Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation


CRD summary
This review concluded that there was some evidence, from three trials, to suggest that both etanercept and infliximab are efficacious treatments for psoriatic arthritis. Short-term benefits for joint and psoriasis symptoms and functional status were observed with both drugs, but further research is needed to assess the long-term benefits. The review was well conducted and its conclusions are likely to be reliable.

Authors' objectives
To assess the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis in patients with inadequate response to standard treatment, including disease-modifying antirheumatic drug therapy.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register, the National Research Register, Current Controlled Trials, CenterWatch, ClinicalTrials.gov, ISI Science and Technology Proceedings, the Social Sciences Citation Index and Science Citation Index were searched from inception to 2004. Additional databases were searched for economic evaluations (details given in the report). The bibliographies of included studies and industry submissions to the National Institute for Health and Clinical Excellence were also checked. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Long-term experimental or observational studies of at least 24 weeks' duration and with a minimum of 100 patients were also included for adverse events.

Specific interventions included in the review
Studies of etanercept given by injection and infliximab given by intravenous infusion, compared with placebo or any other active agent, were eligible for inclusion. The included studies assessed etanercept (25 mg twice weekly for up to 24 weeks) compared with placebo and infliximab (5 mg/kg at baseline and at 2, 6 and 14 weeks) compared with placebo.

Participants included in the review
Studies of adults with psoriatic arthritis were eligible. Average patient ages in the studies of etanercept and infliximab ranged from 43.5 to 47.6 years, and the proportion of men ranged from 45 to 60%. All patients had active psoriatic arthritis, defined as more than three or more than five tender and swollen joints. The mean duration of psoriatic arthritis ranged from 9 to 11 years.

Outcomes assessed in the review
The primary outcomes specified by the inclusion criteria were:

- any measure of disease activity, including the American College of Rheumatology (ACR) joint count, Psoriatic Arthritis Response Criteria (PsARC) and Psoriatic Area and Severity Index (PASI);

- function and quality of life (Health Assessment Questionnaire, HAQ);

- radiological assessment of disease progression; and

- adverse events.
Other measures of these outcomes reported by the studies were also included.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for the review. Any discrepancies were resolved by consensus or by referral to a third reviewer.

Assessment of study quality
Study quality was assessed using the following criteria: specification of patient eligibility criteria; a priori sample size calculation; adequate sample size for the analysis of the primary outcome; randomisation method; double-blinding; allocation concealment; blinded treatment providers; blinded outcome assessors; blinded patients; success of the blinding procedure; sufficient patient baseline data reported; comparability of the treatment groups at baseline; comparability of the treatment groups with respect to cointerventions; adequate treatment compliance; all randomised patients accounted for at end of trial; intention-to-treat analysis; at least 80% of the randomised patients provided primary outcome data. The studies were classed as excellent, good, satisfactory or poor quality. One reviewer assessed the studies for quality and a second reviewer checked the assessment. Any disagreements were resolved by consensus or by referral to a third reviewer. The quality of adverse event studies was not assessed.

Data extraction
One reviewer extracted the data and a second checked the extraction. Any disagreements were resolved by consensus or by referral to a third reviewer. Relative risks (RRs) or mean differences, along with the corresponding 95% confidence intervals (CIs), were calculated for the primary outcome variables of joint count (ACR 20, 50 and 70), PsARC, PASI and HAQ.

Methods of synthesis
How were the studies combined?
Where pooling was appropriate, pooled RRs or weighted mean differences were obtained using a fixed-effect model.

How were differences between studies investigated?
Differences between the studies regarding adult status, minimum PASI score and concomitant medication were described narratively. Statistical heterogeneity was assessed using a chi-squared test.

Results of the review
Three RCTs, two evaluating etanercept (n=60 and n=205) and one evaluating infliximab (n=104), provided results on efficacy. Twenty-five studies provided data on adverse events (10 for etanercept and 15 for infliximab; number of participants not reported).

Etanercept.
The two etanercept trials were both considered good quality. They satisfied all quality criteria except an assessment of whether blinding had been successful. At 12 weeks, patients treated with etanercept demonstrated statistically significant improvements in arthritis-related symptoms compared with placebo. Etanercept patients were more likely to achieve ACR response criteria relating to 20, 50 or 70% reductions in tender and swollen joint counts: 65% achieved ACR20 (RR 4.19, 95% CI: 2.74, 6.42), 45% achieved ACR50 (RR 10.84, 95% CI: 4.47, 26.28) and 12% achieved ACR70 (RR 16.28, 95% CI: 2.20, 120.54). Almost 85% of etanercept patients achieved a PsARC (RR 2.60, 95% CI: 1.96, 3.45). Etanercept patients also experienced a statistically significant improvement in functional status. Similar results were observed after 24 weeks of follow-up. There was no evidence of statistical heterogeneity for any outcome.

Infliximab.
The one trial of infliximab was assessed as being of good quality. At 16 weeks, 65% of patients treated with infliximab achieved ACR20 (RR 6.80, 95% CI: 2.89, 16.01), 46% achieved ACR50 (RR 4.90, 95% CI: 3.06, 785.06) and 29% achieved ACR70 (RR 31.00, 95% CI: 1.90, 504.86); infliximab was significantly superior to placebo for all these outcomes.
outcomes. For PsARC, the response rates were 75% for infliximab and 21% for placebo (RR 3.55, 95% CI: 2.05, 6.13). Infliximab patients also experienced a statistically significant improvement in functional status (mean difference of improvement from baseline 51.4%, 95% CI: 48.1, 54.7).

Adverse events. Etanercept appeared to be well-tolerated for short- and long-term use. The most common adverse effects reported were injection site reactions and mild infections. Infusion reactions, antibody development and infections were the most common adverse events for infliximab.

Cost information
The economic model developed as part of the review showed that etanercept was more cost-effective than infliximab. The incremental cost per quality-adjusted life-year (QALY) gained with etanercept compared with palliative care ranged from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon), assuming that when patients failed on treatment their disability (as measured by HAQ score) deteriorated by an amount equal to their initial treatment response. Under an alternative assumption that when patients failed on treatment their disability level returned to what it would be if they never responded to treatment, the incremental cost per QALY for etanercept ranged from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon).

Authors' conclusions
The limited data available suggest that both etanercept and infliximab are efficacious for treating psoriatic arthritis, with benefits for joint and psoriasis symptoms and functional status. Further data is required to confirm the findings of current trials and to show that response is maintained and long-term disease progression delayed.

CRD commentary
This review had a thorough literature search that involved a number of relevant databases and handsearching, with no language restrictions. The inclusion criteria specified eligible interventions, participants, study designs and outcomes. The studies were selected by two reviewers independently, whilst the data extraction and quality assessment were performed by one reviewer and checked by another; this helps limit potential errors and bias in the review process. Study validity was assessed using criteria applicable to RCTs and was taken into account. This was a well-conducted review and the authors’ conclusions 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 made recommendations for further research. Specifically, long-term controlled trials to provide confirmation that symptomatic benefits for functional status, joint and skin disease are maintained and to look at joint disease progression; a 2-year controlled trial of etanercept versus best care (methotrexate or leflunomide), collecting data on functional status and radiographic progression; controlled trials of combinations with methotrexate, with reference to any synergistic effect and the possibility of tachyphylaxis; long-term monitoring of adverse events and treatment withdrawal rates; further research into the therapeutic impact of arthritis and psoriasis on quality of life using a generic preference-based instrument; and further research into intermittent biologic therapy for psoriatic arthritis.

Funding
NHS R&D Health Technology Assessment (HTA) Programme, project number 04/04/01.

Bibliographic details

PubMedID
17083854

Original Paper URL
http://www.hta.ac.uk/1407

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /adverse effects /therapeutic use; Cost-Benefit Analysis; Etanercept; Female; Humans; Immunoglobulin G /adverse effects /therapeutic use; Immunosuppressive Agents /adverse effects /therapeutic use; Male; Psoriasis /classification /drug therapy /economics; Randomized Controlled Trials as Topic; Receptors, Tumor Necrosis Factor /therapeutic use; Severity of Illness Index; Treatment Outcome

AccessionNumber
12006008418

Date bibliographic record published
30/09/2007

Date abstract record published
30/09/2007

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.