Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials

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Our objective was to determine whether methotrexate is an effective steroid-sparing agent for patients with severe asthma. Published reports of controlled trials assessing the use of methotrexate in asthma were identified by a search of the MEDLINE, EMBASE, CINAHL, Biological Abstracts on CD, and Current Contents databases. Bibliographies from identified studies and from review articles were manually searched. Published and unpublished reports in any language were identified and assessed for inclusion in the meta-analysis. We selected randomized, double-blind, placebo controlled trials in which low dose methotrexate was administered to corticosteroid-dependent asthmatics, and oral steroids were subsequently tapered according to the patients' clinical status.

Data were extracted independently by two reviewers. For all eligible trials, the mean reduction in oral corticosteroid dose, the mean change in FEV₁, and the standard deviations, were calculated for the treatment and control groups. Data concerning side-effects of therapy were also extracted. Data from 12 studies, reporting on a total of 250 patients, were pooled using a weighted average method, with weights proportional to the inverse of the variance of the treatment effect. Compared to placebo, the use of methotrexate was associated with a pooled 6.0% improvement in FEV₁ (95% 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⁻¹ greater reduction in oral steroid use for patients taking methotrexate than for those taking placebo (95% CI, 2.1-4.4 mg day⁻¹). Gastrointestinal complications and transient increases in liver enzymes were more common in patients randomized to methotrexate. Three potentially life-threatening side-effects (two pneumonias and one liver dysfunction) occurred in 159 patients randomized to methotrexate vs. none in those patients on placebo. It was concluded that methotrexate allowed a modest reduction in oral corticosteroid compared to patients receiving placebo. The benefit is relatively small, however, and should be balanced against the potential for side-effects associated with the use of methotrexate.

Introduction

Asthma is an inflammatory disorder of the airways characterized by variable airflow obstruction. For most asthmatics, airway inflammation and asthma symptoms are adequately controlled with inhaled corticosteroids and bronchodilators, medications which are associated with minimal systemic side-effects. However, a subgroup of patients with severe asthma do not achieve adequate control with inhaled medications, and instead require prolonged courses of oral corticosteroids to control their disease. These corticosteroid-dependent patients are often subject to debilitating complications associated with the long-term use of systemic prednisone therapy (1).

The need for alternatives to long-term steroid therapy has prompted investigators to search for other agents which might help to control severe asthma and enable patients to reduce their reliance on systemic steroids (2). In 1986 a case report was published, describing a steroid-dependent asthmatic who was weaned off oral steroids after methotrexate was coincidently prescribed for psoriasis (3). Since this initial case report, numerous studies have been published in the world literature evaluating the use of methotrexate in steroid-dependent asthma (4-23). Many of the published trials have been small and lacking power, and different studies have often yielded conflicting results. Most narrative reviews of past clinical trials have provided equivocal conclusions as to whether the drug is effective and safe in this population (24,25).

We undertook a quantitative analysis of all randomized, placebo controlled trials in which methotrexate was used to treat steroid-dependent asthma, in order to determine methotrexate's efficacy, and to estimate the magnitude of its corticosteroid sparing effect in patients with severe asthma.
Methods

We attempted to identify and include all randomized, placebo-controlled trials assessing the effects of methotrexate in steroid-dependent asthma. Since the primary outcome variable of all the trials assessed was a reduction in oral corticosteroid use, and since reduction in steroid use was dependent on the investigators who controlled the steroid tapering process, only those trials which were placebo-controlled and double-blinded were considered free of potential bias, and therefore only these trials were included in the meta-analysis.

LITERATURE SEARCH

We identified potential trials published in any language by searching MEDLINE (1966–January 1998), EMBASE (1980–1997), CINAHL (Cumulated Index to Nursing and Allied Health 1982–1997), Biological Abstracts on CD (1990–1997), and Current Contents (1996–January 1998). For this search we used the following items: (exp asthma, asthma tw., bronchial hyperreactivity tw.) and (exp methotrexate, methotrexate tw, methotrexate rn). No restrictions for the language of publication or the study design were made.

We obtained a list of published and unpublished trials from the pharmaceutical company which manufactures methotrexate in Canada, Wyeth-Ayerst. The reference lists of all relevant trials and review articles obtained via the previous searching strategies were manually searched. In addition, we contacted investigators of the studies included in the meta-analysis in order to locate any unpublished material, and to obtain any incomplete data that was missing from the published papers.

Two reviewers (S.D.A. and R.E.D.), independently assessed and selected randomized controlled trials for inclusion in the meta-analysis. To be included in the meta-analysis the trial had to satisfy the following three inclusion criteria:

1. **Target population**—We accepted trials which studied adults or children with documented asthma (defined as reversible airflow obstruction with at least a 15% improvement in forced expiratory volume in 1 s (FEV₁) either spontaneously or after bronchodilator therapy), who were dependent on daily oral corticosteroid therapy (at least 5 mg day⁻¹ of prednisone or equivalent), before entry into the trial.

2. **Intervention**—The treatment protocols consisted of low-dose methotrexate (7.5–30 mg) administered once weekly, orally or intramuscularly.

3. **Study design**—The studies had to be randomized, placebo-controlled, double-blind trials for inclusion into the meta-analysis. Parallel and cross-over studies were accepted. In order to be eligible for the meta-analysis, the patients taking placebo or methotrexate had to have been placed on identical steroid-tapering regimens, and the reduction in oral steroid requirements of each group had to have been reported.

ASSESSMENT OF TRIAL QUALITY

Those studies meeting the inclusion criteria were then assessed by using a validated three-item scale (26) designed to measure trial quality. The scale assessed the quality of randomization, double-blinding, and inclusion of data for dropouts and withdrawals. The scale scores range from 0 to 5, with a score of 5 indicating superior quality of reporting. In cases where there was disagreement between the two reviewers, a consensus quality score was arrived at.

DATA COLLECTION

Two reviewers independently abstracted data from identified studies regarding the trial design, patient characteristics, dosages and treatment periods. The mean daily oral steroid dose at baseline for the treatment and control groups and the standard deviations or standard error for steroid doses were collected. These were compared to the mean daily steroid dose used by the treatment and control groups at the end of the trial period. Similar data was collected for FEV₁. In cases where data was available, results for individual patient steroid use within each study was recorded as well.

STATISTICAL ANALYSIS

To standardize the data and determine the relative reduction in oral steroid requirement for each group, the percentage change from baseline in mean daily oral steroid dose for each group was calculated as $100 \times \frac{\text{final value} - \text{baseline value}}{\text{baseline value}}$. For each trial, the net steroid-sparing effect of methotrexate vs placebo was calculated as the difference in the percent change in oral steroid use from baseline in the methotrexate group minus the difference observed in the placebo group. Similar calculations were used to assess the percentage change in FEV₁.

Data on the net steroid-sparing effect of the intervention vs placebo was pooled using weighted averages, with weights equal to the inverse of the variance of the observed effect (27) (see Appendix). This allowed us to calculate an overall weighted mean difference as an estimate of the effectiveness of methotrexate. For studies which did not report the variance measures needed to calculate weights for the pooled analysis, we used a sample-size based weighted average of the reported variances.

Individual patient data was collected when it was available, from publications or correspondence with authors, to determine the proportion of patients in the treatment and control groups who achieved a ≥20% reduction in oral steroid use. A pooled odds ratio was estimated from this data using the DerSimonian and Laird random-effects model (28). Between-trial heterogeneity was evaluated using Cochran’s Q-test. Inter-reviewer agreement in the selection of relevant studies and the assessment of methodological quality was calculated using the weighted kappa statistic.

We identified, a priori, three potential sources of heterogeneity among trial findings. We postulated that the design of the trial might affect its findings, specifically that cross-over trials might show a more significant treatment effect.
Table 1. Randomized, placebo-controlled studies of methotrexate in asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of randomized patients</th>
<th>No. of patients completing study</th>
<th>Study design</th>
<th>Mean entry prednisone dose mg day$^{-1}$ (± SD)</th>
<th>MTX dosage mg week$^{-1}$*</th>
<th>Duration of treatment with MTX (weeks)</th>
<th>Trial quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart, 1994 (4)</td>
<td>24</td>
<td>21</td>
<td>Cross-over</td>
<td>21.0 ± 7.9</td>
<td>15</td>
<td>12</td>
<td>4/5</td>
</tr>
<tr>
<td>Erzurum, 1991 (5)</td>
<td>19</td>
<td>17</td>
<td>Parallel</td>
<td>19.7 ± 4.6</td>
<td>15 (IM)</td>
<td>13</td>
<td>4/5</td>
</tr>
<tr>
<td>Mullarkey, 1988 (6)</td>
<td>14</td>
<td>13</td>
<td>Cross-over</td>
<td>24.8 ± 15.3</td>
<td>15</td>
<td>12</td>
<td>4/5</td>
</tr>
<tr>
<td>Dyer, 1991 (7)</td>
<td>12</td>
<td>10</td>
<td>Cross-over</td>
<td>13.1 ± 5.3</td>
<td>15</td>
<td>12</td>
<td>4/5</td>
</tr>
<tr>
<td>Hedman, 1996 (14)</td>
<td>13</td>
<td>12</td>
<td>Cross-over</td>
<td>10.9 ± 8.4</td>
<td>15</td>
<td>12</td>
<td>4/5</td>
</tr>
<tr>
<td>Coffey, 1994 (15)</td>
<td>14</td>
<td>11</td>
<td>Cross-over</td>
<td>20.8 ± 15.6</td>
<td>15</td>
<td>12</td>
<td>3/5</td>
</tr>
<tr>
<td>Ogirala, 1995 (8)‡</td>
<td>15</td>
<td>13</td>
<td>Parallel</td>
<td>6.6 ± 7.7</td>
<td>15</td>
<td>26</td>
<td>4/5</td>
</tr>
<tr>
<td>Shiner, 1990 (9)</td>
<td>69</td>
<td>60</td>
<td>Parallel</td>
<td>14.0 ± 5.5</td>
<td>15</td>
<td>24</td>
<td>4/5</td>
</tr>
<tr>
<td>Taylor, 1993 (10)</td>
<td>69</td>
<td>60</td>
<td>Parallel</td>
<td>14.0 ± 5.5</td>
<td>15</td>
<td>24</td>
<td>4/5</td>
</tr>
<tr>
<td>Kanzow, 1995 (11)</td>
<td>24</td>
<td>21</td>
<td>Parallel</td>
<td>27.8 ± 11.5</td>
<td>15</td>
<td>16</td>
<td>4/5</td>
</tr>
<tr>
<td>Trigg, 1993 (12)</td>
<td>24</td>
<td>21</td>
<td>Parallel</td>
<td>27.8 ± 11.5</td>
<td>15</td>
<td>16</td>
<td>4/5</td>
</tr>
<tr>
<td>Caldwell, 1992 (13)‡</td>
<td>17</td>
<td>12</td>
<td>Cross-over</td>
<td>17.7 ± 8.4</td>
<td>30</td>
<td>12</td>
<td>4/5</td>
</tr>
</tbody>
</table>

*MTX dose given orally unless otherwise indicated.
†Study included a third triamcinolone arm, data from this arm was not included in the meta-analysis.
‡Unpublished study.

than parallel studies. We also postulated that those trials which attempted a pretrial steroid tapering phase before randomizing patients into the trial might show a different magnitude of treatment effect, since these patients would be entering into the trial while already receiving the lowest steroid dose needed to control their asthma. Finally, we sought to do a subgroup analysis to determine whether trials which enrolled patients taking higher doses of prednisone (≥ 20 mg day$^{-1}$), showed similar results to those trials in which patient's baseline corticosteroid doses were lower.

**Results**

One hundred and thirty-five potentially relevant studies were identified and screened for retrieval. Ninety-three studies were excluded as not being clinical trials. Forty-one studies were retrieved for more detailed evaluation. Twenty of the 41 studies retrieved were excluded since they were review articles, or abstracts of studies later published as full papers. The 21 remaining studies, 20 in English, one in French, were independently reviewed by two reviewers. Nine studies were rejected by both reviewers since they were non-randomized, uncontrolled studies (3,16-23). Twelve studies were independently selected by both reviewers as being randomized, placebo-controlled trials suitable for inclusion in the meta-analyses (4-15). One of these studies was published only in abstract form, however, a copy of the unpublished manuscript was obtained directly from the investigators (13). The two reviewers independently agreed on the studies to be included and excluded in 100% of cases.

Table 1 contains summary information concerning the 12 included trials and an assessment of each trial's quality score. There was agreement between the two reviewer’s quality scores for 11/12 trials, with the weighted kappa statistic being 0.92.

Of 12 trials, 11 reported FEV$_1$ measurements; one trial (9), measured peak expiratory flows rather than FEV$_1$, and this trial was not included in the calculation of the weighted mean difference. The effect of methotrexate vs placebo on FEV$_1$ measurements is shown in Fig. 1. Compared to placebo, the use of methotrexate was associated with a pooled 6.0% improvement in FEV$_1$ over the course of the trial (95% CI, 1.0–11.0%).

All 12 trials analysed reduction in oral steroid dose as a primary endpoint. Figure 2 displays the data concerning steroid-sparing effects of methotrexate vs placebo for each trial and the pooled estimate across all trials. Compared to placebo, methotrexate was associated with an 18.2%
The pooled estimate for parallel studies revealed a 19.6% reduction in oral steroid use (95% CI, 9.6-29.6%) and was similar to the overall pooled estimate for all the trials (Fig. 3).

Two subgroups analyses were performed. Studies which employed a pretrial steroid tapering phase were analysed separately. Pooled results from the five trials which used this strategy showed a 24.6% reduction in oral steroid use (95% CI, 15.6-33.6%) and was similar to the overall pooled estimate for all the trials (Fig. 3).

For six studies in which individual patient data were available we determined the likelihood of an individual patient achieving a 20% or greater reduction in oral steroid dose. The pooled odds ratio was 2.36 for methotrexate compared to placebo (95% CI, 1.25-4.48%).

**WITHDRAWALS**

The 12 trials enrolled 250 patients of which there were 15 patient withdrawals from the placebo arm and 14 withdrawals from the methotrexate arm. Eleven of the 14 methotrexate-arm withdrawals occurred due to side effects of the therapy (five had gastrointestinal intolerance, four developed liver function test abnormalities, two developed pneumonia). Two withdrawals from the methotrexate arm, and three from the placebo arm, were due to severe uncontrolled asthma.

**ADVERSE EFFECTS ASSOCIATED WITH METHOTREXATE**

Eleven of the 12 trials reported on adverse effects. Minor gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhoea) occurred more often in those patients taking methotrexate (45%) vs placebo (31%) ($\chi^2=6.79$, $P=0.01$). Similarly, increases in liver function tests occurred in more patients on methotrexate (21.4%) than in those on placebo (1.3%) ($\chi^2=30.4$, $P<0.001$). There were no significant differences in rates of infection or stomatitis, which occurred infrequently in both groups. Bone marrow suppression and methotrexate pneumonitis were not observed.

Three potentially life-threatening side-effects (two pneumonias and one case of liver dysfunction) occurred in 159 patients randomized to methotrexate vs none in those on placebo. Both cases of pneumonia occurred in patients who were enrolled in the study which used a higher dose of methotrexate, 30 mg week$^{-1}$ instead of 15 mg week$^{-1}$ (12). There were no deaths reported in any of the study patients.

**Discussion**

Compared to placebo, the addition of methotrexate allowed an 18% (3.3 mg of prednisone day$^{-1}$) reduction in patients' use of oral corticosteroids.

Trials which enrolled patients taking higher doses of oral steroids (≥20 mg day$^{-1}$ of prednisone) did not show a greater steroid-sparing effect of methotrexate than those trials with patients on lower baseline doses of steroid. This finding is disappointing, since patients on high doses of oral corticosteroids are most likely to develop steroid-induced adverse effects, and they represent the patient population who would most benefit from an effective steroid-sparing medication.

Seven of the 12 trials included in this meta-analysis (4,5,7-9,13,15) were able to achieve a ≥15% reduction in the oral steroid requirements of placebo-treated patients. The largest reported placebo effect was a dose reduction of 39-6% (5). This suggests that intensive follow-up and monitoring of these patients improved asthma control, or that some of the patients entering into the trials were on more...
oral steroid than was actually needed to control their asthma.

It is also somewhat disturbing that some patients enrolled in these trials had not been receiving high-dose inhaled steroids when they were enrolled into these steroid-sparing trials. Most of the trials only included patients if they were taking at least 800 μg day$^{-1}$ of beclomethasone or its equivalent (7–12,14,15), however, several of the trials (4,5,13) simply required that the patient had undergone ‘a previous adequate trial of inhaled steroid’. Some patients in these trials were therefore not receiving inhaled steroids at all at trial entry. The implication of this is that some of these patients may not have been oral steroid dependent if they had been on high-dose inhaled steroids and should therefore not have been entered into a steroid-sparing trial.

The steroid-sparing effect of methotrexate was accomplished without deterioration in the patient’s status, as evidenced by a pooled 6% improvement in FEV$_1$ for those on methotrexate vs those on placebo. All the trials included in this meta-analysis progressively tapered the study participant’s oral steroid dose according to the status of their asthma. Therefore it is not surprising that the FEV$_1$ was similar between the methotrexate and placebo groups at the end of the trials.

Minor gastrointestinal complications and transient increases in liver enzymes were more common in patients randomized to methotrexate. The two cases of pneumonitis occurred in patients enrolled in a study which caused a relatively high dose of methotrexate, 30 mg week$^{-1}$, rather than the standard dose of 15 mg week$^{-1}$ used in the other 11 studies. Although no deaths were reported during the double-blind study period, one study reported a death from Pneumocystis carinii pneumonia in a patient who was still taking methotrexate and prednisone several months after the study had ended (5). Similar sporadic reports exist in the literature of deaths of patients with asthma who were taking methotrexate and developed fatal methotrexate pneumonitis or infections (29–32).

Meta-analysis is a powerful statistical tool for pooling data from several sources. By synthesizing available scientific evidence, a meta-analysis can provide empirical answers to scientific research questions. However, one potential weakness of any meta-analysis is publication bias.

Theoretically, for our meta-analysis, publication bias could have led to an overestimation of the steroid-sparing effects of methotrexate, because reports of trials with negative results may have been less likely to be published. However, six of the 12 trials included in this analysis reported negative results – either a CI that included 1 or a $P$ value greater than 0.02. Furthermore, our literature search identified only one abstract that was not subsequently published as a full article, and this unpublished article was included in the meta-analysis. A funnel plot of the effect size of the studies plotted against sample size was constructed to assess for publication bias (Fig. 4). There was no evidence for publication bias: the plot reveals a wide dispersion of results among studies of small sample size and a narrower range of study results for larger studies.

Although this meta-analysis indicates that methotrexate allows a reduction in oral steroid use that is statistically significant, it is unclear whether the magnitude of the observed steroid-sparing effect of methotrexate is clinically significant. The mean baseline dose of prednisone for all the patients entering into the 12 trials was 17.9 mg day$^{-1}$; adding methotrexate allowed an average 3.3 mg day$^{-1}$ reduction in patients’ steroid dose over placebo. If we assume that 17.9 mg day$^{-1}$ of prednisone achieves asthma control equivalent to 14.6 mg day$^{-1}$ of prednisone plus 15 mg week$^{-1}$ of methotrexate, then choosing between these two treatment options depends on costs, convenience, and adverse effects.

The actual drug acquisition costs for methotrexate are higher than for prednisone. The annual cost, in the Province of Ontario, of 15 mg week$^{-1}$ of methotrexate is $227.76 vs $56.72 for 5 mg day$^{-1}$ of prednisone. Methotrexate also requires monthly blood work, thus adding to costs and inconvenience for the patient. Patients on methotrexate experience significantly more minor gastrointestinal complaints and liver enzyme changes, and these adverse effects can be expected to further increase medical costs and patient inconvenience. Finally, it is unclear whether an average 3.3 mg day$^{-1}$ reduction in oral corticosteroid use will help to prevent steroid-related adverse effects. For instance, studies of glucocorticoid-induced osteoporosis have shown that significant bone loss occurs even in patients taking less than 10 mg day$^{-1}$ of prednisone when compared to controls (33), and it is not currently known whether there is a threshold dose of glucocorticoid below which bone loss does not occur (34). The benefits of an 18% steroid-reducing effect of methotrexate are therefore unclear, since it is not possible to determine a priori in which patients this degree of steroid dose reduction can be expected to significantly retard bone loss. The issue is further complicated by recent reports which suggest that methotrexate itself can cause osteopathy and osteoblast inhibition, even at low doses (35,36).

Shortly after completion of our meta-analysis, a similar meta-analysis examining the effects of methotrexate in steroid-dependent asthma was published by Marin (37). This meta-analysis found that methotrexate allowed a 23.7% (4.3 mg day$^{-1}$) reduction in prednisone dose, and
the author concluded that ‘low-dose methotrexate has a significant steroid-sparing effect in steroid-dependent asthmatic patients’.

While results of Marin’s meta-analysis are somewhat similar to ours, we feel that our meta-analysis is a more rigorous study. We contacted authors of the original studies to retrieve additional data, and we obtained results from an additional unpublished paper which was not included in Marin’s analysis. We had two different reviewers select studies and abstract data from each study so as to improve the reliability and validity of our findings. We also did a meta-analysis of side-effects, something not done in Marin’s study. Based on the considerable side-effects in the methotrexate group documented in our meta-analysis, we were able to conclude that the very modest steroid-sparing benefits of methotrexate do not seem to outweigh its disadvantages.

Our meta-analysis included an additional unpublished, negative study not analysed in Marin’s paper, and our estimate of the overall steroid sparing effect of methotrexate is therefore less than that found by Marin (3.3 mg prednisone spared day^{-1} vs 4.3 mg prednisone day^{-1} found in the Marin study). It is however, reassuring that the two results are somewhat similar, and certainly not discordant. This adds to the external validity of the results of both studies, since two independent meta-analyses were able to reach similar statistical results.

In summary, we estimate that treating steroid-dependent asthmatics with low-dose methotrexate allows for a mean 18% greater reduction in oral steroid requirements than placebo. Although methotrexate appears to have modest steroid-sparing effects, in absolute terms adding methotrexate only allowed a mean decrease in oral steroid dose of 3.3 mg day^{-1} greater than placebo. Furthermore, the benefits of methotrexate must be weighed against the potential complications of therapy, such as increased GI and hepatic side-effects, as well as the lack of clinical predictors for response. Given these results, 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.

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References


**Appendix**

Let $T_i$ denote the estimate of the treatment effect in trial $i$, $T_i = D_{Ti} - D_{Ci}$, where $D_{Ti}$ and $D_{Ci}$ are the average percent changes in oral steroid dose between baseline and follow-up in the treatment and control groups, respectively. Let $\delta_{Ti}^2$ and $\delta_{Ci}^2$ be the variance of $D_{Ti}$ and $D_{Ci}$, respectively. The variance of any average percent change (i.e. either $\delta_{Ti}^2$ or $\delta_{Ci}^2$), was derived from the variances of the absolute mean prednisone doses at baseline and end of treatment. This variance calculation involved the following steps: (1) the percent change was converted to log-scale so that the variance calculation of the ratio of two random variables involved only the addition of the transformed variables. (2) Variance of a log-transformed variable was derived using the delta method and (3) a correlation of 0.8 was assumed for prednisone doses at baseline and end of treatment.

An inverse-variance weighted estimate was used to combine the treatment effect $T_i$ across $i$ studies. The weighted estimate of the pooled treatment effect is

$$\frac{\sum (T_i/V_i)}{\sum (1/V_i)}$$

and the standard error of the pooled treatment effect is

$$\frac{1}{\sum (1/V_i)^{\frac{1}{2}}}$$