting distribution of HAQ scores*

HAQ	0.25	0.75	1.5
%	25	50	25

Notice also that, for a particular strategy, the same total sequence of DMARDs is used in the non-anakinra branch whether anakinra appears in the middle or last. However, the point of divergence is different, and so the total costs and QALYs counted will also be different.

Data used in the BRAM for anakinra

What follows is a list of the data used in the BRAM for anakinra. Data for anakinra are essentially drawn from this review; other data have been taken from the literature.

Table 15 shows the initial age and gender distribution, based on Wiles and colleagues.[8]

The starting distribution of HAQ scores is shown in *Table 16*, based on Wiles and colleagues.[66] Note that although only three different values were used at the start, natural HAQ increases mean that a much greater variety applies at the point of divergence between branches in any strategy.

Time spent on any DMARD is drawn from a Weibull distribution. A random variable X has a Weibull distribution with shape parameter a and scale parameter b if $\left(\frac{X}{b}\right)^a$ has an exponential distribution with unit mean. The Weibull distribution is more general than the constant-risk exponential distribution in that it reduces to the exponential distribution when $a = 1$. If $a < 1$, then the risk decreases over time, while if $a > 1$,

TABLE 17 *Times to quitting DMARD*

DMARD	*a*	*b* (years)	Mean (years)	Source
Anakinra	1	1.77	1.77	See text
Azathioprine	0.73	1.60	1.95	Hawley and Wolfe[137]
Ciclosporin	0.79	7.62	8.71	Marra *et al.*[138]
Etanercept	0.73	12.34	15.03	Geborek *et al.*[139]
Gold	0.71	3.08	3.85	Maetzel *et al.*[43]
Hydroxychloroquine	1	3.62	3.62	Maetzel *et al.*[43]
Infliximab	0.73	5.96	7.26	Geborek *et al.*[139]
Leflunomide	0.66	1.7	2.28	Siva *et al.*[140]
Methotrexate	0.77	4.62	5.39	Maetzel *et al.*[43]
Penicillamine	0.62	1.86	2.69	Pincus *et al.*[52]
Sulfasalazine	0.71	2.76	3.45	Maetzel *et al.*[43]
Combination	1	1.74	1.74	Tugwell *et al.*[141] Gerards *et al.*[142]

Penicillamine appears in this table as it has the lowest value of the shape parameter *a*; this value was used in the sensitivity analysis for anakinra.

the risk increases over time. Parameters a and b are shown in *Table 17*. For convenience, the mean of the distribution is also shown.

For anakinra, the review gave a withdrawal rate of 23% at 24 weeks. With no data beyond this point, an exponential distribution was fitted to this one point, to be varied in sensitivity analysis. (Although some information was available about timing of withdrawals up to 24 weeks, this was not felt to be a sensible basis on which to extrapolate the shape of the curve.)

Toxicity of DMARDs was only an issue for methotrexate and ciclosporin because toxicity to either of these agents would mean that combination therapy with methotrexate and ciclosporin would not be included as a therapeutic option. For other DMARDs cessation because of toxicity or inefficacy has the same consequence in this model; that is, use of the DMARD next in sequence. For ciclosporin it was assumed drug cessation was due to toxicity with a probability of 0.8 regardless of time spent on the drug.[143] 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.[43]

Costs are made up of drug costs plus monitoring costs. For all DMARDs, there are higher costs on starting than there are for continued use. The total cost for time on any treatment is modelled as a one-off starting cost followed by a steady annual usage cost. The only ones that are relevant for the comparisons in this report are for treatments that come after the point of divergence. For completeness, all costs are shown. The price year is 2002 in each case. The unit costs of the various inputs are shown in *Tables 18* and *19*. The monitoring assumptions are listed in *Table 20*.

Combining the information in *Tables 18–20* leads to the model inputs shown in *Table 21*. It should be noted that palliation does not include hospitalisation, although this may be higher for RA patients with no DMARD options, as this could not be quantified.

The base model does not include costs for hospitalisation as a result of RA. This is because of wide variation in rates dictated by local facilities and practice. ERAS shows a large range of hospitalisation for RA and there are no data for the impact of DMARDs on this.[68] The effect of DMARDs on joint replacement has not been included in the base model. Again, this is because of the absence of data on the effects of DMARDs on joint replacement rates. However, these uncertainties are explored later in a sensitivity analysis.

Basic mortality comes from standard life tables. A relative risk of 1.33 per unit HAQ is applied.[147]

In the base case, it is assumed that there is a mean time of 4 years between each 0.125 unit increase in HAQ. This reflects a mean decline (increase) of 0.031/year.[136]

If the patient's HAQ score at the time of starting a DMARD is less than the reduction given, then the HAQ score reduces to zero. The reduction actually

TABLE 18 *Unit costs for tests and visits*

Test	Cost (£)	Source
FBC	3.77	Newchurch, 2002[144]
ESR	2.91	
BCP	3.63	
CXR	14.75	Newchurch, 2001[145]
Urinalysis	0.08	Newchurch, 2002[144]
Visits		
GP	18.00	PSSRU[146]
Hospital outpatient	86.00	
Hospital inpatient (per day)	191.00	
Specialist nurse visit	43.00	Assumed half of outpatient visit

FBC, full blood count; BCP, biochemical profile; CXR, chest X-ray.

TABLE 19 *Unit costs for drugs*

Treatment	Cost	Assumptions
Anakinra	£20.47 per day	100 mg/day
Azathioprine	3 × 15.2p per day	150 mg per day
Ciclosporin	£5.187 per day	70 kg patient; 3.25 mg/kg per day
Etanercept	£89.38 per dose	102 doses per year
Gold	£9.36 per month	50 mg ampoule, administered at GP visit
Hydroxychloroquine	11.4p per day	300 mg per day
Infliximab	£451.20 per vial	70 kg patient, drug wastage if full vials not used, cost per administration £124
Leflunomide	£1.55 per day	20 mg per day
Methotrexate	11.4p per 2.5 mg tablet	15 mg per week
Sulfasalazine	37.5p per day	2.5 g per day

Sources: Drug tariff/Mims, December 2002.

TABLE 20 *Monitoring assumptions*

Treatment	Pretreatment	On treatment
Palliation		Outpatient visit every 3 months
Anakinra	FBC, ESR, BCP, 4 specialist nurse visits	FBC, ESR, BCP monthly at specialist nurse visit, GP visit every 3 months
Azathioprine	FBC, ESR, BCP	FBC and BCP weekly for 6 weeks, then every 2 weeks for 3 visits, then monthly
Ciclosporin	FBC, 2 × BCP, ESR, urinalysis	FBC, BCP every 2 weeks for 4 months, then BCP monthly
Etanercept	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 4, 8 and 12, then every 3 months
Gold	FBC, ESR, BCP, urinalysis	FBC, BCP, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, then monthly. Treatment given by intramuscular injections
Hydroxychloroquine	FBC, ESR, BCP	FBC, ESR, BCP every 3 months
Infliximab	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2 and 6 and every 8 weeks (at time of infusions)
Leflunomide	FBC, ESR, BCP, urinalysis	FBC every 2 weeks for 6 months, every 8 weeks thereafter. BCP monthly for 6 months, every 8 weeks thereafter
Methotrexate	FBC, ESR, BCP, CXR	FBC, BCP every 2 weeks for 4 months then monthly
Sulfasalazine	FBC, ESR, BCP	FBC every 2 weeks and BCP every 4 weeks for 12 weeks, then FBC and BCP every 3 months

TABLE 21 *Treatment costs*

Treatment	Start-up (£)	Annual usage (£)
Palliation	0	344
Anakinra	182.31	8080.32
Azathioprine	656.71	1286.78
Ciclosporin	331.22	2963.63
Etanercept	473.61	9513.64
Gold	2538.55	1450.08
Hydroxychloroquine	96.31	426.74
Infliximab	1758.51	9867.24
Leflunomide	933.81	1124.60
Methotrexate	484.66	1156.37
Sulfasalazine	552.42	510.10
Combination	331.22	2999.20

applied is used for the increase in HAQ score on quitting the DMARD, except that HAQ cannot go above 3. For example, a patient starting methotrexate with a HAQ score of 0.25 would improve to a HAQ of 0. If the same patient has a HAQ score of 0.125 when quitting methotrexate, the HAQ score increases to 0.375 (see *Table 22*).

Conversion from HAQ to QALYs is by the formula $QoL = 0.862 - 0.327\ HAQ$ calculated from the data set supplied by Nigel Hurst, and reported by Hurst and colleagues.[151] It was assumed that start and end effects can be modelled as one-off deductions equal to 0.2 years times the change in QoL score.

Results

Results from the model are in the form of comparisons between two options, one containing anakinra ('with Ana') and one not ('no Ana'). In each case, the mean cost and QALYs per patient are given. These are calculated from the point of divergence between the options, and discounted to that point at 6% per annum for costs and 1.5% for QALYs, in accordance with Treasury guidelines. The results are subject to statistical error from the sampling used in the model. Quasi-standard errors (QSE) are quoted for costs and QALYs. These reflect the sample sizes used and are given simply to show that an adequate number of replications of the model was made. For each option, the percentage of (virtual) patients ending on palliation has been quoted. This shows what proportion of patients completed a sequence of DMARDs. The results from the two branches must be treated as unpaired data, so the square of the QSE of the difference is the sum of the squares of the individual QSEs. ICERs are quoted as the ratio of mean differences, followed by an approximately 95% quasi-confidence interval obtained using the formula on page 91 of Armitage and Berry[152] to the reciprocal of the ICER.

Strategies 1 and 2 are as defined in *Table 14*. Strategies 1A and 2A include etanercept; strategies 1B and 2B do not. The effect of removing etanercept is that patients reach the divergence point earlier, and therefore tend to be younger.

Base-case results

The base-case costs, QALYs and ICERs for anakinra used in either treatment strategy, with and without the availability of etanercept, are shown in *Table 23*. For fuller details refer to Appendix 8.

Sensitivity analysis

As the best base-case ICER estimate was over £100,000/QALY, which is above that which is generally accepted as value for money within the current NHS budget envelope, sensitivity analyses were undertaken only in the direction that would favour anakinra. The effect of the following

TABLE 22 *Improvement in HAQ for starting each DMARD*

DMARD	HAQ reduction	Source
Anakinra	0.25	This review
Azathioprine	0.25	Assumed to be at the lower end of effectiveness as there are no reliable data on which to base estimates
Ciclosporin	0.375	Zeidler *et al.*[148]
Etanercept	0.5	Jobanputra *et al.*[39] Based on meta-analysis of available trials
Gold	0.375	Munro *et al.*[41]
Hydroxychloroquine	0.25	HERA study group[149]
Infliximab	0.5	Jobanputra *et al.*[39] Based on meta-analysis of available trials
Leflunomide	0.375	Scott and Strand[136]
Methotrexate	0.5	Wyeth Laboratories[150]
Sulfasalazine	0.375	Scott and Strand[136]
Combination	0.25	As for azathioprine

TABLE 23 *Base-case ICER calculations*

Place in DMARD sequence	DMARD sequence	Is etanercept available?	Difference in cost per patient (£)		QALYs per patient		ICER (£/QALY)		
			Mean	QSE	Mean	QSE	ICER	Low	High
Middle	1	Yes	9,477	7.8	0.016	0.0030	604,000	436,000	985,000
		No	9,647	11.1	0.025	0.0046	379,000	278,000	597,000
	2	Yes	9,639	16.0	0.025	0.0054	385,000	270,000	674,000
	(early HCQ and gold)	No	9,843	16.3	0.035	0.0059	278,000	209,000	415,000
Last	1	Yes	11,508	24.3	0.088	0.0106	131,000	106,000	173,000
		No	11,682	17.3	0.111	0.0082	105 000	92,000	124,000
	2	Yes	11,441	24.1	0.105	0.0100	109,000	91,000	134,000
	(early HCQ and gold)	No	11,551	24.3	0.109	0.0110	106,000	88,000	132,000

Low/high: low and high ends of ~95% quasi-confidence intervals (reflecting only sampling uncertainty within the model).

assumptions was explored: time on anakinra, utilities, start and end effects, effectiveness of anakinra, effectiveness of other DMARDs, inclusion of offset costs, and disease progression. A best-case scenario for anakinra was then produced. The effect on the ICER is summarised in *Table 24*. See Appendix 9 for full details of the simulations for the sensitivity analyses.

Time on anakinra

As noted above, the time on anakinra was based on a single time-point in the base case. As an alternative to the exponential distribution, the lowest value (0.62) of the shape parameter a was tried for any of the DMARDs in *Table 17*. (This is the most favourable to anakinra.) To fit 23% withdrawal at 24 weeks requires $b = 4.02$. The mean of the new distribution is 5.80 years, compared with 1.77 years in the base case.

Utilities

The equation used in the BRAM was derived from a regression analysis on the Hurst data set. Tests were done for non-linearity, and for variation with age and gender. These tests suggested that QoL could be best predicted by a linear function of HAQ alone. Accordingly, the BRAM uses such a relationship. Therefore, to test the Amgen utility values in the BRAM, it is necessary to fit a linear relationship between HAQ and QoL. The equation $QoL = 0.915 - 0.269\ HAQ$ fits the Amgen utilities with $R^2 = 0.975$.

Start and end effects

For the sensitivity analysis the one-off loss of QALYs at the start and end of DMARDs was omitted.

Effectiveness of anakinra

In the base-case analysis, the HAQ improvement due to anakinra was rounded from 0.29 to 0.25. To test the effect of this rounding, the model was rerun with the HAQ improvement due to anakinra set to the nearest possible value above 0.29, namely 0.375.

Effectiveness of other DMARDs

It is suggested that the comparator DMARDs may be less effective if used late in the sequence. The importance of this was tested by reducing the HAQ improvement for azathioprine, ciclosporin and gold, each by 0.125. The effect was also tested of replacing the pooled value for anti-TNFs by a HAQ improvement of 0.625 for etanercept and 0.25 for infliximab and, in a separate analysis, reducing the HAQ improvement for methotrexate to 0.125.

Inclusion of offset costs

As the model does not include joint replacement and hospitalisation, the potential effect of these was explored in a sensitivity analysis. It was assumed that disability, as reflected by HAQ, is related to the likelihood of hospitalisation and joint replacement; that is, there is an average cost for being in a given health state and this cost increases with HAQ. The effect was examined of including offset costs at £860/HAQ; thus, these range from £0 at HAQ 0 to £2580 at HAQ 3. (These figures were based on the Wyeth etanercept model reported by Jobanputra and colleagues.[39]) Results show that inclusion of these costs has very little effect on the ICER. (See *Table 24* for summary figures and Appendix 9 for full details.)

TABLE 24 *ICER calculations for sensitivity analyses*

Parameter varied	Place in DMARD sequence	DMARD sequence	Is etanercept available?	ICER (£/QALY)		
				ICER	Low	High
Time on anakinra (mean 5.8 years instead of 1.77)	Middle	1	Yes	364,000	263,000	593,000
			No	240,000	190,000	327,000
		2	Yes	182,000	147,000	240,000
			No	176,000	141,000	232,000
	Last	1	Yes	77,300	66,100	93,300
			No	79,900	67,300	98,400
		2	Yes	89,000	79,000	101,000
			No	85,900	71,800	107,000
Utilities (equation based on Amgen figures)	Middle	1	Yes	554,000	391,000	947,000
			No	405,000	307,000	597,000
		2	Yes	479,000	359,000	682,000
			No	294,000	208,000	499,000
	Last	1	Yes	142,000	116,000	183,000
			No	137,000	103,000	204,000
		2	Yes	124,000	105,000	152,000
			No	137,000	112,000	176,000
Start and end effects (there is no loss of QALYs at start and end of DMARDs)	Middle	1	Yes	277,000	205,000	431,000
			No	199,000	156,000	272,000
		2	Yes	188,000	141,000	281,000
			No	145,000	114,000	200,000
	Last	1	Yes	97,100	82,400	118,000
			No	88,400	75,200	107,000
		2	Yes	84,300	73,400	98,900
			No	82,400	71,200	97,700
Effectiveness of anakinra (effect of anakinra on HAQ score increased to 0.375)	Middle	1	Yes	153,000	117,000	221,000
			No	117,000	101,000	140,000
		2	Yes	119,000	105,000	138,000
			No	99,500	83,900	122,000
	Last	1	Yes	76,800	64,100	95,700
			No	75,000	65,300	88,200
		2	Yes	72,600	61,500	88,400
			No	69,400	58,600	85,200
Effectiveness of azathioprine, ciclosporin and gold each reduced by 0.125	Middle	1	Yes	203,000	162,000	271,000
			No	173,000	140,000	224,000
		2	Yes	166,000	129,000	233,000
			No	144,000	114,000	195,000
	Last	1	Yes	124,000	101,000	160,000
			No	107,000	93,100	126,000
		2	Yes	104,000	92,500	120,000
			No	112,000	97,600	132,000
Effectiveness of etanercept increased to 0.625 and infliximab reduced to 0.25	Middle	1	Yes	531,000	396,000	803,000
			No	367,000	271,000	566,000
		2	Yes	364,000	259,000	611,000
			No	264,000	201,000	385,000
	Last	1	Yes	125,000	102,000	163,000
			No	102,000	89,500	120,000
		2	Yes	104,000	88,000	127,000
			No	117,000	101,000	138,000
Effectiveness of methotrexate reduced to 0.125	Middle	1	Yes	467,000	328,000	809,000
			No	439,000	309,000	761,000
		2	Yes	368,000	261,000	622,000
			No	271,000	205,000	399,000
	Last	1	Yes	123,000	100,000	159,000
			No	109,000	94,200	128,000

continued

TABLE 24 *ICER calculations for sensitivity analyses (cont'd)*

Parameter varied	Place in DMARD sequence	DMARD sequence	Is etanercept available?	ICER (£/QALY)		
				ICER	Low	High
		2	Yes	101,000	86,000	123,000
			No	115,000	99,800	136,000
Offset costs (for hospitalisation and joint replacement) included	Middle	1	Yes	604,000	435,000	985,000
			No	378,000	277,000	595,000
		2	Yes	382,000	268,000	669,000
			No	276,000	207,000	412,000
	Last	1	Yes	128,000	103,000	169,000
			No	102,000	89,200	120,000
		2	Yes	106,000	89,100	131,000
			No	103,000	86,000	129,000
Disease progression removed	Middle	1	Yes	79,400	69,800	92,100
			No	63,200	56,900	71,200
		2	Yes	57,400	50,300	66,900
			No	59,700	51,800	70,300
	Last	1	Yes	36,100	33,200	39,500
			No	33,800	31,200	36,900
		2	Yes	36,500	33,600	39,900
			No	36,000	33,100	39,500
Disease progression removed and mean time on anakinra increased to 5.8 years	Middle	1	Yes	59,300	52,900	67,500
			No	49,100	45,900	52,800
		2	Yes	50,600	47,400	54,200
			No	41,500	38,500	45,000
	Last	1	Yes	30,900	29,700	32,200
			No	28,500	27,500	29,600
		2	Yes	31,900	30,100	33,900
			No	29,800	28,700	31,100
Best case scenario (without offset costs)	Middle	1	Yes	42,400	39,700	45,400
			No	36,700	33,900	40,000
		2	Yes	39,200	36,300	42,700
			No	32,900	30,800	35,300
	Last	1	Yes	29,200	27,900	30,500
			No	27,300	26,200	28,500
		2	Yes	28,900	27,700	30,300
			No	28,400	27,200	29,600
Best case scenario (with offset costs)	Middle	1	Yes	40,900	38,400	43,900
			No	35,400	32,700	38,600
		2	Yes	37,700	34,900	41,000
			No	33,600	31,900	35,400
	Last	1	Yes	27,800	26,100	29,700
			No	26,600	25,100	28,400
		2	Yes	27,300	26,200	28,600
			No	26,700	25,200	28,400

Disease progression

In the base case, patients' HAQ scores increase naturally at an average rate of 0.031/year. The effect was tested of removing this progression while on any DMARD. In the base-case analysis, there is a mean time of 4 years between each 0.125 unit increase in HAQ. However, the model allows this figure to be varied according to treatment. The authors do not accept that anakinra should be treated any differently from other treatments in this regard. However, they do accept that it is reasonable to slow progression on all DMARDs. The following additional analysis tests the importance of this parameter. As can be seen, this is a very important issue as regards the cost-effectiveness of DMARDs. If the rate of HAQ progression on a DMARD is slower than it would otherwise have been, then the DMARD has lasting effect beyond the end of its use.

Best case scenario
Many of the above alternative model parameters led to a noticeable improvement in the ICER in favour of anakinra, as expected. Exceptions were the inclusion of offset costs, and changes to the HAQ improvement due to DMARDs before the divergence point. The effects of the single changes (except for the DMARDs before the divergence point) were combined to produce a best case scenario for anakinra, with and without offset costs. The following changes were made to the base-case data set.

- The mean time on anakinra was increased from 1.77 years to 5.08 years.
- The equation $QoL = 0.915 - 0.269\ HAQ$ for utilities was used (based on the Amgen model).
- The start and end effects for DMARDs were removed.
- The HAQ improvement for anakinra was increased from 0.25 to 0.375.
- The HAQ improvement for each of azathioprine, ciclosporin and gold was reduced by 0.125.
- Disease progression while on any treatment except for palliation was completely removed.

Chapter 5

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 great range of potential costs that cannot readily be explained by socio-economic or clinical factors. However, it is apparent that a minority of patients may account for a great 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 forgone paid work, forgone leisure time and other factors greatly exceed costs incurred by individuals and healthcare services. Clearly, this could have an impact on the QoL of patients and carers. Further, physical disability resulting in difficulties in self-care and work disability has implications for personal social services.

Chapter 6

Factors relevant to the NHS

Use of anakinra can be anticipated to place a demand on outpatient rheumatology facilities, with particular implications for outpatient nurse workload. These professionals are likely to take the lead in teaching patients and carers to self-administer injections, provide back-up support, and provide disease and drug monitoring services. The availability of such specialist nurses in rheumatology varies across the NHS.

There are currently no data on which to base an assessment of the potential impact of anakinra on joint damage in patients with RA. If a reduction in joint damage is apparent this has the potential to reduce the need for surgery in patients with RA. This may in turn lead to a reduced demand for orthopaedic services.

On the basis of the evidence available the most difficult issue for professionals is likely to be identifying the true place in therapy of anakinra among other treatments for RA.

Chapter 7
Discussion

Main clinical effectiveness results

Anakinra, at the higher doses evaluated, demonstrated modest efficacy compared with control, in terms of improving symptoms of RA, when used as both monotherapy and in combination with methotrexate. The effect seen was relatively consistent across the trials, with a RR with the 'licensed dose' of anakinra of achieving an ACR20 of 1.6, ACR50 2.3 and ACR70 3.1, with respective NNTs of 7, 11 and 33, based on the public domain data. A response was generally evident early (within 4 weeks), with no waning of treatment effect evident over the medium term.

Three of the trials evaluated ranges of doses of anakinra. Although a clear dose response was not evident across all of the dose-ranging studies there was a suggestion of increased response with increasing dose. Optimal efficacy was seen at the higher doses, which are in line with the licensed dose of 100 mg daily. No evidence of efficacy was apparent with the low doses of anakinra (≤ 30 mg/day) studied in trial 0182.

For the composite end-point ACR response, benefit with anakinra was slightly greater when used in combination with methotrexate than when used as monotherapy. This may reflect differences in study designs and populations and perhaps late response to continued methotrexate. No subset of patients was identified who had greater or lesser likelihood of response to anakinra.

ACR end-point data for study 0757, a large pragmatic safety study, have not been made available. This is of concern, owing to the size and 'real-life' design of this trial. The authors consider that this study and the ACR end-point data collected are absolutely valid in informing clinical practice. Pragmatic trials that reflect average clinical practice tend to have more external validity than those conducted on highly selected patient populations. We do not believe that because the primary purpose of this trial was to look at safety it is "inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study". The key issue is whether the study design used (in this case a randomised, double-blinded placebo-controlled trial with before and after measurements of effectiveness outcomes) is an appropriate design from which to be able to draw valid conclusions about effectiveness. It clearly is.

Although a trial undertaken in an everyday clinical setting will have more heterogeneity among the participants than a trial undertaken on a highly selected population with restrictive inclusion criteria, this does not necessarily mean that the results will be confounded. One of the benefits of the randomised design is that not only does it reduce selection bias, but it also minimises or avoids the effects of both known and unknown confounders by ensuring that the groups compared have a similar distribution of baseline characteristics. In this trial the patient characteristics of disease duration, concomitant medications and co-morbid conditions, that the company allude to as potential confounders, are randomly distributed between the arms, reducing the risk that they will confound the analysis. Moreover, the large size of this trial helps to minimise the risk of this happening by chance. Indeed, the reported baseline characteristics of the two groups in this trial confirm that there were no significant imbalances in NSAID, corticosteroid, methotrexate or other DMARD use between the anakinra and placebo participants, or in baseline demographic characteristics or disease status (Tables 8-7 and 8-8 of the trial report). In the light of this an analysis of differences in clinical outcomes is methodologically sound and valid.

Because about half the relevant data on effectiveness have been withheld and these are the data that most reflect the average RA clinic population, it is difficult to make an accurate estimate of the likely effectiveness of anakinra in actual clinical practice. It is probable that the data that have been released into the public domain overestimate the effectiveness that would be seen in a clinic context. In the absence of data an educated estimate was made about the effectiveness of anakinra seen in trial 0757 (described earlier). The derived estimate combined with data from earlier trials, using a random effects model, gives the best summary

estimate of effectiveness for the ACR20 response: RR 1.43 (95% CI 1.16 to 1.76), RD 0.11 (95% CI 0.04 to 0.18) and NNT 9 (95% CI 6 to 25).

No conclusion can be made on the effect on disease progression given current data. Study 0560 (monotherapy) suggested that treatment may be associated with a slowing of disease progression as measured by the Larsen score. This end-point was not presented for the other studies. Trial 0145 evaluated disease progression using the modified Sharp score. This trial is now complete but full data are not yet available. There should be serious reservations about post-hoc analyses that claim benefits in clinical non-responders, especially because of the problems of measurement error with radiographic outcomes. Rheumatologists may feel justified in using therapeutic agents in essence for prophylactic purposes where patients experience no immediate benefits. However, whether patients find this approach acceptable allowing for ISRs and other hazards of IL-1Ra would need to be determined. In addition, since other DMARDs also inhibit radiographic damage and have the potential for improving clinical outcomes for patients who have not previously used them, it would seem appropriate for rheumatologists to use untried DMARDs rather than continue with anakinra in the face of continued disease activity.[153]

Anakinra has not been compared head to head with other DMARDs. Such trials are required to inform clinical practice in order to place this drug among other DMARDs for the treatment of RA. In the absence of head-to-head trials an adjusted indirect comparison of NNTs for ACR suggests that anakinra is less effective than other biological agents and other DMARDs. This could be due to different trial conditions or populations, or could represent a true treatment difference.

ISRs were common with anakinra treatment, but were generally mild or moderate and transient. Less than 10% of patients withdrew from treatment because of ISRs. These reactions may, however, have led to unblinding of treatment. Only study 0145 used adjusted methodology to protect against this. Unblinding owing to ISRs has the ability to influence the perceived response for subjective markers (e.g. SJC, ACR response). However objective end-points (e.g. ESR, CRP) should be less subject to unblinding. Benefits with anakinra at therapeutic doses were demonstrated in both subjective and objective end-points across the clinical trials.

SAEs were uncommon and included serious infections and neutropenia. To date, an increase in opportunistic infections such as tuberculosis has not been reported. Increased incidence of malignancy was not evident, but data and exposure are still limited. The BSR biologics register is monitoring adverse events over the longer term.

Economic evaluation

There are no relevant economic evaluations in the published literature. The economic model included in the Amgen submission to NICE contains structural flaws that make its estimate of the cost–utility of anakinra unreliable.

Results of the BRAM

- The BRAM gives a base-case estimate of the ICER of anakinra of between £106,000 and £604,000/QALY.
- This model uses data from public domain trial results only. These recruited a highly selective patient population and may well give a more favourable estimate of cost-effectiveness than would be achieved in an average clinic population.
- Used as a last resort treatment it has a more favourable ICER than when used earlier in the treatment pathway. This is because anakinra displaces cheaper drugs when used earlier.
- In the current situation, where supplies of etanercept are limited, the ICER appears to be slightly more favourable than it would be were etanercept readily available.
- Although the ICER is slightly more favourable when used in drug sequence 2 (with early hydroxychloroquine and gold), the choice of this drug sequence is usually determined by the patient characteristics and disease presentation.[47]
- In the sensitivity analyses quite substantial variations were made in key parameters and ICERs were shown to be responsive.
- The only univariate analysis in which ICERs dropped below £50,000/QALY was the case where anakinra was used last and it was assumed that disease progression was completely halted when on anakinra.
- The best-case scenario produced ICERs between £26,000 and £43,000/QALY. These figures, however, are highly improbable as they are based on combining a number of assumptions, each of which favours anakinra, in some cases beyond the limit of plausibility of empirical evidence.

Assuming that anakinra is used as a last resort DMARD, the Amgen model estimate of £16,545/QALY is lower than the best case scenario and appears to be unsustainable. This is due to multiple inappropriate structural assumptions and errors in the Amgen model.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. This finding is consistent with the indirect comparison of effectiveness for ACR responses (a parameter not used in the model) which suggest that anakinra has a substantially higher NNT. However, it must be borne in mind that patients may respond to anakinra when they have not responded to TNF inhibitors, as these drugs have different mechanisms of action. Thus, anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Assumptions, limitations and uncertainties

A key strength of this review was the expert input received at all stages, which ensured that a clinically relevant perspective was maintained throughout. Sensitive searches were conducted to maximise retrieval of relevant data.

Included studies were of high quality as judged by the Jadad scale. Withdrawal from treatment was handled variously using LOCF or non-responder imputation. It is not known whether these methods of analyses could have introduced unforeseen biases. However, the FDA and EMEA evaluated the robustness of this approach with sensitivity analyses assuming a worst case scenario. Other than for study 0560, this did not alter the conclusions of the trials in relation to ACR response.

The double-blind trials conducted can be considered of short duration (up to 6 months, with the exception of 0145) for a chronic disease such as RA. Longer term open-label follow-up studies are, however, available. Evaluation of the studies is complicated by the use of a wide range of doses, both fixed dose and doses by body weight, across the clinical trial programme.

Approximately 75% of patients completed the trials. Reasons for withdrawal varied across the treatment and control groups. In general, adverse events were a more frequent reason for withdrawal with the higher doses of anakinra evaluated, and lack of efficacy with control.

There is the potential for bias due to unblinding owing to adverse events, most notably ISRs. Only one study used additional methods to protect against this.

Efficacy data were not available for the large pragmatic trial 0757. This is a major weakness in evaluating the effectiveness of anakinra in patients with RA. Given the size of this trial its findings are likely to overshadow those seen in the smaller studies. (See earlier comments.) In the absence of the published results of this trial, an educated guess was made on the trial's likely findings. Although this analysis should be interpreted with caution, it provides a sensitivity analysis around the primary outcome of ACR20 response. Full data on the disease progression end-points for study 0145 were not available.

No direct comparisons of anakinra with DMARDs or anti-TNFs are available. These are required to inform clinical practice. In the absence of this, an adjusted indirect comparison was undertaken to help to inform practice; this should be interpreted with caution and the findings tested in direct head-to-head trials.

An assessment of dose response across all end-points using individual patient data is required to identify whether a true dose response exists in studies 0560 and 0180. Sensitivity analysis assuming no dose response did not alter the findings in relation to ACR response.

Anakinra is too new to know whether it has any effect on the need for joint replacement. Therefore, joint replacement effects have not been modelled.

Although mortality benefits have been included in the model, these have been assumed to relate solely to HAQ scores.

There is very limited evidence, if any, reliably relating ACR responses to QoL. Consequently, the BRAM uses HAQ score changes as a predictor of QALY scores. However, all studies, including those for the comparator drugs, have limited data on HAQ scores. Therefore, the model is based on crude estimates of the effect on HAQ of all treatments.

Trial data are only available to 24 weeks; therefore, continued benefit has been derived by extrapolation. There is a very wide range of time on anakinra, consistent with the current data; consequently, there is a large degree of uncertainty in the results.

The economic evaluation takes an NHS perspective and may therefore underestimate the true cost-effectiveness of anakinra, as a considerable proportion of the cost of uncontrolled disease falls on patients and carers.

Need for further research

Other therapeutic approaches in RA are currently being investigated and these are summarised in Appendix 10.

For research that has already been conducted with anakinra, research needs are:

- the publication of the efficacy data from the large pragmatic study (0757) to enable the benefit of treatment to be fully evaluated
- publication of the 1 year radiology outcome data from study 0145 to evaluate the potential effects of treatment on disease progression. It is also important to identify whether any benefits on radiological measures are limited to patients who demonstrate a symptomatic response.

Current clinical trials with anakinra are of limited duration. RCTs are required to evaluate the efficacy, safety and cost of anakinra over the longer term in patients with such a chronic disease.

Comparative trials of anakinra with other DMARDs and biological modifiers are needed to identify the comparative efficacy of these drugs and to guide clinical practice to optimise patient care. Trials are also required to assess the role of anakinra in the treatment of patients who have failed to achieve a benefit while taking infliximab or etanercept.

Studies with IL-1Ra given by continuous infusion to rats with collagen-induced arthritis produced dramatic effects on soft-tissue swelling and disease progression. Blood levels achieved in clinical trials with once-daily subcutaneous dosing in humans with RA were much lower than those seen in the animal models. It is not known whether daily subcutaneous administration is sufficient to achieve continuous saturation of IL-1 receptors. A clinical trial in which IL-1Ra is delivered by continuous infusion or a slow-release delivery system would address whether this apparent difference between species is related to suboptimal dosing in humans.[26,154]

Suggestions that newer biological therapies reduce radiographic damage without necessarily improving clinical outcomes need to be confirmed if treatment in the absence of a clinical response is to be justified.

Further research is required to assess the impact of DMARDs on joint replacement, mortality and QoL.

As the pathogenesis of RA is complex, it may not be fully suppressed by blocking a single mediator. Optimal treatment in the future may require combinations of therapeutic agents that inhibit more than one mediator in a complex pathogenic network.[25] Controlled clinical trials are required in this area to inform clinical practice, before any such approaches are widely adopted.

Further research is needed to improve the utility of radiographic outcomes in clinical trials of RA, either by building on existing efforts with plain radiographs or through the use of newer imaging methods.

Chapter 8
Conclusions

Anakinra offers a new therapeutic approach for the management of RA. The clinical trials establish the efficacy of anakinra in reducing the signs and symptoms of RA, most notably at the higher doses studied. Although modest efficacy is established, the degree of clinical effectiveness is difficult to gauge because of the absence of data from a large pragmatic safety study. There are no studies of a direct comparison with other DMARDs or anti-TNF therapies. An adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. Such indirect comparisons should be interpreted with caution and assume generalisability of study results. Although safety over the short term is established, duration of exposure to anakinra is still limited. Safety over the longer term is not yet known.

The independent economic model developed to evaluate the cost-effectiveness of anakinra in clinical practice gives a base-case estimate of the ICER for anakinra of between £106,000 and £604,000/QALY.

Patients may respond to anakinra when they have not responded to other TNF inhibitors, as these agents have a different mechanism of action. Thus, anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

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Contributions of authors

Wendy Clark carried out the searches, applied the inclusion and exclusion criteria, and extracted data. She wrote parts of the introduction and background, and the narrative on key studies, conducted the meta-analyses, wrote the discussion, responded to peer review and edited the report.

Dr Paresh Jobanputra wrote the majority of the introduction and background, carried out data extraction, developed the cost and utility inputs for the Birmingham Rheumatoid Arthritis Model (BRAM), responded to peer review and edited the report.

Dr Pelham Barton constructed and analysed the Birmingham Rheumatoid Arthritis Model (BRAM), appraised the industry models, responded to peer review and edited the report.

Dr Amanda Burls supervised the project, conducted the analysis of study 0757, assisted in the economic analysis, responded to peer-review and edited the report.

Publication information

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. Most of our members are based in the Department of Public Health and Epidemiology, University of Birmingham; however, other members are drawn from a wide field of expertise, including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, and pharmacists and methodologists from the Department of Medicines Management, Keele University, and the Centre of Evidence-Based Pharmacotherapy, Aston University.

WMHTAC produces systematic reviews and economic evaluations for the NHS R&D HTA programme (NCCHTA), the National Institute for Clinical Excellence (NICE) and the health service in the West Midlands. WMHTAC also undertakes methodological research on health technology assessment, and provides training in systematic reviews and health technology assessment.

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Appendix 1

Health Assessment Questionnaire[155]

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 WHICH 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:	2.	3.	4.	5.
- Dress yourself including tying shoelaces and doing buttons?				
- Shampoo your hair				
2. RISING – ARE YOU ABLE TO:	3.	4.	5.	6.
- 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?				
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 5lb 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 to 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

ACR response criteria[59]

- 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 figures refer to percentage improvement of the clinical measures shown above.

European League Against Rheumatism (EULAR) response criteria[156,157]

This measure is referred to as the DAS (disease activity score). 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 visual analogue scale)

Paulus response criteria[158]

Responses in four out 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% or 70%, as for ACR responses):

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

Appendix 3

Notes on radiographic scoring methods

Modified Sharp Method[159]

Radiographs of hands, wrists and feet are scored. Forty-six joints are scored for erosions. Erosions are scored on a six-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. Forty-two joints are scored for narrowing on a five-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.

Larsen scoring method

Radiographs of the hands and wrists are scored. Fifteen areas are examined. Dislocation and bony ankylosis are considered; if they are present, the scoring is based on the concomitant bone destruction. Maximum score (total for both hands) is 150.[160]

0 = normal
1 = slight abnormality, including one or more of the following lesions:
periarticular soft-tissue swelling, periarticular osteoporosis and slight joint space narrowing
2 = definite early abnormality, including definite erosion, with or without joint space narrowing
3 = medium destructive abnormality
4 = severe destructive abnormality
5 = mutilating abnormality (the original articular surfaces have disappeared).

Appendix 4

American College of Rheumatology revised criteria for classification of functional status in rheumatoid arthritis[161]

Class	Description
I	Completely able to perform usual activities of daily living (self-care, vocational and avocational)
II	Able to perform usual self-care and vocational activities, but limited in avocational activities
III	Able to perform usual self-care activities, but limited in vocational and avocational activities
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 gender specific.	

Appendix 5

Yield from MEDLINE and EMBASE searches

Date: 10 December 2002
Database: MEDLINE (1966 to present)

Set	Search	Results
1	exp Arthritis, Rheumatoid/	64,573
2	exp Receptors, Interleukin-1/ or receptors interleukin 1.mp.	2,357
3	(IL-1RA or IL 1RA).mp.	1,768
4	anakinra.mp..	17
5	kineret.mp.	3
6	SIALOGLYCOPROTEINS/	5,095
7	Recombinant Proteins/	92,451
8	or/2-7	99,041
9	1 and 8	494
10	randomized controlled trial.pt.	169,545
11	controlled clinical trial.pt.	62,509
12	randomized controlled trials/	26,378
13	random allocation/	46,502
14	double blind method/	71,756
15	single blind method/	6,954
16	or/10-15	286,786
17	(animal not human).sh	2,624,439
18	16 not 17	273,317
19	clinical trial.pt.	345,108
20	exp clinical trials/	138,904
21	(clin$ adj15 trial$).ti,ab.	86,668
22	(singl$ or doubl$ or trebl$) adj25 (blind$ or mask$).ti,ab.	70,784
23	Placebos/	21,852
24	placebo$.ti,ab.	75,840
25	random$.ti,ab.	251,875
26	research design/	40,192
27	or/19-26	605,915
28	27 not 17	563,903
29	28 not 18	301,805
30	29 or 18	575,122
31	9 and 30	95
32	from 31 keep 1-95	95

Date: 10 December 2002
Database: EMBASE (1988 to present)

Set	Search	Results
1	exp Rheumatoid Arthritis/	38,527
2	Interleukin 1 Receptor Blocking Agent/ or Interleukin 1 receptor antagonist.mp.	3,022
3	exp Interleukin 1/ or interleukin 1.mp.	21,123
4	(IL-1RA or IL 1RA).mp.	1,619
5	exp Recombinant Interleukin 1 receptor blocking agent/	196
6	anakinra.mp.	35
7	kineret.mp.	21
8	or/2-7	22,483
9	1 and 8	1,129
10	limit 9 to human	990
11	randomized controlled trial/	67,095
12	exp clinical trial/	246,318
13	exp controlled study/	1,425,624
14	double blind procedure/	44,637
15	randomization/	4,695
16	placebo/	58,995
17	single blind procedure/	3,771
18	((control$ adj (trial$ or stud$ or evaluation$ or experiment$).mp.	85,364
19	((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.	64,321
20	placebo$ or matched communities or matched schools or matched populations).mp.	97,807
21	(comparison group$ or control group$).mp.	93,788
22	(clinical trial$ or random$).mp.	417,278
23	(quasiexperimental or quasi experimental or pseudo experimental).mp.	813
24	matched pairs.mp.	1,325
25	or/11-24	1,734,786
26	10 and 25	478
27	from 26 keep 1-478	478

Appendix 6

List of included and excluded studies for effectiveness review

Citation		Inclusion?	Publication type and reason for exclusion/comment
1	Cohen *et al*., 2001[162]	Yes	Abstract. Trial 0180 HAQ scores at numerous time-points
2	Bresnihan *et al*., 2001[163]	Yes	Abstract. Trial 0560. Modified Sharp score
3	Bresnihan *et al*., 2001[164]	Yes	Abstract. Trial 0560. Productivity
4	Emery *et al*., 2001[165]	Yes	Abstract. Trial 0560. Subgroup analysis NHP data
5	Cohen *et al*., 2001[166]	Yes	Abstract. Trial 0180. HAQ component parts
6	Jiang *et al*., 2000[160]	Yes	FP. Trial 0560. Genant sharp scores vs Larsen scores
7	Cohen *et al*., 2001[105]	Yes	Abstract. Trial 0145
8	Bresnihan *et al*., 1998[102]	Yes	FP. Trial 0560
9	Cohen *et al*., 2002[104]	Yes	FP. Trial 0180
10	Fleishman *et al*., 2001[106]	Yes	Abstract. Trial 0757. Safety study
11	Emery *et al*., 2001[167]	No	Abstract. Data duplication
12	Miller *et al*., 2001[168]	No	Abstract. Combined analysis of 2 separate trials
13	Cravets *et al*., 2001[169]	No	Abstract. Post-hoc analysis of Larsen scores from trial 0560 using imputed data from bootstrapping
14	Bresnihan, 2001[26]	No	FP. Review
15	Bresnihan, 1999[170]	No	FP. Review
16	Bresnihan, 1996[171]	No	Abstract. Data duplication
17	Bresnihan, 2001[172]	No	FP. Review
18	Campion *et al*., 1996[173]	No	FP. No comparator arm
19	Cunnane *et al*., 2001[174]	No	FP. Not an RCT, end-points not appropriate
20	Snaith, 2002[175]	No	Abstract. Open-label extension, insufficient details to identify study
21	Cohen *et al*., 1999[176]	No	Abstract. Data duplication from trial 0180
22	Cunnane *et al*., 1996[177]	No	Abstract. Data duplication. Subgroup analysis, end-point not appropriate
23	Cunnane *et al*., 1998[178]	No	Abstract. Data duplication. Subgroup analysis, end-point not appropriate
24	Dayer and Bresnihan, 2002[179]	No	FP. Review
25	Jiang *et al*., 2001[180]	No	Abstract. Data duplication
26	Jiang *et al*., 1998[181]	No	Abstract. Data duplication
27	Genant, 2001[182]	No	FP. Data duplication
28	Lebsack *et al*., 1992[97]	No	Abstract. Pharmacokinetic study
29	Nuki *et al*., 1997[183]	No	Abstract. Non-comparative extension of trial 0560
30	Schiff, 2000[184]	No	FP. Review
31	Watt and Cobby, 2001[185]	No	FP. Duplicate data
32	Drevlow *et al*., 1996[186]	No	FP. IL-1 receptor type 1, not anakinra
33	Bresnihan *et al*., 2000[187]	No	Abstract. Non-comparative extension of trial 0560 and duplicate data
34	Bresnihan *et al*., 2001[188]	No	Abstract. Duplicate data, and data on non-comparative extension of trial 0560

continued

Citation		Inclusion?	Publication type and reason for exclusion/comment
35	Caldwell *et al*., 2001[189]	No	Abstract. All treatment arms contained anakinra
36	Cohen *et al*., 2001[190]	No	Abstract. Not an RCT
37	Nuki *et al*., 2001[191]	No	Abstract. Non-comparative extension of trial 0560
38	Schiff *et al*., 2001[192]	No	Abstract. No comparator treatment arm
39	Genant *et al*., 2000[193]	No	Abstract. Duplicate data, and data on non-comparative extension of trial 0560
40	Wallis *et al*., 2002[194]	No	Abstract. Review
41	Wallis *et al*., 2002[195]	No	Abstract. Review and duplicate data
42	Yang *et al*., 2002[196]	No	Abstract. Pharmacokinetic study
43	Hochberg *et al*., 2002[131]	No	Abstract. Cost-minimisation study
44	Brennan *et al*., 2002[132]	No	Abstract. Preliminary economic evaluation
45	Fleischmann *et al*., 2002[197]	Yes	Abstract. Subgroup analysis of trial 0757
46	Fleischmann *et al*., 2002[198]	No	Abstract. Duplicate data trial 0757
47	Schiff *et al*., 2002[199]	No	Abstract. Subgroup analysis and duplicate data for trial 0757
48	Tesser *et al*., 2002[200]	Yes	Abstract. Subgroup analysis of trial 0757
49	Fleischmann *et al*., 2002[201]	No	Abstract. Duplicate data trial 0757
50	Rooney *et al*., 2002[202]	No	Abstract. Duplicate data
51	Caldwell *et al*., 2002[203]	No	Abstract. Duplicate data
52	Edwards *et al*., 2002[204]	No	Abstract. No control arm
53	Andrias *et al*., 2002[205]	No	Abstract. Juvenile RA
54	Schiff *et al*., 2002[206]	No	Abstract. Duplicate data
55	Hochberg *et al*., 2002[207]	No	Abstract. Review
56	Shergy *et al*., 2000[208]	Yes	Abstract. Trial 0145 1 year end-point data
57	Shergy *et al*., 2002[112]	No	Abstract. Duplicate data. Trial 0145 1 year end-point data
58	Cohen *et al*., 2002[209]	No	Abstract. Duplicate data

FP: Fully published.

Appendix 7

Scoring using modified Drummond checklist for Amgen economic evaluation

Study design		
(1)	The research question is stated	Yes
(2)	The economic importance of the research question is stated	Unclear
(3)	The viewpoint(s) of the analysis are clearly stated and justified	Yes
(4)	The rationale for choosing the alternative programmes or interventions compared is stated	Stated yes, but of questionable appropriateness
(5)	The alternatives being compared are clearly described	Yes
(6)	The form of economic evaluation used is stated	Yes
(7)	The choice of form of economic evaluation is justified in relation to the questions addressed	Yes
Data collection		
(8)	The source(s) of effectiveness estimates used are stated	Yes
(9)	Details of the design and results of effectiveness study are given (if based on a single study)	Yes
(10)	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes
(11)	The primary outcome measure(s) for the economic evaluation are clearly stated	Yes
(12)	Methods to value health states and other benefits are stated	Yes
(13)	Details of the subjects from whom valuations were obtained are given	Yes
(14)	Productivity changes (if included) are reported separately	NA because of perspective
(15)	The relevance of productivity changes to the study question is discussed	NA
(16)	Quantities of resources are reported separately from their unit costs	Unclear
(17)	Methods for the estimation of quantities and unit costs are described	Yes
(18)	Currency and price data are recorded	Yes
(19)	Details of currency of price adjustments for inflation or currency conversion are given	NA
(20)	Details of any model used are given	Yes
(21)	The choice of model used and the key parameters on which it is based are justified	Authors outline their reasons but these are not thought to be justified (see text)
Analysis and interpretation of results		
(22)	Time horizon of costs and benefits is stated	Yes
(23)	The discount rate(s) is stated	Yes
(24)	The choice of rate(s) is justified	Determined by NICE guidance
(25)	An explanation is given if costs or benefits are not discounted	NA
(26)	Details of statistical tests and confidence intervals are given for stochastic data	No: transition probabilities are best estimates with no sampling variability explored

continued

(27)	The approach to sensitivity analysis is given	Yes
(28)	The choice of variables for sensitivity analysis is justified	No (see 26)
(29)	The ranges over which the variables are varied are stated	Yes
(30)	Relevant alternatives are compared	Only if interpreted as a last resort treatment
(31)	Incremental analysis is reported	Yes
(32)	Major outcomes are presented in a disaggregated as well as aggregated form	NA, as model
(33)	The answer to the study question is given	Yes
(34)	Conclusions follow from the data reported	Not in the authors' opinion
(35)	Conclusions are accompanied by the appropriate caveats	Partially

NA: not applicable.

Appendix 8

Base-case ICER calculations

Individual sampling models such as the BRAM need to be run for a large number of patients so that the results of the model are a good approximation to the assumed population mean. It is desirable that the number of patients is determined in a systematic way. The following procedure was followed to ensure that a sufficient number of patients has been used.

Start with 10,000 patients in each arm. If this proves insufficient, increase to 20,000, then to 40,000, then to 100,000, then to 200,000, and so on. If the results are not securely in one quadrant of the cost-effectiveness plane, then the number of patients is necessarily insufficient. If the results are either securely in the NW quadrant or securely in the SE quadrant, indicating dominance, then there is no need to increase the number of patients. If the results are either securely in the NE quadrant or securely in the SW quadrant, then the magnitude of the ICER is important to the decision-maker. A quasi-confidence interval (L, U) can be calculated for the ICER (in £/QALY). The number of patients was increased according to the criteria shown in the following table.

	Extend if
$U < 5000$ or $L > 200{,}000$	$U/L > 2.5$
$U < 10{,}000$ or $L > 100{,}000$	$U/L > 2.0$
$U < 20{,}000$ or $L > 50{,}000$	$U/L > 1.5$
$U < 30{,}000$ or $L > 30{,}000$	$U/L > 1.2$
$L < 30{,}000$ and $U > 30{,}000$	$U/L > 1.1$

Strategies 1 and 2 are as defined in *Table 14*. Strategies 1A and 2A include etanercept; strategies 1B and 2B do not. The effect of removing etanercept is that patients reach the divergence point earlier, and therefore tend to be younger. Since all patients are followed through to death, the total costs and QALYs are higher than for the corresponding strategy with etanercept. Similarly, although the patient pathways in the 'no anakinra' options in each strategy are the same whether anakinra is in the middle or last, the point from which costs and QALYs are counted is different, and the criterion for reaching the point of divergence is also different.

Results with anakinra in the middle

Strategy 1A with etanercept (4,000,000 patients used)

	Cost (£)	**QSE (£)**	**QALYs**	**QSE**	**% Pall**
With Ana	26,088	6.5	5.119	0.0022	48.1
No Ana	16,611	4.4	5.103	0.0021	53.0
Difference	9,477	7.8	0.016	0.0030	

ICER (£/QALY): 604,000 (436,000 – 985,000).
Ana: anakinra; Pall: Patient's teaching palliation.

Strategy 1B without etanercept (2,000,000 patients)

	Cost (£)	**QSE (£)**	**QALYs**	**QSE**	**% Pall**
With Ana	27,075	9.2	6.178	0.0033	52.5
No Ana	17,429	6.3	6.153	0.0033	57.3
Difference	9,647	11.1	0.025	0.0046	

ICER (£/QALY): 379,000 (278,000 – 597,000).

Strategy 2A with etanercept (1,000,000 patients)

	Cost (£)	**QSE (£)**	**QALYs**	**QSE**	**% Pall**
With Ana	23,498	13.1	4.109	0.0038	54.5
No Ana	13,859	9.2	4.084	0.0038	60.6
Difference	9,639	16.0	0.025	0.0054	

ICER (£/QALY): 385,000 (270,000 – 674,000).

Strategy 2B without etanercept (1,000,000 patients)

	Cost (£)	**QSE (£)**	**QALYs**	**QSE**	**% Pall**
With Ana	24,353	13.3	4.947	0.0042	58.2
No Ana	14,510	9.4	4.912	0.0041	64.0
Difference	9,843	16.3	0.035	0.0059	

ICER (£/QALY): 278,000 (209,000 – 415,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	**QSE (£)**	**QALYs**	**QSE**	**% Pall**
With Ana	14,171	24.0	3.149	0.0075	90.3
No Ana	2,662	3.4	3.061	0.0075	100
Difference	11,508	24.3	0.088	0.0106	

ICER (£/QALY): 131,000 (106,000 – 173,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,523	17.2	3.840	0.0058	91.6
No Ana	2,841	2.5	3.729	0.0058	100
Difference	11,682	17.3	0.111	0.0082	

ICER (£/QALY): 105,000 (92,000 – 124,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,021	23.8	2.844	0.0071	89.8
No Ana	2,581	3.4	2.739	0.0071	100
Difference	11,441	24.1	0.105	0.0100	

ICER (£/QALY): 109,000 (91,000 – 134,000).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,293	24.1	3.447	0.0078	91.2
No Ana	2,742	3.5	3.337	0.0077	100
Difference	11,551	24.3	0.109	0.0110	

ICER (£/QALY): 106,000 (88,000 – 132,000).

Appendix 9

Sensitivity analyses

Time on anakinra

The time on anakinra was based on a single time-point. As an alternative to the exponential distribution, the lowest value (0.62) of the shape parameter a for any of the DMARDs in *Table 17* was tried. (This is the most favourable to anakinra.) To fit 23% withdrawal at 24 weeks requires $b = 4.02$. The mean of the new distribution is 5.80 years, compared with 1.77 years in the base case.

Results with anakinra in the middle

Strategy 1A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	34,789	37.2	5.160	0.0069	40.9
No Ana	16,625	13.8	5.110	0.0068	53.0
Difference	18,164	39.6	0.050	0.0096	

ICER (£/QALY): 364,000 (263,000 – 593,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	36,347	38.0	6.232	0.0074	45.3
No Ana	17,434	14.0	6.153	0.0073	57.3
Difference	18,914	40.5	0.079	0.0104	

ICER (£/QALY): 240,000 (190,000 – 327,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	32,063	52.3	4.176	0.0086	46.2
No Ana	13,838	20.5	4.076	0.0085	60.7
Difference	18,225	56.2	0.100	0.0121	

ICER (£/QALY): 182,000 (147,000 – 240,000).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	33,438	53.6	5.010	0.0093	49.9
No Ana	14,518	21.0	4.902	0.0092	63.8
Difference	18,920	57.5	0.108	0.0131	

ICER (£/QALY): 176,000 (141,000 – 232,000).

Results with anakinra last

Strategy 1A with etanercept (40,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,361	120.2	3.322	0.0171	77.0
No Ana	2,655	7.7	3.042	0.0167	100
Difference	21,706	120.4	0.281	0.0239	

ICER (£/QALY): 77,300 (66,100 – 93,300).

Strategy 1B without etanercept (40,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,218	122.9	4.002	0.0188	78.8
No Ana	2,838	7.8	3.722	0.0183	100
Difference	22,380	123.1	0.280	0.0262	

ICER (£/QALY): 79,900 (67,300 – 98,400).

Strategy 2A with etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,725	73.9	2.967	0.0102	76.0
No Ana	2,577	4.8	2.729	0.0100	100
Difference	21,148	74.0	0.238	0.0143	

ICER (£/QALY): 89,000 (79,000 – 101,000).

Strategy 2B without etanercept (40,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,404	119.9	3.587	0.0177	78.3
No Ana	2,732	7.7	3.335	0.0172	100
Difference	21,672	120.2	0.252	0.0247	

ICER (£/QALY): 85,900 (71,800 – 107,000).

Utilities

The equation used in the BRAM was derived from a regression analysis on the Hurst data set. Tests were done for non-linearity, and for variation with age and gender. These tests suggested that QoL could be best predicted by a linear function of HAQ alone. Accordingly, the BRAM uses such a relationship. Therefore, to test the Amgen utility

values in the BRAM, it is necessary to fit a linear relationship between HAQ and QoL. The equation $QoL = 0.915 - 0.269\ HAQ$ fits the Amgen utilities with $R^2 = 0.975$.

Results with anakinra in the middle

Strategy 1A with etanercept (4,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,088	6.5	6.908	0.0025	48.1
No Ana	16,611	4.4	6.891	0.0025	53.0
Difference	9,477	7.8	0.017	0.0036	

ICER (£/QALY): 554,000 (391,000 – 947,000).

Strategy 1B without etanercept (4,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,073	6.5	8.061	0.0027	52.5
No Ana	17,427	4.4	8.037	0.0027	57.3
Difference	9,646	7.9	0.024	0.0038	

ICER (£/QALY): 405,000 (307,000 – 597,000).

Strategy 2A with etanercept (4,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,503	6.6	5.834	0.0023	54.5
No Ana	13,864	4.6	5.814	0.0022	60.7
Difference	9,639	8.0	0.020	0.0032	

ICER (£/QALY): 479,000 (359,000 – 682,000).

Strategy 2B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,353	13.3	6.763	0.0049	58.3
No Ana	14,510	9.4	6.730	0.0049	64.0
Difference	9,843	16.3	0.034	0.0069	

ICER (£/QALY): 294,000 (208,000 – 499,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,181	17.0	4.892	0.0064	90.4
No Ana	2,664	2.4	4.811	0.0064	100
Difference	11,517	17.1	0.081	0.0091	

ICER (£/QALY): 142,000 (116,000 – 183,000).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,515	24.3	5.649	0.0098	91.6
No Ana	2,838	3.5	5.564	0.0098	100
Difference	11,677	24.5	0.085	0.0139	

ICER (£/QALY): 137,000 (103,000 – 204,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,017	16.8	4.529	0.0061	89.8
No Ana	2,576	2.4	4.437	0.0061	100
Difference	11,442	17.0	0.092	0.0086	

ICER (£/QALY): 124,000 (105,000 – 152,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,307	17.0	5.216	0.0066	91.1
No Ana	2,745	2.4	5.132	0.0066	100
Difference	11,562	17.2	0.084	0.0093	

ICER (£/QALY): 137,000 (112,000 – 176,000).

Start and end effects

In this analysis the one-off loss of QALYs at the start and end of DMARDs was omitted.

Results with anakinra in the middle

Strategy 1A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,092	13.0	5.235	0.0043	48.1
No Ana	16,613	8.7	5.200	0.0043	53.0
Difference	9,479	15.6	0.034	0.0061	

ICER (£/QALY): 277,000 (205,000 – 431,000).

Strategy 1B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,071	13.0	6.303	0.0047	52.6
No Ana	17,429	8.8	6.254	0.0046	57.3
Difference	9,641	15.7	0.049	0.0066	

ICER (£/QALY): 199,000 (156,000 – 272,000).

Strategy 2A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,498	20.7	4.202	0.0060	54.6
No Ana	13,855	14.5	4.151	0.0060	60.7
Difference	9,643	25.3	0.051	0.0085	

ICER (£/QALY): 188,000 (141,000 – 281,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,373	21.0	5.044	0.0066	58.4
No Ana	14,509	14.8	4.976	0.0065	63.9
Difference	9,863	25.7	0.068	0.0093	

ICER (£/QALY): 145,000 (114,000 – 200,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,171	24.0	3.180	0.0075	90.3
No Ana	2,662	3.4	3.061	0.0075	100
Difference	11,508	24.3	0.119	0.0106	

ICER (£/QALY): 97,000 (82,000 – 118,000).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,515	24.3	3.857	0.0082	91.6
No Ana	2,838	3.5	3.725	0.0082	100
Difference	11,677	24.5	0.132	0.0116	

ICER (£/QALY): 88,000 (75,000 – 107,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,021	23.8	2.874	0.0071	89.8
No Ana	2,581	3.4	2.739	0.0071	100
Difference	11,441	24.1	0.136	0.0100	

ICER (£/QALY): 84,000 (73,000 – 99,000).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,293	24.1	3.478	0.0078	91.2
No Ana	2,742	3.5	3.337	0.0077	100
Difference	11,551	24.3	0.140	0.0110	

ICER (£/QALY): 82,000 (71,000 – 98,000).

Effectiveness of anakinra

In the base-case analysis, the HAQ improvement due to anakinra was rounded from 0.29 to 0.25. To test the effect of this rounding, the model was rerun with the HAQ improvement due to anakinra set to the nearest possible value above 0.29, namely 0.375. The results are shown below.

Results with anakinra in the middle

Strategy 1A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,146	20.4	5.172	0.0068	48.2
No Ana	16,625	13.8	5.110	0.0068	53.0
Difference	9,521	24.6	0.062	0.0096	

ICER (£/QALY): 153,000 (117,000 – 221,000).

Strategy 1B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,118	13.0	6.233	0.0047	52.6
No Ana	17,429	8.8	6.151	0.0046	57.3
Difference	9,689	15.7	0.083	0.0066	

ICER (£/QALY): 117,000 (101,000 – 140,000).

Strategy 2A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,550	13.1	4.165	0.0038	54.6
No Ana	13,859	9.2	4.084	0.0038	60.6
Difference	9,691	16.0	0.081	0.0054	

ICER (£/QALY): 119,000 (105,000 – 138,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,411	21.0	5.007	0.0066	58.5
No Ana	14,509	14.8	4.907	0.0065	63.9
Difference	9,902	25.7	0.100	0.0093	

ICER (£/QALY): 99,500 (83,900 – 122,000).

Results with anakinra last

Strategy 1A with etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,241	34.0	3.206	0.0105	90.6
No Ana	2,666	4.8	3.055	0.0105	100
Difference	11,575	34.4	0.151	0.0149	

ICER (£/QALY): 76,800 (64,100 – 95,700).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,550	24.3	3.881	0.0082	91.9
No Ana	2,838	3.5	3.725	0.0082	100
Difference	11,711	24.6	0.156	0.0116	

ICER (£/QALY): 75,000 (65,300 – 88,200).

Strategy 2A with etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,045	33.8	2.887	0.0100	90.0
No Ana	2,577	4.8	2.729	0.0100	100
Difference	11,468	34.1	0.158	0.0142	

ICER (£/QALY): 72,600 (61,500 – 88,400).

Strategy 2B without etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,350	34.2	3.496	0.0110	91.4
No Ana	2,736	4.9	3.328	0.0109	100
Difference	11,614	34.5	0.167	0.0155	

ICER (£/QALY): 69,400 (58,600 – 85,200).

Effectiveness of other DMARDs

It is suggested that the comparator DMARDs may be less effective if used late in the sequence. The importance of this was tested by reducing the HAQ improvement for azathioprine, CyA and gold, each by 0.125. Although these are the minimum changes permitted by the model, they represent reductions of either 33% or 50%. The effect of these changes is shown below. As expected, there is a substantial improvement in the ICER for anakinra.

Results with anakinra in the middle

Strategy 1A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,005	12.9	4.841	0.0042	47.6
No Ana	16,509	8.7	4.795	0.0042	52.5
Difference	9,496	15.6	0.047	0.0059	

ICER (£/QALY): 203,000 (162,000 – 271,000).

Strategy 1B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,991	13.0	5.885	0.0045	52.1
No Ana	17,333	8.8	5.829	0.0045	56.8
Difference	9,658	15.7	0.056	0.0064	

ICER (£/QALY): 173,000 (140,000 – 224,000).

Strategy 2A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,416	20.7	3.909	0.0059	54.2
No Ana	13,768	14.5	3.851	0.0058	60.2
Difference	9,648	25.3	0.058	0.0083	

ICER (£/QALY): 166,000 (129,000 – 233,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,303	21.0	4.737	0.0064	58.0
No Ana	14,430	14.8	4.669	0.0064	63.5
Difference	9,873	25.7	0.069	0.0091	

ICER (£/QALY): 144,000 (114,000 – 195,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,180	24.0	3.167	0.0075	90.5
No Ana	2,673	3.4	3.074	0.0075	100
Difference	11,507	24.2	0.093	0.0106	

ICER (£/QALY): 124,000 (101,000 – 160,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,537	17.1	3.858	0.0058	91.7
No Ana	2,852	2.5	3.749	0.0058	100
Difference	11,685	17.3	0.109	0.0083	

ICER (£/QALY): 107,000 (93,100 – 126,000).

Strategy 2A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,048	16.9	2.859	0.0050	89.9
No Ana	2,585	2.4	2.749	0.0050	100
Difference	11,464	17.0	0.110	0.0071	

ICER (£/QALY): 104,000 (92,500 – 120,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,332	17.0	3.457	0.0055	91.2
No Ana	2,753	2.4	3.354	0.0055	100
Difference	11,578	17.2	0.103	0.0078	

ICER (£/QALY): 112,000 (97,600 – 132,000).

It has also been suggested that the use of the same value for the HAQ improvement under both anti-

TNFs is inappropriate. The analysis was rerun with the HAQ improvement for etanercept set to 0.625 (rounded from 0.62) and for infliximab set to 0.25 (rounded from 0.30). The results are shown below.

Results with anakinra in the middle

Strategy 1A with etanercept (4,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,128	6.5	5.135	0.0022	48.2
No Ana	16,640	4.4	5.118	0.0021	53.2
Difference	9,488	7.8	0.018	0.0030	

ICER (£/QALY): 531,000 (396,000 – 803,000).

Strategy 1B without etanercept (2,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,129	9.2	6.205	0.0033	52.7
No Ana	17,473	6.2	6.179	0.0033	57.5
Difference	9,656	11.1	0.026	0.0046	

ICER (£/QALY): 367,000 (271,000 – 566,000).

Strategy 2A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,536	13.1	4.123	0.0038	54.6
No Ana	13,887	9.2	4.097	0.0038	60.8
Difference	9,649	16.0	0.027	0.0054	

ICER (£/QALY): 364,000 (259,000 – 611,000).

Strategy 2B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,421	13.3	4.976	0.0042	58.5
No Ana	14,555	9.4	4.939	0.0041	64.2
Difference	9,866	16.3	0.037	0.0059	

ICER (£/QALY): 264,000 (201,000 – 385,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,168	24.0	3.154	0.0075	90.3
No Ana	2,663	3.4	3.062	0.0075	100
Difference	11,505	24.2	0.092	0.0106	

ICER (£/QALY): 125,000 (102,000 – 163,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,525	17.2	3.849	0.0058	91.6
No Ana	2,843	2.5	3.735	0.0058	100
Difference	11,681	17.3	0.114	0.0082	

ICER (£/QALY): 102,000 (89,500 – 120,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,047	23.9	2.854	0.0071	89.8
No Ana	2,585	3.4	2.744	0.0071	100
Difference	11,461	24.1	0.110	0.0100	a

ICER (£/QALY): 104,000 (88,000 – 127,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,321	17.0	3.450	0.0055	91.1
No Ana	2,751	2.4	3.351	0.0055	100
Difference	11,570	17.2	0.099	0.0078	

ICER (£/QALY): 117,000 (101,000 – 138,000).

It has also been suggested that a value of 0.125 is more appropriate for the HAQ improvement under methotrexate when used late. Although methotrexate is always used early in any of the strategies considered in this report, the following tables show the result of changing the HAQ improvement under methotrexate to 0.125. They show that the results of the model are highly insensitive to the value used for the HAQ improvement under methotrexate. Indeed, as the previous set of results also suggests, changing the value of the HAQ gain for any DMARD used before the divergence point makes very little difference to the outcome. This is because the analysis is based on what happens after the divergence point between strategies: changing the value of the HAQ improvement for a DMARD before the divergence point merely changes slightly the starting population to which the analysis is applied.

Results with anakinra in the middle

Strategy 1A with etanercept (2,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,110	9.2	5.129	0.0030	48.2
No Ana	16,631	6.2	5.108	0.0030	53.1
Difference	9,479	11.0	0.020	0.0043	

ICER (£/QALY): 467,000 (328,000 – 809,000).

Strategy 1B without etanercept (2,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,112	9.2	6.194	0.0033	52.7
No Ana	17,458	6.2	6.172	0.0033	57.4
Difference	9,654	11.1	0.022	0.0046	

ICER (£/QALY): 439,000 (309,000 – 761,000).

Strategy 2A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	23,517	13.1	4.113	0.0038	54.5
No Ana	13,863	9.2	4.087	0.0038	60.6
Difference	9,655	16.0	0.026	0.0054	

ICER (£/QALY): 368,000 (261,000 – 622,000).

Strategy 2B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,371	13.3	4.955	0.0042	58.4
No Ana	14,519	9.4	4.918	0.0041	64.1
Difference	9,852	16.3	0.036	0.0059	

ICER (£/QALY): 271,000 (205,000 – 399,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,167	24.0	3.157	0.0075	90.3
No Ana	2,662	3.4	3.064	0.0075	100
Difference	11,504	24.2	0.093	0.0106	

ICER (£/QALY): 123,000 (100,000 – 159,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,516	17.1	3.844	0.0058	91.6
No Ana	2,844	2.5	3.737	0.0058	100
Difference	11,672	17.3	0.107	0.0082	

ICER (£/QALY): 109,000 (94,200 – 128,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,025	23.9	2.847	0.0071	89.8
No Ana	2,579	3.4	2.734	0.0071	100
Difference	11,446	24.1	0.113	0.0100	

ICER (£/QALY): 101,000 (86,000 – 123,000).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,318	17.0	3.443	0.0055	91.1
No Ana	2,748	2.4	3.342	0.0055	100
Difference	11,570	17.2	0.100	0.0078	

ICER (£/QALY): 115,000 (99,800 – 136,000).

Inclusion of offset costs

This analysis included an annual cost of being in a given health state of £860 per HAQ unit, ranging from 0 at HAQ 0 to £2580 at HAQ 3.

Results with anakinra in the middle

Strategy 1A with etanercept (4,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	35,942	8.7	5.119	0.0022	48.1
No Ana	26,473	6.9	5.103	0.0021	53.0
Difference	9,470	11.0	0.016	0.0030	

ICER (£/QALY): 604,000 (435,000 – 985,000).

Strategy 1B without etanercept (2,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	36,610	12.0	6.178	0.0033	52.5
No Ana	26,995	9.5	6.153	0.0033	57.3
Difference	9,615	15.3	0.025	0.0046	

ICER (£/QALY): 378,000 (277,000 – 595,000).

Strategy 2A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	33,820	17.5	4.109	0.0038	54.5
No Ana	24,258	14.1	4.084	0.0038	60.6
Difference	9,562	22.4	0.025	0.0054	

ICER (£/QALY): 382,000 (268,000 – 669,000).

Strategy 2B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	34,544	17.4	4.947	0.0042	58.3
No Ana	24,767	13.9	4.912	0.0041	64.0
Difference	9,777	22.3	0.035	0.0059	

ICER (£/QALY): 276,000 (207,000 – 412,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,492	32.8	3.149	0.0075	90.3
No Ana	14,257	20.8	3.061	0.0075	100
Difference	11,235	38.8	0.088	0.0106	

ICER (£/QALY): 128,000 (103,000 – 169,000).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,822	23.0	3.840	0.0058	91.6
No Ana	14,446	14.6	3.729	0.0058	100
Difference	11,376	27.2	0.111	0.0082	

ICER (£/QALY): 102,000 (89,200 – 120,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,366	32.8	2.844	0.0071	89.8
No Ana	14,206	21.0	2.739	0.0071	100
Difference	11,160	38.9	0.105	0.0100	

ICER (£/QALY): 106,000 (89,100 – 131,000).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,658	32.6	3.447	0.0078	91.2
No Ana	14,365	20.8	3.337	0.0077	100
Difference	11,293	38.7	0.109	0.0110	

ICER (£/QALY): 103,000 (86,000 – 129,000).

Disease progression

In the base-case analysis, there is a mean time of 4 years between each 0.125 unit increase in HAQ. However, the model allows this figure to be varied according to treatment. The authors do not accept that anakinra should be treated any differently from other treatments in this regard. However, they do accept that it is reasonable to slow progression on all DMARDs. The following additional analysis tests the importance of this parameter. As can be seen, this is a very important issue as regards the cost-effectiveness of DMARDs. If the rate of HAQ progression on a DMARD is slower than it would otherwise have been, then the DMARD has lasting effect beyond the end of its use.

Using mean time on anakinra of 1.77 years (base case)

Results with anakinra in the middle

Strategy 1A with etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	26,588	13.0	8.639	0.0059	50.6
No Ana	17,030	8.8	8.519	0.0058	55.5
Difference	9,558	15.7	0.120	0.0083	

ICER (£/QALY): 79,400 (69,800 – 92,100).

Strategy 1B without etanercept (1,000,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	27,548	13.1	9.374	0.0062	55.1
No Ana	17,777	8.9	9.219	0.0060	59.5
Difference	9,770	15.9	0.154	0.0086	

ICER (£/QALY): 63,200 (56,900 – 71,200).

Strategy 2A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,067	20.9	7.732	0.0086	57.0
No Ana	14,272	14.8	7.561	0.0084	62.9
Difference	9,795	25.6	0.171	0.0121	

ICER (£/QALY): 57,400 (50,300 – 66,900).

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,811	21.1	8.317	0.0090	60.7
No Ana	14,885	15.1	8.150	0.0088	66.1
Difference	9,926	26.0	0.166	0.0126	

ICER (£/QALY): 59,700 (51,800 – 70,300).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,367	24.1	6.178	0.0100	91.2
No Ana	2,745	3.4	5.856	0.0096	100
Difference	11,623	24.4	0.322	0.0138	

ICER (£/QALY): 36,100 (33,200 – 39,500).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,681	24.4	6.617	0.0103	92.3
No Ana	2,914	3.5	6.270	0.0100	100
Difference	11,768	24.6	0.348	0.0144	

ICER (£/QALY): 33,800 (31,200 – 36,900).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,204	24.0	5.975	0.0097	90.8
No Ana	2,660	3.4	5.658	0.0094	100
Difference	11,544	24.2	0.317	0.0135	

ICER (£/QALY): 36,500 (33,600 – 39,900).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	14,489	24.1	6.380	0.0101	91.8
No Ana	2,824	3.4	6.057	0.0098	100
Difference	11,665	24.4	0.324	0.0141	

ICER (£/QALY): 36,000 (33,100 – 39,500).

Using mean time on anakinra of 5.08 years (best case)

Results with anakinra in the middle

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	35,588	53.6	8.822	0.0137	43.6
No Ana	17,028	19.7	8.509	0.0130	55.4
Difference	18,560	57.1	0.313	0.0189	

ICER (£/QALY): 59,300 (52,900 – 67,500).

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	37,203	38.6	9.604	0.0101	47.9
No Ana	17,765	14.1	9.208	0.0096	59.4
Difference	19,439	41.1	0.396	0.0139	

ICER (£/QALY): 49,100 (45,900 – 52,800).

Strategy 2A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	32,948	37.7	7.931	0.0089	48.9
No Ana	14,272	14.8	7.561	0.0084	62.9
Difference	18,677	40.5	0.369	0.0123	

ICER (£/QALY): 50,600 (47,400 – 54,200).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	34,401	54.6	8.612	0.0132	52.6
No Ana	14,870	21.3	8.142	0.0125	66.1
Difference	19,531	58.6	0.470	0.0182	

ICER (£/QALY): 41,500 (38,500 – 45,000).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,794	54.5	6.571	0.0107	78.5
No Ana	2,745	3.4	5.856	0.0096	100
Difference	22,050	54.6	0.715	0.0144	

ICER (£/QALY): 30,900 (29,700 – 32,200).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,646	56.1	7.067	0.0112	80.3
No Ana	2,914	3.5	6.270	0.0100	100
Difference	22,733	56.2	0.798	0.0151	

ICER (£/QALY): 28,500 (27,500 – 29,600).

Strategy 2A with etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,363	76.2	6.358	0.0148	77.9
No Ana	2,666	4.8	5.678	0.0133	100
Difference	21,697	76.4	0.681	0.0199	

ICER (£/QALY): 31,900 (30,100 – 33,900).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,302	55.3	6.810	0.0109	79.4
No Ana	2,824	3.4	6.057	0.0098	100
Difference	22,478	55.4	0.753	0.0147	

ICER (£/QALY): 29,800 (28,700 – 31,100).

Best case for anakinra

For this analysis, the following changes were made to the base-case data set.

- The equation $QoL = 0.915 - 0.269\ HAQ$ for utilities (based on the Amgen model) was used.
- The start and end effects for DMARDs were removed.
- Disease progression while on any treatment except palliation was completely removed.
- The HAQ improvement for each of azathioprine, ciclosporin and gold was reduced by 0.125.
- The HAQ improvement for anakinra was increased from 0.25 to 0.375.
- The mean time on anakinra was increased from 1.77 to 5.08 years.

The analysis was run both with and without offset costs.

Results without offset costs

Results with anakinra in the middle

Strategy 1A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	35,698	38.0	10.091	0.0107	43.1
No Ana	16,945	14.0	9.649	0.0102	55.0
Difference	18,753	40.4	0.442	0.0148	

ICER (£/QALY): 42,400 (39,700 – 45,400).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	37,241	54.7	11.034	0.0158	47.6
No Ana	17,688	20.0	10.502	0.0150	59.1
Difference	19,553	58.2	0.533	0.0218	

ICER (£/QALY): 36,700 (33,900 – 40,000).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	33,030	53.4	9.149	0.0141	48.6
No Ana	14,213	20.9	8.669	0.0134	62.5
Difference	18,817	57.3	0.480	0.0194	

ICER (£/QALY): 39,200 (36,300 – 42,700).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	34,448	54.7	9.965	0.0147	52.4
No Ana	14,807	21.3	9.368	0.0140	65.7
Difference	19,642	58.7	0.598	0.0203	

ICER (£/QALY): 32,900 (30,800 – 35,300).

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,956	54.8	7.984	0.0124	78.9
No Ana	2,754	3.4	7.222	0.0114	100
Difference	22,203	54.9	0.761	0.0168	

ICER (£/QALY): 29,200 (27,900 – 30,500).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,800	56.4	8.610	0.0129	80.6
No Ana	2,923	3.5	7.773	0.0119	100
Difference	22,877	56.5	0.837	0.0176	

ICER (£/QALY): 27,300 (26,200 – 28,500).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	24,535	54.2	7.709	0.0121	78.2
No Ana	2,668	3.4	6.954	0.0111	100
Difference	21,868	54.3	0.756	0.0164	

ICER (£/QALY): 28,900 (27,700 – 30,300).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	25,461	55.6	8.280	0.0126	79.8
No Ana	2,833	3.4	7.482	0.0116	100
Difference	22,629	55.7	0.798	0.0171	

ICER (£/QALY): 28,400 (27,200 – 29,600).

Results with offset costs

Results with anakinra in the middle

Strategy 1A with etanercept (400,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	40,509	39.7	10.091	0.0107	43.1
No Ana	22,400	18.1	9.649	0.0102	55.0
Difference	18,109	43.6	0.442	0.0148	

ICER (£/QALY): 40,900 (38,400 – 43,900).

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	42,511	57.0	11.034	0.0158	47.6
No Ana	23,637	25.8	10.502	0.0150	59.1
Difference	18,873	62.6	0.533	0.0218	

ICER (£/QALY): 35,400 (32,700 – 38,600).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	37,772	55.6	9.149	0.0141	48.6
No Ana	19,700	25.9	8.669	0.0134	62.5
Difference	18,072	61.3	0.480	0.0194	

ICER (£/QALY): 37,700 (34,900 – 41,000).

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	39,556	40.10	9.936	0.0104	52.4
No Ana	20,778	18.6	9.376	0.0099	65.7
Difference	18,778	44.2	0.559	0.0143	

ICER (£/QALY): 33,600 (31,900 – 35,400).

Results with anakinra last

Strategy 1A with etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	30,615	79.1	7.972	0.0175	78.8
No Ana	9,699	21.9	7.219	0.0160	100
Difference	20,917	82.1	0.753	0.0237	

ICER (£/QALY): 27,800 (26,100 – 29,700).

Strategy 1B without etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	31,935	80.1	8.597	0.0183	80.5
No Ana	10,424	22.6	7.789	0.0168	100
Difference	21,511	84.0	0.808	0.0248	

ICER (£/QALY): 26,600 (25,100 – 28,400).

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	29,967	55.2	7.709	0.0121	78.2
No Ana	9,332	15.1	6.954	0.0111	100
Difference	20,635	57.2	0.756	0.0164	

ICER (£/QALY): 27,300 (26,200 – 28,600).

Strategy 2B without etanercept (100,000 patients)

	Cost (£)	QSE (£)	QALYs	QSE	% Pall
With Ana	31,318	80.1	8.263	0.0178	79.9
No Ana	10,005	22.1	7.464	0.0164	100
Difference	21,313	83.1	0.799	0.0242	

ICER (£/QALY): 26,700 (25,200 – 28,400).

Appendix 10

Therapeutic approaches being investigated in RA

A number of other therapeutic approaches in RA are currently being investigated, many of which involve modulation of the cytokine network. These include receptor antagonists, soluble receptors and monoclonal antibodies to other cytokines, e.g. IL-6, as well as the direct use of anti-inflammatory cytokines, e.g. IL-10, IL-4 and IL-11.[21,210–212]

Further developments around TNF blockade are being actively investigated: D2E7 (adalimumab) a fully humanised anti-TNF-α monoclonal antibody and PEG sTNF-RI, a pegylated soluble p55 TNF receptor.[213] Adalimumab has been submitted for a product licence in both the USA and Europe.[214]

Clinical trials of experimental IL-1Ra gene therapy in RA are also underway. The human IL-1Ra gene is transferred to synovium by a retroviral vector. Clinical benefits in patients with RA are yet to be evaluated.[215]

A novel biological agent for the treatment of RA, CTLA4Ig, which is the first of a new class of drugs, the co-stimulation blockers, is in Phase 3 trials. This drug blocks T-cell activation and pro-inflammatory cytokine release. It is hoped that this drug will be launched in 2004.[216]

Other therapeutic targets being investigated are oral toleragen therapy, adhesion molecules, modulation of T-cell activity, blockade of effector function, vaccination with T-cell receptors, major histocompatibility complex antigens and autologous haematopoietic stem-cell transplantation.[211]

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We look forward to hearing from you.

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