Rheumatoid arthritis: the effectiveness of infliximab and etanercept

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

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Executive summary

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Executive summary

Background

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

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

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

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

Methods

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

Results

Number and quality of studies

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

Direction of evidence

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

Size of treatment effect

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

Costs

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

Conclusions

Recommendations for research

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

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

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

Publication

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