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A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Adjuvant Methotrexate Treatment for Giant Cell Arteritis

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***Objective*. To evaluate treatment with methotrexate (MTX) in patients with newly diagnosed giant cell arteritis (GCA) to determine if MTX reduces GCA relapses and cumulative corticosteroid (CS) requirements and diminishes disease- and treatment-related morbidity.**

***Methods*. This was a multicenter, randomized, double-blind study. Over 4 years, 16 centers from the International Network for the Study of Systemic Vasculitides enrolled patients with unequivocal GCA. The initial treatment was 1 mg/kg/day (≤60 mg every day) prednisone, plus either 0.15 mg/kg/week MTX (increased to 0.25 mg/kg/week, for a maximum weekly dosage of 15 mg) or placebo. Two physicians, both blinded to treatment allocation, evaluated each patient at every trial visit. One physician was responsible for providing global medical care. The other assessed GCA status according to a standard protocol. Treatment**

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failure was defined as 2 distinct relapses or persistence of disease activity after the first relapse, in spite of increased CS therapy.

***Results*. Ninety-eight patients were enrolled. No significant differences between treatment groups were noted with regard to age, frequency of positive findings on temporal artery biopsy (placebo 87%, MTX 79%), or comorbidities at the time of enrollment. The median dosage of MTX was 15 mg/week. The incidence of treatment failure was comparable between groups after 12 months: 57.5% in the MTX group failed treatment (95% confidence interval [95% CI] 41.6–73.4%) compared with 77.3% in the placebo group (95% CI 61.9–92.8%) ($P = 0.26$). In a Cox regression analysis, MTX was not associated with a reduced risk of treatment failure (relative risk 0.72; 95% CI 0.41–1.28). There were no significant differences between groups with regard to abnormal elevations of the erythrocyte sedimentation rate following initial remissions, serious morbidity due to GCA, cumulative CS dose, or treatment toxicity. In the MTX group, there were fewer cases of GCA relapse heralded by symptoms of isolated polymyalgia rheumatica (1 case versus 5 in the placebo group; $P = 0.05$).**

***Conclusion*. The results of this randomized, multicenter trial do not support the adjunctive use of MTX to control disease activity or to decrease the cumulative dose and toxicity of CS in patients with GCA.**

Giant cell (temporal) arteritis (GCA) is a disease of unknown cause that affects large- and medium-sized arteries. GCA generally occurs in individuals >50 years of age. Women are affected at least twice as often as men (1,2). In the US, the annual incidence is ~2.5/100,000 population, and 18/100,000 among persons >50 years old. The disease prevalence in this age group in the US has been estimated to be 223/100,000 population (1).

Treatment of GCA consists of corticosteroids (CS), which may be required for 1–5 years and often results in substantial toxicity. Essentially all patients develop Cushing's syndrome. In addition, 20–50% of individuals develop other CS-related toxicity, including fractures, cataracts, peripheral edema, myopathy, infections, and diabetes (3–5). Following initial improvement and CS dose reduction, 1 or more relapses of GCA occur in 27–62% of patients (6–10). Relapses require reintroduction or dose escalation of CS, which often results in additional toxicity.

Morbidity from GCA itself is substantial. In the era preceding the availability of CS, 30–60% of patients experienced vision loss, compared with 5–20% of CS-treated patients in more recent series (11–17). In 1 population-based study, 17% of GCA patients developed aortic aneurysms that were sometimes associated with dissection or vessel rupture (18). Aortic branch vessel stenoses may cause extremity (upper more frequently than lower) claudication (15%). Patients may also experience polymyalgia rheumatica (PMR) (~50%), constitutional symptoms (~50%), and stroke (3–5%) (13,19,20).

Studies of other vasculitides, including Wegener's granulomatosis (21–24) and Takayasu arteritis (25), have demonstrated that methotrexate (MTX) is an effective treatment and may reduce CS requirements. The treatment combination of MTX and CS for GCA has never been evaluated in a multicenter, randomized, double-blind, placebo-controlled trial.

This trial was conducted to determine if treatment with MTX 1) reduces the risk of treatment failure after induction of remission with CS; 2) diminishes GCA-related morbidity; and 3) decreases treatment-induced toxicity in patients with newly diagnosed GCA.

PATIENTS AND METHODS

Members of the International Network for the Study of Systemic Vasculitides (INSSYS) designed a randomized, double-blind, placebo-controlled trial to evaluate the benefits of adjunctive use of MTX in newly diagnosed GCA. Between 1994 and 1998, patients were enrolled at 16 INSSYS centers. In the absence of early withdrawal, treatment failure, or loss to followup, every patient was followed up for a minimum of 1 year.

Eligibility criteria. All patients were required to be >50 years old and to have a Westergren erythrocyte sedimentation rate (ESR) of ≥40 mm/hour. In addition, patients had to have at least 1 of the following: 1) a temporal artery biopsy revealing features of GCA; 2) unequivocal symptoms of GCA (e.g., new-onset atypical headaches, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain); 3) circumstantial proof of large-vessel vasculitis (angiographic abnormalities); and 4) symptoms of PMR plus ischemia-related vision loss, newly identified tenderness over a temporal artery, or new onset of jaw or mouth pain. All patients had to have had onset of GCA symptoms within 6 months of entry.

Exclusion criteria. Patients were excluded from the study for any of the following criteria: prednisone therapy initiated >21 days prior to study entry, renal impairment (serum creatinine ≥2.0 mg/dl), white blood cell count <4,000/mm^3, platelet count <120,000/mm^3, inability to comply with the protocol, history of medical noncompliance, liver disease, ingestion of >2 ounces of 100-proof liquor or >1 beer per week, insulin-dependent diabetes plus morbid obesity (>33% ideal body weight), prior diagnosis of GCA or PMR that had been previously treated with CS and had relapsed, peptic ulcer disease within the prior 3 months, serologic proof of infection

with human immunodeficiency virus, or malignancy within 6 months of enrollment.

Because it is characteristic for GCA to markedly improve following ≤72 hours of CS therapy, the absence of such a response within 5 days constituted a dubious diagnosis and the patient was deemed ineligible for the study. This clause was included because other forms of vasculitis, less responsive to CS, may affect temporal arteries (26–31).

Frequency of visits. Patients were evaluated 2 weeks after the baseline visit and then every month. Additional visits were arranged as needed.

Treatment. Therapy was initiated with 1 mg/kg/day of prednisone, not to exceed 60 mg. Each patient either received oral MTX at a dosage of 0.15 mg/kg/week (rounded to the nearest 2.5-mg tablet increment) or identical placebo tablets. Twenty-four hours after taking the experimental therapy, all patients also received folinic acid (5 mg/week). In the absence of adverse effects, the MTX/placebo was increased within 2 weeks to a maximum of 0.25 mg/kg or 15 mg/week MTX (or matching placebo). The protocol called for continuation of experimental therapy for 12 months after the achievement of remission. At that juncture, experimental therapy was to be tapered by 1 tablet/month until discontinuation.

CS tapering. Four weeks after trial entry, prednisone was reduced by 5 mg every 4 days according to an alternate-day schedule. Dosage reduction calendars were provided to patients. In the absence of relapse, this dosage reduction schedule led to a dosage of 60 mg every other day after 3 months. If remission continued, the alternate-day prednisone dosage was reduced by 5 mg/week until discontinuation (total duration of prednisone use = 6 months). If a relapse occurred, the patient resumed taking the last dosage of prednisone that effectively controlled the disease, plus an additional 10 mg. After maintenance of the higher dosage for 1 month, another slow prednisone taper was attempted, using the same schedule originally used.

Bone-conserving therapy. All patients received 1,000 mg of elemental calcium/day and 0.5 μg of 1,25 vitamin D twice a week (32). Other therapy for osteoporosis was left to the discretion of the physician.

Monitoring disease status and therapy. Two investigators, both blinded to treatment allocation, evaluated each patient at every visit. One physician was responsible for providing complete medical care and the other for assessing GCA activity with a formal score, using a standardized form. Laboratory studies were performed at least once a month. Complete blood counts, serum creatinine, albumin, hepatic transaminase levels, and an ESR were obtained at least once a month.

Monitoring advisory committee (MAC). The MAC reviewed adverse events and the progress of the trial at least every month. The MAC possessed the treatment code. Unequivocal differences between treatment groups in toxicity or efficacy (intent-to-treat analyses) were grounds for the MAC to terminate the trial.

Adjustment of medications in the setting of toxicity. A standardized protocol for reduction or discontinuation of the experimental medication was followed in the event of thrombocytopenia, leukopenia, elevations in hepatic transaminase values, or dermatologic or mucosal abnormalities. When adverse events necessitated the temporary discontinuation of the experimental medication, after resolution of toxicity, the medication could be restarted at a dosage of 2 tablets/week less than the dosage at which the side effect occurred.

Indications for permanent removal from the trial included 1) drug-induced pneumonitis; 2) severe dermatitis (>10% total surface area); 3) severe oral ulcerations (no improvement after 2 weeks of experimental therapy discontinuation); 4) hepatic transaminase values ≥3 times the upper limits of normal, that did not diminish to <1½ times the upper limits of normal within 1 month after drug withdrawal; 5) severe hemocytopenia; 6) elevations of the serum creatinine to >2.0 mg/dl; 7) alcohol abuse; 8) newly discovered malignancy; 9) life-threatening infections; or 10) patient's decision to leave the trial.

Outcome measures. Outcome measures included the number of disease relapses and treatment failures in the 2 groups (see definitions below), the clinical features associated with relapse, disease-related morbidity, the total dose and duration of CS treatment, treatment-associated toxicities, and death. Because of the inherent difficulties in interpreting the clinical significance of some symptoms and signs of disease relapses (e.g., an isolated headache, the occurrence of PMR symptoms alone, and ESR elevation in the absence of symptoms), we required that 2 features meet the protocol definition of disease relapse.

Definition of relapse. GCA relapse was defined as a change in ESR from normal to ≥40 mm/hour, plus at least 1 other feature of GCA not attributable to other conditions. These additional features could include 1) fever (≥38°C for at least 7 days); 2) PMR; 3) headache, scalp pain, or tenderness; 4) vision loss; 5) jaw or mouth pain; 6) extremity claudication; 7) angiographic abnormalities compatible with vasculitis; 8) cerebral ischemia/infarction; or 9) other features judged by the 2 evaluating physicians and confirmed by the MAC after review to be consistent with a relapse.

Definition of treatment failure. Treatment failure was defined as the occurrence of 2 distinct disease relapses, or a relapse treated with prednisone (10 mg greater than the previously effective dosage) that did not lead to improvement. Following the occurrence of treatment failure, patients discontinued the experimental treatment and were treated according to usual medical care.

Patient randomization. All 16 centers enrolled patients. The randomization process was administered centrally at the coordinating center (the Cleveland Clinic Foundation). Random permuted blocks (size 2 or 4) were designed to ensure balance between the groups.

Statistical analysis. All analyses were performed on an intent-to-treat basis. The primary end points for this trial were first disease relapse and treatment failure. Clinical characteristics were compared between groups, with Wilcoxon's rank sum test for continuous variables and with a chi-square test or Fisher's exact test for proportions. The cumulative incidence of relapse, and the occurrence of elevated ESR, headache, vision loss, PMR, and treatment failures were estimated with the Kaplan-Meier method. Relapse rates and morbidity between groups were compared using log-rank tests. Total prednisone dose and time on therapy were compared with Wilcoxon's rank sum test. Using a Cox proportional hazards model, relative risks were calculated to quantify the relationships between

Table 1. Baseline characteristics*

Characteristic	All patients (n = 98)	CS + placebo (n = 47)	CS + MTX (n = 51)	*P*
Female	70/98 (71)	29/47 (62)	41/51 (80)	0.04
White race	91/98 (93)	45/47 (96)	46/51 (90)	0.44
Headache or scalp pain	87/94 (93)	43/47 (91)	44/47 (94)	0.69
Unexplained tongue or jaw pain	56/93 (60)	29/46 (63)	27/47 (58)	0.58
Temporal artery biopsy positive	79/95 (83)	41/47 (87)	38/48 (79)	0.29
Polymyalgia rheumatica	52/94 (55)	24/47 (51)	28/47 (58)	0.48
Vision loss	17/93 (18)	8/45 (18)	9/48 (19)	0.90
Fever >38°C	5/93 (5)	1/45 (2)	4/48 (8)	0.36
Age, median (range)	74.0 (55–89)	75.0 (57–85)	73.5 (55–89)	0.49

* Except for age, values are the number (%). CS = corticosteroids; MTX = methotrexate.

treatment, relapse, and treatment failure. All statistical tests were 2-sided.

Sample size calculations. The trial was originally designed to enroll 300 patients. Assuming a 30% relapse rate during the first year of followup, the study would have had 80% power to detect a 50% reduction in GCA relapses ($\alpha = 0.05$). However, a later review of the cumulative data by the MAC revealed an observed relapse rate in the placebo group that was much higher, 60%. This resulted in the trial having 80% power to detect a 50% reduction in relapses with 98 patients enrolled.

RESULTS

Among the 98 patients enrolled, 47 were randomized to receive CS + placebo and 51 to receive CS + MTX. Apart from an overrepresentation of women in the MTX group, there were no significant differences in baseline characteristics (Table 1). The median age was 74 years (range 55–89). Eighty percent of patients had been treated with CS (median 11 days) prior to enrollment. There was no difference between groups in the number of patients treated with CS before entry ($P = 0.71$).

Treatment failures and disease relapses. Six months following trial entry, 35.4% of the patients in the placebo group and 24.4% of patients in the MTX group had failed therapy. At 12 months, 77.3% in the placebo group and 57.5% in the MTX group had failed therapy (Table 2). These differences were not statistically significant ($P = 0.26$). When all relapses and treatment failures were considered for each month through the first 12 months following trial entry, there were no differences between groups (Figure 1). The risk of treatment failure was not significantly reduced for the MTX group (relative risk 0.72, 95% confidence interval [95% CI] 0.41–1.28). A separate analysis of only the first observed relapse (as opposed to treatment failure as defined) in each group also failed to reveal significant differences (Figure 2). Significant differences in relapse rates and treatment failures between men and women were not apparent ($P = 0.90$).

Timing and clinical features of relapse. The number of relapses increased as CS therapy was reduced: 15% occurred during daily therapy (first 3 months of the trial), 51% occurred during the period of every-other-day therapy, and 34% occurred after CS discontinuation. Table 3 outlines the 1-year cumulative incidences of clinical manifestations of GCA at the time of a relapse in both treatment groups. The most com-

Table 2. Cumulative incidence of first relapses and treatment failures (Kaplan-Meier analyses)*

Outcome	Time in study, months	CS + placebo (n = 47)				CS + MTX (n = 51)				Log-rank *P*
		N_R	N_E	%	95% CI	N_R	N_E	%	95% CI	
First relapse†	6	11	24	66.1	50.2–82.0	13	29	68.9	54.8–82.9	0.31
	12	1	31	91.3	80.6–100.0	8	31	74.8	61.2–88.4	
Treatment failure‡	6	21	12	35.4	19.2–51.6	29	10	24.4	11.2–37.6	0.26
	12	5	24	77.3	61.9–92.8	15	22	57.5	41.6–73.4	

* CS = corticosteroids; MTX = methotrexate; N_R = number of patients at risk who have not had a relapse at 6 months and 12 months followup; N_E = number of patients who experienced a relapse at 6 months and 12 months followup; % = percent of patients who have had the outcome on or before 6 months or 12 months; 95% CI = 95% confidence interval for the estimated percentage.
† One patient in the placebo group and 1 in the MTX group relapsed after 1 year.
‡ Outcome of a second relapse or treatment failure. One patient in the MTX group had a second relapse after 1 year.

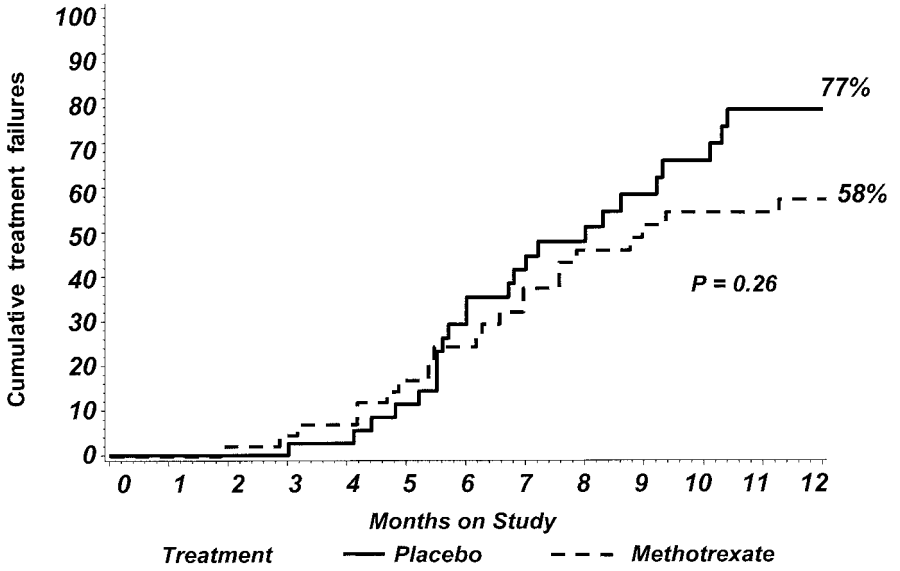

Figure 1. Cumulative incidence of treatment failure by treatment group. The rates of treatment failure over time were not statistically different between the 2 treatment groups. (Treatment failure is defined as 2 distinct relapses or failure to improve following an increase in therapy after 1 relapse.)

mon features of relapse in both groups were an increase in ESR plus recurrent headache or scalp pain and/or PMR. At the time of relapses, no differences were seen between groups in rates of new increases in ESR, headache, jaw, tongue, or mouth pain, or vision loss. However, significantly more patients in the CS + placebo group had either PMR or fever at the time of relapse than patients in the CS + MTX group.

The cumulative incidences of isolated occurrence of headache or scalp pain ($P = 0.50$), tongue, jaw, or other oral pain ($P = 0.14$), or vision loss ($P = 0.29$) did not differ significantly between groups. Isolated occur-

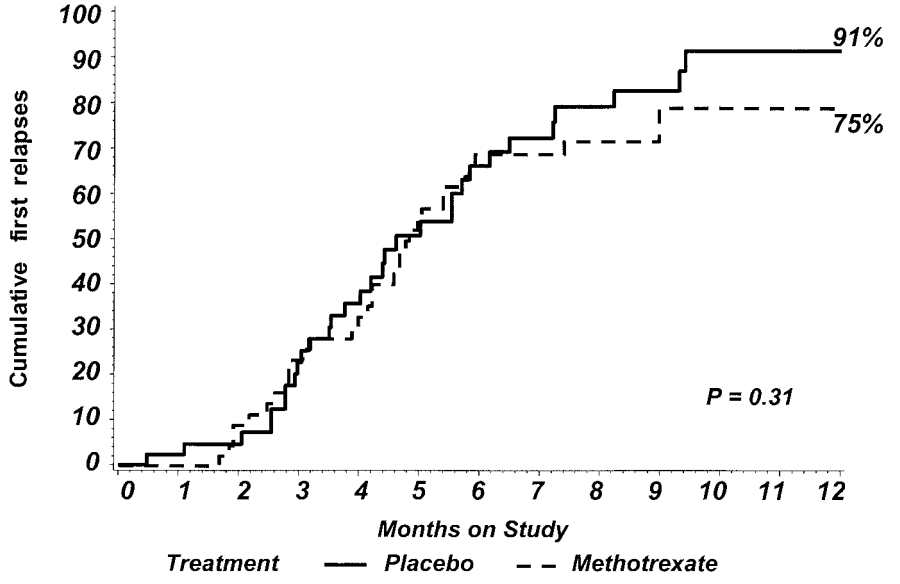

Figure 2. Cumulative incidence of first relapse by treatment group. The rates of first relapse over time were not statistically different between the 2 treatment groups.

Table 3. One-year cumulative incidence of clinical characteristics identified at the time of a relapse*

Characteristic	CS + placebo, % (n = 47)	CS + MTX, % (n = 51)	Log-rank *P*
Headache or scalp pain	55.2 ± 9.0	48.7 ± 8.0	0.62
Tongue or jaw pain	4.8 ± 3.3	20.0 ± 7.9	0.23
Polymyalgia rheumatica	73.7 ± 10.8	39.9 ± 9.0	0.009
Vision loss	19.7 ± 11.5	10.2 ± 4.9	0.83
Sustained fever	18.1 ± 7.0	3.9 ± 3.8	0.04
ESR increase	76.1 ± 9.4	61.7 ± 8.2	0.28

* Relapse defined as a rise in erythrocyte sedimentation rate (ESR) (from normal to ≥40 mm/hour, not attributable to a comorbid event), and at least 1 other feature of giant cell arteritis. Exceptions could be considered by the monitoring advisory committee (see Patients and Methods). Values are the mean ± SEM cumulative rate. CS = corticosteroids; MTX = methotrexate.

rence of PMR in the absence of any other feature defining relapse occurred in only 6 patients, 5 in the placebo group and 1 in the MTX group ($P = 0.05$). Following the development of isolated PMR, protocol-defined relapses eventually occurred in all 6 patients, over intervals that ranged from 4 weeks to 13 weeks.

ESR as a predictor of disease relapse. The numbers of patients with ESR elevations (≥40 mm/hour) following achievement of normal values were the same between groups, regardless of relapse status ($P = 0.49$) (Figure 3). Among 20 patients with isolated increases in ESR, subsequent relapses were noted in 16 cases (positive predictive value of ESR elevation for relapse = 80%). The 16 relapses occurred at a median of 7 weeks (range 2–21 weeks, interquartile range [IQR] 8 weeks) after the detection of an isolated increase in ESR. In 4 cases, a significant rise in ESR occurred in the absence of a subsequent relapse (false-positive results). Eight patients had relapses, as judged by both the evaluating physicians and the MAC, without concomitant elevations of ESR (false-negative results). In 18 patients, the ESR remained normal throughout the period of observation, and relapses did not occur (true-negative results). An isolated increase in ESR had a relative risk for relapse of 4.32 (95% CI 1.87–10.01) compared with patients whose ESRs did not increase ($P < 0.001$).

GCA-associated morbidity. Serious disease-associated morbidity included subclavian artery stenosis (2%) and vision loss. The prevalence of vision loss at study entry was 18%. New vision loss at 1 year was 13.8% (4 patients in each group). Three patients who had already had 1 episode of vision loss at study entry experienced additional vision loss during the first year after enrollment. Stroke did not occur in any patient.

Treatment. The median dosage of MTX was 15 mg/week (range 5–15; 13 patients received 5–12.5 mg/

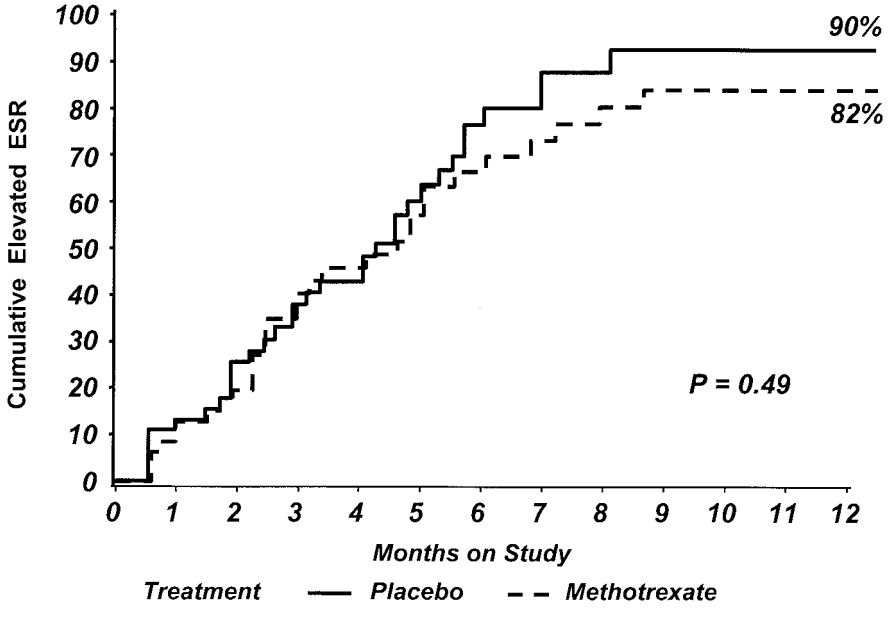

Figure 3. Number of patients with erythrocyte sedimentation rate (ESR) elevations. Following remission, significant differences were not observed between the incidence of increases in ESR from normal to ≥40 mm/hour in the prednisone group and in the prednisone + methotrexate group.

week). The mean and median cumulative doses of CS were comparable in both groups. The median total dose of prednisone in the placebo group was 5,275 mg (range 1,020–8,605 mg, IQR 1,695 mg), versus 5,375 mg in the MTX group (range 1,980–8,270 mg, IQR 1,560 mg) ($P = 0.5$). The median duration of CS treatment was 5.6 months in the placebo group (range 0.6–20.4 months, IQR 2.4 months) and 5.4 months in the MTX group (range 1–10 months, IQR 2.1 months) ($P = 0.5$).

Treatment-related morbidity. Treatment-related toxicity was infrequent apart from universal, but transient, cushingoid features. Only 3 patients experienced fractures. One patient in the placebo group had a pelvic fracture and 2 in the MTX group had vertebral compression fractures. Three patients with serious infections required hospitalization and were withdrawn from the trial (2 placebo, 1 MTX). Four patients required MTX reductions, of whom 3 were withdrawn from the trial because of persistent elevation in hepatic transaminase values, MTX-related fever, and persistent thrombocytopenia, respectively. There were no withdrawals because of drug-induced pneumonitis, oral ulcers, dermatitis, enteric symptoms, or leukopenia.

Deaths. Three deaths occurred, 2 in the MTX group (1 related to congestive heart failure, the other cause unknown) and 1 in the placebo group (pneumonia). No deaths were attributed to GCA.

DISCUSSION

This is the first large multicenter, randomized, double-blinded, placebo-controlled trial of any form of adjunctive therapy for new-onset GCA. The results suggest that MTX does not have a substantial effect on the course of GCA, the incidence of strictly defined relapse, cumulative CS dose, or treatment-related morbidity. In a secondary analysis of isolated disease features, the only discernible benefit of MTX treatment was a significant reduction in the emergence of isolated PMR (5 cases in the placebo group versus 1 case in the MTX group). In all 6 cases, isolated PMR heralded eventual GCA relapses within 4–13 weeks.

Our trial has a number of important strengths. This trial 1) is the first multicenter comparison of CS + MTX versus CS alone; 2) included a relatively large sample size from an international group of academic medical centers; 3) involved a rigorous protocol for patient evaluation, in which all patients were monitored by 2 physicians, both blinded to treatment assignment; 4) used a standardized regimen for medication dosage reduction during remission; and 5) included patients whose clinical characteristics at presentation were similar to those of patients in previously reported studies (3,11,33–38). Thus, our results are broadly applicable to the population of GCA patients at large.

The incidence of GCA relapse that we observed in the course of CS reduction (58% and 77% in the MTX and placebo groups, respectively) is similar to rates previously reported by others. In recent years, the relapsing nature of GCA and its long-term associated morbidity have become more apparent. Reports from the 1980s described the frequency of relapse to be in the range of ~30% (6,7,9). In contrast, more recent reports have described relapse frequencies of 60–84% among patients followed up for periods of 12–52 months (8,39,40). A population-based analysis of 125 GCA patients revealed that only about half were able to discontinue CS therapy within 2 years (41).

The effectiveness of conventional long-term treatment with CS in GCA has also recently been questioned by Weyand and colleagues (40), who found that soluble interleukin-6 (IL-6) concentrations correlated better with GCA activity than either the ESR or C-reactive protein level. In two-thirds of their patients, IL-6 levels did not normalize after treatment, even in the setting of apparent clinical remission. The notion that some patients with GCA, who appear to be clinically well, may continue to have active disease is further supported by findings of active GCA in aortic bypass specimens or postmortem examinations in patients whose disease was thought to be in remission (18,42).

While findings of recent studies have succeeded in changing concepts about the long-term effectiveness of CS therapy in GCA, differing opinions persist about preferred CS dosage and treatment regimens for GCA. During the planning of this trial, investigators achieved consensus on a standardized plan for CS therapy. The process of consensus revealed a broad range of clinical practices, even among individuals regarded as experts. There was unanimity among investigators that severe systemic vasculitis, including GCA, requires high daily dosages of CS at the start of treatment (34). The investigators also acknowledged the importance of avoiding long-term daily CS exposure. The conversion of CS dosage from daily to an alternate-day regimen has been the basis of numerous National Institutes of Health–based protocols for several types of vasculitis and has been tested in GCA (43–46). Agreement was reached on a strategy of 1 month of daily prednisone (1 mg/kg), followed by gradual tapering, to eventually achieve a 60-mg dosage on alternate days after 3 months. In reaching this consensus, the investigators recognized

that the optimal schedule of CS therapy in GCA remained uncertain.

The rationale for choosing MTX as adjunctive therapy for GCA was based on its success in other vasculitides (21–25). Some of these studies used a similar CS tapering protocol (21–23,25). Previous studies have attempted to assess MTX or other agents in GCA. The interpretations of these studies have been confounded by several factors, including both the enrollment of patients with GCA and patients with isolated PMR (47,48), lack of controls (49), the use of low dosages of MTX (e.g., 7.5 mg/week) (47), and the inclusion of patients with longstanding, relapsing disease (48). One randomized, double-blind, placebo-controlled trial of 21 patients failed to demonstrate significant differences between CS treatment and CS + MTX. The authors' conclusions were cautiously interpreted because of the limited numbers of patients enrolled (50).

In a recently published article, Jover and colleagues from Madrid (39) reported that adjunctive therapy with MTX had beneficial effects in GCA, in regard to both maintenance of remission and decreasing the cumulative requirement for CS. The results of that single-center trial, which enrolled 42 patients and used a less intensive regimen of MTX and CS than ours, are difficult to reconcile with our own. The clinical and demographic features of the patient populations in both studies, apart from geographic residence, appear to be comparable. In the Madrid trial, CS tapering was actually more rapid than in our trial. Although Jover et al did not convert prednisone dosing to every other day after 3 months, their patients, barring relapse, achieved prednisone dosages of 40 mg daily at the end of 1 month and a dosage of 20 mg daily at the end of 2 months. In the absence of relapse, complete CS withdrawal was accomplished in 4 months in the Madrid trial.

In contrast, our protocol called for the treatment of patients with 60 mg of prednisone daily for 4 weeks and then tapering according to an alternate-day schedule, such that by the end of 2 months patients were still receiving 60 mg on 1 day and 20 mg the next. In the absence of relapse, total CS withdrawal was accomplished by 6 months. The median dosage of MTX in our trial was 15 mg/week, whereas Jover et al (39) used 10 mg/week (mean/median values were not provided). Both trials included folic or CS folinic acid supplementation to diminish or prevent MTX toxicity. In both trials, relapses occurred in the majority of patients, most often when CS dosages were very low or CS had been discontinued. Most of the relapses in the Madrid study (39) were in the form of PMR, and no patient in either treatment group experienced new-onset vision loss. In our trial, protocol-defined relapses were characterized by an increase in ESR plus either PMR and/or cranial symptoms. In the course of relapse, 13.8% of our patients had new-onset vision loss.

Several factors may have contributed to the differences in outcomes reported between our study and that of Jover et al. Most important, it is likely that differences in guidelines for defining relapses partly explain the disparate results. For example, although the study by Jover et al obtained ESR values on all patients, it is not clear how those data were applied to the assessment of disease activity. It is also not clear whether isolated PMR symptoms or headaches, in the absence of other findings (e.g., ESR elevation), were sufficient to constitute relapses. In our study, isolated increases in ESR were not considered to represent relapses. Eighty percent of our patients who had an isolated increase in ESR eventually experienced a relapse during the ensuing 2–21 weeks (median 7 weeks). In our trial, the relative risk of relapse following an isolated rise in ESR was 4.32, compared with patients in whom ESR values remained normal. Even in retrospect, we believe the decision not to use an isolated elevation in ESR as a measure of relapse was clinically correct. Whereas an ESR elevation has a high positive predictive value for relapse, that event may not occur for months in some patients. Intensifying treatment in response to only a change in ESR may lead to additional and unnecessary CS-induced morbidity. However, a rise in ESR should indicate a need for more vigilant clinical surveillance.

In our trial, all 6 patients with isolated PMR (not judged to be a relapse) eventually satisfied relapse criteria. Patients in our MTX group had a significant reduction in isolated PMR (at 12 months followup, MTX group 2.6% versus placebo group 25.8%; $P = 0.05$). One could argue that our protocol may have been too restrictive in identifying relapses that would otherwise have led to providing earlier increases in CS therapy. More liberal criteria would have led to earlier treatment in the 6 patients who had isolated PMR, and subsequently relapsed, and in earlier increased treatment of the 20 patients who had isolated increases in ESR, of whom 16 later relapsed.

Our aggressive CS tapering schedule may have led to a high rate of relapse. However, when one compares the relapse rates in our trial with those of other recent prospective studies (6–9,39,40), including that from Madrid, the outcomes for CS therapy alone are not dissimilar. More important, if MTX contributed substantially to the maintenance of remission in GCA, it

should have allowed for aggressive CS reduction without the high incidence of relapse observed. It is also possible that higher doses of MTX may have achieved greater efficacy. However, previous publications and investigators' experience with MTX in the elderly cautioned against the use of higher doses. Age-related reductions in renal clearance and serum albumin may lead to greater numbers of MTX-associated complications (51–53). Even so, the finding that only 8% of our MTX-treated patients had side effects of that drug that required dosage reductions indicates that higher doses may be safe in a subset of carefully selected elderly individuals.

In conclusion, this large, randomized, double-blinded, placebo-controlled trial did not demonstrate statistically significant effects of MTX in reducing either the relapse rate of strictly defined GCA remissions, cumulative doses of CS, or serious CS- and disease-related morbidity. However, adjunctive treatment with MTX did appear to diminish recurrences of isolated PMR in a small number of patients.

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