A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis

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CRD summary
This review concluded that gold, sulfasalazine, leflunomide and tumour necrosis factor inhibitors are effective in treating psoriatic arthritis compared to controls, but toxicity was greater. Given the methodological differences between included studies, and limitations in the reporting of the review, such as inconsistencies between the conclusions and statistical analysis, the reliability of the authors' conclusions is uncertain.

Authors' objectives
To assess the efficacy and tolerability of treatments for psoriatic arthritis (PsA).

Searching
MEDLINE/PubMed and EMBASE were searched from 1966 to June 2006 for publications in English; the search terms were reported. In addition, the bibliographies of relevant articles were manually searched.

Study selection
Randomised controlled trials (RCTs) comparing currently licensed disease-modifying antirheumatic drugs (DMARDs) or biological agents with a control in patients with PsA, and reporting withdrawals due to toxicity (adverse events) and lack of efficacy as the primary outcomes, were eligible for inclusion. Eligible studies were required to report adequate allocation concealment and double-blinded assessment. The included studies were of patients with established PsA and peripheral arthritis. The majority of included studies assessed DMARD monotherapy using a number of different treatments. Withdrawal rates for lack of efficacy were mainly measured using the psoriatic arthritis response criteria (PsARC) or the American College of Rheumatology response criteria (ACR20).

The authors did not state how many reviewers screened studies for relevance, or how any discrepancies were resolved.

Assessment of study quality
Validity was assessed using criteria from the Jadad scale, but the authors did not state how many reviewers performed the assessment.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous data on the number of patients withdrawn due to toxicity. Comparisons were made of withdrawal due to lack of efficacy between those with ACR20 and PsARC responses.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The ORs were pooled using the Peto fixed-effect model. Sensitivity analyses were conducted on agents used and outcomes measured. The benefit versus risk of each treatment was calculated from the ratio of numbers-needed-to-treat (NNT) to numbers-needed-to-harm (NNH). Heterogeneity was assessed using the $\chi^2$ and I^2 tests.

Results of the review
Eighteen RCTs (n=2,148: 1,109 receiving treatment and 1,039 controls) were included in the review. The sample sizes ranged from 6 to 315 participants.

Three studies scored 5 on the Jadad scale, but the majority scored 3 (72%).
Efficacy.

Participants receiving the intervention reported significantly greater benefit compared with controls (OR 0.35, 95% CI: 0.25, 0.49, p=0.00001). Tumour necrosis factor (TNF) inhibitors (4 RCTs) and gold salts (2 RCTs) were shown to have the greatest treatment effect, while sulfasalazine (4 RCTs) and leflunomide (1 RCT) reported moderate effect sizes. One RCT of methotrexate was terminated early and it was not possible to report on the remaining 6 studies as no events occurred.

Toxicity.

The intervention group reported a significantly higher number of withdrawals compared with controls (OR 2.33, 95% CI: 1.61, 3.37, p=0.00001), with the most significant differences being reported for patients treated with leflunomide (1 RCT) and gold salts (2 RCTs), and a relatively high withdrawal rate with sulfasalazine (5 RCTs). The number of withdrawals in the TNF inhibitors group compared with controls was not significantly different (4 studies).

Sensitivity analyses did not significantly alter the results. There was no significant heterogeneity among studies for the overall pooled result for either outcome. Treatment with TNF inhibitors reported the most benefit when using the NNT:NNH ratio.

Authors' conclusions
Gold, sulfasalazine, leflunomide and TNF inhibitors are effective in treating PsA, with gold and TNF inhibitors showing the greatest effects. However, toxicity was greater in the intervention groups, with gold and leflunomide reporting the greatest number of withdrawals.

CRD commentary
The review question was clear and was supported by appropriate inclusion criteria. The literature search was somewhat limited, using only two electronic databases and one other source. Publications were restricted to those in English, which means that language bias cannot be ruled out. Together with the fact that there was no apparent search for unpublished articles, it is possible that relevant papers might have been missed. Validity was assessed, but no details were given on how many reviewers performed the assessment, or how the studies were selected and the data extracted, thus reviewer error and bias cannot be ruled out. Appropriate methods were used to investigate heterogeneity, but the data synthesis was a little unclear as there were inconsistencies between the statistical analysis that was stated to be undertaken and that reported, and the results were reported as risk ratios but presented in forest plots as ORs. In addition, it may not have been appropriate to use the Peto method for statistical analysis as this can introduce bias. There were also several limitations of the included studies, such as small sample sizes for some studies, wide CIs and the use of different outcome measures. Given the above considerations and limitations in the reporting of the review, the authors’ conclusions may not 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 a definitive RCT of methotrexate is needed.

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