Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials

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CRD summary
This generally well-conducted review assessed the tumour necrosis factor-α (TNF-α) inhibitors adalimumab, etanercept and infliximab for the management of psoriatic arthritis (PsA). The authors concluded that TNF-α inhibitors were effective treatments for psoriatic arthritis with no important risks associated with short-term use. The conclusion reflected the results of the review and is likely to be reliable.

Authors' objectives
To assess the efficacy and safety of tumour necrosis factor-α (TNF-α) inhibitors in the management of psoriatic arthritis (PsA).

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials were searched without language or publication restriction from inception to May 2007. Search terms were reported. The websites of the FDA and the European Medicines Evaluation Agency were also searched, as were the references of identified trials and reviews.

Study selection
Double-blinded randomised controlled trials (RCTs) that compared adalimumab, etanercept or infliximab at licensed therapeutic dosages with placebo or other active treatments in patients with at least three swollen joints and three tender or painful joints were eligible for inclusion. RCTs were required to report efficacy or safety outcomes. The primary outcome was American College of Rheumatology 20 (ARC20) response at 12 to 16 weeks. Secondary efficacy outcomes were: Psoriatic Arthritis Response Criteria (PsARC), ARC50 and ARC70; Psoriasis Area Severity Index (PASI) 50, PASI 75, and PASI90; and Disability Index of the Health Assessment Questionnaire (HAQ-DI). Safety outcomes included upper respiratory tract infections, serious adverse events, malignancies, withdrawals, withdrawals due to adverse events and injection site or infusion reactions. The included studies had durations of between 12 to 24 weeks. Adalimumab was given subcutaneously at 40 mg bi-weekly, etanercept at 25 mg subcutaneously twice-weekly and infliximab at 5 mg/kg at increasing intervals. Some included studies used concomitant medications such as methotrexate, corticosteroids and non-steroidal anti-inflammatory agents.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the studies for validity using the Jadad scale, which awards up to 5 points for the criteria of randomisation, blinding and treatment of withdrawals and dropouts. Studies scoring fewer than 2 points were excluded from the review. Differences were resolved through discussion.

Data extraction
Two reviewers independently performed the data extraction; disagreements were resolved through discussion. The frequency of events in each group was extracted for dichotomous data, along with the number of patients treated. The change in response from baseline, its standard deviation and the number of patients intended to be treated were extracted for continuous data.

Methods of synthesis
The studies were combined in a random-effects meta-analysis. Pooled relative risks (RRs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for each outcome. Subgroup analyses were conducted for each individual treatment. Statistical heterogeneity was assessed using $X^2$ and $I^2$ tests. Indirect comparisons were performed using the method of Bucher et al; data on outcomes at week 12 were used for adalimumab
and etanercept and data at weeks 14 to 16 were used for infliximab.

Results of the review
Six RCTs (n=982) were included in the review.

All three TNF-α inhibitors were significantly more effective than placebo as assessed by ACR20. The pooled RR for all trials was 4.35 (95% CI: 3.24, 5.84). Results for each individual treatment were significant (adalimumab RR 3.42, 95% CI: 2.08, 5.63, etanercept RR 5.50, 95% CI: 2.15, 14.04 and infliximab RR 5.71, 95% CI: 3.53, 9.25). The indirect comparisons found no significant differences between the treatments in achieving response assessed by ACR20. The same pattern of results was found for outcomes assessed by PsARC at 12 weeks and 24 weeks. Indirect comparisons found no significant differences in efficacy.

Outcomes assessed using PASI also showed significant and consistent benefits of all three treatments. There were no significant differences between TNF-α inhibitors and placebo in the numbers of patients withdrawing from the study or withdrawing due to an adverse reaction. Nor were there significant differences in the numbers experiencing serious adverse events or respiratory tract infections. More patients experienced injection site reactions with etanercept than with placebo (RR 4.27, 95% CI: 2.25, 8.13), but no significant difference was found with adalimumab or in infusion site reactions with infliximab versus placebo. Only one incidence of malignancy (in a placebo group) was found in five trials that monitored malignancy. Quality of life outcomes were reported.

Authors’ conclusions
TNF-α inhibitors were effective treatments for psoriatic arthritis with no important risks associated with short-term use. There was a need for long-term risk-benefit assessment of TNF-α inhibitor use for the management of psoriatic arthritis.

CRD commentary
The review question and the inclusion criteria were clear and specific. The authors searched several relevant databases and other sources and took steps to reduce the possibility of language or publication bias. The authors reported using methods designed to reduce reviewer bias and error in the extraction of data and the assessment of validity, but not in the selection of papers. An appropriate validity assessment was conducted, although this was not used to inform the synthesis. The decision to use meta-analysis and indirect comparisons appeared appropriate. Heterogeneity was investigated using appropriate techniques. The authors’ conclusions reflected the results of the review and appear 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 there was a need for longitudinal observational studies with sufficient numbers of patients to investigate the long-term comparative safety of TNF-α inhibitors in the management of psoriatic arthritis.

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