Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

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Executive summary

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Executive summary

Background

Rheumatoid arthritis (RA) is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Description of technology

Drugs that inhibit joint destruction are known as disease-modifying antirheumatic drugs (DMARDs). There are around eight DMARDs, which are not biologics, in common use in the UK. These drugs are not always effective, may lose effectiveness with time or may cause adverse effects. Alternative DMARDs are therefore needed and tumour necrosis factor (TNF) inhibitors are one class of new agents that has been developed.

Tumour necrosis factor-α (TNF-α) is a cytokine that plays an important role in joint inflammation. TNF inhibitors have been designed to inhibit its actions. Three are currently licensed for use in the UK:

- *adalimumab*: given by subcutaneous injections (40 mg) every other week, but the dose may be increased to weekly if the disease is poorly controlled
- *etanercept*: given by a once-weekly subcutaneous injection (50 mg) or twice weekly (25 mg each)
- *infliximab*: given by intravenous infusion (3 mg kg^{-1}) at 0, 2 and 6 weeks and at 8-weekly intervals thereafter. It is only licensed for use concomitantly with methotrexate.

Current recommendations and service provision

National Institute for Health and Clinical Excellence (NICE) 2002 guidance for the use of TNF inhibitors recommended that:

- etanercept and infliximab be used in patients with clinically active disease that has not responded adequately to at least two DMARDs including methotrexate (unless contraindicated)
- details of patients and their treatment should be recorded in a registry.

There is variable implementation of the guidance, with limited access to these agents in some areas. Where used, these drugs have tended to be used after people have failed two or more DMARDs (as recommended), but they are also being used sequentially, after patients fail on a TNF inhibitor (not recommended). There are currently around 10,000 patients (about 2% of the RA population) on these drugs in the UK, with an estimated annual cost to the NHS of around £100 million. These figures are rising.

Since 2002 more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. In addition, all three agents have been licensed for use in early disease.

Objective to the report

This report reviews the clinical and cost-effectiveness of adalimumab, etanercept and infliximab when used in the treatment of RA in adults.

Methods

Systematic reviews of the literature on effectiveness and cost-effectiveness were undertaken. A wide range of databases was searched and information sought from researchers and industry. Industry submissions to NICE were reviewed. Meta-analyses of effectiveness data were undertaken for each agent.

The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model, was further developed and used to produce an incremental cost-effectiveness analysis.

Results

Number and quality of studies

Twenty-nine randomised controlled trails (RCTs), most of high quality, were included: nine on adalimumab, 11 on etanercept and nine on infliximab. There were 14 economic ▶

evaluations: three from industry submissions, one from the British Society for Rheumatology and ten from published literature.

Direction of evidence and size of treatment effect

Direct comparison with standard treatments

The only head-to-head comparisons were against methotrexate. For patients with short disease duration (≤ 3 years) who were naïve to methotrexate:

- adalimumab was marginally less and etanercept was marginally more effective than methotrexate in reducing symptoms of RA; etanercept was better tolerated than methotrexate
- both adalimumab and etanercept were more effective than methotrexate in slowing radiographic joint damage.

Etanercept was also marginally more effective and better tolerated than methotrexate in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate.

TNF inhibitors versus placebo

All the three agents, either alone (where so licensed) or in combination with ongoing DMARDs, were effective in reducing the symptoms and signs of RA in patients with established disease. At the licensed dose the numbers needed to treat (95% CI) required to produce an American Colleague for Rheumatology (ACR) response compared with placebo were: ACR20: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0); ACR50: adalimumab 4.2 (3.7 to 5.0), etanercept 3.1 (2.7 to 3.6), infliximab 5.0 (3.8 to 6.7); ACR70: adalimumab 7.7 (5.9 to 11.1), etanercept 7.7 (6.3, to 10.0), infliximab 11.1 (7.7 to 20.0).

Combination (TNF inhibitor plus methotrexate) versus methotrexate

In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. Infliximab combined with methotrexate had an increased risk of serious infections (relative risk 2.74, 95% CI 1.12 to 6.70; number needed to harm 25, 95% CI 16.7 to 100).

Existing economic evaluations

All ten published economic evaluations met standard criteria for quality, but the incremental cost-effectiveness ratios (ICERs) ranged from being within established thresholds to being very high because of varying assumptions and parameters. All three sponsors submitted economic models. All made assumptions favourable to their product (e.g. assuming that 'responders' can be separated from 'non-responders' and choosing the most favourable trial data for effectiveness).

Cost-effectiveness

BRAM incorporates improvements in quality of life and mortality, but assumes no effect of TNF inhibitors on joint replacement. For use in accordance with current NICE guidance as the third DMARD in a sequence of DMARDs, the base-case ICER was around £30,000 per quality-adjusted life-year (QALY) in early RA and £50,000 per QALY in late RA. Sensitivity analyses showed that the results were sensitive to the estimates of Health Assessment Questionnaire (HAQ) progression while on TNF inhibitors and the effectiveness of DMARDs, but not to changes in mortality ratios per unit HAQ.

TNF inhibitors are most cost-effective when used last. The ICER for etanercept used last is £24,000 per QALY, substantially lower than for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). First line use as monotherapy generates ICERs around £50,000 per QALY for adalimumab and etanercept. Using the combination of methotrexate and a TNF inhibitor as first line treatment generates much higher ICERs, as it precludes subsequent use of methotrexate, which is cheap. The ICERs for sequential use are of the same order as using the TNF inhibitor alone.

Conclusions

Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function and slowing radiographic changes in joints. When used alone, adalimumab is marginally less effective and etanercept is marginally more effective than methotrexate, in methotrexate-naïve patients. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in early RA, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well-established effectiveness of MTX alone. In addition, an increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab or infliximab.

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Results of published economic evaluations vary: some analyses suggest that the use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, whereas others report very high ICERs. Although most are of high quality, none of them uses all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. The societal perspective generates more favourable ICERs. All economic evaluations submitted by the manufacturers report ICERs that fall within the currently accepted thresholds of cost-effectiveness. However, in the authors' opinion, these models make assumptions and use data that favour the TNF inhibitor being evaluated, the appropriateness of which can be questioned.

The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (£24,000 per QALY) being significantly lower than the ICER for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). Other things being equal, etanercept would be, therefore, the TNF inhibitor of choice based on this evidence. However, the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance, which gives ICERs around £30,000 per QALY using early RA effectiveness data. Using data for late RA, however, gives an ICER of around £50,000 per QALY for etanercept, with higher figures for adalimumab and infliximab. First-line use gives ICERs around £50,000 per QALY for adalimumab and etanercept as monotherapies with much higher figures for combinations with methotrexate.

Sequential use of TNF inhibitors was modelled, with the TNF inhibitors starting as third line therapy and using the 'late RA' values for the TNF inhibitors. The results are similar to those using the given TNF inhibitor as the sole TNF inhibitor in third place, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept.

Recommendations for further research

Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs, and sequential use in patients who have failed a previous TNF inhibitor, are needed. Longer term studies of the quality of life in patients with RA and the impact of DMARDs on this are needed, as are longer studies that directly assess effects on joint replacement, other morbidity and mortality.

Publication

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Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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