

Short communications

Methotrexate in steroid-dependent asthma: long-term results

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Treatment of 21 steroid-dependent asthmatic patients with methotrexate (MTX) 15 mg/week was prospectively evaluated for a mean of 14.7 (SD 3.7) months. Before MTX, therapy consisted of a mean prednisone dose of 16.6 (SD 9.2) mg, in addition to inhaled beclomethasone/budesonide (mean daily dose 1157 (SD 330) µg) and bronchodilators. Thirteen patients were weaned from all regular systemic steroid therapy, a 50% or more reduction was achieved in four patients, and a less than 50% reduction in four patients. Abnormal liver function tests were noted in six of the 21 patients; this resolved despite continuation of MTX in five. In one patient, MTX was stopped because of symptoms as well as a fivefold rise in serum transaminases, and a speedy resolution was noted. Gastrointestinal side-effects were reported in six patients but were resolved in five with intramuscular MTX. There were no hematologic or pulmonary complications. We conclude that MTX appears to be both safe and efficacious as a steroid-sparing agent in most steroid-dependent asthmatic patients when taken over a long period.

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Most (5, 10, 13), though not all (6) short-term studies have demonstrated the efficacy of MTX as a systemic, steroid-sparing agent in patients with steroid-dependent asthma. Potential long-term toxicity of MTX treatment in the asthmatic population remains a worry, as it may be invalid to extrapolate from the experience in psoriasis or rheumatoid arthritis. In addition, efficacy may decrease when treatment is maintained for a longer period of time (7). To date, there has been only one published report of MTX treatment in asthma for more than 24 weeks (11).

Patients and methods

All patients who were aged 20–75 years were considered for inclusion. All patients met the updated American Thoracic Society criteria for asthma (2). Steroid dependence was defined as requirement of treatment for at least 1 year with the equivalent of 7.5 mg or more prednisone daily, in addition to at least 800 µg inhaled beclomethasone/budesonide and regular bronchodilator therapy (4-h beta-agonist

as well as theophylline when tolerated). Exclusion criteria were pregnancy or lack of adequate contraception, and renal, hepatic, or hematologic disease. Informed consent was obtained from all patients.

Nineteen patients had taken prednisone and two patients had received every 3 weeks intramuscular depot (diprosan-sterile aqueous suspension providing 5 mg of betamethasone as the dipropionate in suspension and 2 mg of betamethasone as sodium phosphate in solution) injections for at least 1 year, despite repeated attempts at weaning by a specialist in respiratory medicine. In addition, weaning was reattempted over a period of 2 months before the 1-month run-in before prescription of MTX. Once a month, two physicians (RJS, PS) saw the same patients, who were asked to 1) complete daily diary cards, 2) record the number of night wakings, and 3) record the best of three PEFr measurements twice daily. In addition, patients were required to record a daily symptom score on a scale of 0–5.

Pulmonary function tests (including diffusing capacity) and chest radiograph were performed every 3 months. All patients were treated with 15 mg MTX

Table 1. Patient characteristics and base-line treatment

Male/female ratio	7/14
Mean age (SD; range) in yr	52 (13; 20–73)
No. of cigarette smokers*	2
Mean (SD; range)	
Base-line prednisone dose (mg) (two patients – diprospan IM)	16.6 (9.2; 7.5–40)
Inhaled beclomethasone/budesonide dose (µg)	1157 (330; 800–2000)

* More than 10 pack-years.

once a week after food. The daily prednisone dose was reduced by 2.5 mg/d at the monthly visit if the diary card criteria were unchanged or had improved. Inhaled steroid and bronchodilator treatments were not changed for the duration of the study.

The amount of prednisone taken before MTX treatment was compared for each patient for each 3-month treatment period by the two-tailed paired t-test.

Results

Twenty-one patients were recruited for the study. Patient characteristics are outlined in Table 1; pulmonary function data in Table 2. None of the pulmonary function values changed significantly during the trial. The mean prednisone dose in the group decreased significantly during the trial, as shown in Table 3. Two of the patients were being treated with monthly injected steroids and therefore were not included in the tables, but they were both totally weaned from systemic steroids and had taken MTX for 16 and 12 months, respectively. Mean duration of MTX treatment was 14.7 (SD 3.7) months. The mean cumulative MTX dose was 957.9 (SD 242.5) mg. When individual patients were considered, it was clear that the reduction in prednisone dose was not related to the original base-line dose of systemic steroid (Fig. 1). The study was designed so that mild worsening of the asthma resulted in no steroid reduction over the following 4-week period. In four patients, the steroid dose had to be temporarily increased because of exacerbation of asthma. In two patients, a small increase in steroid dose was nec-

Table 2. Pulmonary function data-mean (SD; range)

Peak flow (l/min)	
Morning	244 (88; 120–460)
Evening	279 (92; 150–500)
FEV ₁ *	61.4 (22; 24–89)
FVC*	77.1 (17; 39–117)
RV*	179 (39; 120–254)
TLC*	111 (16; 72–133)
Transfer factor for carbon monoxide*	96.9 (16; 65–118)

* % Predicted; FEV₁=forced expiratory volume in 1 s; FVC=forced vital capacity; RV=residual volume; TLC=total lung capacity.

Table 3. Mean prednisone dose taken during study (mg/d)

Months	0	3	6	9	12	15	18
n (patients)	19	19	19	19	15	9	6
Mean dose	16.6	11.6	7.8	5	4.2	5.9	7.1
SD	9.5	8.4	7	6	7	8.3	8.4
P<		0.001	0.001	0.001	0.001	0.005	0.03

The two additional patients receiving depot steroid have been successfully weaned from systemic steroid treatment and have taken MTX for 16 and 12 months, respectively.

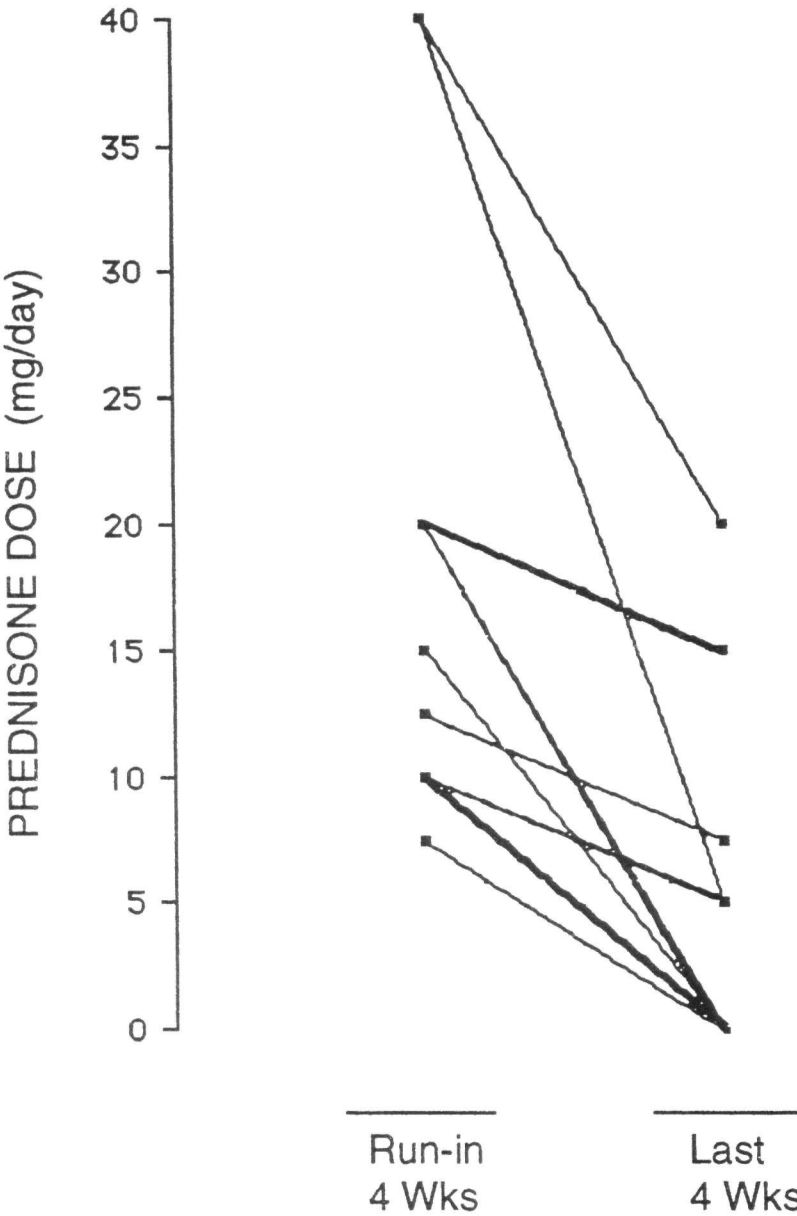


Fig. 1. Effect of methotrexate on individual prednisone doses.

essary, and in two additional patients (in one patient on two occasions), the systemic steroid dose had to be temporarily increased to above the original dose taken before MTX treatment. Night waking, symptom score, and mean PEFR did not significantly change during the study.

An increase in liver function test scores (mainly serum aminotransferases) occurred in six of the 21 patients, but the condition resolved in five despite continuation of MTX treatment. Only in one patient did they exceed four times base-line values, and that patient also complained of general weakness, abdominal discomfort, and nausea without clinical

jaundice. Cessation of MTX resulted in a speedy resolution of both symptoms and abnormal laboratory findings. Six patients complained of nausea, which was severe in one and was also accompanied by heartburn. The symptoms disappeared in five patients and greatly improved in one patient when they switched to weekly intramuscular injections of MTX (15 mg/week). There was no evidence of adverse hematologic effects or of pneumonitis.

With the exception of the patient with hepatotoxicity, all patients continued with MTX treatment, and the improvement was maintained.

Discussion

Our study tends to confirm the safety and efficacy of MTX both in the short and long term. All the asthmatic patients were followed by senior specialist respiratory physicians, with repeated well-documented attempts to wean the patients from systemic corticosteroid therapy. In addition, all patients were taking at least 800 µg of inhaled beclomethasone or budesonide, a treatment that has been shown to have a systemic, steroid-sparing effect in its own right (4). Although these patients were truly steroid-dependent at the outset of the study, 13 of the 21 (62%) were completely weaned and four (19%) partially weaned after the addition of MTX therapy. As in our previous study (13), the steroid-sparing effect was slow in onset and only became apparent after 3 months of treatment. One group of researchers who could not show that MTX treatment was of benefit studied the effect of MTX over only a 13-week period (6). This same group also demonstrated a steroid reduction of 40.2% in the placebo group, an effect which might suggest a difference in the patient populations studied in the various trials. The mechanism of action of low-dose MTX is unclear, although it has been postulated that it acts at an inflammatory level rather than earlier on an immunologic pathway (3). Open studies are always problematic when assessing the efficacy of a drug in asthma. However, randomized, placebo-controlled trials over the long term (more than 6–8 months in duration) are unfeasible. In addition, there are enough data from the shorter randomized, placebo-controlled trials to suggest that MTX is significantly superior to placebo in its ability to reduce dependency on systemic corticosteroid therapy. There was no evidence that this effect lessens with time.

MTX therapy was stopped after 7 months in one patient (after she had been successfully weaned from systemic corticosteroids) because of hepatotoxicity. It is worrying that the hepatotoxicity was not apparent until after some months of low-dose MTX treatment; careful long-term follow-up of all patients on MTX is indicated. None of the patients had taken

a cumulative dose of 1.5 g of MTX (1); therefore, we did not feel justified in performing liver biopsies.

Most of the reported cases of pneumonitis associated with low-dose MTX therapy have been rheumatoid arthritis (9, 12), but there is frequently considerable underlying lung involvement in this disease. Pneumonitis appears to be much rarer in psoriatic patients treated with MTX, and it is probably relatively uncommon in asthmatic patients. However, more experience with long-term, low-dose MTX treatment in this patient population is required before this statement can be made with confidence. *Pneumocystis carinii* pneumonia has been associated with low-dose MTX treatment in rheumatoid arthritis (16), psoriasis (15), and asthma (6). Most of these patients were concurrently taking either systemic corticosteroids or nonsteroidal anti-inflammatory drugs, and patients on MTX who have been successfully weaned from systemic steroids may be at less risk. A raised mean corpuscular volume was noted in some cases (MTX is a dihydrofolate reductase inhibitor), but there was no evidence of serious hematologic abnormalities. MTX treatment failures may result from too short a treatment trial (6) (less than 3 months), or possibly individual variations in MTX pharmacokinetics (8, 14).

Our study provides further evidence that long-term MTX treatment in steroid-dependent asthma is both safe and efficacious. Further follow-up is clearly indicated. In addition, the questions of optimal dose and route of administration should be addressed.

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