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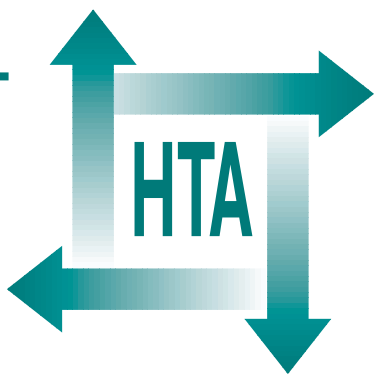

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A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept

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Competing interests: Dr Carole Cummins is an investigator on a research proposal approved by the British Paediatric Rheumatology Group for a biologics and new drug paediatric rheumatology register, which will include patients taking etanercept. Funding is to be sought from Wyeth Laboratories. None of the other authors have any competing interests.

Wyeth Laboratories submitted some information to the National Institute for Clinical Excellence in confidence and references to this information have been removed from this HTA report. However, it should be noted that the Institute's Appraisal Committee had access to the full report when drawing up their guidance on the use of etanercept for children with juvenile idiopathic arthritis.

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Contents

List of abbreviations and glossary

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.

List of abbreviations

ACR	American College of Rheumatology
ANA	antinuclear antibody
BPRG	British Paediatric Rheumatology Group
CAHP	Childhood Arthritis Health Profile
CHQ	Childhood Health Questionnaire
CHAQ	Child Health Assessment Questionnaire
CRP	C-reactive protein
DMARD	disease-modifying anti-rheumatic drug
EQ-5D	EuroQol-5 dimensions
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GP	general practitioner
HAQ	Health Assessment Questionnaire
HLA	human leucocyte antigen
IgG1	immunoglobulin G (class I)
ILAR	International League of Associations for Rheumatology
IL	interleukin
JIA	juvenile idiopathic arthritis (ILAR terminology)
JRA	juvenile rheumatoid arthritis (ACR terminology)
JCA	juvenile chronic arthritis (EULAR terminology)
MHC	major histocompatibility complex
NICE	National Institute for Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
PRINTO	Paediatric Rheumatology International Trials Organisation
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RF	rheumatoid factor
RCT	randomised controlled trial
SF-36	Short Form with 36 items
TNF-α	tumour necrosis factor-alpha
VAT	value added tax

Glossary

ACR 20 A scoring system for determining if 20% improvement in RA disease state has been achieved. It employs measures in six key outcome variables according to the ACR response criteria.

Amyloidosis A very serious and often fatal complication of uncertain cause in RA and other diseases, particularly those involving inflammation. It is characterised by essentially irreversible and non-physiological glycoprotein deposition in many tissues, the function of which is consequently compromised.

Anti-tumour necrosis factor agent (TNF) Agents that block the action of TNF-α by mechanisms such as binding to TNF-α so that it is unable to complex with its receptor or binding to cell surface TNF-α receptors so that their function is antagonised (as opposed to agonists, which potentiate the function of receptors).

Cyclosporin An immunosuppressive drug used to prevent organ transplant rejection and as a therapy for JIA and RA. It is a complex cyclic peptide that is the natural product of certain bacteria and fungi and which blocks signalling pathways dependent on calcineurin.

C-reactive protein A globulin protein that, in the presence of calcium ions, precipitates the C substance of pneumococcal cells. The presence of this protein correlates with radiographic disease progression in RA.

Cytokine Peptide or protein that functions as part of signalling pathways that act as local mediators in cell–cell communication; examples include TNF-α and the ILs. They may represent targets of natural products such as cyclosporin, or of chemically or biologically synthesised putatively therapeutic agents.

Disease-modifying anti-rheumatic drug (DMARD) A drug that can modify the course of RA by slowing or stopping disease progression, as assessed by radiographic analysis of involved joints (in contrast to providing only symptomatic relief with no effect on disease course).

Etanercept A genetically engineered fusion protein consisting of two copies of the extracellular part of the p75 TNF-α receptor each linked to one constant region (Fc) of human IgG1. The elimination half-life and the TNF-α affinity are respectively fivefold and 1000-fold greater than the corresponding monomeric TNF-α receptor. The protein is produced in a line of Chinese hamster ovary cells. Its molecular mass is approximately the same as an IgG molecule.

Erythrocyte sedimentation rate (ESR) The rate at which erythrocytes settle in a test tube in 1 hour under standard conditions. ESR is a non-specific indicator of disease including RA, and correlates with radiographic disease progression in RA.

Fc 'Fragment crystallising'; part of the constant region of IgG immunoglobulin molecules. When first investigated, these fragments, produced from the parent molecules by enzyme hydrolysis, were found to precipitate out of solution as crystals thus indicating a highly homogeneous structure.

Hydroxychloroquine An anti-malaria drug employed sometimes in RA therapy. Its mechanism of action is uncertain.

JRA 30 A scoring system for determining if 30% improvement in JRA disease state has been achieved. It employs measures in six key outcome variables according to the ACR response criteria.

Metalloproteinases Metal-containing enzymes whose substrates are proteins, which they degrade by hydrolysis of peptide bonds. Matrix metalloproteinases play a pivotal role in the breakdown of the extracellular matrix. They contain the metal zinc, which greatly enhances their catalytic power above that which could be provided by their amino acid side chains alone. Under normal physiological circumstances they are tightly controlled and regulated.

Methotrexate A cytostatic drug used in cancer therapy and as an immunosuppressive agent. Chemically related to the B class vitamin folic acid it inhibits the synthesis of the coenzyme tetrahydrofolate, which is

continued

Glossary *contd*

important in one carbon (methyl) transfer reactions (e.g. in the biosynthesis of purines and pyrimidines).

Nitric oxide Nitrogen monooxide (NO) is a gas with free radical properties that render it chemically reactive and therefore short-lived in a biological environment. It is generated by complex cellular enzymes (NO synthases) from the amino acid arginine. Depending on circumstances NO can function as a signalling molecule (e.g. resulting in relaxation of cardiac muscle or of artery walls) or as a potent free radical antibacterial agent. When generated by pro-inflammatory cells its reactivity is deleterious to surrounding tissues.

Oligoarthritis JIA with four or fewer joints involved on initial presentation, usually wrists, knees, ankles (ILAR terminology). May extend to further joint involvement.

Pauciarthritis JIA with four or fewer joints involved on initial presentation, usually wrists, knees, ankles (predating ILAR terminology).

Polyarticular JIA with more than four joints involved at presentation.

Prostaglandins Signalling molecules derived after the action of cyclooxygenases upon certain polyunsaturated fatty acids (particularly those with 20 carbon atoms – the eicosanoids) that are released from cell membrane phospholipid molecules by the action of phospholipases after appropriate stimulation. They are chemically unstable and are short-lived. Their production can be blocked by inhibiting cyclooxygenase action with NSAIDs such as aspirin.

Rheumatoid factor (RF) Antibodies that are able to bind slightly denatured human IgG class antibodies and which are frequently present in serum of patients with RA.

Steinbrocker functional classification One of the radiological scoring methods employed for evaluating change and joint damage in peripheral joints of RA patients.

Sulphasalazine A drug used in the treatment of RA and inflammatory bowel conditions (Crohn's disease and ulcerative colitis). It is a conjugate drug that is split into two parts by colonic bacteria; one part is a salicylate and the other a sulfonamide. Its mechanism of action is uncertain.

Uveitis Inflammation of the uveal tract of the eye including the iris, ciliary body and choroid. It may be associated with pain and lacrimation (tearing), and can result in damage to vision. Complication of JIA.

Executive summary

Background

Juvenile idiopathic arthritis (JIA) comprises a group of painful conditions involving persistent swelling of the joints with variable presentation and course. A high proportion of affected children develop destructive joint disease, 30–40% of children with polyarticular onset disease, often requiring early joint replacement.

While some patients respond to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular or pulsed steroids, others require further treatment. There is evidence that methotrexate is an effective second-line drug for such children, and it is increasingly used earlier in the course of the disease with the aim of preventing long-term joint damage. Some children, however, have disease that does not respond adequately to methotrexate or they cannot tolerate methotrexate treatment. These patients are treated with other disease-modifying anti-rheumatic drugs (DMARDs), which are also used in the treatment of rheumatoid arthritis (RA) in adults. In this patient group, however, these drugs have limited effectiveness and often carry a high risk of adverse effects. Such patients are likely to experience substantial morbidity persisting into adult life, with a serious impact on their quality of life.

Tumour necrosis factor-alpha (TNF-α) is a cytokine that plays an important role in mediating joint inflammation. Its actions may be inhibited by etanercept (Enbrel®, Wyeth Laboratories; Maidenhead), a synthetic receptor for TNF-α licensed for use in the UK for the treatment of methotrexate-resistant JIA. Etanercept is given by twice-weekly subcutaneous injection and can be given for an indefinite period.

Aims

- To provide a background review on JIA, including epidemiology, current and emerging therapeutic options, and impact of disease on individuals and health services.
- To conduct a systematic review of the clinical benefits and hazards of the anti-TNF agent etanercept in JIA compared with currently available treatments.
- To review economic evidence about the cost-effectiveness of this agent compared with other treatment options.

Methods

A systematic review of effectiveness was undertaken. Databases (MEDLINE, EMBASE, Science Citation Index and the Cochrane Library) were searched from 1966 to the end of 2000. Randomised controlled trials (RCTs) comparing etanercept with any agent in JIA and other rheumatic diseases of childhood were considered. Manufacturer and sponsor submissions to the National Institute for Clinical Excellence (NICE) were reviewed.

Data extraction focused on clinical outcomes, commonly measured by six core outcome variables: physician's global impression; parent/patient global impression; number of active joints; number of joints with limited range of motion; functional ability; and erythrocyte sedimentation rate.

For the health economic and cost studies the databases MEDLINE, DARE and UK health economic websites were searched from 1997 to the end of February 2001 and Manufacturer and sponsor submissions to NICE were reviewed.

Results

Number and quality of studies

One RCT of etanercept in patients with methotrexate-resistant JIA was identified. The trial involved a total of 69 patients, all of whom received etanercept. Etanercept was compared with placebo in a withdrawal trial that included patients who had responded to etanercept in the first phase of the study. The trial was given a high quality score.

Direction of evidence

Etanercept improves the outcomes in children and young people with JIA when compared with placebo. No comparisons between etanercept and

other drugs used in this patient group were found. Other such drugs, however, are believed to have only limited efficacy in this patient group. The trial results are consistent with the results of trials of etanercept in adults with RA.

Size of treatment effect

In an open phase, 51 out of 69 children (74%) improved while on etanercept (30% response based on the six outcome variables). In the randomised phase of the study, 28% of the etanercept arm experienced disease flare compared with 81% of the placebo arm. At the end of the study, 20 (80%) of the etanercept double-blind phase group compared with nine (35%) of the placebo group still met the definition of improvement ($p < 0.01$). Eighteen (72%) compared with six (23%) met the definition of improvement set at 50% improvement, and 11 (44%) compared with five (19%) met the definition of improvement if it was set at 70%.

The trial continued with an open-label extension phase. At 20 months, 83% of all patients had achieved a 30% response, 78% a 50% response, and 63% a 70% response. Adverse events occurred infrequently and were comparable with placebo.

Economic analysis

Cost/QALY

The manufacturer's submission included a cost–utility analysis. No other economic analyses were found.

In the cost–utility analysis, for a patient starting on etanercept rather than placebo, the incremental benefit per person was estimated as 1.74 QALYs, with a total discounted cost per QALY of £16,082.

Sensitivity analyses

Sensitivity analyses ranged between £3900 (cost offsets assumption changed to exclude nursing home and home help costs but to include indirect costs) and £34,000 (SF-36 used), though changes in most variables did not make a great difference.

Limitations of the calculations (assumptions made)

The validity and accuracy of this estimate must be questioned because:

- there is insufficient knowledge about the outcomes of JIA, in particular the quality of life and long-term outcomes
- the model was constructed for RA in adults
- the strong assumptions used were not based on evidence
- technical problems were identified with the model.

The limitations of the research base at present means that the construction of a JIA model with greater validity presents considerable problems.

Drug costs

The annual cost of etanercept for a child with JIA is £8996. It was estimated that about 400 (range, 230–560) JIA patients might be receiving treatment with etanercept in 5 years' time, yielding annual drug costs at that point in time of £3,589,400 (current prices, licensed use). Further patients would accrue.

Notes on the generalisability of the findings

The strong assumptions used in the economic analysis limit the usefulness and generalisability of the model.

Conclusions

Need for further research

Given the novel biological action of etanercept, long-term follow-up is desirable, and is required by regulatory agencies, in order to detect any unexpected adverse events.

There is no evidence comparing etanercept with other treatments in this patient group. Safety concerns and relative lack of efficacy would place ethical constraints on trials of relative effectiveness.

The effectiveness of etanercept in the treatment of other forms of JIA including psoriatic and enthesitis arthritis is unknown. International trials would be required, on account of the rarity of these conditions.

Greater health gains might be possible if etanercept was used earlier in the disease process and in less severe disease. Trials to test these hypotheses are required.

Chapter 1

Aims and background

Aims of the review

The aims of this review are as follows:

- to provide a background review on juvenile idiopathic arthritis (JIA), including epidemiology, current and emerging therapeutic options, and impact of disease on individuals and health services
- to conduct a systematic review of the clinical benefits and hazards of the anti-tumour necrosis factor (TNF) agent etanercept in JIA compared with currently available treatments. Etanercept is licensed for the treatment of patients with JIA who have not responded to methotrexate treatment, that is, patients with a severe form of the condition
- to review the economic evidence about the cost-effectiveness of using these agents compared with other treatment options.

Background

Description of the underlying health problem

Epidemiology

This report focuses on children and young people with severe JIA.

JIA (formally known as juvenile rheumatoid arthritis (JRA) in the USA) comprises a heterogeneous group of painful conditions involving persistent swelling of the joints with variable presentation and course. A high proportion of affected children develop destructive joint disease, 30–40% of children with polyarticular onset disease (*Table 1*).[1–5] Young children, however, may not complain of pain at presentation, and detection of swelling may require close examination. Non-specific symptoms such as lethargy and irritability are common.[1] Growth retardation may be a feature of severe JIA.

The current, but still unvalidated,[6,7] classification of JIA is the recently developed International League of Associations for Rheumatology (ILAR) classification (*Table 1*).[5,6] Previously, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) classifications used different terminology.[8] Caution should therefore be used in comparing studies using different classifications. In this report, JIA is the preferred term; however, where reference is made to studies that have used JRA (usually ACR classification) or juvenile chronic arthritis (JCA; usually the EULAR classification), those terms are used. The ILAR classification identifies clinically homogeneous groups, as knowledge of genetic and other factors is not yet adequate to arrive at a classification based on pathology. Important differences are that spondylarthropathies are excluded from the ACR definition, but included in the EULAR definition, and that rheumatoid factor (RF)-positive cases are called JRA under EULAR rather than JCA. This multiplicity of classifications complicates the interpretation of studies from different regions and periods.

The reported distribution of JIA subgroups varies from country to country, but in Europe and North America oligoarthritis accounts for more than half of the cases, with about a quarter of prevalent cases having polyarthritis and about 10% having systemic disease.[8,9] Data from two of the centres included in a National Diagnostic Register indicate that there is an annual incidence of 10 per 100,000 population aged under 16 years, and it has been estimated that about 1000 new cases are referred to hospital in England each year.[9] The distribution of subtypes of incident cases is not known.

One serious complication of JIA is chronic uveitis, which can lead to visual impairment or blindness in up to 12% of children with JIA who develop the condition and can result in the development of cataracts and glaucoma. Thus children with JIA are screened for early signs. Uveitis is most common in oligoarthritis, with 30% developing uveitis over 6 years[10] and is more in antinuclear antibody- (ANA-)positive patients than in ANA-negative patients. Therapy is with non-steroidal anti-inflammatory drugs (NSAIDs), oral and topical steroids (which themselves carry a risk of ocular damage), and immune suppressants such as methotrexate and cyclosporin, but these therapeutic options have not been evaluated in randomised controlled trials (RCTs).[11]

TABLE 1 *International League of Associations for Rheumatology (ILAR) classification of JIA, disease characteristics and treatment*[5,7]

Classification	Characteristics and treatment
Systemic arthritis	*Diagnosis*: Spiking fever, transient rash, high ESR and C-reactive protein, negative autoantibodies *Characteristics*: Peak age onset 2 years, typically followed by polyarthritis, no HLA association *Typical prognosis*: Polyarthritis progresses, systemic features may regress over 3–4 years. Uncontrolled systemic disease can progress to amyloidosis with renal failure and high mortality *Typical treatment*: NSAIDs, high-dose steroids, methotrexate (for persistent polyarthritis, equivocal benefit for systemic features)
Oligoarthritis (persistent)	*Diagnosis*: Four or fewer joints involved, usually wrists, knees, ankles *Characteristics*: Mainly girls, peak age of onset 3 years, often localised and mild, associated with uveitis that may lead to visual impairment or blindness *Typical prognosis*: Remission in 4–5 years *Typical treatment*: NSAIDS, intra-articular or other steroids (may remove need for NSAIDs), physiotherapy
Oligoarthritis (extended)	*Diagnosis*: Often raised ESR, four or fewer joints, extending to more within first year *Characteristics*: Mainly girls, peak age of onset 3 years, associated with uveitis, chronic disease *Typical prognosis*: Chronic disease, risk of functional disabilities *Typical treatment*: NSAIDS, intra-articular or other steroids, low-dose methotrexate, resistant cases subcutaneous methotrexate at higher doses, resistant cases other DMARDs
Polyarticular arthritis	*Diagnosis*: More than four joints involved at presentation *Characteristics*: Most RF-negative *Typical prognosis*: Poor, widespread joint destruction, often joint replacement as young adults *Typical treatment*: NSAIDs, intra-articular or oral steroids, low-dose methotrexate, resistant cases subcutaneous methotrexate at higher doses, resistant cases other DMARDs
Enthesitis arthritis	*Diagnosis*: HLA B27 associated, RF-negative, ANA-positive, peripheral arthritis *Characteristics*: Mainly boys, teen and pre-teen, uveitis *Typical prognosis*: Functional outcome aside from hips and progression usually good, some hip joint erosion, many progress to spondylarthropathies *Typical treatment*: NSAIDs, sulphasalazine, methotrexate
Psoriatic arthritis	*Diagnosis*: Inflammation of fingers, toes and polyarthritis, psoriasis in child or first-degree relative *Characteristics*: Psoriasis in child or relative *Typical prognosis*: Can be highly erosive *Typical treatment*: Generally treated with methotrexate, but efficacy not established in childhood disease
Unclassified	Includes patients with overlapping features

ESR, erythrocyte sedimentation rate, HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drug; DMARD, disease-modifying anti-rheumatic drug; RF, rheumatoid factor; ANA, antinuclear antibody

Pathogenesis

The causes of JIA and the mechanisms through which it develops remain unclear. An autoimmune origin for JIA is suggested by associations of subtypes with major histocompatibility complex (MHC) types, by the presence of autoantibodies in some patients and by the association of JIA with selective immune system deficiencies.[4,5,12] Subtypes show different genetic features, primarily involving MHC. In common with many other conditions with an autoimmune component, JIA does not show a Mendelian inheritance pattern and can be characterised as a complex genetic trait, as members of a patient's family have a small increased risk of developing the disease. This risk might result from an increased disposition to autoimmunity.[12] Environmental factors are also involved, possibly a common infection, but studies have been inconclusive.[5]

Incidence

A wide range of estimates for the incidence of JIA is found in the literature.[8] Some of the difference is attributable to differences in disease definition

and some to differences in case-finding and the population covered. The most reliable information comes from studies with populations covering clearly defined geographic areas. One such Swedish study found a rate of 11 cases per 100,000 population per year,[13] and a UK study found a similar rate of 10 cases per 100,000 population per year.[9] Both of these studies used the EULAR classification.

Prognosis

The prognosis of JIA varies with the subtype. Estimation of the proportions of patients with persistent disease is complicated by:

- lack of a consensus on the definition of remission
- referral bias inherent in hospital-based series
- differences in the length of follow-up
- potential problems with loss to follow-up.

The applicability of existing reports of prognosis to the current cohort of children may be limited. It is possible that the prognosis of the cohort of children currently being treated for JIA may be better than previous cohorts as no cohort of children with JIA has hitherto left paediatric services with as well-controlled disease, following the wider evidence-based use of methotrexate (see *Current service provision* below). As yet, follow-up is too short to identify any impact on long-term outcomes.

While many children presenting with oligo-arthritis will experience remission within 5 years, as many as 50% progress to extended oligo-arthritis by 6 years from diagnosis,[10] with 35% developing joint erosions. About one-third to one-half of children with polyarticular arthritis will have active arthritis persisting into adult life, and about one-third of those presenting with systemic disease will develop severe polyarthritis.[14]

Patients with polyarticular and systemic disease score more highly (i.e. do badly) on the Disability Index of the Child Health Assessment Questionnaire (CHAQ) than children with pauciarticular disease and controls.[15] In terms of generic health-related quality of life, children with JIA do worse than controls in terms of pain, self-esteem, general health perceptions and impact on emotions, and on all physical functioning scales, but their scores were high for behaviour, mental health and family functioning (based on a study of 208 JRA patients using the Childhood Arthritis Health Profile (CAHP), which uses generic scales based on the Childhood Health Questionnaire (CHQ) and disease-specific scales).[16]

Patients with JIA of any type, particularly those who are positive for RF, may need multiple soft-tissue release operations and joint replacement. Amyloidosis is a rare but usually fatal complication of severe chronically active JIA of any type, particularly of systemic onset disease.

A study from a tertiary referral centre has shown that school attendance of children and young people can be good, but the range of days off school is wide, indicating that some children do experience problems. However, attendance is poorer in polyarticular disease,[17] and high rates of psychological deviance (i.e. departure from expected values) were reported. In a case–control study, JCA patients unexpectedly did well compared with controls with respect to perceived competence and self-image, depression, social functioning, family functioning and social support.[18]

A population-based case–control survey (n = 44 cases) in Minnesota found that in adult life 75% described their symptoms to be mild or absent. However, 21% reported moderate symptoms and 5% reported joint symptoms occurring even when at rest. Functional status was examined using the Health Assessment Questionnaire (HAQ) score, and more cases than controls had abnormal scores. Cases also scored badly compared with controls on the Health Status Questionnaire on scales including vitality, bodily pain, health perception and physical functioning. There were higher rates of unemployment in patients who had had JRA than in controls.[19]

In a Danish study, 11% of those subjects who could be followed-up were in Steinbrocker[20] functional class III and IV (i.e. were severely disabled), and 22% had undergone major surgery. Eighty per cent of patients had had extended pauciarticular or polyarticular JCA, indicating referral and follow-up bias. A UK study reported 14% to be severely disabled, but again may have incorporated referral and follow-up bias.[3] It is apparent, however, that a proportion of adults with JIA have severe persisting morbidity. There is other important long-term morbidity: a further UK study and others have shown that many adults have osteoporosis or growth abnormalities or visual loss.[21]

In a UK study of education and employment status in adults who had JIA,[22] 20% had attended schools

for the physically disabled for at least part of their education. Only a minority left school without any qualifications, and more patients than siblings were in tertiary education. Despite relatively high school achievement, 30% of patients compared with 11% of siblings were unemployed and most attributed this to their disability. Although most patients were sexually active, the majority (58%) had experienced problems relating to their arthritis. Thirty-two per cent of patients had high anxiety levels, and while only 5% had high depression levels, 23% had experienced depression previously.[23]

In the same UK centre, a cross-sectional study of adults with JIA[2] (mean age, 35 years) showed that 36% had severe functional limitation (Steinbrocker class III and IV), with 42% having a HAQ score of 1.5 or more. A total of 51% had at least one prosthetic joint, with 47% having had hip replacements and 28% having had knee replacements. The number of prosthetic joints correlated with duration of disease, function and disease-modifying anti-rheumatic drug (DMARD) use. The highest frequency of joint replacements was in patients with systemic or polyarticular JIA.

A further study from Minnesota[24] was able to assess mortality in a population-based cohort of adults with a history of JRA. There were no deaths in childhood. Out of 57 adults, four deaths had occurred where one would have been expected and all were from autoimmune diseases other than JRA.

In summary, the more severe forms of JIA are associated with severe morbidity that persists into adult life and which has profound consequences for the patients' quality of life.

Patient perspective

JIA patients suffer disability, pain, decreased physical functioning in every-day events and increased fatigue. Thus, the circumstances in which JIA patients find themselves may impede their personal and social functioning and development.[25] Although some studies document a high level of social adjustment among JIA patients in the longer term,[17,18] a high incidence of depression has been documented.[23] Cohesiveness of family life and the quality of care are important, and the British Paediatric Rheumatology Group (BPRG) has identified the negative impact that severe JIA can have on family and social life, for parents as well as patients, and on education.[26] Where quality of life measures (e.g. the Short Form with 36 items (SF-36)) were used in adults with JIA, significant differences in psychosocial functioning and activities of daily living were identified, but were not reflected in functional disability as measured by the HAQ scale.[21]

A report on a small group of patients receiving etanercept (Gardner-Medwin J, University of Birmingham: personal communication, April 2001) provides an indication of outcomes that are important to young patients. These outcomes include:

- injections not as bad as previous treatment
- no longer dependent on a wheelchair
- improved mobility
- reduction in social isolation and increased independence
- increased energy and interest in sport
- confidence to go out with peers, and
- improved school/college attendance.

These benefits may not be encapsulated in functional status as measured by change in the CHAQ score.[27] Other benefits from more effective treatment might include reduced side-effects from other drugs, and reduction in steroid dose and steroid-related side-effects, which include osteoporosis and growth retardation.

Operative treatment

A further indication of the burden of disease caused by JIA is given by figures on operations and procedures for patients with JIA. In the 4 years from 1996 to 2000, 4850 episodes of hospital care involving operations and procedures were recorded for JIA patients in English hospitals (Wilson R, National Safe Havens Pilot Project, University of Birmingham: personal communication, May 2001). Some numerically insignificant categories were not obviously related to JIA.

The 12 most performed procedures accounted for nearly 70% of all episodes, with a steady increase in episodes by year from 1996–97 to 1999–2000. Operations and procedures for JIA that were directed (therapy or diagnosis) at joints and associated structures (tendons and bones) accounted for approximately 85% of all episodes and encompassed 150 categories of operation/procedure. The number of episodes in these categories increased year on year. By far the greatest number of episodes were for "puncture of joint with injection, aspiration or arthrography", intra-articular joint injections, which accounts for 44% of all episodes (276 episodes in 1996–97 rising to 513 episodes in 1999–2000), indicating the increasing popularity and availability of this treatment, which is used across the spectrum of JIA.

The most serious morbidity caused by the disease is reflected in the incidence of joint replacements in adolescence and early adult life. There were 141 hip joint replacements, 95 knee joint replacements and 45 other joint replacements in patients with JIA over 4 years. Although these procedures were carried out more often in older age groups, some were carried out in patients aged less than 20 years. It is unclear what the denominator should be in terms of disease type and severity, if rates were to be calculated, but some children and young adults have suffered considerable joint destruction by early adult life.

Current service provision

Treatment of oligoarticular, polyarticular and systemic JIA involves progressively NSAIDs, intra-articular or intravenous steroids, methotrexate and, if no response is achieved, further DMARDs. Progression to more extensive treatment depends upon the initial presentation and classification of the disease, and upon response to initial therapies.[5] *Table 1* shows typical treatment options for different forms of JIA, but for any individual patient progression to more intensive treatment will depend upon the patient's response, and children initially presenting as any subtype may go on to have severe disease, intensive treatment and a poor prognosis. *Figure 1* illustrates referral pathways and treatments likely to be offered in different settings. In the UK, the majority of children who develop severe JIA will ultimately be seen by consultant paediatric rheumatologists, the majority of whom work in tertiary specialist centres, some of which are able to offer shared care, and this is the setting in which etanercept treatment would be available. Patients will either have been referred directly by their general practitioners (GPs) (currently only sporadically in at least some centres), or else via general paediatricians, orthopaedic surgeons or rheumatologists. Treatment of JIA is best provided by a multi-disciplinary team, which includes physiotherapists, occupational therapists, nurses, psychologists and social workers, with easy access to other paediatric subspecialties including ophthalmology and orthopaedic surgery.[1,5]

On initial presentation, unless systemic disease is present, patients are likely to be treated symptomatically with NSAIDs. Following referral, treatment with pulsed corticosteroids may follow where symptoms have not resolved, administered either orally or intravenously, for example methylprednisolone (30 mg/kg over 3 days) for polyarticular disease. Multiple intra-articular joint injections[28] are widely used, but as this treatment in children often requires general anaesthesia and theatre time, rapid treatment can present

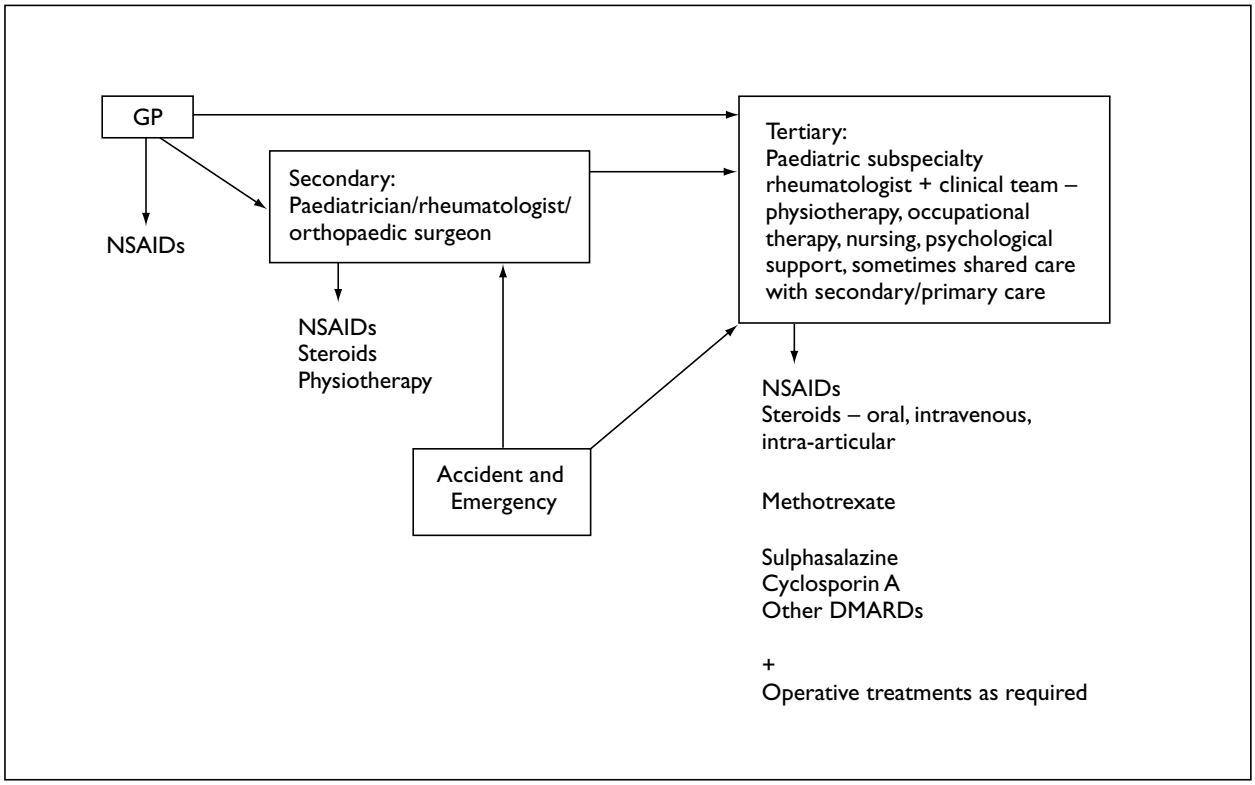

FIGURE 1 *Patient care path and treatment options in JIA*

logistical problems, particularly in smaller centres. This treatment has not yet been evaluated in controlled clinical trials in children. A proportion of children, most commonly with oligoarthritis, will respond to intra-articular or pulsed steroids alone and will not require escalation of treatment, but the outcome is poorer for children with multiple joint involvement.

Children with systemic disease are likely to require more aggressive initial treatment, as they are often severely ill on initial presentation, and children without an adequate response to initial treatment will require further treatment. It is important to avoid long-term treatment with corticosteroids in children wherever possible, as in addition to the problems caused by steroid dependency in people of all ages (including adrenal and immune suppression), steroid treatment in children can restrict growth and cause osteoporosis.

There is no one treatment that universally controls the disease. Methotrexate is an immunosuppressant agent, and low-dose oral methotrexate (10–20 mg/m^2)[14,29] is now an established treatment for relatively severe and longstanding JIA, following an RCT that established its efficacy compared with placebo over 6 months.[29] A further crossover placebo RCT confirmed that it was effective over 4 months in treating extended oligoarthritis with equivocal results for systemic arthritis, two of the most disabling forms of the disease.[14] At the standard low dose, 60–70% of children might be expected to benefit. Higher doses up to 25–30 mg/m^2 administered subcutaneously are often used when there is no or only a partial response, and a trial organised by the Paediatric Rheumatology International Trials Organisation (PRINTO) is underway to establish whether higher doses are more effective in children resistant to the low-dose regimen.[30] Methotrexate may be an effective treatment of uveitis.[31,32] Methotrexate is of equivocal benefit in treating systemic features, but effective in treating other aspects of systemic disease. Although the positive short- and medium-term outcomes with methotrexate have been established, further information on outcomes in the long-term is needed.[30] Despite the limited evidence on methotrexate's long-term impact, as magnetic resonance imaging has shown that joint damage occurs early in JIA and radiographic joint disease is a common early finding in children with JIA,[30] there could be benefits in starting more aggressive treatment earlier in the course of the disease.[32] Although there is good quality evidence that methotrexate is an effective treatment for JIA, it is not licensed for this indication.

While methotrexate is considered to be a relatively safe treatment when used in JIA, lymphomas have been reported in methotrexate-treated patients including children and this may be a phenomenon related to rheumatic disease or a complication of treatment.[30] Although liver fibrosis and cirrhosis have been reported in adults following treatment with methotrexate, clinically significant fibrosis has not been reported in children,[30] and treatment with the commonly used doses is considered to be safe. Even so, a high prevalence of adverse events, around 40%, has sometimes been reported. Common problems include gastrointestinal toxicity (when administered orally) and transient raised liver enzymes.[30] Haematological and liver enzyme monitoring necessitates regular monthly blood tests during treatment. Methotrexate is a folic acid analogue that suppresses the utilisation of folic acid-derived coenzymes, so folic acid is commonly prescribed with methotrexate. It is unclear how long methotrexate treatment needs to be continued if remission is achieved.[30]

In clinical practice the trend is now to introduce methotrexate earlier in the disease course with more aggressive treatment policies, with the aim of minimising destructive joint damage and improving patient quality of life.

Methotrexate is one of several agents collectively known as DMARDs. It is currently the drug of choice and most frequently used of these drugs in children with JIA.[30] These drugs, which include sulphasalazine, gold preparations, penicillamine, azathioprine, hydroxychloroquine and cyclosporin, act relatively slowly in comparison with corticosteroids, but may induce disease remission in adults with rheumatoid arthritis[33] (RA) and reduce the risk of permanent structural joint damage. Most of these agents cause immune suppression in one way or another, although the mechanisms are not always fully understood. They have complex and different side-effect profiles that complicate treatment. The use of cyclosporin, for example, has a high risk of renal complications. Results in children with JIA have often been disappointing with lack of efficacy and high rates of side-effects.[34]

Where children do not respond to methotrexate, one or other of these drugs will be tried, often in conjunction with oral steroids and pulsed or intra-articular steroids. Although there are few reports to support the practice, it is common for methotrexate to be used in combination with other drugs including sulphasalazine and cyclosporin in these circumstances. The need for trials is acknowledged.[30]

Systematic searches were made for trials of DMARDs in JIA. MEDLINE, EMBASE and the Cochrane Control Trials Register were searched. The search strategy used a sensitive control trial filter as described in appendix 1, effectiveness searches, in conjunction with generic drug names. Citations to the following studies were found:

- two placebo controlled trials of methotrexate (see above)[14,29]
- one placebo controlled trial of penicillamine and hydroxychloroquine[35]
- one placebo controlled trial of penicillamine[36]
- one double-blind study of azathioprine and placebo[37]
- one placebo controlled trial of auranofin[38]
- one randomised double-blind placebo controlled trial of sulphasalazine[39]
- two trials comparing gold sodium thiomalate and penicillamine[40,41]
- one randomised trial of hydroxychloroquine, gold sodium thiomalate, and penicillamine[42]
- one double-blind study of penicillamine and hydroxychloroquine (in Russian, reference not retrieved)[43]
- one RCT of sulphasalazine and Delagil (chlorochinum diphosphoricum).[44]

No trials including cyclophosphamide or cyclosporin were found.

Brief details of these trials and findings are given in *Table 2*. The trials are not reported in detail, as they mostly concern drugs rarely used in current practice. Placebo responses tended to be high, and this must introduce a note of scepticism regarding positive results found where two active drugs are compared. Azathioprine appeared to have limited efficacy, but with important adverse events. Concerns regarding malignancy limit its use in children. Evidence in favour of sulphasalazine in oligoarticular or polyarticular JCA was found only in patients' assessments. D-penicillamine was no more effective than placebo in one trial and effective on only some measures in a second. There was evidence from one trial that hydroxychloroquine had some effect. Oral gold was not effective compared with placebo, and there were conflicting results for parenteral gold compared with D-penicillamine. The patients in these trials often do not come from that same patient population as JIA patients eligible for etanercept under the BPRG prescribing guidelines, so the generalisability of the trials to such patients may be limited.

Studies concerning the use of therapies apart from methotrexate in severe JRA have been discussed in a narrative review that summarises evidence from case series, including reports of drugs used in combination and pulsed steroids.[32] Methotrexate combined with cyclosporin has been reported to be effective, but nephrotoxicity is very common. Case series reporting use of cyclosporin alone claim mixed results. Positive results have also been reported for cyclophosphamide in combination with pulse methylprednisolone and methotrexate. Sulphasalazine case series have been separately reviewed.[45]

In summary, the evidence base for the effectiveness of therapies for JIA patients who have not responded to methotrexate is weak, and no one therapy stands out as the first choice once methotrexate has failed.

The main drugs currently used in the UK for children for whom methotrexate has not been successful are hydroxychloroquine, cyclosporin, sulphasalazine and cyclophosphamide. Such children are also likely to be receiving oral steroids and therefore are at risk of steroid-related complications including growth retardation and osteoporosis. They will also sometimes receive pulse intravenous steroids and multiple intra-articular joint injections. A survey of US and Canadian paediatric rheumatologist identified the drugs most frequently used in polyarticular arthritis. Methotrexate, NSAIDs and steroids were most often used but sulphasalazine and hydroxychloroquine were also relatively frequently used.[46] Commonly used NSAIDs are naproxen, ibuprofen, indomethacin and piroxicam.

Autologous stem cell transplantation as a treatment for children with severe JIA, refractory to conventional therapy is as yet experimental and currently being evaluated.[47] A high proportion of patients receiving transplants have died,[48] however, and this treatment is not considered in routine clinical practice. To date the results from short-term follow-up are encouraging, but this treatment carries a significant morbidity and mortality.

Traditionally, the treatment of JIA has focused on relief of symptoms. However, as magnetic resonance imaging has led to an increased understanding of the early occurrence of destructive joint damage, the importance of achieving complete remission and of extending disease-free months has received a new emphasis.[49] The argument for more aggressive treatment to avoid joint destruction, in practice the earlier introduction of methotrexate, is widely accepted.

TABLE 2 *Trials of DMARDs other than methotrexate used in JIA*

	Patients	Intervention	Comparison	Design	Result
Giannini *et al.*, 1990[38]	231 patients with clinically active JRA not controlled by NSAIDs, ≥ 3 joints	Auronofin (oral)	Placebo	Double-blind RCT	No statistically significant differences at 6 months. High placebo response rate
Kvien *et al.*, 1986[37]	32 JRA patients	Azathioprine	Placebo	Double-blind RCT	Statistically significant improvement in patient's own assessment at 16 weeks. Azathioprine three withdrawals (two leucopenia), placebo 0 withdrawals
van Rossum *et al.*, 1998[39]	69 oligoarticular or polyarticular JCA patients	Sulphasalazine	Placebo	Double-blind RCT	Statistically significant improvements in sulphasalazine group in many disease activity measures at 24 weeks. 29% withdrew from sulphasalazine because of adverse events
Prieur *et al.*, 1985[36]	74 JCA patients	PEN	Placebo	Double-blind RCT	Fewer painful and stiff joints with PEN at 6 months. High placebo response rate
Brewer *et al.*, 1986[35]	162 patients with severe JRA	1. PEN 2. HC	Placebo	Double-blind RCT	PEN: no significant differences from placebo at 12 months HC: less pain on movement, only difference at 12 months. High placebo response rate
Kvien *et al.*, 1985[42]	72 pauciarticular and polyarticular JCA patients needing SAARD therapy	1. GSTM (parenteral) 2. HC	3. PEN	Open RCT	No statistically significant differences at 50 weeks except six PEN patients vs 0 HC and three GSTM withdrew because of adverse reactions
Kvien *et al.*, 1985[40]	77 pauciarticular and polyarticular JIA patients needing SAARD therapy	GSTM (parenteral)	PEN	Open RCT	Some statistically significant improvements in favour of GSTM at 50 weeks
Schairer *et al.*, 1975[41]	55 patients with active JRA	Gold (natrium-aurothiomalate, tauredon)	PEN	RCT	No significant differences at least 3 months
Hoza *et al.*, 1991[44]	Pauciarticular and polyarticular JCA patients	Sulphasalazine	Chlorochinum disphosphoricum	RCT	No significant differences at 6 months

GSTM, gold sodium thiomalate; HC, hydroxychloroquine; PEN, D-penicillamine; SAARD, slow-acting anti-rheumatic drug

Description of new intervention

Description of technology

Both JIA and RA are diseases that involve the immune system. Understanding of the role of the natural (or innate) immune system (the host defence mechanisms involving neutrophils, monocytes, macrophages and natural killer cells) as opposed to adaptive or acquired immunity (production of specific antibodies or cells in response to foreign agents), and of the protein mediators produced in its activation (cytokines), in the inflammatory processes of rheumatoid disease has advanced sufficiently to allow the development of therapeutic agents that target these pathological immune responses.[4,50,51] The first of these new biologic agents to be licensed for human use are TNF-α agents.

The TNF cytokine family first attracted attention because of its involvement in programmed cell death (apoptosis), but TNF is also involved in the inflammatory process and possibly in the joint destruction found in rheumatic disease. Many cytokines are present in the synovial compartment

in rheumatic disease, both pro-inflammatory, including TNF-α and interleukin-1 (IL-1), and anti-inflammatory, including IL-10 and transforming growth factor-beta, but with a net inflammatory effect. The types and quantities of serum cytokines and soluble cytokine receptors found in JIA varies according to JIA subtype.[4] TNF-α is a regulator of IL-1, a pro-inflammatory cytokine in turn involved in the regulation of other pro-inflammatory cytokines. Both have been implicated in joint inflammation and destruction as they induce the synthesis and release of metalloproteinases, prostaglandins and nitric oxide within cells.[50] Agents that inhibit the action of TNF-α or of IL-1 thus might be expected to have the potential to modify the inflammatory processes of rheumatic disease, and perhaps protect joints from damage.[51] It is possible that children might experience most benefit because of the regenerative potential of cartilage and bone.

The intervention

Two TNF-α inhibitors are currently licensed for use in the UK: etanercept (Enbrel®, Wyeth Laboratories; Maidenhead) for use in JIA and RA and infliximab (Remicade™, Schering-Plough; Welwyn Garden City) for use in RA and Crohn's disease. Etanercept is a soluble TNF-α receptor and is a 'designer molecule' consisting of two of the normal receptors for TNF (extra-cellular p75 ligand) and a portion of a human immunoglobulin protein (Fc portion of IgG1). It is administered as a twice-weekly subcutaneous injection and may be given for an indefinite period. In clinical paediatric rheumatology practice expected duration of the use of etanercept is likely to be comparable to that of methotrexate. Once a child had had 2 disease-free years, the drug would be stopped, but 30% of children might be expected to relapse. It works by competitively binding to TNF-α, thus preventing binding to cellular receptors. It also binds to lymphotoxin-α, known to be active in JIA.[52] Infliximab is a chimeric monoclonal anti-body that binds soluble and cell-attached TNF-α, inhibiting TNF-α activity. Infliximab is given as periodic intravenous infusions, but is not currently licensed for use in children in the UK. Adult patients with RA who are treated relatively frequently with infliximab must also be treated with methotrexate. This reduces the risk of formation of antibodies against the drug and thus the risk of allergic reactions. Etanercept can be administered alone.

Indication and criteria for treatment

Etanercept is currently licensed for the treatment of active polyarticular course JIA in children aged 4–17 years who have had an inadequate response to or are intolerant of methotrexate.[53,54] Such children are most likely to have a diagnosis of extended oligoarthritis, polyarticular arthritis or systemic arthritis, and will have developed or will be at risk of developing functional disabilities and damage to joints. Further biologic agents targeting cytokines or inflammatory cells are likely to come into clinical use in the next few years and would raise similar questions over short- and long-term outcomes and safety to those that arise with etanercept, the first licensed agent.

Setting

Children and young people with JIA of such severity that they are candidates for etanercept treatment should be treated by specialist paediatric rheumatologists, and whether or not they receive etanercept, also require regular follow-up and support from a multi-disciplinary team. The BPRG has developed prescribing guidelines for etanercept,[26] and etanercept for JIA should only be prescribed by consultant paediatric rheumatologists or in shared care with paediatricians or rheumatologists. Etanercept can be prescribed indefinitely.

Burden of disease and degree of diffusion of technology

A survey of paediatric rheumatology centres in the UK in October 2000 identified 101 children and young people who had an immediate need for etanercept. Of these, only 25 had started etanercept as funding was not available for the remainder. In one large centre, 20% more children have been identified subsequent to the survey and it is estimated that a further 5–10% would start etanercept each year (Gardner-Medwin J, University of Birmingham: personal communication, April 2001). If these increments are applied to the BPRG survey, then over 5 years between 160 and 190 patients may well have been identified. However, there is reason to think that these estimates do not reflect the true burden of disease and are too conservative, as the experience in one centre indicates that these initial cases represented a backlog of patients with the worst disease and in whom treatments additional to etanercept had already failed.

If, however, etanercept appears more effective than alternative treatments and maintains a good safety profile, children and young people are likely to be considered candidates for etanercept after methotrexate has failed and before other, more toxic, drugs are tried (Gardner-Medwin J, University of Birmingham: personal communication, April 2001). Thus, the patients identified in October 2000 represent a limited degree of

technology diffusion (i.e. there is potential for further take-up of the technology and an increase in patient numbers), with funding difficulties and the current supply problems acting as barriers to further diffusion, and estimates of potential patient numbers based on the survey are likely to be unrealistically low. If these barriers were removed, then it might be expected that the number of candidates for treatment identified would increase.

It has been suggested that one-third of patients treated with methotrexate are resistant.[55] If all such patients were considered candidates for etanercept (again extrapolating from one centre's figures and applying the results to the BPRG survey), then there might be as many as 750 candidate patients over 5 years. Assuming that about 75% of patients respond and continue on etanercept in the medium term, about 560 patients would continue to be prescribed the drug. Some of these would not maintain the initial response and might stop the drug, further reducing patient numbers.[56,57]

It can be seen that even on the highest estimates, numbers requiring etanercept on current indications for prescribing are relatively small compared with adults who might be prescribed it for RA. It is not known how long patients will require the drug, and should patients remain on etanercept indefinitely, patient numbers would continue to accumulate. The number of patients who remain on etanercept after a trial of the drug at the end of 5 years' use might therefore be expected to fall in the range 230–560, with about 400 as the most likely figure. If clinicians follow current practice with regard to methotrexate, patients who maintain response over 2 years would stop the drug, but a proportion would relapse and then restart etanercept. Further patients will accrue but estimation of future patient numbers presents difficulties.

The industry submission[53] derives a UK prevalence of 10,000 from the literature on incidence[9] and the somewhat limited data on prevalence. It is then assumed that of 4000 patients with active polyarticular course JIA, 600 will have failed methotrexate therapy, and 420 will respond to etanercept. This yields a comparable estimate to that given above on a pragmatic definition based on identified cases.

In summary, new treatments have been developed as a result of advances in genetic engineering, mass culture of mammalian cells and improved understanding of the immune system pathology in JIA, including anti-TNF agents. The effectiveness of the currently licensed agent, etanercept, and any further new interventions, needs to be evaluated in two areas.

- The treatment of children with JIA refractory to methotrexate therapy presents a challenge to clinicians. Typically this has involved agents that may have limited efficacy and substantial potential for adverse effects. Is the anti-TNF agent etanercept effective in the treatment of the relatively small number of JIA patients who have not responded to, have not tolerated or have not complied with methotrexate treatment?
- Such patients are likely to have aggressive and relatively longstanding disease, and thus may already have structural joint damage. The question arises whether the anti-TNF agent etanercept and methotrexate have the potential to alter the course of disease: if they are of proven efficacy in the later stages of disease, could they also prevent structural damage and improve longer-term outcomes if used earlier in the course of disease?

These questions will arise with regard to any further new therapeutic agents for JIA.

Chapter 2

Effectiveness

Methods for reviewing effectiveness

Search strategy

MEDLINE (Ovid), EMBASE (Ovid), the Science Citation Index and the Cochrane Library were searched from 1966 to the end of 2000 using MeSH subject headings (arthritis, juvenile rheumatoid) and keywords that encompass JIA ('juvenile idiopathic arthritis', 'juvenile rheumatoid arthritis' and 'juvenile chronic arthritis'), TNF, TNF receptors, anti-TNF, quality of life, etanercept and infliximab. Data were also sought in abstracts from relevant rheumatology and paediatric rheumatology meetings. Manufacturer and sponsor submissions to the National Institute for Clinical Excellence (NICE) were reviewed in detail. Safety data available on regulatory authority websites were reviewed.

Systematic reviews and RCTs of DMARDs were to be sought in order to inform the economic analysis and provide a context for biological anti-TNF therapies. The search strategies were based on that developed by the Aggressive Research Intelligence Facility (available on request) and by the Centre for Reviews and Dissemination. Reviews were sought in *Clinical Evidence*, MEDLINE, *Bandolier*, health technology assessment databases, in-house databases and the Cochrane Library.

Searches for relevant health economic analyses were conducted.

Inclusion and exclusion criteria

In order to assess clinical effectiveness, all RCTs of etanercept versus any agent (including placebo) in JIA (including disease described as JCA) and in other rheumatic diseases of childhood were considered. Only populations of patients aged 18 years or under were considered, as the age at which young people transfer to adult services varies according to the practice current in particular treatment centres. Studies reporting entirely on laboratory measures aimed at investigating disease or treatment mechanisms were not included unless relevant clinical outcomes not described elsewhere were provided.

Data extraction strategy

Data were extracted independently by two reviewers. Discussion or involvement of a third reviewer was used to resolve discrepancies where no agreement could be reached. One reviewer screened foreign language publications using English abstracts if available. Translations were obtained where necessary.

Data extraction focused on clinical outcomes, including the standard definition response in terms of changes to the Core Outcome Variables, but included accepted radiographic outcomes where available. Outcomes in JIA in both clinical practice and research are now commonly measured by a core set of six outcome variables:

- physician's global impression
- parent/patient global impression
- number of active joints
- number of joints with limited range of motion
- functional ability as measured by the CHAQ
- ESR or C-reactive protein (CRP) level.

An improvement of at least 30% in at least three of these, and a deterioration of more than 30% in no more than one variable constitutes a validated endpoint for improvement.[58,59] But as this endpoint was validated on mainly polyarticular patients, it may be less appropriate as an endpoint for other subgroups. For example, co-evaluation of uveitis in cases with single-joint involvement might be appropriate.[59] Research that pre-dates this consensus on outcomes is likely to measure similar outcomes, but may not use the same definition of response. In clinical practice the aim of treatment is for the patient to have no joint disease; therefore responses of 50% or more are clinically important outcomes.

Health-related quality-of-life measures were included where available, as were other outcomes relevant to the quality of life of children and young people, for example days off school. The characteristics of patients included in studies were sought in detail in order to allow comparisons between studies and to judge relevance to routine care.

For many patients, JIA is a chronic disease that requires long-term treatment. Immediate response,

medium-term and long-term outcomes were therefore all considered.

Quality assessment strategy

The quality of identified RCTs was examined using a validated quality assessment checklist developed by Jadad and colleagues.[60]

Methods of analysis and synthesis

Study characteristics including patient details, quality scores and clinical outcomes were tabulated. Key points were highlighted by a commentary. As only one RCT was included, the question of whether data from several trials should be combined did not arise.

Quantity and quality of the research available

The results of the effectiveness searches are summarised in *Table 3*. Citations were examined by two independent reviewers who agreed that only one study met the inclusion criteria. Only one RCT was included.[56] The number of studies excluded and the reasons for the exclusions are also given in *Table 3*.

Five other clinical studies were found but were excluded as they were not randomised clinical trials (a small pilot study of etanercept and methotrexate combined;[61] a case series of eight patients treated with high-dose etanercept;[62] a non-randomised comparison of etanercept and infliximab ($n = 15$);[63] a case series describing poorer response in systemic disease[64] and a further case series[65]). An abstract describing a survey of use and response to etanercept in systemic disease was found.[66] Survey results suggested that etanercept is well tolerated in systemic disease but that response may be different. Two papers in German were retrieved and read by one reviewer. These were excluded as they were commentaries.

Trials planned or in progress

[Confidential information removed].

Assessment of effectiveness

Quality and characteristics of study

The included study[56] was evaluated with regard to design factors that have been shown to introduce bias. The study was randomised, double-blind and withdrawals and follow-up were completely described. The method of randomisation was not described in the main trial publication and on published evidence would have only scored 4 on the Jadad scale.[60] **[Confidential information removed]**.

Preparation of adequate placebos for injectable drugs presents difficulties. Correspondence concerning one of the adult RA trials[67] suggested

TABLE 3 *Number of studies identified in searches of electronic databases*

	No. of citations retrieved	Retrieved	Included	Excluded	Reason excluded
National Research Register	0				
Cochrane Control Trials Register	1	1*	1		
MEDLINE	7	1*	1		
				2	Not intervention study
				4	Narrative review
Science Citation Index	16	1*	1		
				2	Clinical studies, not RCTs
		2		6	Editorial
				4	Reviews
				3	Case reports
EMBASE	42	1*	1		
				24	Not intervention study
				12	Narrative review
		3		3	News summary of trial*(1) Editorials (2)
				2	Not JIA/JRA

* *All citations were of Lovell* et al. [56]

BOX 1 ***Design of etanercept in JIA trial***[56]

Months 1–3		Months 4–7		Months 8–12
Open-label etanercept Pharmacokinetic study	⇒	Randomised etanercept or placebo Parallel-group study Outcome: flare	⇒	Open-label etanercept
All patients		**Responders**		**Responders**

that it had been possible to distinguish vials containing drug and placebo. Adequate blinding can be particularly important in withdrawal trials. **[Confidential information removed]**. For one of the core outcome variables, CRP or ESR, lack of blinding would have been unlikely to influence trial results.

Trial design

The study was a withdrawal trial. This unusual study design (*Box 1*), began with an open phase with all patients receiving etanercept. The open phase provided an opportunity for a pharmacokinetic study of etanercept in children with JIA. Responders in the open phase were then randomised to either continue with etanercept or receive placebo in a double-blind phase. At the end of the double-blind phase, the remaining patients continued with etanercept, providing a cohort of patients with longer-term use of the drug.

The choice of this design was dictated by the ethical constraints of carrying out clinical research in children and young people. To be ethically acceptable, such research should not cause undue harm and distress.[68,69] As children typically find injections distressing, and placebo treatments can be considered to offer no benefit to the child, placebo-control trials involving injections present ethical problems. The design of trial used minimised this problem, as the placebo-control phase addresses the question of whether the benefit of the open phase persists when the drug is withdrawn.

- The advantage of this trial design is that a trial of etanercept in JIA that is ethically acceptable to the relevant bodies has been carried out.
- The disadvantage is that it is harder to interpret: although time to relapse following response is evaluated in a comparative study, initial response to etanercept therapy is not evaluated against a control.

Inclusion criteria of the trial

Patients had to be aged between 4 and 17 years. They had to have active polyarticular JRA with greater or equal to five swollen joints, and three joints or more with limitation of motion or pain or tenderness. Initial presentation could have been pauciarticular, systemic or polyarticular. Patients must have been unresponsive to treatment with NSAIDs and to methotrexate at doses greater or equal to 10 mg/m^2/week. Platelet, white cell and neutrophil counts, and liver and renal function tests had to be normal. **[Confidential information removed]**.[70]

NSAIDs and low-dose steroids (≤ 0.2 mg/kg prednisolone) and pain medication (except for 12 hours before assessment period) were allowed.

Exclusion criteria of the trial

Pregnant and lactating females and patients with concurrent major medical conditions were excluded. Methotrexate had to be withdrawn 14 days before entry and DMARDs discontinued for 28 days. Intra-articular steroids were not allowed during or for 1 month before the trial.

Intervention

Patients received 0.4 mg/kg etanercept up to a maximum of 25 mg by subcutaneous injection twice a week. In the randomised phase of the study they received the same dose of etanercept or placebo.

Outcome measures

The primary outcome measure was flare in a 4-month period after entry into the double-blind phase of the trial following a response in a 3-month open phase.

Outcomes in JIA were measured by the six core outcome variables:

- physician's global impression
- parent/patient global impression
- number of active joints
- number of joints with limited range of motion
- functional ability as measured by the CHAQ
- ESR.

Response in the open phase was defined in line with a previous definition[58] but was modified to

allow for existing contractures, as these were thought unlikely to respond to medication over the trial period. Patients had to have 30% improvement from baseline in at least three core outcome variables out of six, with worsening of 30% or more in no more than one. Flare was defined by change in the core outcome variables from the beginning of the double-blind study. Patients had to be worse by 30% or more in three out of six measures and have a minimum of two active joints, but could also have at least 30% improvement in one variable. Global assessments had to change by at least two out of a score of 10. Fifty per cent and 70% improvements were also measured.

Assessments were made at day 1, day 15, and at the end of each month, with data analysed using a Last Observation Carried Forward algorithm where patients withdrew from the study.

Trial results

The trial results are described in *Figure 2*. In the open phase, 51 out of 69 children (74%) responded to etanercept. In the randomised phase of the study, 28% of the etanercept arm experienced flare compared with 81% of the placebo arm. Detailed results are given in *Table 4*.

At the end of the study 20 (80%) of the etanercept double-blind phase group compared with nine (35%) of the placebo group still met the definition of improvement ($p = 0.003$). Eighteen (72%) compared with six (23%) met the definition of improvement set at 50% improvement ($p = 0.001$), and 11 (44%) compared with five (19%) met the definition of improvement if it was set at 70% ($p = 0.08$).

In the first part of the trial (all patients receiving etanercept) the most common adverse events were injection site reactions (39%), upper respiratory tract infections (35%), headache (20%), rhinitis (16%), abdominal pain (16%), vomiting (14%), pharyngitis (14%), nausea (12%) and rash (10%).

2-Year results

The trial continued with an open-label extension phase. The 2-year results of the study are now available,[57] with median duration of use of etanercept of 26 months (range, 4–31 months). Of the 58 patients entering the open-label extension study, 12 had withdrawn, seven for disease flare or lack of efficacy, two for adverse events, one was lost to follow-up, one was in remission and one switched to commercially available etanercept. There were safety and efficacy evaluations every 3–4 months. At 20 months, 83% of all patients had achieved a 30% response, 78% a 50% response, and 63% a 70% response. Patients whose disease had flared while receiving placebo regained their initial response.

Additional safety information

Additional safety information including evaluation of reports subsequent to regulatory approval can be found on regulatory authority websites. A summary[54,71] is given here.

- The most common adverse events in adults with RA were injection site reactions (42% of patients) and infections (58%). In adult studies seven out of 531 patients developed cancer, although this was not different to that seen in the placebo group or expected in the general population.
- In the JIA trial, slightly more infections were reported in the etanercept-treated patients (60% of patients, 0.33 events per month) than in the placebo group (31%, 0.28 events per month).
- Post-marketing, ten cases of blood dyscrasias, including five with fatal sepsis, have been reported associated with the use of etanercept,[71] confirming the need for continuing safety monitoring.
- Regulatory bodies remain concerned that long-term patients might "develop an as yet unidentified immune defect" putting them at increased risk of malignancy and infections, and requiring ongoing monitoring.[54]

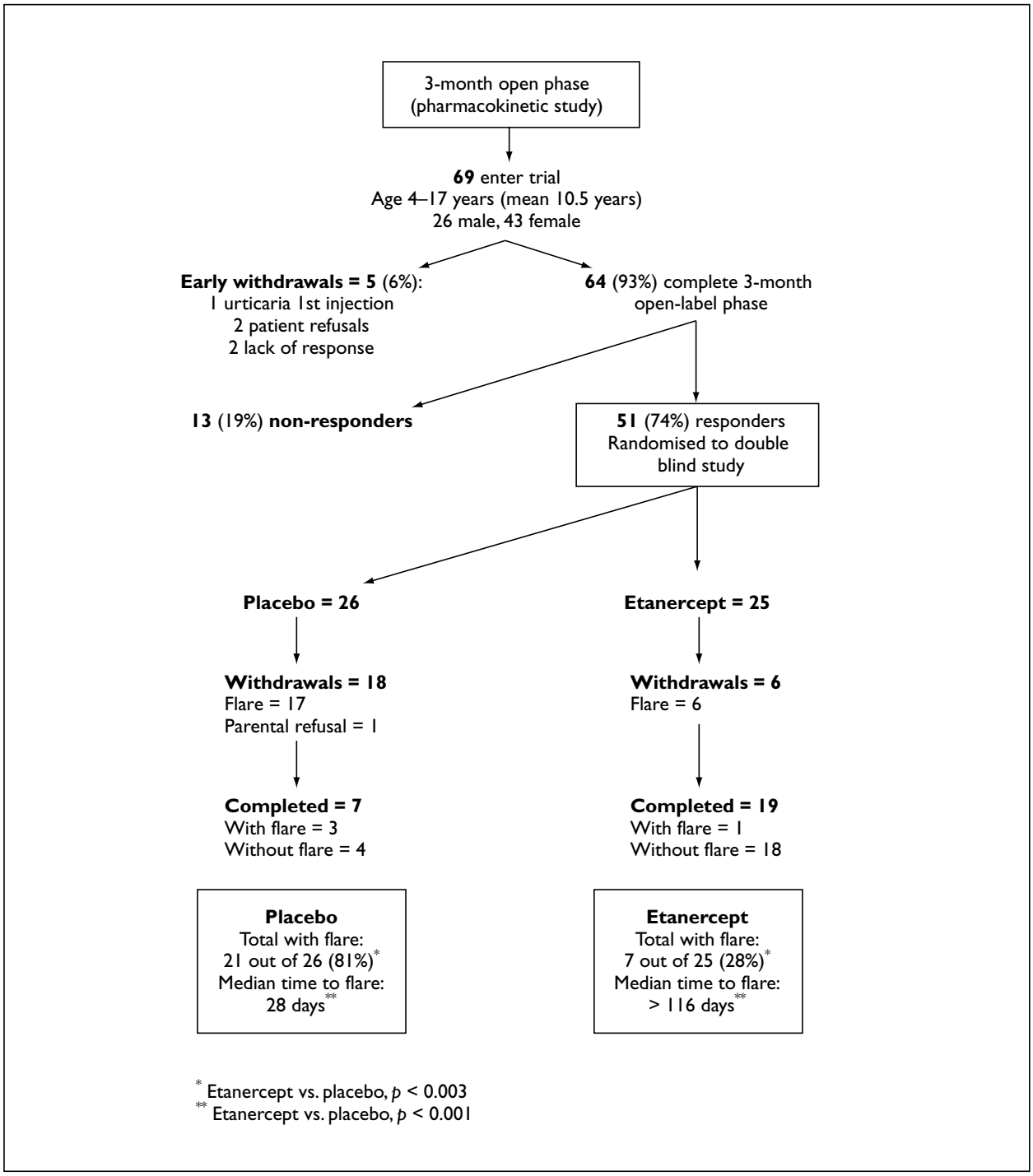

FIGURE 2 *Trial progress and results*

TABLE 4 *Measures of disease activity in etanercept trial*

Variable measured	Open-label study *n* = 69				Double-blind study placebo *n* = 26			Double-blind study etanercept *n* = 25		
	Range	Baseline	Month 3	% Improvement	Baseline	Month 3	Month 7	Baseline	Month 3	Month 7
No. of active joints	0–73	28	13	56	27.0	7.5	13	32.0	13.0	7.0
No. joints with limited motion plus pain or tenderness or both	0–71	10	2	79	6.5	1.0	4.5	8.0	2.0	1.0
Physician's global assessment of disease severity	0 (worst) – 10 (best)	7	2	60	6	1	5	7	2	2
Patient/parent's global assessment of disease severity	0 (worst) – 10 (best)	5	2	50	5	1	5	5	2	3
CHAQ score (functional ability)	0 (best) – 3 (worst)	1.4	0.9	37	1.3	0.4	1.2	1.6	0.9	0.8
ESR (mm/h)	1–30(F)/1–13(m) (normal)	35	20	50[a]	27	12	30[a]	41	15	18
Articular severity score	0 (best) – 962 (worst)	88	45	50	84	36	66	90	35	38
Duration of stiffness (min)		45	15	75	60	5	38	45	15	5
Pain (on VAS)	0 cm (best) – 10 cm (worst)	3.6	1.4	63	3.5	0.3	3.5	3.5	1.3	1.5
CRP (mg/dl)	0–0.79 (normal)	3.5	0.8	60[a]	1.8	0.3	3.0[a]	3.5	0.2	0.4
No. of swollen joints	0–66	25	9	58	22.5	6.0	11.0	27.0	12.0	4.0
No. joints with limited motion	0–71	23	15	23	23	17	22	24	12	9
No. 30% improved at 3 or 7 months versus start				51/69 (74%)			9/26 (35%)[b]			20/25 (80%)[b]
No. 50% improved at 3 or 7 months versus start				44/69 (64%)			6/26 (35%)[c]			18/25 (72%)[c]
No. 70% improved at 3 or 7 months versus start				25/69 (36%)			5/26 (35%)[d]			11/25 (44%)[d]

Values for measured variables are medians. The first six variables listed are the six core variables used in the determination of the primary end point (disease flare) in the double-blind part of the study

[a] *baseline to endpoint,* $p \leq 0.03$ (χ^2)
[b] *placebo versus etanercept,* $p = 0.003$ (χ^2)
[c] *placebo versus etanercept,* $p = 0.001$ (χ^2)
[d] *placebo versus etanercept,* $p = 0.08$ *(Fisher)*

CHAQ, Child Health Assessment Questionnaire; F, female; m, male; VAS, visual analogue scale

Chapter 3

Review of economic analysis

MEDLINE, DARE and UK health economic websites were searched from 1997 to the end of February 2001 for health economic and cost studies. No health economic studies were found. The MEDLINE search strategy and numbers of citations retrieved is given in appendix 1. The industry submission contained a cost–utility analysis.

Cost–utility model

The industry submission cost–utility model uses the results of the JIA trial[56] in an economic model based upon one developed for RA in adults.[53] The adult model uses the results of an etanercept placebo-controlled trial and modelled outcomes over the life-course. The model assumed that in RA in adults there was a relationship between response and HAQ score, and a further relationship between HAQ score and excess mortality in the RA population compared with the general population, and is based on mean HAQ scores at each time point. The proportions of responders, non-responders and deaths were estimated at each time point (start, 3 months, 6 months and 1 year, then yearly intervals over the life-course), effectively a time-slice model. At each time point the estimated HAQ scores influenced mortality at the next time point. The inputs are described in the industry submission on RA and are reviewed in the RA appraisal report. In the base-case adult model, a cost offset of £860 per point in HAQ score was used,[72] including drug and monitoring costs and direct costs of NHS care. This excludes any analysis of nursing home, home help or lost productivity (estimates of these were included in sensitivity analyses). Cost offsets were calculated from a Swedish and a US study of RA patients and translated into sterling at 2001 prices. Data from these studies are used to argue that there is a linear relationship between an increase in HAQ score and costs. A US study and a UK study are used to estimate nursing home costs and the Swedish study to estimate lost productivity. As resource use data have not been collected for JIA patients, it was assumed it would be equivalent to that of adults. Costs were assumed equivalent in JIA, but with different and unspecified service use.

The JIA trial was a placebo-controlled trial and thus the model assumes that any incremental benefit from etanercept is best represented by the difference between active therapy and placebo. This assumption has been criticised when applied to models of RA in adults, as patients would receive alternative active treatments for which there is good evidence of effectiveness.[33] While the same criticism can be levelled with regard to JIA, any benefits from alternative drugs to etanercept have not been clearly quantified, and the evidence to provide inputs to an alternative model is missing. The methotrexate-resistant patient population and impressive maintenance of good quality responses to etanercept suggest that the increment chosen presents fewer problems in the case of JIA than in the case of RA.

Further model assumptions are discussed below.

Model assumptions

A separate economic model for JIA was not developed. The main reasons for this were that the JIA trial was not a formal double-blind placebo-controlled trial, presenting problems with the information to feed into a model, and that there are no data relating CHAQ scores in JIA to utility measures. Instead a model developed for RA was used.

To use the adult RA model for JIA, the following assumptions were made.

1. CHAQ was equivalent to HAQ.
2. JRA30 can be equated to ACR20.
3. The relationship between HAQ and utility and mortality claimed for RA applies in children with JIA.

Information from the JIA trial was incorporated into the model, specifically, the change in CHAQ score from the start of the open phase to the end of the randomised phase at 7 months (placebo arm: baseline CHAQ 1.3, 7-month CHAQ 1.2; etanercept arm: baseline CHAQ 1.6, 7-month CHAQ 0.8).

The following further assumptions were made.

4. Assumptions concerning the age distribution and gender of JIA patients to allow the construction of lifetables.
5. The cost of etanercept for children is equal to the cost for adults.
6. A higher placebo response rate is used consistent with that found in the adult trial used in the RA model (23% versus 19%).
7. Etanercept response assumed to be 74% at 3 months and 72% at 6 months.
8. CHAQ scores are calculated from the trial report for both responders and non-responders in each arm. Responder CHAQ scores in the etanercept group are calculated from responder and non-responder averages and proportions.
9. The placebo effect is assumed to last 3 months with the same scale of effect as in the adult RA trial used in the adult model.
10. The levels of CHAQ score increase in non-responders is taken from the increase observed in the placebo arm of the adult trial.
11. The baseline CHAQ score in the etanercept arm is used in the base-case, that for the placebo arm in a sensitivity analysis.
12. As no data were collected on resource use, this was assumed to be equivalent to adult disease.
13. Costs for adults and children are assumed to be equivalent.
14. Costs were discounted at 6% per annum and benefits at 1% per annum.
15. Cost offsets are assumed to be equivalent between children and adults.

The base-case parameters were:

- the quality of life scale was the EuroQol-5 dimensions (EQ-5D)
- cost offset per HAQ point was £860
- % increase in mortality per point change in HAQ was 38%
- baseline HAQ was 1.3
- relative risk of mortality in JIA was 2.98
- placebo and etanercept HAQ progression: responders 0–4 years 0, responders > 4 years 0.034, non-responders 0.0669
- annual withdrawal from responder to non-responder: placebo 50%, etanercept 13%.

Model results

Table 5 shows the base-case results. For a patient starting on etanercept rather than placebo, the incremental benefit estimated per person was 1.74 quality-adjusted life-years (QALYs), with a total discounted cost per QALY of £16,082. Sensitivity analyses ranged between £3900 (cost offsets assumption changed to exclude nursing home and home help costs but to include indirect costs) and £34,000 (SF-36 regression used), though changes in most variables did not make a great difference.

Discussion

The cost–utility model has uncertain validity. Challenges to model validity arise in several areas. There is limited evidence on health-related quality of life in JIA. There is limited evidence on the long-term prognosis of methotrexate-resistant JIA, and very little evidence on the effectiveness of current treatments, raising questions over the value of any cost-effectiveness model in this area. Because of these problems, a model of etanercept treatment of acute RA in adults has been used. The application of this model to JIA has involved making some very strong assumptions for which there is no evidence-base. Furthermore, some technical problems have been identified with the adult model that suggest that an improved utility estimate could be derived.

Economic analyses in JIA

Cost–utility analyses present major problems in JIA. Little is known about health-related quality of life in JIA. Measurements such as the EQ-5D, which have been used in adult studies, have usually not been tested in children.[27] Relatively little is known about the long-term outcomes of JIA, certainly about the impact of JIA over the whole lifespan. Thus, modelling will inevitably incorporate probable mis-specification and will extrapolate beyond the evidence-base. Little is known about the effectiveness of alternative treatments to etanercept in methotrexate-resistant JIA, calling

TABLE 5 *Base-case results*

	Placebo (£)	Etanercept (£)	Incremental (£)
Drug and monitoring costs	0	33,335	33,335
Cost offsets	12,602	7,289	–5,313
Total cost	12,602	40,624	28,022
QALY	13.3	15.0	1.7
Cost per QALY			16,082

into question the validity of cost-effectiveness modelling in this instance. A further criticism from the patient perspective might be that such analyses rarely incorporate indirect costs and patient-centred outcomes important to the family.

Assumptions made in the model

The validity of the more important assumptions made in order to apply the adult model to JIA must be questioned. Numbered comments refer to the equivalent numbered assumptions listed above.

Assumption numbers 1, 2 and 3

There are no data to support these assumptions. This is acknowledged by the authors. Only indirect measurement of health-related quality of life was possible, making strong assumptions about the relationship between the CHAQ and the HAQ and the HAQ and the SF-36 a necessity. There is no evidence that the CHAQ is equivalent to the HAQ, or that the relationship assumed between the HAQ, utility and mortality would hold when applied to JIA. Although severe JIA is associated with long-term morbidity and functional disability, there is not enough known to model this relationship and little is known regarding mortality in JIA. Any excess mortality may be related to other autoimmune disease and amyloidosis, rather than functional disability.[24] Equally there is nothing to support the equation of JRA30 with ACR20.

Assumption number 4

The time horizon is the patient's lifetime. This, however, extends well beyond the scope of the best available evidence.

Assumption number 5

Costs for children cannot be assumed to be the same as for adults. See drug costs section below.

Assumption number 6

The assumption of a higher placebo response rate than found in the trial is conservative and consistent with the high placebo response rates found in JIA trials.

Assumption number 7

The trial was a withdrawal trial and the double-blind phase of the trial is based on responders. There was no parallel group comparison of response. This may have generated a selection bias. This is acknowledged by the authors.

Assumption numbers 9 and 10

In relation to duration of the placebo effect and CHAQ score increases in non-responders, the trial design has again meant that data from adult studies have had to be used to populate the model, and the assumed relationship may not hold.

Assumption numbers 12, 13 and 15

It is not plausible that resource use, costs and cost offsets are equivalent for adults and children or for adult disease and JIA.

The conclusion must be that the external validity of the model is compromised. Given the data available, however, it is not possible to construct a model that does not use such strong assumptions. The authors of the model are aware that some of the assumptions are difficult to justify.

Technical aspects of the model

Some technical problems were identified with the adult model.[33]

- The model failed to take into account changes in the age and sex distribution, as there are disproportionately more deaths in the higher-age groups.
- The probability of death in a given year for the normal population was multiplied by a fixed factor for the general RA population and a further factor dependent on HAQ scores, leading to probabilities of over 100% in some cases. These were truncated to 100% for the general RA population, but not for the HAQ-score-dependent adjustment.
- The percentage of responders withdrawing between 3 months and 6 months was based on trial data; after that, a constant annual rate was used, but the full annual rate should not be used as a probability over a 6-month period.
- For placebo group non-responders, a linear annual increase in HAQ score was applied until the HAQ score reached 3; the full annual increase was applied between 6 months and 1 year.

Accordingly, adjustments were made to the model. Following these adjustments, the incremental cost per QALY in the adult model changed from £18,900 (range of sensitivity analyses, £7200–29,700) to £24,000 (range of sensitivity analyses, £9900–48,400). The amended model has not been applied to children with JIA, as to do so would involve making further strong assumptions.

Summary

A cost–utility model of the use of etanercept in JIA uses a model designed to model outcomes for adults with RA. There is insufficient data to construct a model for JIA, and little is known about health-related quality of life in JIA.

Adapting the adult model, however, has required strong assumptions, diminishing the model's claims to validity to such an extent that its relevance to real practice cannot be determined. In addition, changes to the adult model have been advocated. The incremental cost per QALY generated should be viewed with caution.

Etanercept drug costs

In the UK, etanercept is available in cartons containing four single-use vials with four pre-filled syringes and eight alcohol swabs. The cost to hospital pharmacies is £325 per pack plus 17.5% VAT, a total of £382. Alternatively in suitable cases, the drug can be dispensed to patients' homes via the Enbrel Homecare Service. The cost per pack is then £346, but VAT is not payable.

The costs of etanercept in JIA have been estimated in three ways.

The first is calculated using the standard dose dispensed in the licensed manner, that is using one vial per dose, discarding any surplus.

The second is calculated assuming that bacteriostatic water is used to draw multiple doses from a single vial. The etanercept dose for children is weight-related (mostly in the range from 0.2 to 0.4 ml). Etanercept comes in 1 ml vials, so, where usual dispensing instructions are followed, much of the vial is wasted.

The use of bacteriostatic water is usually banned in the UK (it contains benzyl alcohol and there is a risk of brain damage if used intrathecally), but special dispensation has been given by the Medicines Control Agency to use it in this instance in at least one UK centre (Costello I, MacCallum F, Birmingham Children's Hospital NHS Trust: personal communication, April 2001). This means that more than one syringe can be drawn up from the same vial. The Enbrel Homecare delivery service[53] that prepares and delivers the syringes can mix and match doses of different amounts for different sized children, thus eliminating wastage. The Homecare service also prepares and delivers the drug in the standard way.

Using a drug in this unlicensed manner is not to be taken lightly. However, drug stability data were available. In this use of bacteriostatic water, as the drug is delivered by the Homecare service, the risk of accidental intrathecal injection of bacteriostatic water is minimised, as the water is not kept in the hospital pharmacy. The physician prescribing the drug and allowing dispensing in this manner takes personal responsibility for the consequences of the prescription. Much paediatric prescribing (including methotrexate for JIA), however, is unlicensed,[73,74] as the evidence for the appropriate licence does not exist and no regulatory submissions were made. In normal circumstances when a licensed therapy is available then it should be used. In the case of etanercept for JIA, there are two reasons why unlicensed use has been considered. The first reason is that there is a supply problem with etanercept at present and supplies are strictly limited. If drug that otherwise would be wasted could be used, then more patients would be able to start on the drug. The second reason is that substantial cost savings can be made if the drug is used in the unlicensed manner. In these circumstances, it is possible that the use of the drug with bacteriostatic water will become more common in the UK. So the costs in these circumstances have been estimated.

The third and fourth methods of estimating costs consider how the costs would change if different sized vials became available. Only a 25 mg vial is available at present.

Table 6 shows the cost of 1 year's therapy with etanercept. It is assumed that 104 administrations are given per year at a dose of 0.4 mg/kg body weight with a maximum possible dose of 25 mg at one administration. JIA children aged 4–18 years are considered likely on average to fall within 30% decile body weight category for age in the general population. Body weight for 16–18 year olds have been estimated from growth rates over previous years for the appropriate decile. The unit cost of an Enbrel Homecare Service pack is taken as £346; this encompasses four 25 mg vials together with syringes and swabs with home delivery. Where multiple doses are drawn from the vials, the unit cost of an Enbrel Home Service pack is taken as £346; this encompasses four 25 mg vials, syringes and swabs, with home delivery. It is assumed that the cost of the bacteriostatic water, new swabs and syringes is absorbed by the Homecare Service. The unit cost for 10 mg and 15 mg Enbrel packs has been calculated *pro rata* from the existing 4 × 25 mg packs. For the modes of delivery if 10 mg and 15 mg vials were available, it is assumed that a single dose is made up from one or two vials of appropriate size as necessary with remaining vial contents being wasted. The licensed use employs one 25 mg vial for every administration with a single withdrawal from the vial and the remaining vial contents being discarded.

TABLE 6 *Etanercept costs: annual cost (£) of therapy by four modes according to age of patient*

Age (years)	Single-dose size (mg)	Licensed use: single-use vial	Unlicensed multiple-use of vial	Hypothetical costs if different vial sizes were available, assuming *pro rata* unit costs	
		25 mg vial available. Single withdrawals only; vial remains discarded	Complete use of 25 mg vial contents by multiple withdrawals	10 mg and 25 mg vials available. Single withdrawals only; vial remains discarded	15 mg and 25 mg vials available. Single withdrawals only; vial remains discarded
4	6.69	£8996	£2407	£3598	£5398
5	7.38	£8996	£2656	£3598	£5398
6	8.12	£8996	£2922	£3598	£5398
7	9.08	£8996	£3267	£3598	£5398
8	9.98	£8996	£3591	£3598	£5398
9	11.03	£8996	£3969	£7197	£5398
10	12.40	£8996	£4462	£7197	£5398
11	13.86	£8996	£4987	£7197	£5398
12	15.68	£8996	£5642	£7197	£8996
13	17.84	£8996	£6420	£7197	£8996
14	19.59	£8996	£7049	£7197	£8996
15	20.82	£8996	£7492	£8996	£8996
16	22.30	£8996	£8025	£8996	£8996
17	23.78	£8996	£8558	£8996	£8996
18	25.00	£8996	£8996	£8996	£8996

Table 7 shows the savings that would accrue from 5 years' use of multiple-dose vials compared with single-dose vials. Again it has been assumed that JIA patients are lighter than average. Savings are substantial in younger children, reducing in older children. The assumption of some utilisation of multiple-use vials could be incorporated in any future economic analyses, with the impact probably dependent upon the time horizon, as it might be anticipated that patients remain on etanercept

TABLE 7 *Savings from multiple-dose vials (savings by year of treatment and starting age of patient comparing the use of one 25 mg vial for each administration with delivery involving no vial wastage)*

Age at start of treatment (years)	Single dose (mg)	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)	Total over 5 years (£)
4	6.7	6,589	5,960	5,367	4,758	4,220	26,894
5	7.4	6,340	5,710	5,062	4,489	3,925	25,526
6	8.1	6,074	5,385	4,776	4,175	3,540	23,950
7	9.1	5,729	5,081	4,442	3,766	3,130	22,147
8	10.0	5,405	4,725	4,006	3,329	2,618	20,084
9	11.0	5,027	4,262	3,542	2,786	2,012	17,628
10	12.4	4,534	3,768	2,963	2,140	1,520	14,925
11	13.9	4,009	3,152	2,277	1,617	1,174	12,229
12	15.7	3,354	2,422	1,720	1,249	758	9,503
13	17.8	2,576	1,830	1,329	807	342	6,884
14	19.6	1,947	1,414	858	364	0	4,583
15	20.8	1,504	913	387	0	0	2,804
16	22.3	971	412	0	0	0	1,383
17	23.8	438	0	0	0	0	438
18	25.0	0	0	0	0	0	0

indefinitely. Savings are shown for the first 5 years of delivery. Lack of wastage involves multiple withdrawals from each vial.

The assumptions involved in the calculations in *Table 7* are as follows.

- Saved costs when etanercept administration involves no wastage of vial contents.
- Savings are shown for the first 5 years of delivery.
- Lack of wastage involves multiple withdrawals from each vial and mixing and matching of doses according to patient group.
- The alternative procedure employs one 25 mg vial for every administration with a single withdrawal from the vial and the remaining vial contents being discarded.
- The unit cost of an Enbrel Homecare Service pack is taken as £346; this encompasses four 25 mg vials, syringes and swabs, with home delivery.

The annual costs of other drugs commonly used in this patient group is provided for information (*Table 8*). Insufficient data, however, are available to model the use of alternative drugs, and crude comparisons of drug costs are not informative.

The cost of 1 year's therapy of JIA patients of 4, 10 and 17 years of age are given. Low-dose and high-dose costs are given where appropriate. Lower and higher doses were considered to be:

- methotrexate, 15 and 30 mg/m^2 per week, subcutaneous
- cyclophosphamide, 400 and 500 mg/m^2 per intravenous pulse
- cyclosporin, 2 and 5 mg/kg/day, oral liquid
- sulphasalazine, 20 and 50 mg/kg/day tablets
- hydroxychloroquine, 3 and 6 mg/kg/day tablets
- methylprednisolone sodium succinate 30 mg/kg (to 1 g max) (intravenous pulse) repeated four times a year and 30 mg/kg (to 1 g max) on three consecutive days repeated four times a year.

Unit costs include VAT (this assumes dispensing via a hospital pharmacy); more than one unit cost is quoted when different sized preparations are used for various sized children. JIA patients were considered to fall within the lower 30% decile body weight category for age in the general population. While methotrexate treatment is generally relatively cheap, it should be noted that oral treatment for the smallest children who require syrup is expensive, approximately half the cost of etanercept.

Other resource use

In the absence of empirical evidence, the best estimate might be that use of support services and clinic visits/monitoring is likely to be similar on and off etanercept for the currently treated cohort, which has a long disease history and permanent joint damage. Drug costs may change, as children will be able to come off/reduce other drugs, but may also switch between drugs, and increased mobility may reveal a need for surgical treatment.

TABLE 8 *Costs of drugs other than etanercept used in methotrexate-resistant JIA*

Drug	Unit cost (£)	Annual drug costs (£) for patients aged, 4, 10 and 17					
		Age 4 years		Age 10 years		Age 17 years	
		Lower dose	Higher dose	Lower dose	Higher dose	Lower dose	Higher dose
Methotrexate high dose[14,30]	3.08	160*	160	160	160	160	160
Cyclosporin[75–78]	110.87	270	675	500	1251	960	2400
Hydroxy-chloroquine[35†]	5.53	32	32	32	32	65	65
Cyclo-phosphamide[79‡]	1.81 3.15 5.50	13	13	13	17	17	17
Methyl-prednisolone[79,80‡]	8.98 16.18	36	108	65	194	65	194
Sulphasalazine[39,44,81,82]	11.39	37	37	74	74	111	185

* *Part of single-use vial*
† *Assumes part tablets discarded*
‡ *May be used in combination, three pulses per annum assumed*

Chapter 4

Discussion and conclusions

Implications for other parties

See *Patient perspective* (page 4) for a discussion of quality of life for family and carers.

Financial impact for patient and others

No UK studies of the costs of JIA were found. A US study estimated the direct costs of healthcare for families with a child with JIA. In addition special school costs and other non-medical direct costs were also estimated. Costs were related to disease severity. Seventy questionnaires were received. The mean direct healthcare costs were an average of $7905 per year (1989 costs). While US medical costs may be different to those that would be encountered in the UK, the indirect costs recorded are of interest. $328 in salary per family were lost per annum. The mean annual non-medical expense was $1524 per child per year, representing 5% of the mean family income. For 14% of families, this represented 10% of their income. The mean extra school cost per school year for those receiving special school services was $7135. Total annual non-medical costs were $488 dollars.[83] The total cost of JRA to the USA in 1989 was estimated at $285 million. The study may have been biased by non-response, was based on a small sample and included children with variable disease severity, but does provide evidence of the indirect costs to families incurred when children have JIA. Children considered for etanercept would have more severe disease and their families might be expected to have incurred greater costs than those quoted. There is therefore some evidence that substantial indirect costs to families are incurred where children have severe JIA.

Factors relevant to the NHS

Fair access

The BPRG surveyed paediatric rheumatology centres in the UK in October 2000, identifying 101 children and young people who had an immediate need for etanercept. Funding was available for only 25 (Gardner-Medwin J, University of Birmingham: personal communication, April 2001). There was therefore no equity of access to etanercept at that time.

Equity issues

Equity issues arise with regard to children and young people compared with adults when the evidence-base for therapeutic interventions is considered. The difficulties of clinical research in children and the ethical constraints on research designs and drug development (children should not be exposed unnecessarily to potential hazards) mean that very often drugs, although commonly used in clinical practice, are not licensed in children,[74] and the evidence-base for practice in child health is relatively weak. These constraints should be borne in mind when evaluating the evidence. Good quality and ethical clinical research that will improve the evidence-base in child health should be promoted and supported.

The International Conference on Harmonisation has approved guidance on the clinical investigation of medicinal products in the paediatric population.[69] The document provides a framework for drug development, determining what kinds of studies might reasonably be expected in a particular case. When making recommendations for further research and for use of a product contingent upon further research, these guidelines should act as a frame of reference, as further research, particularly randomised trials in children, will generally be required, but sometimes will present ethical or practical difficulties.

Discussion

Main results

Effectiveness

- There was one RCT with a withdrawal design. In an open phase 51 out of 69 children (74%) improved while on etanercept. In the randomised phase of the study, 28% of the etanercept arm experienced flare compared with 81% of the placebo arm.
- The trial continued with an open-label extension phase. At 20 months, 83% of all patients had achieved a 30% response, 78% a 50% response, and 63% a 70% response. Patients whose disease had flared while receiving placebo regained their initial response.
- These results are consistent with those found in trials of etanercept in adults with RA.[34]

- Etanercept has an acceptable safety profile at present, despite some reports of blood dyscrasias. Ongoing monitoring is required.

Economic analysis

- The annual drug cost of treating a child with etanercept is £8996 when used in accordance with the license. It is hoped that etanercept may help reduce long-term joint damage, although the evidence-base is too small and follow-up too short for this to be known.
- There is no good empirical evidence about the other costs of etanercept treatment in JIA. Clinical opinion suggests that use of support services, clinic visits and monitoring is likely to be similar on or off etanercept for children, similar to the currently treated cohort (i.e. those who have a long disease history and permanent joint damage).
- The manufacturer's submission included a cost–utility analysis. No other economic analyses were found.
- In the cost–utility analysis, for a patient starting on etanercept rather than placebo, the incremental benefit estimated per person was 1.74 QALYs, with a total discounted cost per QALY of £16,082.
- Sensitivity analyses ranged between £3900 (cost offsets assumption changed to exclude nursing home and home help costs but to include indirect costs) and £34,000 (SF-36 regression used), though changes in most variables did not make a great difference.
- The validity and accuracy of this estimate must be questioned:
  - insufficient is known about the outcomes of JIA, in particular quality of life and long-term outcomes
  - the model was constructed for RA in adults
  - the strong assumptions used were not based on evidence
  - technical problems were identified with the model.
- The limitations of the research base at present means that the construction of a JIA model with greater validity presents considerable problems.
- The annual cost of etanercept for a child with JIA is £8996. It was estimated that about 400 (range, 230–560) JIA patients might be receiving treatment with etanercept in 5 years' time, yielding annual drug costs at that point in time of £3,589,400 (current prices, licensed use). Further patients would accrue.

Assumptions, limitations and uncertainties

Effectiveness

Given that the only trial had a withdrawal design, beginning with an open phase, no randomised evidence is available comparing etanercept with either placebo or standard treatment with regard to response. Etanercept was superior to placebo on the primary outcome measure of flare rate at 4 months in responders from the open phase who entered the randomised phase and in the proportions of patients with 30% response at the end of the randomised phase (etanercept 80% compared with placebo 35%). The improvement from baseline however is striking, with a high proportion of very good clinically important responses maintained at the end of the double-blind phase (18 (72%) etanercept patients compared with six (23%) placebo patients had 50% improvement, and 11 (44%) compared with five (19%) had 70% improvement). Furthermore, evidence from adult studies detailed in the Technology Assessment Report covering RA[33] and the refractory nature of the JIA patients' disease, suggests that the response in the open phase is unlikely to be attributable to the placebo effect alone, although substantial placebo effects have been described in JIA RCTs. The patients in the trial were non-responders to DMARDs, suggesting that a large placebo effect was in this instance less likely. The randomised phase of the study provides evidence that etanercept can maintain improvements and that relapse is more likely over a 4-month period when it is withdrawn. We conclude that etanercept is an effective treatment of methotrexate-resistant JIA in the medium term (7 months) for a significant number of patients.

The evidence provided by this one small trial however leaves some unanswered questions.

- The response rate relative to placebo is unquantifiable, although relapse is more frequent with placebo. High placebo response rates have been observed in JIA but the very good responses with etanercept and the patients' poor previous response to DMARDs suggest that this may not be true of this trial.
- The expectation might be that children who respond to etanercept remain upon the drug indefinitely. We do not know whether and when the drug can be withdrawn. Longer-term studies are therefore required.
- Given the novel biological action of etanercept, long-term follow-up is desirable, and is required by regulatory agencies, in order to detect any unexpected adverse events.

- There is no evidence comparing etanercept with other treatments in this patient group. It might be possible to compare response to etanercept with some of these drugs in further randomised trials. Such treatments have tended to have safety concerns attached, which means that a treatment such as etanercept, which so far appears to have fewer risks attached, is attractive. Thus, safety concerns might place ethical constraints on trials of relative effectiveness. We do not know how alternative drugs might perform if compared with placebo in a similar design to that of the etanercept trial.
- The effectiveness of etanercept in the treatment of other forms of JIA including psoriatic and enthesitis arthritis is unknown. International trials would be required, on account of the rarity of these conditions.
- Greater health gains might be possible if etanercept was used earlier in the disease process. Trials to test this hypothesis are required.
- Any further trials in patients with methotrexate-resistant JIA will be multi-centre and probably international, given the small number of patients.

Economic analysis

Our evaluation of the industry cost–utility analysis concluded that it was of limited validity due to the constraints of current empirical knowledge and that construction of a model of greater validity was problematic. The choice is therefore to use the incremental cost per QALY estimate as an aid to decision-making, despite the concerns regarding validity, or to attempt to take a holistic view of the evidence presented, recognising that further valid quantification currently presents difficulties.

Need for further research

A summary of other anti-TNF therapies is to be included in the Technology Assessment Report on anti-TNF therapies in adults with RA.

Current practice

The existing evidence-base for the treatment of methotrexate-resistant patients with JIA is weak. There is a need for better evidence on the efficacy of the drugs used in current clinical practice. We do not know how alternative drugs might perform if compared with placebo in a withdrawal trial of similar design to that of the etanercept trial. Clinical trials might be possible to organise, although they would present challenges to the existing paediatric rheumatology clinical trials networks and patient numbers would be a limiting factor. As clinicians believe currently used second-line treatments with the exception of methotrexate to be of limited effectiveness, they would be unwilling to enter patients into trials that used these agents and might consider such trials unethical.

Drugs new to JIA

Two drugs currently licensed for RA but not used in children might have a role in the treatment of methotrexate-resistant JIA. Infliximab, an anti-TNF agent administered by infusion, is currently not licensed for use in children with JIA, but might become a treatment option if appropriate trials are carried out. Leflunomide has an anti-proliferative effect on T cells *in vitro*, and is licensed for adults with RA, but there have as yet been no trials in children with JIA.

Etanercept

- There is no evidence comparing etanercept with other treatments in this patient group. It might be possible to compare response to etanercept with some of these drugs in further randomised trials. Clinicians' opinions as to the relative lack of efficacy of agents apart from methotrexate would limit the possibility for trials. Safety concerns might place further ethical constraints on trials of relative effectiveness. The effectiveness of etanercept in the treatment of other forms of JIA including psoriatic and enthesitis arthritis is unknown.
- Greater health gains and prevention of destructive joint disease might be possible if etanercept was used earlier in the disease process and in a wider range of patients. Trials to test this hypothesis are required. The only trial was in patients with very severe (mean physician's global assessment at baseline, 7 out of 10) and longstanding (mean duration, 5.9 years) disease. Trials are required to establish the benefits of etanercept earlier in the disease course and in patients with less severe disease.
- Any further trials in patients with methotrexate-resistant JIA will be multi-centre and probably international, given the small number of patients.
- It is not known whether and when the drug can be withdrawn. Longer-term studies are therefore required.
- Given the novel biological action of etanercept, long-term follow-up is desirable, and is required by regulatory agencies, in order to detect any unexpected adverse events. An increasing quantity of post-marketing data will become available. The post-marketing safety profile

will be important in continuing assessment of benefits and risks.

Health economics

The problems encountered in constructing a health economic model for the use of etanercept in JIA indicate that further research is required as follows:

- studies of health-related quality of life in children
- high quality epidemiological long-term studies of outcomes of JIA
- economic analyses of etanercept, preferably in RCTs.

Conclusions

Etanercept is an effective treatment for JIA. Estimation of cost–utility presents considerable difficulties, and some uncertainty must be attached to the estimate of an incremental cost per QALY of £16,000, but an estimate with greater validity is not currently achievable.

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Contributions of authors

Carole Cummins, Senior Lecturer, wrote the protocol, reviewed the searches, reviewed the literature, extracted data, and reviewed the economic analysis found and wrote much of the report.

Martin Connock, Systematic Reviewer, reviewed the searches, extracted data, produced the costs analysis and contributed to the writing of the report.

Anne Fry-Smith, Information Specialist, developed and ran the literature searches and advised on information aspects of the report.

Amanda Burls, Senior Clinical Lecturer in Public Health and Epidemiology, contributed to the writing of the protocol and report.

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Appendix 1

Search strategies

Effectiveness searches

Search strategy for Cochrane Library (CCTR)
Date: 19 April 2001

#1	etanercept
#2	infliximab
#3	enbrel
#4	remicade
#5	#1 or #2 or #3 or #4
#6	juvenile rheumatoid arthritis:ME
#7	juvenile idiopathic arthritis
#8	juvenile chronic arthritis
#9	juvenile rheumatoid arthritis
#10	#6 or #7 or #8 or #9
#11	#5 and #10

Date: 19 April 2001
Database: MEDLINE 1966 to December 2000

Set	Search	Results
001	etanercept.mp.	49
002	enbrel.mp.	7
003	infliximab.mp.	70
004	remicade.mp.	8
005	or/1-4	106
006	arthritis, juvenile rheumatoid/	600
007	(juvenile adj idiopathic adj arthritis).ti,ab.	26
008	(juvenile adj chronic adj arthritis).ti,ab.	186
009	(juvenile adj rheumatoid adj arthritis).ti,ab.	316
010	or/6-9	698
011	exp receptors tumor necrosis factor/	4371
012	tumor necrosis factor/	11921
013	tumo?r necrosis factor.ti,ab.	12234
014	tnf.ti,ab.	11858
015	or/11-14	20468
016	5 or 15	20488
017	10 and 16	37
018	limit 17 to human	37
019	randomized controlled trial.pt.	36840
020	controlled clinical trial.pt.	8534
021	randomized controlled trials/	7360
022	random allocation/	5354
023	double blind method/	13842
024	single blind method/	2297
025	or/19-24	59192
026	animal/ not human/	300482
027	25 not 26	55521
028	clinical trial.pt.	76512
029	exp clinical trials/	19055
030	(clin$ adj25 trial$).ti,ab.	20467
031	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mas k$)).ti,ab.	12962
032	placebos/	2285
033	placebo$.ti,ab.	15411
034	random$.ti,ab.	60249
035	research design/	5737
036	or/28-35	136764
037	36 not 26	127676
038	37 not 27	73749
039	27 or 38	129270
040	18 and 39	7
041	40	7

Database: National Research Register
Date: 19 April 2001
Search strategy: Drug names as per MEDLINE, citations examined to identify whether the patient population was relevant.

Database: EMBASE 1980 – present
Date: 19 April 2001

Search strategy

1	etanercept.mp.	290
2	enbrel.mp.	128
3	infliximab.mp.	391
4	remicade.mp.	156
5	(tumo?r adj necrosis adj factor).ti,ab.	30767
6	tnf.ti,ab.	26183
7	or/1-6	39102
8	juvenile rheumatoid arthritis/	3363
9	(juvenile adj idiopathic adj arthritis).ti,ab.	49
10	(juvenile adj chronic adj arthritis).ti,ab.	856
11	(juvenile adj rheumatoid adj arthritis).ti,ab.	1576
12	or/8-11	3759
13	controlled trial/	1152352
14	randomized controlled trial/	52028
15	clinical trial/	194445
16	controlled study/	1152352
17	clinical study/	6816
18	prospective study/	18430
19	double blind procedure/	38357
20	randomization/	2834
21	major clinical study/	717927
22	or/13-21	1769745
23	7 and 12 and 22	42
24	7 and 12	79
25	from 23 keep 1-42	42

Database: Science Citation Index
Date: 19 April 2001
Search strategy: (infliximab or etanercept or remicade or enbrel) and (juvenile rheumatoid arthritis or juvenile idiopathic arthritis).

Health economics searches

Database: MEDLINE 1997 to February Week 4 2001

Search strategy:

1	etanercept.mp.	66
2	infliximab.mp.	93
3	enbrel.mp.	11
4	remicade.mp.	10
5	or/1-4	144
6	juvenile rheumatoid arthritis/	653
7	(juvenile adj idiopathic adj arthritis).ti,ab.	39
8	(juvenile adj chronic adj arthritis).ti,ab.	202
9	(juvenile adj rheumatoid adj arthritis).ti,ab.	345
	or/6-9	10
11	5 and 10	766
12	econimics/	8
13	economics/	0
14	exp "costs and cost analysis"/	252
15	cost of illness/	18166
16	exp health care costs/	1654
17	economic value of life/	5597
18	exp economics medical/	132
19	exp economics hospital/	432
20	economics pharmaceutical/	1671
21	exp "fees and charges"/	331
22	(cost or costs or costed or costly or costing).tw.	2068
23	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	28581
24	or/13-23	12042
25	11 and 24	45003
26	from 11 keep 1-8	0
27	from 11 keep 1-8	8
28	quality of life/	8
29	life style/	10023
30	health status/	3627
31	health status indicators/	5799
32	or/28-31	1700
33	10 and 32	19109
34	from 33 keep 1-31	31

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We look forward to hearing from you.

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