This review found that leflunomide, methotrexate, and sulfasalazine did not differ in their effectiveness for treating rheumatoid arthritis, but leflunomide was more effective than placebo. These conclusions omitted the adverse effect findings and might not be reliable, due to the small number of trials for some comparisons, failure to specify a primary outcome, and high heterogeneity in many analyses.

Authors' objectives
To assess the efficacy and safety of leflunomide, compared with active therapy (methotrexate or sulfasalazine) or placebo, for the single-drug treatment of rheumatoid arthritis.

Searching
PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), two trial registers, and the Internet were searched to December 2011. Search terms were reported; the reference lists of retrieved articles were checked; and drug manufacturers were consulted. The search was restricted to studies published in full-text peer-reviewed journals in English, German, French, or Polish.

Study selection
Eligible studies were single or double-blinded randomised controlled trials (RCTs) comparing leflunomide versus placebo or another active treatment in adults with active rheumatoid arthritis. The outcomes of interest included clinical improvement, tender and swollen joint count, assessment of disease activity, acute phase markers, pain, stiffness, functionality, quality of life, radiographic changes, and safety. Detailed criteria for the outcomes were described in the review.

Most participants in the included trials were women (66% to 88%). The mean participant age was over 50 years; the mean duration of rheumatoid arthritis was three to nine years; and over 60% of participants had the rheumatoid factor in their blood. Trials were conducted in various countries or groups of countries; all included between two and 117 centres. Leflunomide was given at a loading dose of 50 to 100mg and then usually at 20mg orally per day. It was compared with methotrexate (target dose 15mg per week), sulfasalazine (target dose 2g daily), or placebo.

Two reviewers independently selected studies for inclusion, with a third reviewer for arbitration if necessary.

Assessment of study quality
Trial quality was evaluated using the Jadad scale to assess the adequacy of reported randomisation, double-blinding, and withdrawals or dropouts. Each trial was awarded a score out of a maximum of five points. The sample size, number of participating centres, and duration of follow-up were also assessed.

The authors did not state how many reviewers assessed validity.

Data extraction
Mean differences were calculated for continuous data and relative risks for dichotomous (two options) data, both with 95% confidence intervals. In one study, with three intervention groups receiving different doses of leflunomide, only the 10mg group was included.

Two reviewers independently extracted the data, with a third reviewer for arbitration if necessary.

Methods of synthesis
The data were combined using a fixed-effect meta-analysis to calculate pooled risk ratios and weighted mean differences with 95% confidence intervals. Heterogeneity was assessed using $X^2$ and $I^2$. A random-effects model was used if heterogeneity was detected ($X^2 \ p<0.1$) or high ($I^2>50%$).
Results of the review

Seven RCTs were included (2,861 participants, range 15 to 999). Jadad scores were five for two RCTs, four for three RCTs, three for one RCT, and two for one RCT. The reported randomisation was inadequate in three RCTs and one did not adequately describe withdrawals or dropouts. All RCTs were described as double-blind, but three scored only one out of two possible points for the adequacy of reported double-blinding. Follow-up ranged from 12 to 104 weeks.

Placebo: Using American College of Rheumatology criteria, leflunomide was significantly more effective than placebo, at follow-up of six months to one year, in achieving a clinical improvement of 20% (RR 1.98, 95% CI 1.62 to 2.40; three RCTs; $\Gamma^2=0$) or 50% (RR 3.14, 95% CI 1.70 to 5.81; two RCTs; $\Gamma^2=53$%). Leflunomide was superior to placebo for all other reported measures of effectiveness.

Methotrexate and Sulfasalazine: No significant difference was found between leflunomide and methotrexate in clinical improvement at most time points, nor did the two groups differ for most other reported measures of effectiveness (one to three RCTs for each outcome). There was significant heterogeneity for several of these analyses, with $\Gamma^2$ ranging from zero to 95%. In the only trial comparing leflunomide with sulfasalazine, at follow-up of two years leflunomide was significantly more effective in achieving a clinical improvement of 20% (RR 1.37, 95% CI 1.07 to 1.75) or 50% (RR 2.10, 95% CI 1.25 to 3.53).

Side-effects: Leflunomide was significantly more likely than placebo to be associated with withdrawal from the trial due to adverse events (RR 2.69, 95% CI 1.64 to 4.41; three RCTs; $\Gamma^2=0$). Adverse events that were significantly more frequent with leflunomide than with placebo were alopecia, elevation of liver enzymes, diarrhoea, and allergic reactions (one to three RCTs for each outcome). Leflunomide was significantly more likely than methotrexate to cause itching, diarrhoea, or alopecia (two to three RCTs for each outcome), but less likely to cause mouth ulceration (two RCTs) or elevation of liver enzymes (one RCT). Leflunomide was significantly more likely than sulfasalazine to cause back pain or diarrhoea (one RCT).

Authors' conclusions

Leflunomide, methotrexate, and sulfasalazine did not differ significantly in their effectiveness at treating rheumatoid arthritis, but leflunomide was more effective than placebo.

CRD commentary

The objectives and inclusion criteria were clear in most respects. The review objective stated that single drugs were considered, but heterogeneity was attributed to folic acid as a co-intervention in some trials. Relevant sources were searched, but the restrictions by language and publication status mean that some trials may have been missed. The risk of publication bias was discussed but there were too few trials to conduct a formal test. It was unclear whether appropriate steps were taken to minimise the risk of reviewer bias and error in the quality assessment. The use of the Jadad tool for quality assessment was questionable, as it does not address some important aspects of quality, such as allocation concealment and dropout rates.

A large number of effectiveness outcomes were reported and the review did not specify a primary outcome. There were multiple comparisons, which created an increased risk of significant findings by chance. These issues make the review findings difficult to interpret. Appropriate methods were used to combine the trials and to assess statistical heterogeneity, which was very high for some analyses and largely remained unexplained. The review was funded by the manufacturers of leflunomide.

The authors' conclusions did not include their findings on adverse effects and they might not be reliable, due to limitations of the review, including the small number of trials, failure to specify a primary outcome, and high heterogeneity in many analyses.

Implications of the review for practice and research

Practice: The authors stated that patients on leflunomide, methotrexate, or sulfasalazine required close monitoring for adverse reactions.

Research: They stated that the safety of leflunomide compared with placebo, methotrexate, or sulfasalazine should be assessed using clinical data rather than trial data. They referenced further suggestions in another report (see Other...
Publications of Related Interest).

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