Leflunomide: a new disease modifying drug for rheumatoid arthritis
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Authors' objectives
To undertake a rapid review of the effectiveness, cost and utility of leflunomide (LFM) for the treatment of rheumatoid arthritis (RA).

Searching
The authors searched MEDLINE, EMBASE, EconLit, HMIC, GEARs, Best Evidence 3, the National Research Register (NRR), the Cochrane Systematic Reviews Database, the Cochrane Controlled Trials Register and DARE. Search dates were post 1993 and the search terms were 'Leflunomide', 'Avara', 'HWA486', 'disease modifying anti-rheumatic agents', 'DMARD*', and 'rheumatoid arthritis', further refined by limiting the searches to 'systematic reviews', 'meta-analyses', 'RCTs' and articles relating to 'costs/economics'.

The authors also searched the bibliographies of related papers for additional relevant studies. The search was limited to English language publications. The authors used the Internet (Yahoo search engine) for general information and product information. The authors also had contact with the South and West Drug Information Centre, Hoechst Marion Roussel Ltd, four hospitals in the South East, South West, London and West Midlands Regions for additional information.

Study selection
Study designs of evaluations included in the review
Systematic reviews, meta-analyses or randomised controlled trials (RCTs). Included studies were RCTs with a study duration of 24 weeks.

Specific interventions included in the review
Disease modifying anti-rheumatic drugs (DMARDs). Interventions used leflunomide (LFM) compared with sulphasalazine (SSZ) and/or placebo. One study's dosage was 5, 10 or 25 mg daily following a loading dose of 50 mg for the 5 mg group and 100 mg for the 10 and 25 mg groups, while the second study's dosages were LFM 20 mg daily after a 3 day loading dose of 100 mg compared to SSZ 20 g daily after week 4, loading dose of 0.5 g, 1.0 g, and 1.5 g on weeks 1, 2, and 3.

Participants included in the review
People diagnosed with active rheumatoid arthritis based on American College of Rheumatology (ARC) criteria. In one study, the mean age of participants was 51 years, age range 20-76, 83% were female, and the mean length of time with RA was 8.3 years, ranging from 0.8 years to 37.8 years. In the other study, the mean age of participants was 58.3 years (LFM), 58.9 years (SSZ) and 58.8 years (placebo), 72% were female, and the mean length of time with RA was 7.6 years (LFM), 7.4 years (SSZ) and 5.7 years (placebo).

Outcomes assessed in the review
Efficacy and safety outcomes. Primary outcome measures were: tender joint count (TJC), swollen joint count (SJC), tender joint score (TJS), swollen joint score (SJS), and patient and physician overall assessment of RA activity.
Secondary outcome measures were: morning stiffness, grip strength, Stanford health assessment questionnaire (HAQ), patient pain score (visual analogue score), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). Efficacy was assessed every 4 weeks between baseline and week 24 (followed by 8 weeks of observation).

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies for inclusion. It is not stated whether they worked independently. Results were checked by a third reviewer. Disagreements were resolved through discussion.
Assessment of study quality
The authors do not report a method for assessing validity, although an assessment was done by two of the authors. There is some discussion, however, of the quality limitations of the included studies in the text. Two reviewers performed the quality assessment. It is not stated whether they worked independently. Results were checked by a third reviewer.

Data extraction
Two reviewers performed the data extraction. It is not stated whether they worked independently. Results were checked by a third reviewer.

Data were extracted for the categories of: study identification, year of publication and study design, intervention, subject characteristics, outcome measures, results and comments.

Methods of synthesis
How were the studies combined?
The authors state that due to time constraints a statistical meta-analysis was not performed in this review. The included studies are discussed in a narrative review.

How were differences between studies investigated?
The authors do not report a test for heterogeneity.

Results of the review
Two RCTs were included in the review with 860 participants. Two further trials published after the review was finalised are included in an appendix but not in the review analysis.

In the first study, the 25 mg/day and 10 mg/day leflunomide groups showed significant improvement in the primary and secondary outcome measures. Statistically significant differences for all four responder analyses were demonstrated by both the 10 mg/day and 25 mg/day leflunomide groups. The results of the study indicate that daily treatment of leflunomide (above 10 mg) reduces the symptoms of RA. The onset of action for the 10 mg/day and 25 mg/day leflunomide groups was quite rapid, with changes in efficacy outcomes occurring at four weeks after baseline. Twenty-three of patients withdrew from the study due to adverse events. Ten of these 18 events were serious, including one each for anaphylaxis (non-fatal allergic reaction), skin rash and cholecystitis, and five attributed to the progression of RA symptoms.

In the second study, the leflunomide group showed significant improvement in all clinical outcomes. The study suggests that leflunomide was significantly superior for the onset of action of sulphasalazine at four weeks for tender joint count (TJC), swollen joint count (SJC), patient and physicians overall assessment, pain intensity, Health Assessment Questionnaire (HAQ), rheumatoid factor (RF) and C-reactive protein (CRP) (p < 0.05). Most outcome measures showed a significant decrease for the leflunomide group at week four. The responder analyses and mean time/duration of sustained response yielded a similar improvement for both the leflunomide and sulphasalazine groups, as were results for the progression of radiological disease.

Cost information
Leflunomide and associated monitoring of side effects is likely to cost approximately £400 more than sulphasalazine and approximately £300 more than methotrexate per patient per year. The authors state that it is expected that the monitoring requirements for leflunomide will be similar to methotrexate. Details of the cost analysis and monitoring requirements are given in an appendix to this review.

The overall costs of leflunomide in comparison to sulphasalazine and methotrexate are sensitive to the costs associated with the monitoring of side effects. It is expected that, in time and with increased use of leflunomide by clinicians, more prescriptive guidelines relating to the monitoring of side effects may reduce the overall costs of the agent.
Authors' conclusions
The authors state that, of the two trials included in this review, only one directly evaluates the dose of leflunomide likely to be recommended in the UK. Evidence from that trial suggests that leflunomide is similar in efficacy to sulphasalazine, although it has a differential pattern of side effects and, possibly, a more rapid onset of efficacy for outcome measures. These may increase the likelihood of a patient continuing treatment with leflunomide.

CRD commentary
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be very thorough. The authors also included searches for unpublished and grey literature. The quality of the included studies was formally assessed but the method and results are not reported. The authors have reported how the articles were selected, and who performed the selection, and the validity assessment and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in a narrative review and there was no discussion of heterogeneity.

The authors state that one limitation of both included studies is that the treatments were given for only 6 months whereas guidelines recommend that trials of DMARDs should last at least one year.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

Research: The authors state that several topics should be considered for further research. First, there is a need to assess the long-term efficacy and safety of leflunomide particularly with regard to liver function, sustained control of RA symptoms and plasma metabolite levels, and specific attention to the assessment of patterns of adverse effects. Second, the effectiveness of leflunomide in the reduction of RA symptoms needs to be established through direct clinical comparison with existing DMARDs. Finally, future trials need to incorporate a generic quality-of-life (instrument in clinical trials for the estimation of costs per quality-adjusted life-year. This would assist decision-makers in determining the relative cost-effectiveness of leflunomide in comparison with existing pharmaceutical treatments for RA.

Bibliographic details

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Record Status
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.