

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

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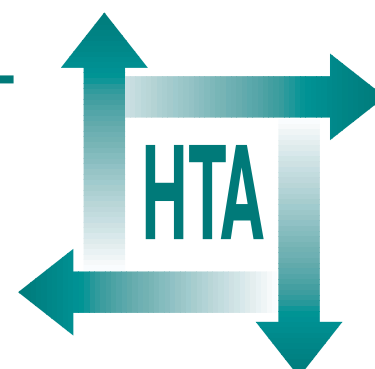
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Executive summary

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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.

Publication

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NHS R&D HTA Programme

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