

Comparison of oral pulse methotrexate with placebo in the treatment of severe glucocorticosteroid-dependent asthma

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Background: This study compared the efficacy of weekly oral administration of methotrexate and placebo in treatment of 24 subjects with chronic glucocorticosteroid-dependent asthma.

Methods: The 33-week randomized, double-blind, placebo-controlled crossover trial compared once weekly 15 mg doses of methotrexate with placebo. At the time of entry, the subjects' mean dosage of prednisone was 23.8 mg/day (range, 12.5 to 85 mg) and glucocorticosteroid therapy had been used continuously for a mean duration of 78 months (range, 5 to 360 months).

Results: Of the 21 subjects who completed the study, 13 tolerated lower daily prednisone doses during methotrexate treatment compared with placebo. When treated with methotrexate, subjects required 14.2% less prednisone than when treated with placebo ($p = 0.0447$), their subjective symptom scores improved 21.4% ($p < 0.05$), and mean forced expiratory volume in 1 second values tended to improve. Mean serum theophylline levels did not change significantly between the methotrexate and placebo arms of the study. Adverse effects were minimal, with nausea and headache occurring twice as often during methotrexate therapy compared with placebo.

Conclusion: Short-term, low-dose, pulse therapy with orally administered methotrexate results in a decrease in the daily glucocorticosteroid requirement in a majority of subjects with severe asthma and is accompanied by improvement in subjective symptom scores without unacceptable side effects or deterioration of pulmonary function. (*J ALLERGY CLIN IMMUNOL* 1994;94:482-9.)

Key words: Asthma, methotrexate, glucocorticosteroids

The mechanism responsible for the reversible bronchial obstruction of asthma remains incompletely understood. Two of the recognized contributors to clinical asthma are bronchial smooth muscle contraction and airway inflammation. Bronchial smooth muscle contraction is rapidly reversible with β -agonists. Airway inflammation is characterized by cellular infiltration, mucus secretion, and edema. The inflammatory component of airway obstruction is not rapidly reversible with

Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
GCS:	Glucocorticosteroid
MTX:	Methotrexate
NSAIDs:	Nonsteroidal antiinflammatory drugs
SGOT:	Serum glutamic-oxaloacetic transaminase
SGPT:	Serum glutamic-pyruvic transaminase

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β -agonists but responds to glucocorticosteroid (GCS) therapy after several hours, days, or weeks. The presence of bronchial inflammation contributes to chronic symptoms, morbidity, and even death, regardless of the triggering mechanisms.

Systemic GCSs are among the most effective agents used in the management of asthma but are associated with undesirable side effects, some of which include: hypertension, cataracts, osteoporosis, sodium retention and edema, glucose intoler-

ance, increased adiposis, myopathy, and immune suppression with increased frequency of infection.

Nonsteroidal, antiinflammatory agents may have a therapeutic role in asthma. During three controlled studies of subjects with severe, GCS-dependent asthma, GCS dosage could be reduced when low-dose methotrexate (MTX) was added to the treatment regimen.¹⁻³ Two other studies confirmed the reduction in GCS requirements when MTX was added but showed similar reductions in the subjects treated with placebo.^{4, 5} The alleged steroid-sparing effect of MTX is believed to be, in part, secondary to its antiinflammatory properties, which include inhibition of: (1) chemotaxis of neutrophils, (2) activity of interleukin-1, and (3) basophil histamine release.⁶ MTX, an antimetabolite with immunosuppressive effects when administered at high doses, is not immunosuppressive at lower doses (15 to 25 mg/wk).

This double-blind, placebo-controlled, crossover study compared the effectiveness of weekly, oral, pulse MTX with placebo in facilitating the reduction of systemic GCS requirements of subjects with GCS-dependent asthma.

METHODS

Subject selection

Twenty-four subjects between the ages of 18 and 70 years were enrolled. All had chronic reversible airway disease, defined as recurring airway obstruction of sufficient severity to require therapy. This was documented by history and at least 15% improvement in forced expiratory volume in 1 second (FEV₁) after inhalation of a β -adrenergic aerosol. Atopic status was documented by history and skin testing during visit 2 (week 0).

Twenty-three subjects were GCS-dependent as defined by an average oral prednisone requirement of at least 450 mg/month (or its equivalent) for the 6-month period before enrollment. One subject (no. 13) with a lower monthly prednisone requirement (375 mg) was enrolled because of the presence of GCS-related adverse effects (cushingoid appearance).

Fertile women were required to maintain accepted contraception for at least 8 weeks before participating in the study, for the duration of the study, and for at least 12 weeks after its completion. The female partners of enrolled male subjects were required to practice similar contraception.

Subjects were excluded because of lack of reliability, ethanol consumption exceeding 7 ounces of 100 proof liquor (or its equivalent) per week, weight greater than 30% of ideal body weight, and diabetes mellitus requiring pharmacologic therapy before the initiation of treatment with GCSs. Other exclusion criteria included liver disease as defined by liver function test results greater than twice normal or hepatomegaly on physical

TABLE I. Study design

Visit	Week	Description of study activity
1	-3	Screening/baseline evaluation
2	0	Begin study drug (MTX or placebo)
3-6	3-12	Double-blind first arm
7	15	End washout; begin second arm of the study
8-11	18-27	Double-blind second arm
12	30	Follow-up; completion of the study

examination, active bacterial infection requiring antibiotic therapy at the time of entry into the study, evidence of renal insufficiency defined as serum creatinine level greater than 1.8 mg/dl, and active peptic ulcer disease. Recent or active hepatitis, interstitial pulmonary disease as noted on chest x-ray films, abnormal diffusing capacity less than 50% of normal value, allergic bronchopulmonary aspergillosis, pregnancy, and breastfeeding were also exclusion criteria.

All subjects, informed that the use of MTX for the treatment of asthma was experimental, were willing to participate in the study and, before enrollment, signed a written consent form approved by the University of South Florida Institutional Review Board.

Study design

This was a randomized, double-blind, placebo-controlled, crossover study. The study design is summarized in Table I. Subjects were seen at 3-week intervals. There was an initial 3-week screening period, after which each subject was randomly assigned to a 12-week course of either placebo or MTX. This was followed by a 3-week washout period, then a second 12-week treatment period. Randomization and medication dispensing were performed by an investigator who was not involved in patient evaluation in order to maintain double-blinding.

Subjects were instructed to take three 2.5 mg tablets of MTX or three tablets of placebo (total dose of MTX, 7.5 mg) in the morning, once a week, beginning after visit 2. Both placebo and MTX doses were doubled at visit 3 (total dose of MTX, 15 mg) and maintained for an additional 9 weeks, through visit 6. After the following 3-week washout period, subjects were instructed, at visit 7, to resume the starting dose of three 2.5 mg tablets of MTX or placebo in the morning once a week. The dose was doubled at visit 8 (total dose of MTX, 15 mg) and maintained for an additional 9 weeks, through visit 11.

Subjects were allowed to continue the use of other medications in their regimen including adrenergic bronchodilators, theophylline, mucolytics, expectorants, nasal steroids, topical decongestants, and oral decongestants. Long-acting steroids and intramuscular steroids were not permitted.

There was no predetermined regimen for GCS ta-

TABLE II. Overall asthma severity

Symptom score	Description
0	No symptoms of asthma
1	Mild asthma symptoms, barely noticeable
2	Moderate asthma symptoms noticed from time to time but not bad enough to cause trouble with daily routine
3	Severe asthma symptoms noticed often and caused significant discomfort to somewhat interfere with daily routine
4	Very severe asthma symptoms present for most of the day, which cause significant discomfort and radically change daily routine

pering. Attempts to decrease oral GCS doses were made at each visit, if indicated in the opinion of the evaluating physician. Reduction of GCS therapy was attempted if symptom scores decreased, medication use indicated stability, and airway obstruction had not increased.

Clinical assessment

Each subject was given a diary and instructed to record daily asthma symptoms according to the scale shown in Table II. The examining physician also assessed asthma symptom severity at each follow-up visit.

Laboratory assessment

FEV₁, serum theophylline, complete blood count, and liver function tests were monitored at each 3-week follow-up visit.

Statistical analysis

Sample size calculations, performed with the hypothesis that 5% of patients treated with placebo would have a decrease in prednisone dose of 5 mg as compared with 35% of patients treated with MTX ($\alpha = 0.05$, $\beta = 0.20$), indicated a sample requirement of 21 subjects. Comparisons of the difference between MTX and placebo in average daily prednisone dose during each 12-week study period were performed with Student's paired *t* test, two-tailed, with a 0.05 significance level. Similar comparisons with Student's paired *t* test were performed for differences in FEV₁ and laboratory tests. The Wilcoxon signed-rank test was used for nonparametric data, such as the physician's assessment of asthma symptoms and the subjects' asthma symptom scores.

RESULTS

Three of the 24 subjects withdrew before completion of the study. One withdrew because of concern over the possibility of side effects from MTX. A second participant withdrew after a severe asthma exacerbation, which required hospitalization and a significant increase in GCS dose. The third subject did not comply with study visits and was ultimately lost to follow-up. All three subjects were in the placebo treatment arm at the time of withdrawal from the study.

As shown in Table III, of the 24 subjects who enrolled in the study, 11 were men and 13 were women, with a mean age of 48 years. Mean daily prednisone dose at entry was 23.8 mg (range, 12.5 to 85 mg) with a mean duration of continuous therapy of 78 months (range, 5 to 360 months).

Results for the 21 subjects who completed the study are summarized in Table IV. The difference between the mean daily prednisone dose at entry into the study (21.05 mg) and the mean daily prednisone dose required during the 12-week placebo treatment arm (21.45 mg) was not statistically significant ($p = 0.9190$). The mean daily prednisone requirement was reduced to 18.40 mg during the MTX treatment arm. This 14.2% decrease in mean daily prednisone dose was statistically significant ($p = 0.0447$).

Mean FEV₁ improved from 1.95 L/sec during the placebo arm to 2.05 L/sec during the MTX treatment arm; however, this 5.1% increase in FEV₁ did not reach statistical significance ($p = 0.1053$).

There were no statistically significant differences in mean serum theophylline, serum glutamic-oxaloacetic transaminase (SGOT), or serum glutamic-pyruvic transaminase (SGPT) levels between the placebo and MTX treatment arms of the study.

Mean subjective asthma symptom scores improved from 2.34 during the placebo treatment arm to 1.84 during the MTX treatment arm. This improvement in symptom scores was statistically significant ($p < 0.05$). The mean physician symptom assessment score during the MTX arm was 2.17 compared with 2.53 during the placebo arm. This improvement in symptom scores was also statistically significant ($p < 0.05$).

The reported adverse events are summarized in Table III. Adverse events were mild and did not necessitate discontinuation of study medication. One subject, a 62-year-old woman with very severe GCS dependency, died of cardiac arrest 1 week after the final study visit. This subject completed the MTX treatment arm 4 weeks before her death, with a reduction in prednisone

TABLE III. Subject characteristics and adverse event summary

Patient No.	Age (yr)	Sex	Months of GCS use	GCS at entry (mg/day)	AEs during MTX	AEs during placebo
1	40	M	60	22.5	Dz, heel pain	N, D
2	60	M	30	30	URI	URI, bursitis
3	65	M	30	15	WD	Blurred vision
4	51	M	120	30	N (2), Dys (3), HA (3), tinea pedis	Dys (2), Ar (2)
5	36	F	6	20	HC, syncope	AP (2), leg cramps
6	40	M	120	22.5	AP	Vomiting, ear pain, CP (2), fever, My
7	58	F	8	20	WD	CP, constipation
8	65	F	12	15	None	None
9	62	F	34	20	UI (4)	UI (2), DVT
10	69	M	30	17.5	My	AP
11	23	F	132	85	WD	D, URI, HA, AP, CP
12	57	M	96	32	URI (2), fever	None
13	42	F	120	12.5	N (2), HA, AP, R (2), Ar	N, URI, (3), HA, fever, R (2)
14	54	F	5	15	N (2), D, URI (2), AP	D, URI, Ar, hoarse (2), arm pain
15	43	M	360	20	Dz, URI (2), My (2), Ar (2), Dpr (2)	URI (3), My, Ar
16	19	M	N/A	30	OE	OE, OM
17	62	F	30	20	HA, fever	None
18	44	F	12	17.5	URI, VB	Ar, hair loss, VB
19	35	F	60	15	None	URI
20	65	M	N/A	45	None	D, URI (2)
21	47	F	48	17.5	Dz, URI, Dpr	URI
22	23	M	264	15	D, URI	URI (3)
23	42	F	120	15	D, Abd bloat, sweating, PED	D, facial flush, dyspepsia
24	56	F	12	20	R, polydipsia, polyphagia, polyuria	N, HA, Ar (3), IB, edema (3), Nb, W (3), pruritis

AEs, Adverse events; *Dz*, dizziness; *N*, nausea; *D*, diarrhea; *URI*, upper respiratory tract infection; *WD*, withdrawn from study; *Dys*, dyspnea; *HA*, headache; *Ar*, arthralgia; *HC*, heel cellulitis; *AP*, abdominal pain; *CP*, chest pain; *My*, myalgia; *UI*, urinary incontinence; *DVT*, deep vein thrombosis; *R*, rhinitis; *Dpr*, depression; *OE*, otitis externa; *OM*, otitis media; *VB*, vaginal bleeding; *PED*, periorbital edema; *IB*, irritable bowel; *Nb*, numbness; *W*, weakness.

TABLE IV. Mean clinical and laboratory values during each 12-week study period for the 21 subjects who completed the study

Variable	MTX	Placebo	p Value
Prednisone (mg/day)	18.40	21.45	0.0447*
FEV ₁ (L/sec)	2.05	1.95	0.1053†
Serum theophylline (μg/ml)	11.2	10.8	0.4520†
SGOT (U/L)	18.98	20.82	0.1861†
SGPT (U/L)	27.10	25.27	0.6428†
Subject symptom scores	1.84	2.34	<0.05*
Physician symptom assessment	2.17	2.53	<0.05*

*Statistically significant.

†Not significant.

dose from 25 mg/day to 7.5 mg/day and improvement in symptom scores from 4 to 3. No increase in continuous symptoms, change in medication, or evidence of hypocortisolism was reported before her death.

DISCUSSION

Most studies of MTX in asthma have reported a moderate to great reduction (33% to 76%) in GCS requirements accompanied by improvement in subjective symptom scores (Table V). Two

TABLE V. Summary of MTX in asthma studies

Ref (yr)	No. of patients	Study design	Length of study	MTX dose (mg)	% GCS change (MTX)	% GCS change (PI)	Comment
28 (1986)	6	CR	6-19 mo	7.5-15	33.3% less	N/A	Open label; no placebo
1 (1988)	14	DB, PI, C	24 wk	15	36.5% less	5.5% more	$p = 0.01$
7 (1990)	25	PCS	18-28 mo	15-50	76.2% less	N/A	No placebo; $p = 0.0001$
2 (1990)	69	DB, PI, R	24 wk	15	50% less	14% less	$p = 0.005$
4 (1991)	17	DB, PI, P, R	13 wk	15	39.6% less	40.2% less	PI equiv. to MTX
3 (1991)	10	DB, PI, C, R	12 wk	15	36% less	9% less	$p < 0.01$
29 (1991)	5	CR	1-3 yr	15-25	$\geq 75\%$ less	N/A	No placebo; age, 10-16 yr
30 (1991)	25	PCS	≤ 24 mo	10-15	39-64% less	N/A	Open label; no placebo
31 (1992)	7	PCS	4-17 mo	7.5-17.5	66.6% less	N/A	Open label; age, 3-14 yr
5 (1994)	11	DB, PI, C, R	24 wk	15	34.7% less	20.4% less	$p < 0.01$
Stewart et al.* (1994)	21	DB, PI, C, R	33 wk	15	14.2% less	1.9% more	$p = 0.0447$

PI, Placebo; CR, case reports; N/A, not applicable; DB, double-blind; C, crossover; PCS, prospectively; R, randomized; P, parallel.

*This study.

studies have shown significant GCS reductions in both MTX and placebo groups without a significant difference between the two groups.^{4, 5} Those subjects were examined at weekly intervals, which probably improved compliance and facilitated a decrease in GCS doses during treatment with placebo. In one of the studies with negative results, the design was parallel as opposed to crossover, and the route of MTX administration was intramuscular instead of oral. One of the studies with positive results was a parallel design, but no positive study utilized intramuscular administration. It is not clear whether these differences from this study influenced the outcome.

The results of this study suggest that short-term, low-dose, pulse therapy with oral MTX may allow a reduction in the daily GCS requirement for the majority of subjects with GCS-dependent bronchial asthma (Fig. 1). Eight subjects required slightly higher doses of GCSs during the MTX treatment arm (mean increase, 2.3 mg/day). These individuals may represent a subset of "nonresponders" to MTX. Responders and nonresponders did not differ significantly in age or average daily GCS requirement at time of entry

into the study. Responders tended to have a shorter mean length of continuous GCS use than nonresponders (50.5 and 123 months, respectively), and this difference approached statistical significance ($p = 0.0932$). The subjects who responded to MTX, when analyzed separately, achieved a 29.8% decrease in their mean daily GCS requirement, from 22.5 mg to 15.8 mg ($p = 0.0009$).

The mean subjective symptom scores during the placebo arm of the study were significantly better than at the time of entry into the study (2.38 vs 3.33, respectively; $p < 0.05$). Factors that may contribute to this decrease in asthma symptoms include the natural variability of asthma, closer monitoring of patients, and the placebo effect. Mean subjective symptom scores were further improved during treatment with MTX when compared with the placebo arm (1.84 vs 2.34, respectively; $p < 0.05$). This is suggestive of symptomatic improvement beyond that of a placebo effect during treatment with MTX. In another published study, Mullarkey et al.⁷ found significant improvement in subjective symptom scores in 25 subjects with GCS-dependent asthma treated

for 18 to 28 months with weekly, pulse MTX; however, controlled studies of MTX in treatment of asthma by Dyer et al.³ and by Shiner et al.² did not show improvement in subjective symptom scores of subjects treated with MTX.

The trend toward improvement in mean FEV₁ with MTX treatment, although not significant ($p = 0.1053$), suggests that GCS dose reduction may be accomplished without adversely affecting pulmonary function. Improvements in FEV₁ were reported in all other studies except for the study by Dyer et al.,³ in which a statistically insignificant decrease in mean FEV₁ was noted.

Mean serum theophylline levels in the MTX and placebo treatment arms were not significantly different (Table IV). This indicates that GCS reduction and symptomatic improvement were not the result of changes in serum theophylline concentration. The double-blind, randomized study of subjects with severe GCS-dependent asthma by Glynn-Barnhart et al.,⁸ which showed an average decrease in theophylline clearance of 19% when low-dose oral MTX was administered, indicates that it is important to monitor serum theophylline concentrations in subjects receiving low-dose MTX.

MTX levels were not measured in this study. MTX was administered orally, which eliminated the need for weekly visits for drug administration. Although some preliminary data suggest that injectable MTX may be more effective than orally administered MTX,⁶ the fact that the largest study that failed to show a beneficial effect of MTX in asthma used the parenteral route of administration⁴ argues against a clinically significant difference between routes.

Only three subjects in the study used nonsteroidal antiinflammatory drugs (NSAIDs) or salicylates. One subject received a brief course of naproxen therapy, 500 mg/day, during the placebo arm; one used ibuprofen, 200 to 400 mg/day, during the 3 weeks before the MTX arm; and the third took a single daily aspirin along with intermittent short courses of ibuprofen during both the placebo and MTX treatment arms. None of these exposures would be expected to make clinically significant alterations in plasma levels of MTX.

MTX was well tolerated in this study. Six subjects reported nausea and headache during methotrexate therapy, and three during placebo therapy. Sixteen subjects had upper respiratory tract infections during MTX treatment, and 10 during the placebo arm. Five subjects reported diarrhea while receiving MTX, and three while

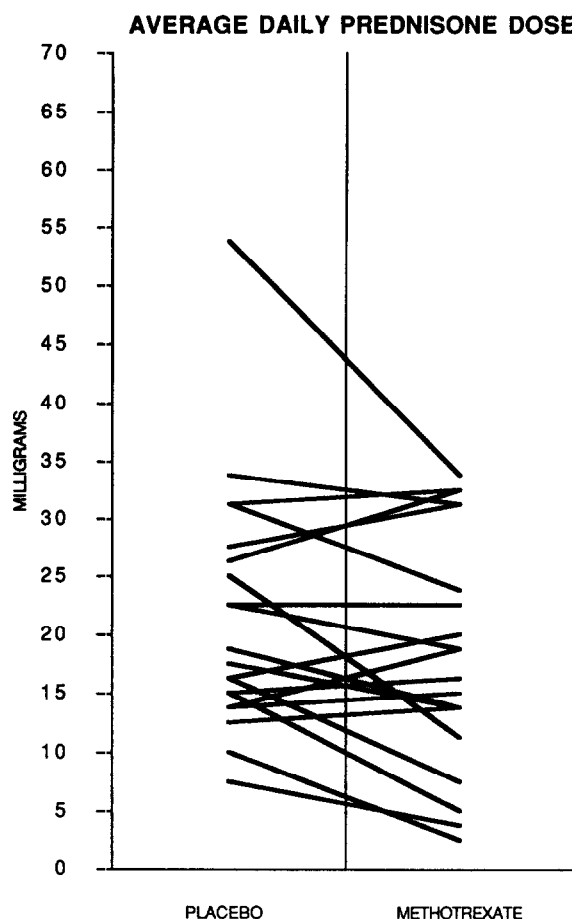


FIG. 1. Effect of MTX or placebo treatment on individual mean daily prednisone dose.

receiving placebo. All adverse effects were mild, especially when compared with the consequences of long-term systemic GCS use. No subjects withdrew from the study because of drug intolerance or adverse events.

Although there is concern about the possibility of opportunistic infections occurring during low-dose MTX treatment, a survey by the Florida Society of Dermatology and the Chicago Dermatological Society (September 1974) showed the incidence of unusual bacterial, fungal, and viral infections to be "virtually zero" among 2419 patients receiving MTX for treatment of psoriasis.⁹ In 1983, Perruquet et al.¹⁰ reported the first case of *Pneumocystis carinii* pneumonia in a patient with rheumatoid arthritis who was treated with salicylates, low-dose MTX, and prednisone. Since 1987, two cases of pulmonary cryptococcosis,¹¹ one case of nocardiosis,¹² and eight other cases of *P. carinii* pneumonia^{4, 13-17} (including three deaths) have been reported in subjects receiving low-dose

MTX. The majority of these opportunistic infections occurred in subjects with rheumatoid arthritis or psoriatic arthritis whose therapy also included GCSs and/or NSAIDs. NSAIDs potentiate the effects of MTX by competing for protein binding sites, competitively inhibiting renal tubular excretion of MTX, and reducing renal blood flow and the glomerular filtration rate through suppression of renal prostaglandin synthesis.¹⁸⁻²¹

GCSs are immunosuppressive, especially when administered in large doses. Important effects of high-dose GCSs include interference with antigen processing by macrophages, reduction of cytolytic effects of T lymphocytes, and inhibition of immunoglobulin synthesis by sensitized B lymphocytes.²² Three of the reports of *P. carinii* pneumonia (including two deaths) occurred in patients with asthma who were receiving concomitant systemic GCS therapy.^{4, 15, 16} The risk of *P. carinii* pneumonia in GCS-dependent subjects treated with adjuvant low-dose MTX alone is very low but may be increased by the concomitant administration of NSAIDs (which may potentiate the effects of MTX) or high-dose GCSs.

The decision of whether to add low-dose MTX to the regimen of a patient with GCS-dependent asthma must take into account the significant risk of adverse events from long-term systemic GCS use. In a study of 286 subjects with GCS-dependent asthma, Miyamoto et al.²³ found more than one adverse event in all subjects, with a higher incidence of adverse events when larger doses and a longer duration were used. Subjects who have received prednisone, 30 mg a day or more, for longer than 1 week are known to have some degree of hypothalamic-pituitary-adrenal axis suppression, which may continue for up to 1 year after discontinuance.²⁴ Gastrointestinal ulceration and perforation are associated with GCS use, and mortality rates associated with intestinal perforation have been reported to increase to more than 80% in subjects receiving daily prednisone, 20 mg or more.²⁵

Questions remain about the potential for irreversible hepatic fibrosis associated with the long-term use of MTX in patients with asthma. Eight subjects in this study experienced brief, self-limited, increases in SGOT (one episode) and SGPT (25 episodes); however, there was no significant difference between mean SGOT and SGPT levels during MTX treatment compared with placebo. Liver function abnormalities are not reliable indicators of severe hepatotoxicity and do not predict the development of fibrosis.²⁶ The risk of

cirrhosis is reduced if subjects are selected to avoid known risk factors, which include impaired liver function, obesity, diabetes mellitus, and alcohol consumption. Subjects were excluded from this study if these risk factors were identified. There is controversy about the need for a liver biopsy after a total dose of MTX of 1500 mg.²⁷

This study agrees with the findings of three of five previous placebo-controlled studies that the addition of MTX to the treatment regimen of patients with GCS-dependent asthma results in lower daily GCS requirements compared with placebo.¹⁻⁵ The amount of GCS reduction achieved was statistically significant but of uncertain clinical value. The question of the risks versus benefits of the addition of MTX to the regimen of a patient with GCS-dependent asthma is extremely complex. The low incidence of major adverse events (e.g., hepatic fibrosis, acute pneumonitis, *P. carinii* pneumonia, and MTX-induced asthma) in a short-term study such as this is encouraging but does not ensure safety in larger populations treated for longer periods of time. Furthermore, there is no evidence of long-term remissions of chronic asthma after MTX therapy. GCS requirements and asthma signs and symptoms increase when MTX is discontinued. Thus low-dose pulse therapy with MTX is a treatment option that may be appropriate for some patients with GCS-dependent asthma but should only be undertaken by clinicians experienced in its use after other treatment alternatives have been carefully considered.

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