The effect of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials

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CRD summary
This review assessed the effectiveness of drug treatments in preventing bone erosion (determined from X-rays) in rheumatoid arthritis. The authors concluded that cyclosporine, infliximab, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin and IL-1-RA are more effective than placebo. This conclusion appears reliable. Conclusions about relative effectiveness of different drugs were derived from indirect comparisons and may not be reliable.

Authors’ objectives
To assess and rank the efficacy of pharmaceutical interventions in preventing radiological progression of rheumatoid arthritis.

Searching
The Cochrane Controlled Trials Register, MEDLINE (from 1966 to 2000) and EMBASE were searched. Bibliographies of reviews, papers and the conference proceedings of the American College of Rheumatology were searched manually, and pharmaceutical companies and authors were contacted for unpublished trials. Only English language reports of trials were reviewed.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials with a follow-up of at least 24 weeks were reviewed.

Specific interventions included in the review
All pharmaceutical interventions were eligible for the review. The included studies were of cyclosporin, infliximab, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin, interleukin I receptor antagonist (IL-1-RA), hydroxychloroquine, chloroquine, pamidronate, minocycline, cyclophosphamide and D-penicillamine. Only placebo (or equivalent) controlled studies were eligible. Trials that permitted the use of concomitant medications were included.

Participants included in the review
Studies of adults with rheumatoid arthritis (according to the American College of Rheumatology criteria), or older trials of patients with active disease, were eligible. Details of the participants in the included trials were not reported in the review.

Outcomes assessed in the review
The primary outcome of interest was the radiographic scoring of bone erosion in joints. A number of scoring systems were accepted.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The methodological quality of the included trials was assessed using a previously used scale (reference given in the paper). The trials were scored 0 to 3 for: blinding of randomisation; intention-to-treat analysis; blinding of the assessors to the treatment allocation; and the comparability of the study groups at baseline. The authors did not state how the
papers were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**
Two authors independently extracted the efficacy data from the published reports. Any disagreements were resolved by discussion involving a third investigator. The primary outcome, the radiographic scoring of bone erosion in joints, was reported using a number of scoring systems. Where necessary, trialists were contacted for further information.

**Methods of synthesis**
How were the studies combined?
To allow the direct comparison and pooling of studies, the authors of the review calculated two dimensionless outcome measures: the standardised mean difference (SMD; changes in erosion score) and the odds of worsening X-ray scores (progression of erosion). Details were given in the review. Only trials of the same agent were pooled. To minimise possible heterogeneity due to different treatment duration, the trials were pooled using follow-up data as close to 12 months as possible. Pooled effect sizes for the SMD and the odds of worsening X-ray scores were calculated, along with 95% confidence intervals, using a fixed-effect model. Standard t-tests were used to compare the mean treatment effects between X-ray trials and disease activity trials. The results were ranked in order of the pooled SMD. Superiority of one treatment over another was defined as the point estimate of the inferior agent not including the 95% confidence interval of the superior agent.

How were differences between studies investigated?
Tests for heterogeneity were performed using the Mantel-Haenszel method.

**Results of the review**
Twenty-five trials (n=3,907) were included in the review.

There were 5 trials of corticosteroids; 3 of parenteral gold; 2 of sulphasalazine; 2 of leflunomide; 2 of auranofin; 2 of hydroxychloroquine; 2 of chloroquine; 2 of pamidronate; and one each of cyclosporin, infliximab, methotrexate, IL-1-RA, minocycline, cyclophosphamide, and D-penicillamine.

The quality scores of the included studies ranged from 7 to the maximum 12. There was no significant association between quality score and efficacy.

For changes in erosion score, in rank order, cyclosporin, infliximab, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin and IL-1-RA were statistically better than placebo. Only infliximab demonstrated superiority over any other agent; it was superior to methotrexate, parenteral gold, corticosteroids, auranofin and IL-1-RA.

For effect of pharmaceutical treatment on the progression of erosions, in rank order, infliximab, leflunomide, methotrexate, parenteral gold, sulphasalazine and corticosteroids were statistically better than placebo. Only infliximab demonstrated superiority over any other agent; it was superior to parenteral gold, corticosteroids, auranofin and IL-1-RA.

**Authors' conclusions**
The authors concluded that there was evidence that nine agents (cyclosporin, infliximab, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin and IL-1-RA) decrease radiological progression in rheumatoid arthritis.

**CRD commentary**
The inclusion and exclusion criteria for the review were well-defined and most of the review methodology were clearly described. The literature search was adequate, although the restriction to English language reports may have excluded
some trials. The possible impact of trials identified but excluded form the review was explored. The quality assessment was thorough; however, the findings of the assessment were not incorporated into the review of efficacy.

The drug versus placebo data were summarised using accepted statistical techniques. However, the ranking of findings according to the size of the treatment effect versus placebo is not a valid statistical technique for comparing levels of the effectiveness of the different agents. The authors' claim that the overlapping of confidence intervals confers equivalence is also incorrect, and their definition of superiority is of doubtful validity. Thus, whilst the review's conclusions about the evidence for all agents when compared with placebo are supported by the data presented, any conclusions about the relative efficacy of the individual agents are not.

Implications of the review for practice and research
Practice: The authors stated that there was evidence that nine agents (cyclosporin, infliximab, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin and IL-1-RA) decrease radiological progression in rheumatoid arthritis.

Research: The authors stated that trials of combination therapy and further trials of pamidronate are warranted.

Bibliographic details

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Other publications of related interest
This additional published commentary may also be of interest. Sander O. Review: 9 drugs prevent an increase in radiographic scores of bone erosion in joints in adult rheumatoid arthritis. ACP J Club 2003;139:46.

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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.