Authors' objectives
To assess the effectiveness, safety and cost implications of leflunomide (LFM) treatment for rheumatoid arthritis (RA).

Searching

Additional information relating to LFM, DMARDs, the clinical treatment of RA and costs, or treatment and monitoring of DMARDs were provided by ten clinicians in the UK, USA and Belgium, and from four hospitals located in different health regions in the UK. Hoechst Marion Roussel, the manufacturers, were contacted for relevant published trials and information on potential administration and monitoring requirements for adverse effects.

A further search of the databases was performed in November 1999 to identify new publications on LFM; this was supplemented by information provided by Hoechst Marion Roussel relating to recent publications. The search was limited to English language publications.

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

Specific interventions included in the review
LFM administered orally compared to placebo or other disease-modifying anti-rheumatic drugs (DMARDs). The first study compared LFM (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) with placebo. The second study compared LFM (20 mg/day after a 3-day loading dose of 100 mg) with sulphasalazine (SSZ; 2.0 g daily after week 4, loading dose of 0.5, 1.0 and 1.5 g on weeks 1, 2 and 3, respectively) and placebo. The third study compared LFM (20 mg/day after a 3-day loading dose of 100 mg) with methotrexate (MTX; 7.5 to 15 mg weekly) and placebo.

Participants included in the review
People diagnosed with RA based on American College of Rheumatology (ACR) criteria. In one study, the mean age of the participants was 51 years (range: 20 - 76), 83% were female, and the mean length of time with RA was 8.3 years (range: 0.8 to 37.8). 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 were assessed. The primary outcome measures were: tender joint count, swollen joint count, tender joint score, swollen joint score, assessment of functioning, Health Assessment Questionnaire, Modified Health Assessment Questionnaire, pain (visual analogue score), erythrocyte sedimentation rate, C-reactive protein, and radiological progression and treatment adverse events. Efficacy was assessed every 4 weeks between baseline and week 24, and was followed by 8 weeks of observation.
How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The studies included in the report were critically appraised using guidelines for assessing the quality of RCTs (see Other Publications of Related Interest nos. 1-2). There was also some discussion of the quality limitations of the included studies in the text. The critical appraisals and full text of the report can be found on the Development Evaluation Committee (DEC) website. Two reviewers performed the quality assessment. It was not stated whether they worked independently. The results were checked by a third reviewer.

Data extraction
Two reviewers performed the data extraction. It was not stated whether they worked independently. The results were checked by a third reviewer. Data were extracted for the categories of study identification and year of publication, participants, design and duration, intervention, and summary of treatment groups. The data extracted included information on the efficacy and safety of LFM.

In addition, statistical analyses of radiographs relating to the effects of treatment on disease progression were extracted, and safety data relating to the frequency and type of adverse events were assessed. Information on the cost of treatment and monitoring for side-effects were obtained from Hoechst Marion Roussel and four hospitals in separate health regions of the UK.

Methods of synthesis
How were the studies combined?
The included studies were discussed in a narrative review.

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

Results of the review
Three double-blinded RCTs were included in the review with 1,242 participants. Two of the studies were reported in a previous systematic review (see Other Publications of Related Interest no.3).

Quality: the trials were generally well designed and executed. The population, inclusion and exclusion criteria, intervention and outcomes were clearly specified. Duration of RA, concomitant medications, and demographic and disease characteristics of patients were similar between treatment groups. Randomisation and concealment were of a high standard in 2 of the 3 studies, and intention to treat analysis was used in each study.

LFM therapy was demonstrated to be significantly superior to placebo in relation to the efficacy outcome measures, e.g., tender joint count, swollen joint count, patient and physician global assessment, pain, erythrocyte sedimentation rate and C-reactive protein. In addition, it slowed the radiological progression of RA in three studies.

ACR responder criteria, treatment success, sustained response and duration of sustained response were also significantly superior to placebo.

Quality of life measures were found to be significantly greater than placebo groups.

LFM treatment was comparable to SSZ and MTX with respect to efficacy, radiological progression and quality of life measures. LFM was found to have a somewhat faster onset of action and provide a slightly longer duration of sustained response.

The percentage of study withdrawals due to lack of efficacy was lower for the LFM groups than for either SSZ or MTX.
The most common adverse effects leading to withdrawal from LFM treatment were gastrointestinal symptoms (rash and pruritus), alopecia, dyspepsia, hypertension, and elevated transaminase levels. Weight loss and dizziness have also been reported for LFM treatment.

**Cost information**
The approximate costs varied from £600 for SSZ to £730 for MTX and £990 for LFM. Estimated costs were presented since the monitoring requirements of LFM are yet to be clinically established. A cost-utility analysis of LFM in relation to existing DMARD treatments was not undertaken.

**Authors' conclusions**
The authors state that, despite the small number of published articles relating to LFM treatment, the evidence suggests that LFM is significantly superior to placebo and similar in efficacy to both SSZ and MTX, although with a differential pattern of side-effects. LFM therapy costs about 1,000 per annum, approximately 400 more than SSZ and 300 more than MTX.

**CRD commentary**
The authors clearly stated the research question and inclusion and exclusion criteria. The literature search appeared to be very thorough, and included searches for unpublished and grey literature. The quality of the included studies was formally assessed, and the method and results were discussed. The authors reported how the articles were selected, and who performed the selection, the validity assessment and the data extraction.

The data extraction was reported in tables and discussed in the text of the review. The studies were combined in a narrative review with some discussion of heterogeneity.

The authors state that one limitation of two of the included studies was that the treatments were given for only 6 months, whereas guidelines recommend that trials of DMARDs should last at least 1 year. The authors' conclusions appear to follow from their results, although the authors do state that further research is needed.

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

**Research:** The authors state that further research is needed to assess the long-term efficacy and safety of LFM, particularly with regard to liver function, sustained control of RA symptoms and plasma metabolite levels, and pay specific attention to the assessment of patterns of adverse effects. Secondly, the effectiveness of LFM 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 LFM in comparison with existing pharmaceutical treatments for RA.

**Bibliographic details**

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10971781

**Other publications of related interest**
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Subject indexing assigned by NLM

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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.