Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials
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Authors' objectives
To determine whether methotrexate is an effective steroid-sparing agent for patients with severe asthma.

Searching
MEDLINE (from 1966 to January 1998), EMBASE (from 1980 to 1997), CINAHL (from 1982 to 1997), Biological Abstracts (from 1990 to 1997), and Current Contents (from 1996 to January 1998) were searched for publications in any language. The search terms used were 'asthma', 'bronchial hyperactivity' and 'methotrexate'. Additional published and unpublished material was identified by manually searching the references of retrieved articles, and by contacting sponsors in the pharmaceutical company and investigators.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled, double-blind trials were included. Parallel and crossover studies were also accepted.

Specific interventions included in the review
Low-dose methotrexate (7.5 to 30 mg, once weekly) versus placebo.

Participants included in the review
The participants were adults or children with asthma who were dependent on daily oral corticosteroid therapy (at least 5 mg/day of prednisone or equivalent). Asthma was defined as a reversible airflow obstruction with at least a 15% improvement in forced expiratory volume in 1 second (FEV1) either spontaneously or after bronchodilator therapy.

Outcomes assessed in the review
The outcomes assessed were the reduction in oral corticosteroid use, the change in FEV1, and side-effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed and selected the trials for inclusion.

Assessment of study quality
Study quality was assessed using the validated scale of Jadad et al. (see Other Publications of Related Interest no.1). Two reviewers independently assessed the trials and any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data from the identified trials on the trial design, patients' characteristics, dosages, treatment period, FEV1 and daily oral steroid dose at baseline and at the end of the trial period.

Methods of synthesis
How were the studies combined?
The results of the individual trials were combined using a weighted average, with weights equal to the inverse of the variance.

How were differences between studies investigated?
Heterogeneity across trials was tested using Cochran's Q-test. Subgroup and sensitivity analyses were also conducted.
Results of the review
Twelve randomised controlled trials (250 patients) were included.

Compared with placebo, the use of methotrexate was associated with a pooled 6.0% improvement in FEV1 (95% confidence interval, CI: 1.0, 11) and an 18.2% reduction in oral steroid use (95% CI: 11.7, 24.7). This corresponded to a 3.3 mg/day greater reduction in oral steroid use for patients taking methotrexate than for those taking placebo (95% CI: 2.1, 4.4). Gastrointestinal complications and transient increases in liver enzymes were more common in patients randomised to methotrexate. Three potentially life-threatening side-effects occurred in 159 patients randomised to methotrexate, whereas there were none in the placebo group.

Cost information
The annual cost of methotrexate (15 mg/week) in the Province of Ontario is $227.76 versus $6.72 for prednisone (5 mg/day). Methotrexate also requires monthly blood work, thus adding to the costs and inconvenience for the patient.

Authors’ conclusions
Methotrexate allowed a modest reduction in oral corticosteroid use when compared with patients receiving placebo. The benefit was relatively small and should be balanced against the potential for side-effects associated with the use of methotrexate.

CRD commentary
This review was methodologically rigorous and the literature search was comprehensive. The inclusion criteria were clearly described and study validity was assessed. Details of the included studies were presented and the identified evidence were appropriately combined. The authors considered the problem of potential publication bias. A funnel plot did not find any association between the sample size and treatment effect. The review’s conclusions were appropriate, based on the research evidence identified.

Implications of the review for practice and research
The authors asked whether an average 3.3 mg/day reduction in oral corticosteroid use will help to prevent steroid-related adverse effects. The benefits of methotrexate must be weighed against the potential complications of therapy, such as increased gastrointestinal and hepatic side-effects, as well as the lack of clinical predictors for response. Therefore, it does not seem appropriate to recommend the use of methotrexate, except for those asthmatics who are already experiencing substantial side-effects from corticosteroid therapy.

Bibliographic details

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Other publications of related interest

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