Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review

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CRD summary
This review assessed the efficacy of folic acid supplementation in patients receiving methotrexate for inflammatory diseases, concluding that was an effective measure to reduce hepatic side-effects associated with methotrexate treatment. However, given the small number of included studies of uncertain quality, the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the efficacy of folic acid supplementation in patients receiving methotrexate treatment for inflammatory diseases.

Searching
MEDLINE, EMBASE, Cochrane Skin Group Specialised Trials Register and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1990 to 2007. Search terms were reported. Reference lists of retrieved articles were manually searched to identify additional studies.

Study selection
Double-blind randomised controlled trials (RCTs) and clinical controlled trials in patients receiving methotrexate for rheumatoid arthritis or psoriasis (with or without arthritis), that compared folic or folinic acid supplementation with placebo, were eligible for inclusion. In patients treated with either oral or parenteral methotrexate receiving a dose of at least 7.5mg per week, the intervention had to comprise folic or folinic acid for at least 12 weeks duration during the double-blind phase.

Inclusion criteria for outcomes were not explicitly stated; the analysis was based on various subgroups of side-effect profiles: gastrointestinal; mucocutaneous; haematological; and hepatic.

In the included trials doses of folic acid ranged from 1mg to 5mg per day (five to seven days per week) and folinic acid from 1mg to 5mg per week; duration of follow-up ranged from eight weeks to 30 months.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed study quality using published criteria, but the results were not reported in the review.

Data extraction
Two reviewers independently extracted or estimated data on the side-effects of supplementation. These were calculated as an absolute risk reduction (ARR) and standard error for each study. Authors of included trials were contacted to provide missing data where necessary.

Methods of synthesis
The trials were pooled in a meta-analysis using a random-effects model to produce combined estimates of absolute risk reduction with 95% confidence intervals (CIs).

Results of the review
A total of six RCTs were included in the review (n=648 patients, range 16 to 411).
Patients receiving methotrexate with folic or folinic acid supplementation had significantly reduced risk of liver enzyme elevation (ARR -0.358, 95% CI -0.467 to -0.248), with the effect similar between patients treated with folic acid (ARR -0.309, 95% CI -0.512 to -0.105) and folinic acid supplementation (ARR -0.389, 95% CI -0.568 to -0.209). No difference was apparent for mucocutaneous and gastrointestinal side-effects. There was insufficient data to assess haematological side-effects.

**Authors' conclusions**

Low-dose supplementation with folic acid reduced hepatic side-effects associated with methotrexate treatment.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria for study design, patients and interventions, but criteria for outcomes were not explicitly stated. The search included a number of appropriate databases, but it was unclear whether unpublished studies were sought; some studies may have been missed, with publication bias a possibility. All stages of the review process were undertaken in duplicate, reducing the potential for error and bias. Seemingly appropriate criteria were used to assess the quality of the included studies, but the criteria and the results were not reported in the review. Suitable methods appear to have been used for the meta-analysis, but statistical heterogeneity was not reported, so it was unclear whether these were entirely appropriate. Given the small number of included studies of uncertain quality, the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors recommend that low-dose folic supplementation can be recommended in clinical practice.

**Research:** The authors did not state any implications for research.

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