CRD summary
The authors concluded that tacrolimus, given at doses from 1.5 to 3mg daily, was found to be effective in patients with active rheumatoid arthritis who were resistant to other disease modifying anti-rheumatic drugs and methotrexate. The potential for some biases in the review means that the reliability of the authors' conclusion is unclear.

Authors' objectives
To evaluate the efficacy and safety of tacrolimus in patients with severe rheumatoid arthritis.

Searching
MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant studies; search terms were reported. Search dates were not specified, but the most recent article included was published in April 2009. Reference lists of the retrieved articles were checked to identify additional studies. It was unclear if there were any language restrictions.

Study selection
Randomised controlled trials (RCT) or open-label trials that evaluated the efficacy and safety of tacrolimus compared with placebo or other disease modifying anti-rheumatic drugs in patients with confirmed rheumatoid arthritis were eligible for inclusion.

The primary outcome for efficacy was the number of patients who received an American College of Rheumatology (ACR) 50% response rate (ACR50); the primary safety outcome was the number of patients withdrawn due to adverse events. Secondary outcomes included the number of patients who achieved ACR 20% and 70% (ACR20 and ACR70) responses, the number of patients withdrawn due to lack of efficacy, other outcomes relating to joint function and pain, and the incidence of all adverse events.

The patients in included trials had rheumatoid arthritis that was resistant to other disease modifying anti-rheumatic drugs, intolerant active rheumatoid arthritis, or methotrexate-resistant rheumatoid arthritis. Tacrolimus was administered at 1.5 to 2mg or 3mg per day. The control treatments in the included RCTs were placebo or mizoribin given at 150mg. In one open-label trial, methotrexate was also administered at a dose of 20mg/week.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The reviewers assessed RCT methodological quality by evaluating the concealment of treatment allocation, the use of blinding and the adequacy of the analyses.

The authors did not state how many reviewers performed the quality assessment, but stated that any disagreements between the reviewers were resolved by consensus.

Data extraction
Data were extracted to calculate mean differences (MDs) for continuous data and relative risks (RRs) for dichotomous data, with corresponding 95% confidence intervals (CIs) for both.

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

Methods of synthesis
Weighted mean differences (WMDs) and 95% confidence intervals were calculated for the continuous data. Where different scales were used to measure the same outcomes, standardised mean differences were used. The Cochran's Q-statistic and I$^2$ were used to assess heterogeneity across the results for each outcome. In the event of significant heterogeneity (p<0.10), a random effect model was used to pool the trial results. If p>0.10, a fixed-effect model was used. Additional meta-analyses were conducted stratified by methodological quality criteria and duration of follow-up. The Egger's test was used to assess publication bias.

**Results of the review**

Eight trials (n=2,059) were included in the review, comprising four open-label trials (n=1,045) and four RCTs (n=1,014); the RCTs were included in the meta-analysis. Sample sizes ranged from 12 to 896 patients in the open-label trials and 135 to 464 patients in the RCTs. Follow-up durations of RCTs ranged from 16 to 28 weeks. The results of the quality assessment were only reported for the four RCTs. The concealment of allocation was unclear in all four RCTs; the random allocation of patients and patient blinding were judged to be adequate in all four RCTs.

Statistically significant benefits were observed with treatment with 3mg tacrolimus compared with control treatments for response rates classified as ACR50 (RR 2.583, 95% CI 1.095 to 6.092; I$^2$=66.6%; four RCTs), ACR20 (RR 3.141, 95% CI 2.327 to 4.240; I$^2$=17.3%; four RCTs) and ACR70 (RR 5.618, 95% CI 1.440 to 21.92; I$^2$=26.3%; two RCTs). Withdrawals due to lack of efficacy were also significantly lower in the tacrolimus group (RR 0.391, 95% CI 0.217 to 0.705, I$^2$=72.7%).

The use of tacrolimus given at doses of 1.5 to 2.0 mg was associated with significant benefits compared with placebo in response rates of ACR50 (RR 2.143, 95% CI 1.097 to 4.187; I$^2$=0%; two RCTs), ACR20 (RR 1.849, 95% CI 1.187 to 2.880; I$^2$=0%; two RCTs) and ACR70 (RR 8.209, 95% CI 1.039 to 64.85; I$^2$=0%; one RCT). There was also a non-significant beneficial difference in withdrawals due to lack of efficacy in the tacrolimus group.

At both dose levels, there were significant improvements for the patients who received tacrolimus for all clinical outcomes related to rheumatoid arthritis disease activity, but there were no differences between the tacrolimus and control groups in physical function. The results did not vary significantly from the main analysis of tacrolimus for results stratified by methodological quality criteria.

In the four open-label trials, tacrolimus appeared to be well-tolerated, safe and was associated with clinical benefits.

The incidence of adverse events was higher for the tacrolimus-treated groups than the control groups (RR1.214, 95% CI 1.066 to 1.384).

There was no evidence of publication bias shown in the Egger's test; however, as the authors acknowledged, the number of studies included in the analysis was insufficient for these analyses.

**Authors' conclusions**

Tacrolimus given at doses from 1.5 to 3mg per day was found to be effective in patients with active rheumatoid arthritis who were resistant to other disease modifying anti-rheumatic drugs and methotrexate, although long term efficacy and toxicity were still to be established.

**CRD commentary**

The review addressed a clear question. Criteria for the inclusion of studies were stipulated. Only two appropriate electronic databases were searched, and it was unclear if there were any language restrictions. This meant that some studies may have been missed, and that there may be a risk of language bias. Although the authors examined the potential for publication biases, these analyses were not likely to detect publication bias as there were only a small number of studies identified and included. There were adequate methods reported to minimise reviewer error and bias for the conduct of the methodological quality assessment, but not for study selection and data extraction.

Methodological quality of the trials was assessed and the results were adequately reported. The authors' decision to statistically combine the results of the trials appeared to be justified. In addition, the authors correctly acknowledged the limitations of the review relating to the small numbers of included trials and the lack of data pertaining to long-term efficacy and toxicity.
The conclusion of the review is based on the evidence presented, but, owing to the potential for some biases, its reliability is unclear.

Implications of the review for practice and research

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

Research: The authors stated that additional trials are required to determine whether tacrolimus has any effect on bone erosion and joint destruction in rheumatoid arthritis. In addition, the focus in open-label studies should be on tolerability of tacrolimus rather than efficacy when using the results of open-label studies in systematic reviews.

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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.