

Combined Treatment of Giant-Cell Arteritis with Methotrexate and Prednisone

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Corticosteroids remain the cornerstone of therapy for giant-cell arteritis, but relapse during dose tapering and corticosteroid-related adverse events often complicate management of this condition. Although several approaches, including combined therapy with cytotoxic agents, have been suggested to overcome these problems, no study has clearly shown benefits of alternate treatments.

Objective: To analyze the safety and efficacy of combined therapy with corticosteroids and methotrexate in giant-cell arteritis.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: University-based clinic.

Patients: 42 patients with new-onset giant-cell arteritis according to biopsy.

Intervention: High initial doses of corticosteroid were given; the dose was then tapered quickly until therapy was completely withdrawn. Methotrexate or placebo was given weekly from the start of corticosteroid therapy for 24 months.

Measurements: Number of relapses, cumulative dose of corticosteroid, and number of adverse events were assessed on completion of follow-up.

Results: Compared with combined prednisone and placebo therapy, treatment with prednisone and methotrexate reduced the proportion of patients who experienced at least one relapse (45% vs. 84.2%; $P = 0.02$) and the proportion of patients who experienced multiple relapses ($P = 0.004$). The mean cumulative dose of prednisone was 4187 ± 1529 mg in the methotrexate group and 5489.5 ± 1396 mg in the placebo group (mean difference, 1302 mg [95% CI, 350 to 2253 mg]; $P = 0.009$). Overall, the rate and severity of adverse events were similar between groups. Treatment was discontinued in 3 patients in the methotrexate group who experienced definite drug-related adverse events. In sensitivity analysis that included patients lost to follow-up, differences between groups in number of relapses and cumulative dose of prednisone were significant.

Conclusions: Treatment with methotrexate plus corticosteroid is a safe alternative to corticosteroid therapy alone in patients with giant-cell arteritis and is more effective in controlling disease.

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Giant-cell (temporal) arteritis is a T-cell-dependent vasculitis in elderly persons that involves large and medium-sized arteries (1). Treatment with high doses of corticosteroids usually suppresses inflammatory activity dramatically, thus improving clinical symptoms and preventing disease-related complications. It is commonly accepted that patients should receive prednisone at an initial dosage of 40 to 60 mg/d, with subsequent tapering to a lower maintenance dose that is given for an average of 2 years (2). However, up to 60% of patients experience disease relapse during corticosteroid tapering (3, 4), and long-term corticosteroid therapy leads to corticosteroid-related adverse events in up to 80% of patients (5–7). Corticosteroid-related side effects are thus a major problem in the management of giant-cell arteritis in already frail patients.

Various agents have been used in an attempt to reduce corticosteroid requirements in corticosteroid-resis-

tant giant-cell arteritis (8–11), but only azathioprine has been shown to reduce maintenance doses of corticosteroid in a double-blind, placebo-controlled study lasting 1 year (12). Methotrexate has proven to be useful in the management of several types of systemic vasculitis, such as Wegener granulomatosis, polyarteritis nodosa, and Takayasu disease (13), and various open studies in small series of patients have shown a potential corticosteroid-sparing effect of methotrexate in giant-cell arteritis (14). After a previous open preliminary study (15), we conducted a trial to assess the safety and efficacy of methotrexate in the management of giant-cell arteritis.

METHODS

Patients with newly diagnosed active giant-cell arteritis were consecutively entered into a randomized, double-blind, placebo-controlled trial to assess the safety

and efficacy of methotrexate therapy combined with corticosteroids in this condition. Patients were enrolled from May 1993 through August 1997. The study protocol was approved by the Ethics and Research Committees of Hospital Clínico San Carlos, Madrid, Spain.

Selection and Randomization

All patients with suspected recent-onset giant-cell arteritis were eligible for entry into the trial after giving informed consent. Patients attending Hospital Clínico San Carlos ($n = 38$) and those referred from other hospitals in the metropolitan area of Madrid, Spain ($n = 12$), were invited to participate in the study. Inclusion criteria were a positive result on temporal artery biopsy and less than 2 weeks of treatment with high-dose corticosteroid (prednisone, >10 mg/d, or equivalent) before randomization. Exclusion criteria were contraindications to methotrexate, such as known liver dysfunction or baseline elevation of serum aminotransferase levels to more than twice the normal values; renal failure (baseline serum creatinine concentration $> 176.8 \mu\text{mol/L}$ [>2 mg/dL]); history of chronic alcohol abuse (consumption of >20 g/d); active chronic infection; history of neoplasm (unless it was treated successfully >5 years before screening) or any other clinical condition that might hinder follow-up; history of poor compliance with other treatment protocols; treatment with low doses of steroids (≤ 10 mg of prednisone per day or equivalent) for more than 3 months before screening; previous use of other immunosuppressive drugs; or lack of written consent.

Patients were randomly assigned in blocks of six and in a 1:1 ratio to receive prednisone plus methotrexate or placebo. The active drug and placebo were identical in terms of physical characteristics.

Baseline Studies and Follow-up

Baseline and follow-up visits were scheduled weekly during the first month, monthly until completion of the first year of therapy, and quarterly during the second year of follow-up. Each scheduled visit included a detailed clinical assessment; a complete physical examination; routine blood tests (including erythrocyte sedimentation rate, complete blood count, serum chemistry studies, and urinalysis); and a structured questionnaire designed to detect symptoms of giant-cell arteritis, oc-

currence of adverse events, and use of concomitant medication. Chest radiography was performed at baseline, at 6 months, and at the end of the protocol. Clinical follow-up was performed by the same two physicians. A third physician who had no contact with patients and did not assess outcomes monitored the laboratory tests before each clinical visit. Results of serum liver enzyme tests and mean corpuscular volume were not made available to the physicians involved in clinical follow-up. No physician on the research team was aware of group assignments.

Treatment Protocol

A single weekly dose of four tablets (each containing 2.5 mg) of oral methotrexate (total weekly dose, 10 mg) or placebo was started on diagnosis, maintained throughout the treatment period, and discontinued after 24 months of follow-up if clinical signs of disease activity were absent. Adherence to therapy was assessed by assigning patients an exact number of tablets for each period and checking the empty package during each scheduled visit.

All patients received oral prednisone, 60 mg/d, in three divided doses during the first week and once daily during the second week. The daily prednisone dose was then gradually tapered by 10 mg per week until a dosage of 40 mg/d was being given at the end of the first month. Thereafter, a tapering schedule of 5 mg per week was used; by the end of the second month, patients were receiving a daily dose of 20 mg. The daily prednisone dose was then tapered by 2.5 mg every 2 weeks until therapy was completely withdrawn. The rate of prednisone tapering could be decreased if complete response to initial therapy was not achieved; if relapse occurred; or if the patient had clinical findings that could be attributed to relapse until a second, unrelated process was ruled out. The prednisone dose could be tapered more quickly if patients presented with serious prednisone-related complications in the absence of clinical activity of giant-cell arteritis. The dose of methotrexate or placebo could also be decreased in the event of comorbid conditions or adverse events attributable to therapy. If relapse occurred, the dose of prednisone was increased to the minimum amount that controlled symptoms and the dose of methotrexate or placebo was increased by one tablet per week. Tapering of the pred-

nisone regimen was then resumed while the new dose of methotrexate or placebo was maintained.

All patients received oral calcium, 1000 mg/d, and oral vitamin D₃, 600 IU/d, as a part of the treatment protocol. Patients with a history of tuberculosis or compatible changes on chest radiography received prophylaxis with oral isoniazid, 600 mg/d, during the first 6 months of treatment. Starting in June 1994, the initial protocol was modified so that all patients received oral folic acid, 5 mg/d, in accordance with current recommendations (16–18). Patients could receive any other concomitant medication needed to control adverse events except those specified in the exclusion criteria.

Assessment of Disease Activity

Initial response to treatment was defined as absence of symptoms of giant-cell arteritis and normalization of laboratory values after initiation of treatment. Relapse was defined as recurrence of symptoms of giant-cell arteritis after definite objective improvement followed by symptom reversal on resumption of or increases in the prednisone dose (5). The research team classified relapses according to their clinical characteristics: presence or absence of cranial symptoms, such as visual or ocular disturbances; jaw claudication; headache; and thickness, tenderness, or ulcers or nodules over the temporal or occipital arteries. Once other causes of symptoms were ruled out, relapses were further classified as “definite” if the clinical presentation was characteristic of giant-cell arteritis or “possible” if there were unclear or atypical symptoms or nonspecific manifestations, such as asthenia or general discomfort, that resolved spontaneously in a few days.

Definition and Classification of Adverse Events

Adverse events were defined as a new diagnosis or incidence of any condition during the treatment protocol. The relationship between adverse events and study drugs was classified as follows: 1) definitely related, if the temporal sequence was compatible, the pattern was consistent with the established toxicity profile, and withdrawal of therapy resolved or improved the adverse event; 2) probably related, if the temporal sequence was compatible, no alternative causes could be established, and withdrawal of therapy resolved or improved the adverse event; 3) possibly related, if the temporal sequence

was compatible but the adverse event could have been due to another, equally likely cause; or 4) unrelated, if the temporal sequence was not compatible and there was another, more likely cause of the adverse event.

The following criteria were used to define the most commonly reported adverse events associated with corticosteroid or methotrexate therapy: arterial hypertension as blood pressure greater than 140/90 mm Hg measured at three routine visits; symptomatic vertebral fractures as spinal pain accompanied by a 20% height loss in a vertebra compared with previous radiographs; diabetes mellitus as fasting plasma glucose levels greater than 7.77 mmol/L (>140 mg/dL) on three routine analyses; glucose intolerance as fasting plasma glucose levels greater than 6.11 mmol/L (>110 mg/dL) but less than 7.77 mmol/L (<140 mg/dL) on three routine analyses; hypercholesterolemia as fasting plasma cholesterol levels greater than 5.18 mmol/L (>200 mg/dL) on three routine analyses; cataracts as loss of visual acuity that was diagnosed or confirmed by an ophthalmologist; weight gain as a 5% increase in baseline body weight; myopathy as clinically detectable proximal muscle weakness; thrombocytopenia as a platelet count less than 130×10^9 cells/L; and leukopenia as a leukocyte count less than 3.5×10^9 cells/L. All other adverse events were defined according to current clinical criteria.

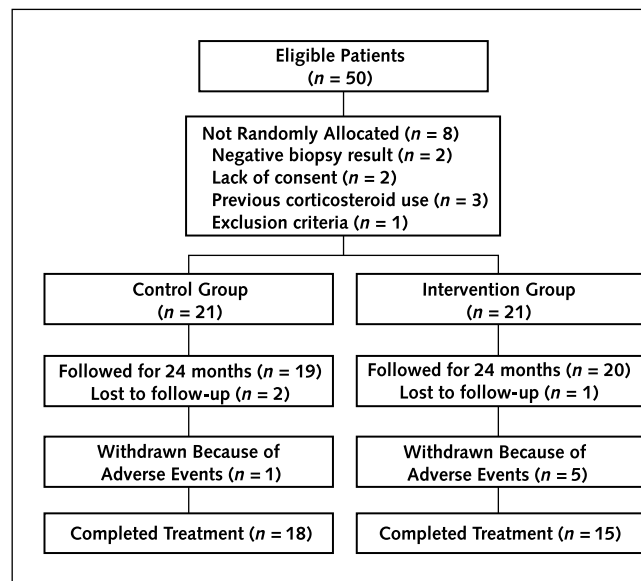
Outcome Measures

The major outcomes studied were number of disease relapses and total cumulative dose of prednisone during follow-up.

Statistical Analysis

Results were analyzed on a completion-of-follow-up basis (which included all patients who completed the intended follow-up) and on a completion-of-treatment basis (which included all patients who completed the treatment protocol). To overcome bias due to loss of patients to follow-up, we performed a sensitivity analysis in which patients in the placebo group who were lost to follow-up were assigned the median or mean value for each variable observed in the methotrexate group at the end of follow-up; conversely, patients in the methotrexate group who were lost to follow-up were assigned the median or mean value for each variable observed in the placebo group at the end of follow-up.

Figure 1. Flow of participants through the study.



A two-sided P value less than 0.05 was considered statistically significant. Categorical variables are presented as frequency distributions; quantitative variables are presented as the mean (\pm SD) if they fit a normal distribution or the median (25th and 75th percentiles) if the distribution was non-normal. Differences between treatment groups were analyzed by using the two-tailed Student t -test for normally distributed data and the Mann-Whitney U test for non-normally distributed data; corresponding 95% CIs are given where appropriate. Chi-square or Fisher exact tests were used to compare categorical variables. Statistical comparisons were made by using Arcus Quickstat Biomedical 1.2 software (Cambridge, United Kingdom).

RESULTS

Patient Characteristics

From May 1993 through August 1997, 42 of 50 eligible patients were enrolled in the trial (Figure 1). Participants and nonparticipants did not differ significantly in terms of clinical presentation and laboratory variables at presentation. Twenty-one patients were randomly assigned to receive methotrexate and 21 to receive placebo. Baseline characteristics of these patients are shown in Table 1. The groups did not differ in demographic characteristics, clinical features, prednisone received in the 2 weeks before random allocation, or

previous comorbid conditions. One patient in the methotrexate group and two patients in the placebo group were lost to follow-up: One moved to another city during the 5th month, 1 experienced cognitive deterioration that adversely affected compliance with the protocol during the 3rd month, and 1 moved to another city during the 10th month. Thus, 39 patients completed follow-up (90.4% of the placebo group and 95.2% of the methotrexate group; $P > 0.05$) and were analyzed on a completion-of-follow-up basis. Six of the 39 patients (5 in the methotrexate group and 1 in the placebo group) experienced adverse events and were withdrawn early from the treatment protocol; therefore, 33 patients completed the treatment protocol (94.7% of the placebo group and 75% of the methotrexate group; $P > 0.05$) and were analyzed on a completion-of-treatment basis.

Disease Activity

All patients had a favorable initial response to corticosteroid therapy. Symptoms improved and laboratory values normalized in the first weeks of treatment. Table

Table 1. Baseline Characteristics of the Study Patients*

Characteristic	Methotrexate Group (n = 21)	Placebo Group (n = 21)
Age, y	78 \pm 8.7	77.6 \pm 7.9
Women, n	14 (66.7)	15 (71.4)
Body weight, kg	60.2 \pm 11.7	58.1 \pm 11.1
Weeks before diagnosis, n	14.3 \pm 12.5	10.9 \pm 8
Clinical features, n (%)		
Polymyalgia rheumatica	12 (57.1)	11 (52.3)
Abnormal temporal artery	16 (76.1)	15 (71.4)
Headache	21 (100)	20 (95.2)
Jaw claudication	12 (57.1)	17 (80.9)
Unilateral blindness†	4 (19)	5 (23.8)
Bilateral blindness‡	2 (9.5)	3 (14.2)
Amaurosis fugax	0 (0)	1 (4.7)
Laboratory values		
Hemoglobin level, g/L	117 \pm 15	112 \pm 15
Platelet count, $\times 10^9$ cells/L	371 \pm 141	358 \pm 115
Leukocyte count, $\times 10^9$ cells/L	9.5 \pm 3.3	10.7 \pm 3.9
Erythrocyte sedimentation rate, mm/h	91 \pm 24	100 \pm 26
Previous concomitant disease, n (%)		
Arterial hypertension	7 (33.3)	10 (47.6)
Diabetes mellitus	2 (9.5)	3 (14.2)
Cataracts	7 (33.3)	3 (14.2)
Glaucoma	2 (9.5)	0 (0)
Tuberculosis	4 (19)	2 (9.5)
Cerebrovascular disease	1 (4.7)	1 (4.7)

* Values with the plus/minus sign are the mean \pm SD. $P > 0.10$ for all paired comparisons between groups. No differences were observed between groups in either completion-of-follow-up or completion-of-treatment analysis.

† Includes complete (one patient) and partial (eight patients) unilateral blindness.

‡ Includes complete (two patients) and partial (three patients) bilateral blindness.

Table 2. Definite Relapses of Giant-Cell Arteritis*

Characteristic	Completion-of-Follow-up Analysis			Completion-of-Treatment Analysis		
	Methotrexate Group (n = 20)	Placebo Group (n = 19)	P Value	Methotrexate Group (n = 15)	Placebo Group (n = 18)	P Value
Patients without relapse, n	11	3	0.004	8	3	0.009
Patients with one relapse, n	7	7		6	7	
Patients with two relapses, n	1	8		1	7	
Patients with three relapses, n	1	1		0	1	
Total patients with relapse, n (%)	9 (45)	16 (84.2)	0.018	7 (46.6)	15 (83.3)	0.06
Total relapses, n	12	26		8	24	
Patients with cranial relapse, n (%)	2 (10)	7 (36.8)	0.06	1 (6.6)	6 (33.3)	0.09
Patients with noncranial relapse, n (%)	7 (35)	9 (47.3)	>0.2	6 (40)	9 (50)	>0.2

* Five cases of relapse (four patients in the control group and one in the methotrexate group) were classified as “possible” and were not included in the analysis.

2 shows the number and characteristics of definite relapses in both groups. Compared with placebo, methotrexate therapy significantly reduced the proportion of patients who experienced at least one relapse and the proportion of patients who experienced multiple relapses. In sensitivity analysis that included the three patients who did not complete follow-up, fewer patients in the methotrexate group still experienced one, two, or three relapses compared with the control group ($P = 0.01$). Only one patient who completed the methotrexate treatment protocol experienced a second relapse after the weekly dose was increased to 12.5 mg, whereas relapse recurred in eight patients receiving placebo.

In both groups, most relapses presented clinically as isolated symptoms of polymyalgia rheumatica. Relapses that included cranial symptoms were much less frequent in patients treated with methotrexate, but this finding was not statistically significant. No patient with cranial relapse experienced transient or permanent visual damage.

Most relapses occurred between the fourth and sixth month after randomization. First relapses occurred at a median of 25 weeks (25th and 75th percentiles, 21 and 31.5 weeks) in the methotrexate group and 21 weeks (25th and 75th percentiles, 17 and 26.7 weeks) in the control group ($P = 0.08$). Five patients in the control group and one in the methotrexate group were taking more than 5 mg of prednisone daily at the time of the first relapse, and only one of these relapses (in the control group) occurred at a prednisone dosage greater than 20 mg/d. In six patients (three in each group), the dose of methotrexate or placebo was reduced because of comorbid conditions or adverse events; only two of these patients (one in each group) experienced relapse while taking 7.5 mg of methotrexate or placebo daily.

Corticosteroid-Sparing Effect

In completion-of-follow-up analysis, the mean cumulative dose of prednisone was 4187 ± 1529 mg in the methotrexate group and 5489.5 ± 1396 mg in the placebo group (difference, 1302 mg [95% CI, 350 to 2253 mg]; $P = 0.009$). In patients who completed the treatment protocol, the mean cumulative dose of prednisone was 4024 ± 1256 mg in the methotrexate group and 5360 ± 1314 mg in the placebo group (difference, 1336 mg [CI, 416 to 2254 mg]; $P = 0.006$). When all randomly allocated patients were included in the sensitivity analysis, the mean cumulative dose of prednisone was 4249 ± 1517 mg in the methotrexate group and 5365 ± 1381 mg in the placebo group (difference, 1116 mg [CI, 210 to 2021]; $P = 0.01$).

Figure 2 shows the median prednisone dose for both treatment groups throughout follow-up. Median duration of prednisone treatment was 29 weeks (25th and 75th percentiles, 22.2 and 65 weeks) in the methotrexate group and 94 weeks (25th and 75th percentiles, 64 and 103 weeks) in the placebo group (difference, 29.25 weeks [CI, 9 to 52 weeks]; $P = 0.0016$). At the end of follow-up, five patients in the placebo group were still receiving 5.0 ± 2.5 mg of prednisone daily and 1 patient in the methotrexate group was still receiving 2.5 mg/d.

Adverse Events

Methotrexate therapy was withdrawn in three patients who experienced adverse events that were clearly drug-related; all were taking 10 mg per week. One patient presented with leukopenia, anemia, and mucositis during the 2nd month of treatment (before folic acid supplementation was included in the treatment proto-

col). One patient developed pancytopenia during the first month of treatment, and one developed oral ulcers during the 12th month of treatment. Baseline serum creatinine concentrations in the latter two patients were 141.4 and 167.9 $\mu\text{mol/L}$ (1.6 and 1.9 mg/dL), respectively.

Two patients in the methotrexate group and one in the placebo group were withdrawn from the treatment protocol because of adverse events that were unrelated to the study drugs. One patient in the methotrexate group received a diagnosis of colonic neoplasm during the 11th month. A 97-year-old woman receiving methotrexate was hospitalized during the 18th month for an episode of syncope secondary to cardiac rhythm abnormalities and choledocholithiasis with cholecystitis requiring endoscopic sphincterotomy. Therapy was discontinued in this patient because her serum levels of liver enzymes remained high after discharge and interfered with follow-up. One patient in the placebo group in whom primary hyperparathyroidism was recently diagnosed stopped therapy because of an episode of acute pancreatitis during the 11th month. No deaths occurred during follow-up.

Figure 2. Median cumulative dose of prednisone in the methotrexate group (solid line) and placebo group (dotted line).

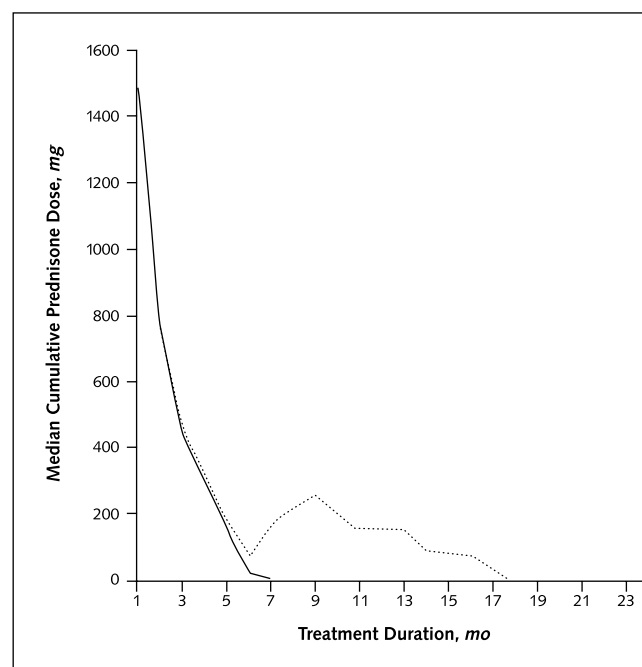


Table 3. Adverse Events in the Completion-of-Follow-up Analysis*

Adverse Event	Methotrexate Group (n = 20)	Placebo Group (n = 19)
	n (%)	
Fracture	4 (20)	2 (10.5)
Neuropsychiatric disorders	10 (50)	8 (42.1)
Cataracts	2 (10)	1 (5.2)
Diabetes mellitus	3 (15)	7 (36.8)
Glucose intolerance	2 (10)	2 (10.5)
Arterial hypertension	12 (60)	16 (84.2)
Cushingoid appearance	3 (15)	6 (31.8)
Weight gain	7 (35)	9 (47.3)
Myopathy	2 (10)	1 (5.2)
Hypercholesterolemia	0 (0)	2 (10.5)
Increase in AST/ALT level	7 (35)	6 (31.8)
Nausea or vomiting	0 (0)	1 (5.2)
Thrombocytopenia	3 (15)	1 (5.2)
Oral ulcers	0 (0)	1 (5.2)
Alopecia	1 (5)	2 (10.5)
Infection†	8 (40)	10 (52.6)
Peptic disease	1 (5)	3 (15.7)
Diarrhea	1 (5)	3 (15.7)

* The adverse events listed were definitely or probably related to the study drugs but were not severe enough to warrant discontinuation of treatment. $P > 0.10$ for all paired comparisons between groups. ALT = alanine aminotransferase; AST = aspartate aminotransferase.
† Infections considered to be severe were cholecystitis in the methotrexate group and pyelonephritis, lymph node tuberculosis, and bacterial pneumonia in the control group. All infections were treated and resolved successfully with discontinuation of methotrexate or placebo treatment.

Table 3 shows the frequency of other drug-related events that were not severe enough to warrant discontinuation of therapy. Adverse events were more frequent during the first 2 months of therapy in both groups. Overall, the groups did not significantly differ in the rate of individual adverse events or the incidence of mild, moderate, or severe adverse events.

DISCUSSION

We conducted a randomized, double-blind, placebo-controlled trial in which patients with giant-cell arteritis on biopsy received high initial doses of corticosteroid and then a quickly tapered corticosteroid regimen plus methotrexate or placebo for 24 months. Our results indicate that methotrexate is effective in controlling disease activity while producing a quantifiable prednisone-sparing effect.

Treatment with methotrexate and prednisone significantly reduced the number of patients who experienced a first relapse after initial remission compared with treatment with placebo and prednisone (45% vs. 84.2%). The rate of relapse observed in the methotrexate group falls in the range of rates reported in the lit-

erature (20% to 60%) in treatment protocols that used higher doses of steroid (3, 4, 19). Furthermore, after slight increases in the weekly dose, methotrexate treatment almost eliminated further episodes of disease activity in patients with a first relapse (6% of patients in the methotrexate group and 53% of patients in the control group experienced more than one relapse). The need for adjustments to the methotrexate dose may imply that higher doses of methotrexate must be used in giant-cell arteritis to achieve long-term remission, as was reported in trials of other types of vasculitis that studied weekly doses of 12.5 to 25 mg (13). However, the efficacy of initial high doses of methotrexate should be balanced against safety. The approach that we used, in which we administered initial low doses of methotrexate and limited higher doses to patients with a clinical course that warranted an increase, may be preferable. An initial conservative approach to methotrexate dosing may be justified given that giant-cell arteritis is a disease of elderly persons, in whom rates of drug clearance are physiologically altered (20).

Methotrexate in combination with prednisone not only reduced the number of relapses but also seemed to improve the course of disease; patients in this group presented with first relapses later and at a lower dose of prednisone compared with controls. Furthermore, one patient in the methotrexate group compared with six in the control group experienced relapse with cranial symptoms. Although they were not statistically significant, differences observed in the quality of relapses might be clinically relevant in long-term control of giant-cell arteritis.

Because of improved disease control, which manifested as persistent remission and decreased severity of the clinical picture, methotrexate-treated patients required less steroid than controls. The median duration of prednisone treatment was 29 weeks in the methotrexate group and 94 weeks in the placebo group, which led to a 25% reduction in the cumulative dose of prednisone during follow-up. The duration of prednisone therapy and the total cumulative dose of prednisone in the methotrexate group contrast with the results of other studies, in which the majority of patients required prolonged corticosteroid therapy until the second year of treatment and higher cumulative doses (4, 21–23). van der Veen and colleagues (24), who used a rapidly tapered steroid regimen, found no corticosteroid-sparing

effect with oral methotrexate, 7.5 mg/wk. However, in that study, most patients had polymyalgia rheumatica alone, the initial methotrexate dose was lower than that used in our protocol and could not be modified during the course of treatment, and methotrexate therapy was discontinued only 6 weeks after treatment with prednisone was withdrawn. These differences might account for the discrepancies between their results and ours.

The differences between groups in the two major outcomes, number of relapses and cumulative dose of prednisone, were statistically significant according to various analytic strategies. Methotrexate therapy was found to be beneficial even though the values assigned to patients who were lost to follow-up tended to eliminate differences in therapeutic effectiveness between methotrexate and placebo. As was expected, the statistical differences, although still significant, were smaller than those obtained by comparing patients who completed follow-up, thus indicating a high level of biological plausibility and consistency of the results.

The incidence of adverse events was similar in the methotrexate and control groups. Most of the adverse events reflected age-related characteristics and greater burden of comorbid conditions in the patients. The adverse events that could be attributed to methotrexate were similar in pattern and frequency to those described in the literature in studies of other diseases (25). Serious methotrexate-related adverse events occurred in patients who did not receive folic acid supplementation and those who had higher baseline serum creatinine concentrations. Although these patients recovered successfully after withdrawal of drug therapy, concomitant use of folic acid supplements in all patients and a cautious approach to use of methotrexate in patients with even slight increases in serum creatinine concentrations should be advised. Despite the lower cumulative dose of prednisone used, all patients in the control group and 90% of patients in the methotrexate group experienced at least one adverse event that was definitely or probably related to corticosteroids. The high incidence of steroid-related adverse events in both groups probably reflects the fact that in our protocol, we chose to induce disease remission quickly by using initially high doses of corticosteroid despite the high risk for corticosteroid-related adverse events (6, 23).

In conclusion, therapy with methotrexate plus corticosteroids is a safe alternative to corticosteroid therapy

alone in patients with giant-cell arteritis and is more effective in controlling disease than standard corticosteroid therapy. Methotrexate plus prednisone was also more efficient than prednisone alone in maintaining disease remission. When disease relapses occurred, they were clinically less severe and prednisone requirements were lower. Further studies should be directed toward establishment of criteria for optimum individualized doses of corticosteroid and methotrexate in an attempt to reduce adverse events without sacrificing disease control.

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“I shall soon be dead, shall I not?” she asked after she had listened to my woes for a good long while and I had exhausted the topic of my hardship.

My master in Padua had always warned about such questions: not least because one might be wrong. He always believed that the patient has no right to confront the physician in such a way; if one is right and the patient does die, it merely makes them morose for the last few days of their life. Rather than composing themselves for their imminent ascent into the Presence of God (an event to be desired rather than regretted, one might think) most people complain bitterly at having this divine goodness thrust upon them. On top of this, they do tend to believe their physicians. In moments of frankness, I confess that I do not know why this is the case; nonetheless, it seems that if a physician tells them they will die, many dutifully oblige, even though there may be little wrong with them.

Iain Pears

An Instance of the Fingerpost

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