Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation


CRD summary
This review, which assessed the clinical effectiveness of anti-tumour necrosis factor-α therapy for patients with ankylosing spondylitis, concluded that the therapy is clinically effective in the short term. The authors’ conclusions are likely to be reliable.

Authors' objectives
To assess the comparative clinical effectiveness and cost-effectiveness of anti-tumour necrosis factor (TNF)-α therapy (adalimumab, etanercept and infliximab) for the treatment of ankylosing spondylitis. This abstract will only deal with the assessment of clinical effectiveness.

Searching
The Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register, DARE, EMBASE, HTA, ISI Web of Science -Proceedings, ISI Web of Science - Science Citation Index Expanded, MEDLINE and NHS EED were searched up to November 2005; the search terms were reported. Reference lists of included studies and company submissions were screened for other relevant studies. Abstracts from three rheumatology conferences (2003 to January 2005) were handsearched: BSR, European League Against Rheumatism (Annual European Congress of Rheumatology) and American College of Rheumatology.

Study selection
Clinical trials of adalimumab, etanercept and infliximab plus conventional treatment for adults with active ankylosing spondylitis were eligible for inclusion. For trials of etanercept and infliximab to be eligible, the participants must have already responded inadequately to conventional therapy. Eligible trials also had to report functional capacity, disease activity, adverse effects, disease progression, health-related quality of life and pain, and other symptoms as outcomes. Randomised studies were excluded if they provided only interim findings, provided data on only a subgroup of patients, were continuing to recruit patients, or if they were trials in which the numbers of patients treated with a specific intervention or disease status could not be determined.

Of the studies included, all used some form of conventional care (such as non-steroidal anti-inflammatory drugs with or without disease-modifying antirheumatic drugs) for all recruited participants. Two studies were of adalimumab, five of etanercept and two of infliximab; all trials used placebo as a comparator. Composite binary measures of response, such as the Assessment in Ankylosing Spondylitis (ASAS) or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were primary outcomes in all studies; ASAS improvement was measured as being at least 20, 50 or 70% (ASAS 20, ASAS 50, ASAS 70). The majority of participants were male (range: 63 to 90%) with a mean age of 32 to 45.4 years. The definition of ‘active AS’, for participant recruitment, varied slightly across trials.

Two independent reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed using criteria based on the Centre for Reviews and Dissemination's guidance on the conduct of systematic reviews. This covers areas such as method of randomisation, allocation concealment, baseline comparability, blinding, withdrawals and use of intention-to-treat analysis.

Two reviewers independently assessed study quality, with any disagreements resolved through discussion.

Data extraction
Outcome data were extracted and relative risks (RRs) for ASAS outcomes, or weighted mean differences (WMDs) for
BASDAI outcomes, were calculated, along with 95% confidence intervals (CIs).

One reviewer extracted the data, which a second reviewer checked.

**Methods of synthesis**

Meta-analyses of pooled estimates of RRs and WMDs were generated using a fixed-effect model. A random-effects model was also used when heterogeneity was found. The studies were weighted, but the method used was not described. Subgroup analyses (for intervention type), tests for heterogeneity (I² and χ²) and indirect comparison analyses were also conducted.

**Results of the review**

Nine randomised controlled trials were included in the review (the total number of participants was unclear, but was approximately 1,500). The sample sizes ranged from 34 to 315.

All studies were of good, and broadly comparable, quality.

Anti-TNF-α therapy was associated with a statistically significant improvement in ASAS 20 criteria, compared with placebo, at 12 weeks (8 trials; RR 2.52, 95% CI: 2.14, 2.98, p<0.00001) and 24 weeks (2 trials; RR 2.80, 95% CI: 2.11, 3.71, p<0.00001); moderate heterogeneity was found at 12 weeks (I²=36%). ASAS 50 was also improved with anti-TNF-α therapy at 12 weeks (7 trials; RR 3.58, 95% CI: 2.72, 4.71, p<0.00001) and 24 weeks (1 trial; RR 3.96, 95% CI: 2.37, 6.63, p<0.00001); there was no evidence of heterogeneity (I²=0%). ASAS 70 was improved with anti-TNF-α therapy at 12 weeks (6 trials; RR 3.94, 95% CI: 2.61, 5.95). Compared with baseline, treatment with anti-TNF-α therapy reduced BASDAI disease activity scores by 1.89 points at 12 weeks (WMD -1.89, 95% CI: -2.23, -1.55), although this result was derived using a random-effects model since moderate heterogeneity was found.

Subgroup analyses showed that, individually, all three drugs were effective. Indirect comparison analyses showed no statistically significant differences between the drugs. Adverse event data were also reported.

**Cost information**

The incremental cost-effectiveness ratios (ICERs) of adalimumab and etanercept were roughly similar, falling below an assumed willingness-to-pay threshold of £30,000. The ICER for infliximab was in the range of £40,000 to £50,000 per quality-adjusted life-year.

**Authors’ conclusions**

Anti-TNF-α therapy is clinically effective in the short term (12 to 24 weeks) for the treatment of ankylosing spondylitis.

**CRD commentary**

This generally well-conducted review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify studies were undertaken by searching electronic databases and checking references, although language restrictions were not reported, so it is difficult to comment on whether any studies not published in English were missed. Attempts were made to identify unpublished studies by searching conference abstracts. Methods were used to minimise the risk of reviewer error and bias in the study selection, quality assessment and data extraction processes. Study quality was adequately assessed. Sufficient study details were provided and the data were pooled using appropriate meta-analyses. However, although the authors assessed heterogeneity, when it was found its possible causes were neither investigated nor discussed. The authors’ conclusions reflect the evidence available and are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that, in order to obtain a robust estimate of the longer-term clinical effectiveness of anti-TNF-α agents for ankylosing spondylitis, clinical trials that aim to address a number of limiting factors need to be
conducted.

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