

Adjunctive Methotrexate for Treatment of Giant Cell Arteritis

An Individual Patient Data Meta-Analysis

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Objective. To reevaluate the efficacy and safety of adjunctive low-dose methotrexate (MTX) in giant cell arteritis (GCA).

Methods. An individual patient data meta-analysis of 3 randomized placebo-controlled trials in patients with newly diagnosed GCA was performed. Treatment consisted of initial high-dose corticosteroids and randomly assigned oral MTX therapy (7.5–15 mg/week) or placebo. Time-to-event outcomes were compared between groups using Cox proportional hazards models stratified by trial, and continuous outcomes were compared by calculating weighted mean differences.

Results. The combined data set comprised 161 patients, of whom 84 received MTX and 77 received placebo. The mean duration of followup was 54.7 weeks (SD 39.2 weeks). Hazard ratios (HRs) for a first and second relapse of GCA were 0.65 ($P = 0.04$) and 0.49 ($P = 0.02$), respectively, in patients receiving MTX as compared with patients receiving placebo. Accordingly, a predicted 3.6 individuals (95% confidence interval [95% CI] 2.2–56.8) and 4.7 individuals (95% CI 3.3–

21.9) need to be treated with MTX to prevent the occurrence of one first or one second relapse, respectively, up to 48 weeks. Use of MTX resulted in a reduction in the corticosteroid cumulative dose by 842 mg within 48 weeks ($P < 0.001$). Moreover, MTX treatment was associated with a higher probability of achieving sustained discontinuation of corticosteroids for ≥ 24 weeks (HR 2.84, $P = 0.001$). Dropout rates and occurrence of adverse events did not differ between treatment groups.

Conclusion. In GCA, adjunctive treatment with MTX lowers the risk of relapse and reduces exposure to corticosteroids. These findings indicate that MTX could be considered as a therapeutic option in addition to standard-of-care treatment with corticosteroids for patients with GCA.

Giant cell arteritis (GCA), also named temporal arteritis, is a systemic vasculitis involving large- and medium-size vessels, particularly the extracranial branches of the carotid arteries (1,2). This disorder almost exclusively affects individuals older than age 50 years and is characterized by a combination of constitutional symptoms and cranial manifestations, such as headache, jaw claudication, scalp tenderness, visual loss, and, in ~50% of patients, polymyalgia rheumatica. GCA is considered a medical emergency because of the potential for severe general and ophthalmic complications, with blindness being the most feared consequence (1,2).

For patients with GCA, the treatment of choice consists of systemic corticosteroids, and guidelines usually recommend administration of prednisone or its equivalent for 1–2 years at an initial dosage of 40–60 mg/day (1,2). This corticosteroid regimen almost always controls the disease and prevents progressive blindness but is associated with substantial toxicity. Approximately 50% of patients with GCA experience at least 1 severe

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disease flare that requires prolonged corticosteroid therapy (3,4). Moreover, 53–86% of patients develop major side effects related to corticosteroid treatment, including fractures, diabetes, infections, cataracts, and other problems (4–6).

The high rate of relapse and potential toxicity of corticosteroids have prompted investigations of alternative therapies for GCA. Notably, several randomized, double-blind, placebo-controlled trials have studied the effect of combining low-dose methotrexate (MTX) with corticosteroids for treatment of patients with GCA (7–9) or for a mixed population of patients with GCA and isolated polymyalgia rheumatica (10). These trials have yielded inconsistent conclusions, in that the findings have suggested that MTX provides either a clear advantage (8) or no benefit (9,10) in terms of a lowered risk of relapse or reduced exposure to corticosteroids, or that MTX has only a preventive effect on relapses of GCA presenting as isolated polymyalgia rheumatica (7).

Thus, the utility of adjunctive treatment with MTX in the management of GCA remains highly controversial. Accurate appraisal of this matter is hampered by the possibility that the discrepancies among trials reflect differing trial designs or inadequate sample sizes (11) or by the lack of uniformity in the choice of outcome measures. We therefore performed a meta-analysis of individual patient data from 3 randomized placebo-controlled trials to reevaluate the effects of MTX and its potential toxicity in patients with GCA.

PATIENTS AND METHODS

Selection of studies. All randomized placebo-controlled trials assessing the efficacy and safety of MTX in GCA were considered for the present study. We performed a literature search of the MEDLINE, EMBASE, and Cochrane Library databases, using the keyword terms giant cell arteritis, temporal arteritis, methotrexate, and randomized trial (and combinations thereof) for the period 1966–2006. Beyond the 4 studies cited above (7–10), none of the searches revealed additional trials relevant to our present study. We approached the principal investigators of the 4 trials identified and asked for permission to use their individual patient data in our meta-analysis. Data from the 3 largest studies (7–9) were obtained, whereas for the remaining trial, data were no longer available (10). The latter trial (10) included only 9 patients with GCA, and the remaining study participants had isolated polymyalgia rheumatica.

Collection and checking of data. For each of the 3 trials, the following data were requested: unique patient identifier, demographic characteristics, clinical presentation at diagnosis, date of randomization, treatment allocation (MTX or placebo), outcome (occurrence, timing, and type of relapse), doses of corticosteroids and MTX over time, and

adverse events. All data were checked for consistency against the published report; in the case of any differences or ambiguities, the participating investigators were contacted to resolve these issues. Subsequently, data were recoded and merged into a single data set for the pooled analysis. The main characteristics of the MTX- and placebo-treated patients were compared to identify any potential between-group differences in distribution.

Outcome measures. Comparisons were performed by treatment group for the following end points: time to first relapse, time to second relapse, number of patients needed to be treated to prevent a first or second relapse, cumulative dose of corticosteroids, time to sustained discontinuation of corticosteroids, and adverse events. Relapses were defined in accordance with the definitions given in the original studies. Time to relapse and time to sustained discontinuation of corticosteroids were calculated from the date of randomization to date of censoring, date of relapse, or date of corticosteroid withdrawal. For the calculation of the time to second relapse, individuals who had been withdrawn from the trial after a first relapse were censored on the date of withdrawal. Sustained corticosteroid discontinuation was defined as a corticosteroid-free period of ≥ 24 weeks; additional analyses were performed for periods of ≥ 12 weeks, ≥ 36 weeks, and ≥ 48 weeks. Cumulative doses of corticosteroids were measured for the prespecified time points of 12 weeks, 24 weeks, 36 weeks, 48 weeks, 72 weeks, and 96 weeks after randomization.

To test the possibility that a treatment benefit might be confined to particular subsets of patients, we performed subgroup analyses with patients stratified by age (according to the median value), sex, and histologic proof of diagnosis by temporal artery biopsy. We also evaluated the treatment effect on relapses involving only cranial signs or symptoms, as defined by the presence of at least 1 of the following variables: headache, scalp tenderness, jaw claudication/tongue pain, tenderness of the temporal artery, or abnormalities identified on temporal artery examination.

To evaluate if differences in the length of followup between trials or between treatment groups might have affected the results, we also performed a sensitivity analysis that censored all time-to-event outcomes at a maximal followup of 12 weeks, 24 weeks, 36 weeks, or 48 weeks. All between-group comparisons were made on an intent-to-treat basis. We also performed a per-protocol analysis in which we excluded patients who dropped out, defined as those individuals who had neither experienced a relapse nor completed a followup of 12 months (52 weeks) for 2 of the trials (7,9) or 96 weeks for the remaining trial (8).

Statistical analysis. Descriptive data are reported as the mean \pm SD or frequency. Quantitative variables were compared using Student's *t*-test or, when appropriate, Wilcoxon's rank sum tests. Categorical variables were compared using chi-square or Fisher's exact tests. Time-to-event outcomes were analyzed using Cox proportional hazards models stratified by trial, with results expressed as the hazard ratio (HR); by definition, an HR lower than unity indicated that an event was more likely to occur with placebo treatment. The assumption of proportional hazards for the effect of MTX on the risk of a first or second relapse was verified by examining Kaplan-Meier logarithmic plots of the negative log of survival probabilities against time, and by assessing the statistical significance of an

Table 1. Pooled baseline demographic and clinical characteristics of the patients in the 3 randomized controlled clinical trials included in the meta-analysis

Variable	Treatment group			P, methotrexate versus placebo
	All	Methotrexate	Placebo	
No. of patients	161	84	77	
Demographic				
Age, mean ± SD years	74.6 ± 8.0	74.6 ± 8.0	75.3 ± 6.9	0.55
Female, no. (%)	113 (70)	64 (76)	49 (64)	0.08
Baseline characteristic, no./total no. (%)				
Headache	137/154 (89)	71/79 (90)	66/75 (88)	0.71
Tongue or jaw pain	98/154 (64)	47/80 (59)	51/74 (69)	0.19
Scalp tenderness	84/111 (76)	43/58 (74)	41/53 (77)	0.69
Tenderness of TA and/or TA abnormalities*	66/128 (52)	37/67 (55)	29/61 (48)	0.39
Vision loss	37/153 (24)	15/80 (19)	22/73 (30)	0.10
Polymyalgia rheumatica	78/155 (50)	41/80 (51)	37/75 (49)	0.81
Positive findings on TA biopsy†	137/156 (88)	69/81 (85)	68/75 (91)	0.30
Duration of followup, mean ± SD weeks	54.7 ± 39.2	58.9 ± 41.5	50.1 ± 36.3	0.16

* Findings determined on examination of the temporal artery (TA).
 † Positive for giant cell arteritis.

interaction between treatment and the log of time as included in the Cox regression models. For the cumulative dose of corticosteroids, groups were compared by calculating the weighted mean differences, with a fixed-effect inverse variance model. The predicted number of patients needed to be treated with MTX to prevent a first or second relapse was computed as the reciprocal of the absolute risk reduction.

Heterogeneity in clinical characteristics or trial methods was assessed by reviewing the differences in the characteristics of the patients in each randomized treatment group across trials and the differences in the dosing protocols across trials. Evidence of statistical heterogeneity across trials was examined by including, in the Cox regression models, a treatment-trial interaction indicator variable, and by comparing the value of -2 times the log-likelihood in this model with that in a model without inclusion of the interaction term (12). A similar approach was applied to evaluate the interaction between treatment and other selected covariates that might

contribute to variability in the treatment effect between trials. The other covariates examined included age (stratified according to the median value), sex, and histologic proof of GCA by temporal artery biopsy.

All statistical analyses were computed using SAS statistical software for Windows, version 9.1 (SAS Institute, Cary, NC). P values less than 0.05 were considered significant.

RESULTS

Characteristics of the study participants. Individual patient data on demographic characteristics (age, sex), temporal artery biopsy findings, time-to-event outcomes, and doses of corticosteroids and MTX over time were provided for all 3 of the trials. Data on baseline clinical characteristics and posttreatment adverse events

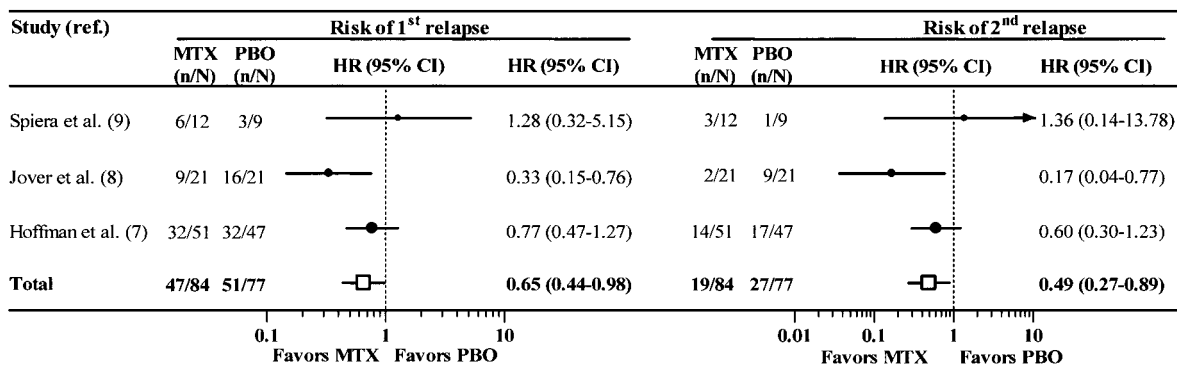


Figure 1. Hazard ratios (HRs) for the occurrence of a first or second relapse of giant cell arteritis in patients receiving adjunctive methotrexate (MTX) versus those receiving placebo (PBO). Values under each treatment group are the number of events (n) among the total number of subjects exposed (N). 95% CI = 95% confidence interval.

were available at the individual patient level for 2 of the 3 studies (7,8), whereas for 1 study (9), we used aggregate baseline clinical data and adverse event data extracted from the published report. Clinical characteristics were gathered for the following variables: headache, scalp tenderness, jaw claudication or tongue pain, tenderness of the temporal artery or abnormalities of the temporal artery on examination, vision loss, and poly-myalgia rheumatica.

Of the total of 161 individuals randomized to a treatment group in the 3 trials, 84 were assigned to receive MTX and 77 to receive placebo. One hundred twenty patients (75%) completed the specifically defined protocol for their respective trial, whereas 41 patients (25%) did not complete the protocol. Overall, the proportions of patients who dropped out were similar between the treatment groups ($P = 0.83$). Among the 41 patients who dropped out, the reasons for withdrawal were as follows: lost to followup ($n = 7$ [17%]), protocol violation ($n = 6$ [15%]), diagnosis of cancer ($n = 3$ [7%]), death ($n = 2$ [5%]), study drug-related adverse event ($n = 8$ [20%]), or withdrawals for other reasons based on the treating physicians' or study participants' decisions ($n = 15$ [37%]). The distributions of the abovementioned reasons for study withdrawal were equally balanced between the MTX and placebo groups.

Table 1 shows the main comparisons of the demographic and clinical characteristics of the 161 individual patients in total and according to their therapy assignment. Distributions of the main demographic and clinical characteristics as well as lengths of followup did not differ between the MTX and placebo groups. Comparisons between patients who were treatment completers and those who dropped out of the trials showed that the latter were slightly older (mean \pm SD 77.5 ± 7.9 years versus 74.1 ± 7.1 years; $P = 0.01$), but the sex distribution did not differ between these 2 groups ($P = 0.38$). Moreover, there were no differences between the treatment completers and noncompleters in the proportions of patients with positive findings of GCA on temporal artery biopsy ($P = 0.11$).

For the individuals receiving MTX, the mean starting dosage was 9.4 mg/week (SD 1.6 mg/week) and the mean dosage over the total period of intake of MTX was 11.1 mg/week (SD 2.5 mg/week). MTX was administered at a maximum dosage ranging between 7.5 mg/week and 15 mg/week, except in 1 patient whose dosage of MTX was gradually increased to 17.5 mg/week.

MTX treatment effects on risk of first and second relapse. Ninety-eight (61%) of the 161 participants experienced a first relapse of GCA, and 46 (29%) experienced a second relapse. Among the individuals who had a first relapse, 59 (60%) had relapses of cranial signs and symptoms and 39 (40%) had relapses without cranial involvement. At 48 weeks and 96 weeks after randomization, the rates of first relapse were 72% (95% confidence interval [95% CI] 64–79%) and 74% (95% CI 66–82%), respectively, and the rates of second relapse were 31% (95% CI 23–40%) and 43% (95% CI 33–53%), respectively.

The HRs for the risk of a first or second relapse are presented in Figure 1 for all trials separately and as

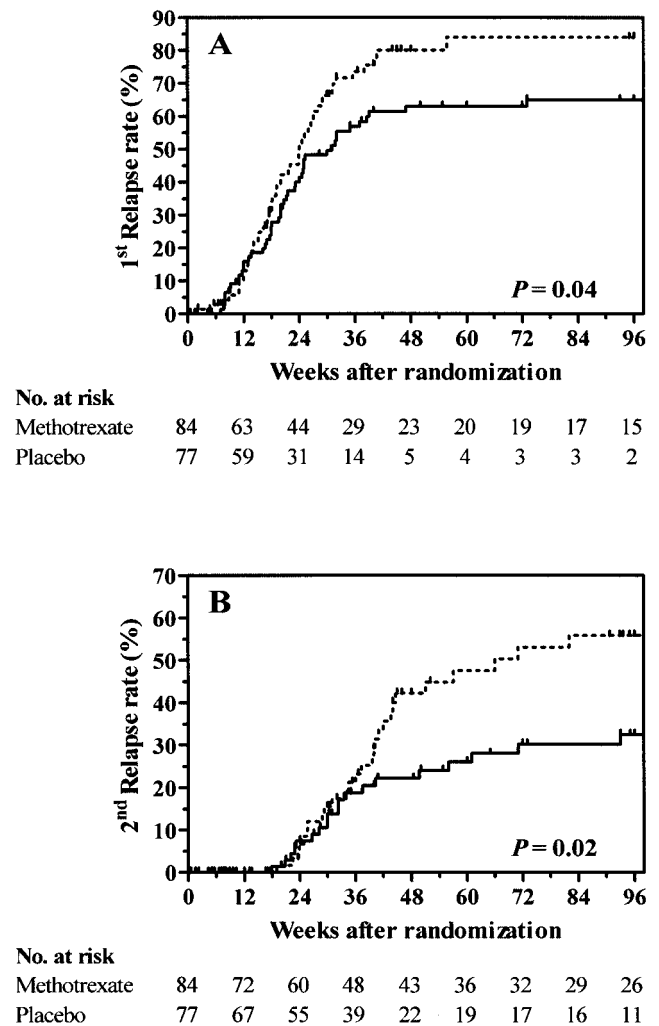


Figure 2. Rates of first (A) and second (B) relapse of giant cell arteritis among patients receiving adjunctive methotrexate (solid lines) versus those receiving placebo (broken lines).

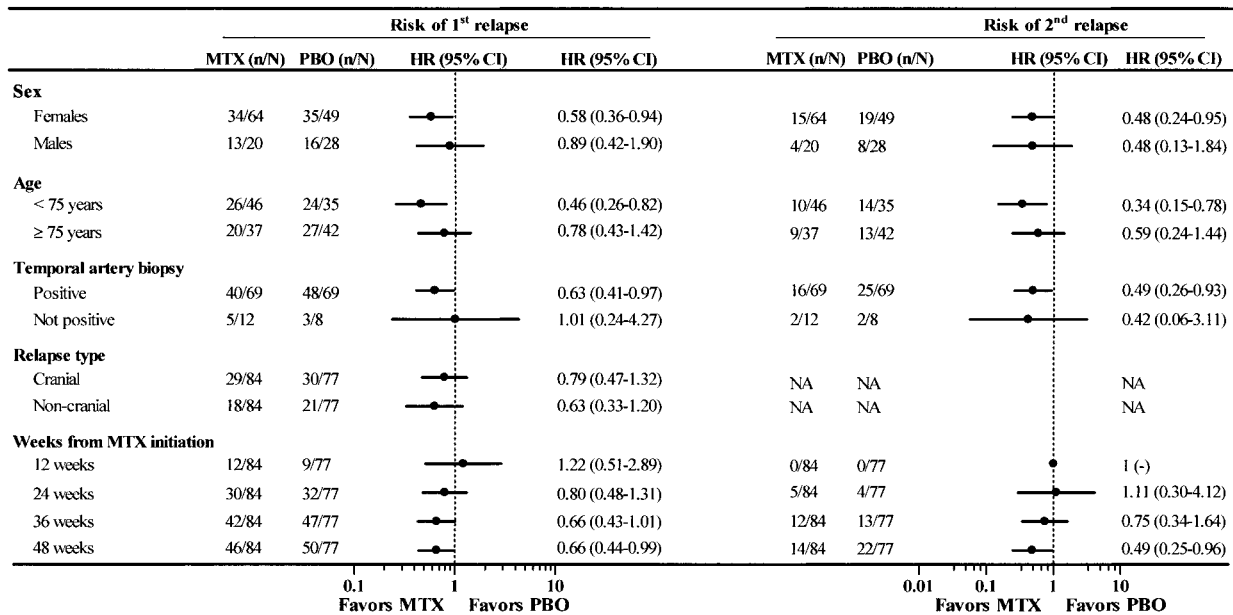


Figure 3. Subgroup and sensitivity analyses of hazard ratios (HRs) for the occurrence of a first or second relapse of giant cell arteritis in patients receiving adjunctive methotrexate (MTX) versus those receiving placebo (PBO). Values under each treatment group are the number of events (n) among the total number of subjects exposed (N). 95% CI = 95% confidence interval; NA = information not available.

pooled data. In the pooled analysis, MTX significantly reduced the risk of a first relapse and second relapse, with HRs of 0.65 (95% CI 0.44–0.98, *P* = 0.04) and 0.49 (95% CI 0.27–0.89, *P* = 0.02), respectively. Both the first relapse model and the second relapse model satisfied the assumption of proportional hazards, as evident graphically and on statistical analysis.

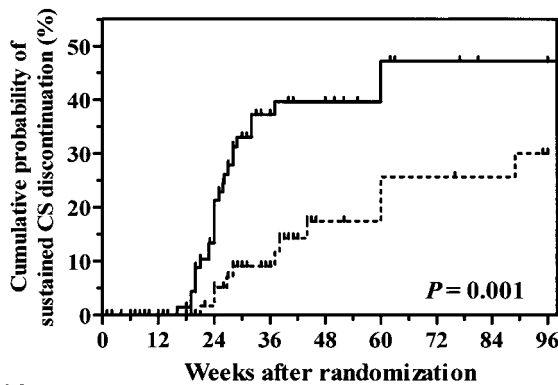
Figure 2 shows the Kaplan-Meier plots for the rate of first or second relapse over time by treatment group. At 48 weeks, among patients receiving MTX, the rates of a first and second relapse were 63% (95% CI 52–74%) and 22% (95% CI 12–32%), respectively, and among patients receiving placebo, the rates of a first and second relapse were 80% (95% CI 69–91%) and 42% (95% CI 29–56%), respectively. The rates of a first relapse of cranial signs and symptoms at 48 weeks were 40% (95% CI 28–51%) among the MTX group and 47% (95% CI 34–59%) among the placebo group.

Subgroup analyses (Figure 3), according to patients’ sex, age, temporal artery biopsy findings, relapse type, and duration of followup, demonstrated treatment effects of a similar magnitude as those observed overall. The sensitivity analyses in which the data were censored for maximum followups of 12 weeks, 24 weeks, 36 weeks, or 48 weeks following randomization showed a strengthening of the protective effect of MTX in reducing the relapse risk as the censoring time was increased (Figure

3). Sensitivity analyses involving only patients who were treatment completers also yielded a reduction in relapse risk both for the risk of first relapse (HR 0.65, 95% CI 0.42–0.99, *P* = 0.04) and for the risk of second relapse (HR 0.52, 95% CI 0.28–0.95, *P* = 0.03). Results from the per-protocol analyses of treatment effect within the specified subgroups or at specified time points were largely comparable with those from the intent-to-treat analysis (results not shown).

Based on the pooled estimates of reductions in relapse risk with the use of MTX, and using the 48-week relapse frequency in the placebo group as the expected event rate, we estimated the number of patients who would need to be treated with MTX to prevent the occurrence of one relapse. The number of individuals who would need to be treated with MTX to prevent one first relapse was 3.6 (95% CI 2.2–56.8), and for prevention of one second relapse, 4.7 individuals would need to be treated (95% CI 3.3–21.9). Similarly, for prevention of one first relapse of cranial signs and symptoms by 48 weeks, the predicted number of patients to be treated with MTX was 10.1 (95% CI –6.8 to 4.1).

MTX treatment effects on cumulative corticosteroid dose and time to sustained discontinuation of corticosteroids. The mean cumulative corticosteroid dose for the entire study population after 48 weeks of treatment was 3,754 mg (SD 1,231 mg), and after 96



No. at risk	84	72	54	27	21	15	12	10	9
Methotrexate	84	72	54	27	21	15	12	10	9
Placebo	77	68	56	37	22	19	18	17	14

Figure 4. Cumulative probability of achieving a sustained discontinuation of corticosteroids (CS) for at least 24 weeks in patients receiving methotrexate (solid line) versus patients receiving placebo (broken line).

weeks was 4,264 mg (SD 1,670 mg). According to calculations of the weighted mean differences, treatment with MTX reduced the cumulative exposure to corticosteroids by 124 mg (95% CI 28–220 mg, $P = 0.01$) at week 12, by 319 mg (95% CI 77–561 mg, $P = 0.01$) at week 24, by 681 mg (95% CI 300–1,063 mg, $P < 0.001$) at week 36, by 842 mg (95% CI 358–1,325 mg, $P < 0.001$) at week 48, by 1,015 mg (95% CI 435–1,594 mg, $P < 0.001$) at week 72, and by 1,101 mg (95% CI 308–1,894 mg, $P = 0.007$) at week 96.

Use of MTX also significantly increased the probability of achieving a sustained discontinuation of corticosteroids for ≥ 24 weeks (HR 2.84, 95% CI 1.52–5.28, $P = 0.001$) (Figure 4). Analyses for periods of corticosteroid discontinuation of ≥ 12 weeks, ≥ 36 weeks, or ≥ 48 weeks yielded HRs of 2.55 (95% CI 1.45–4.49, $P = 0.001$), 3.13 (95% CI 1.50–6.54, $P = 0.003$), and 3.47 (95% CI 1.47–8.18, $P = 0.005$). In the per-protocol analysis, the HR for discontinuation of corticosteroids for ≥ 24 weeks was 2.75 (95% CI 1.45–5.24, $P = 0.002$).

Adverse events. Comparisons of reported adverse events did not reveal any significant differences between treatment groups (Table 2). Among all patients, 8 withdrew early because of adverse events; 4 of these patients were MTX recipients and 4 were placebo recipients ($P = 1.0$).

Investigation of between-trial heterogeneity. Clinical heterogeneity was assessed by reviewing and comparing the designs and principal characteristics of the 3 trials identified (Table 3). All 3 trials included

patients with newly diagnosed GCA. In 1 of the studies (8), only individuals with positive temporal artery biopsy findings of GCA were enrolled, whereas in the remaining 2 studies (7,9), GCA could also be defined on the basis of a combination of clinical, laboratory, and/or angiographic criteria. Therapeutic regimens were comparable between 2 of the studies (7,8), whereas in 1 study (9), MTX had been initiated only secondarily, and a less stringent scheme for tapering of the corticosteroid dose was used.

Comparisons of the main demographic and clinical characteristics at baseline among the participants in the 3 studies revealed only slight, nonsignificant variations (results not shown). Conversely, there were significant differences in the lengths of followup, with mean durations of followup of 56.3 weeks (SD 23.2 weeks) (9), 90.9 weeks (SD 19.2 weeks) (8), and 38.8 weeks (SD 38.1 weeks) (7) ($P < 0.001$ for all pairwise comparisons). When the trials were compared for the time to date of first relapse or to date of censoring, we also found that substantial variations existed in the lengths of followup, with mean values of 42.3 weeks (SD 23.3 weeks) (9), 47.4 weeks (SD 35.6 weeks) (8), and 24.4 weeks (SD 27.7 weeks) (7) ($P = 0.54$, $P < 0.001$, and $P < 0.001$, respectively, for pairwise comparisons). Similarly, in the 3 trials, the mean time to date of second relapse or to date of censoring was 52.1 weeks (SD 21.5 weeks) (9), 80.2 weeks (SD 25.4 weeks) (8), and 38.8 weeks (SD 38.1 weeks) (7) ($P < 0.001$ for all pairwise comparisons).

In analyses using the treatment–trial interaction term, statistical heterogeneity in the treatment effect across studies was not found in the models that analyzed the risk of first relapse ($P = 0.12$) or second relapse ($P = 0.16$). Analyses of the variability of treatment effect showed no interactions of the risk estimates of a first or

Table 2. Types and frequency of adverse events*

Type of adverse event	Treatment group			<i>P</i> , methotrexate versus placebo
	All patients (n = 161)	Methotrexate (n = 84)	Placebo (n = 77)	
Infection	35 (22)	17 (20)	18 (23)	0.63
Abnormal liver function test findings	28 (17)	14 (17)	14 (18)	0.80
Fractures	13 (8)	7 (8)	6 (8)	0.90
Diabetes	13 (8)	4 (5)	9 (12)	0.11
Malignancy	6 (4)	4 (5)	2 (3)	0.68
Thrombocytopenia	6 (4)	4 (5)	2 (3)	0.68
Leukopenia	1 (1)	1 (2)	0 (0)	1.0

* Values are the number (%) of patients.

Table 3. Summary of the study protocol characteristics of the randomized controlled trials included in the meta-analysis*

	Hoffman et al, 2002 (7)	Jover et al, 2001 (8)	Spiera et al, 2001 (9)
Inclusion criteria	Study specific†	Positive temporal artery biopsy findings	Study specific†
MTX therapy			
Dosage	0.15 mg/kg/week, increased to maximum of 0.25 mg/kg/week or 15 mg/week (within 2 weeks)	10 mg/week	7.5 mg/week (maximum 20 mg/week)
Time of initiation relative to CS regimen	Simultaneous	Simultaneous	Delayed until prednisone dosage decreased to 30 mg/day
Duration	~18–24 months	24 months	~12–18 months
Foli(ni)c acid supplementation	Yes	Yes (after protocol amendment)	Yes
CS therapy			
Initial prednisone dosage	1 mg/kg/day (maximum 60 mg/day)	60 mg/day	1 mg/kg/day‡
Administration scheme	Daily then alternate day	Daily	Daily
Duration	~6 months	~6 months	Not stated
Relapse dosage	Increase to last effective dosage plus additional 10 mg/day	Increase to minimum amount that controlled disease	Increase upon decision of the treating physician
Definition of relapse	Change in ESR from normal to ≥ 40 mm/hour plus at least 1 study-specific clinical and/or angiographic feature	Recurrence of GCA symptoms that reversed on resumption or increase of prednisone dosage	Recurrence of GCA symptoms that reversed on resumption or increase of prednisone dosage
Study duration	Mean 12 months	96 weeks	12–24 months

* MTX = methotrexate; CS = corticosteroids; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis.

† For details of inclusion criteria, see Results.

‡ Three of 21 patients also received methylprednisolone intravenously (1,000 mg/day) for 1–3 days.

second relapse with age ($P = 0.45$ and $P = 0.73$, respectively), sex ($P = 0.45$ and $P = 0.86$, respectively), or positive findings on temporal artery biopsy ($P = 0.50$ and $P = 0.97$, respectively). Furthermore, no statistical heterogeneity between trials was detected for the probability of a sustained discontinuation of corticosteroids for ≥ 24 weeks ($P = 0.99$).

DISCUSSION

This individual patient data meta-analysis of 3 randomized placebo-controlled trials in patients with newly diagnosed GCA demonstrates that adjunctive MTX administered in dosages of 7.5–15 mg/week reduces the risk of first relapse by 35% and the risk of second relapse by 51%. In addition, this regimen reduces the cumulative exposure to corticosteroids and increases the probability of achieving a sustained discontinuation of corticosteroid treatment. Sensitivity and subgroup analyses consistently favored adjunctive MTX, notably in showing comparable effect sizes among patients with biopsy-proven GCA and for relapses of cranial signs and symptoms, and suggest that the pooled estimates are both robust and applicable to various clinical situations. Furthermore, at the prescribed dosages, MTX appeared to be well tolerated in patients with GCA.

By pooling the data from the 3 principal trials addressing this question, we aimed to obtain a more reliable estimate of the treatment effect of adjunctive low-dose MTX in GCA. In contrast to the use of summary statistics (as has been done in the majority of published meta-analyses [13]), analysis of the data at an individual patient level enabled us to homogenize the outcome measures and to evaluate time-to-event outcomes in order to maximally exploit the information available. An additional advantage of conducting meta-analyses of individual patient data is that it allows a more powerful exploration of potential sources of between-trial inconsistencies (14,15). With respect to the possible shortcoming that the data pooling was inappropriate because of dissimilarities between studies, we did not identify statistical heterogeneity in the primary outcomes across trials, and comparison of the respective study samples did not demonstrate any major clinical heterogeneity that would have suggested that the trials had enrolled dissimilar populations.

The findings of our meta-analysis support the possibility that the differences in length of followup might have contributed to the disparate results of the individual trials (11). The appearance of the relapse curves, and our sensitivity analyses that censored the

duration of followup at different time points, indeed suggest that the superiority of the treatment effect of MTX over placebo fully appears only after 24–36 weeks. This observation is consistent with that from a placebo-controlled trial of MTX in patients with isolated polymyalgia rheumatica (16), in whom a beneficial effect on relapse risk became apparent only after 24 weeks of treatment. The most likely explanation for these findings may be that there is a latency period before MTX exerts its pharmacologic action in patients with GCA and in those with isolated polymyalgia rheumatica.

The benefit conferred by MTX demonstrated in our study has to be balanced against several realizations. The absolute reduction in relapse risk by MTX remains moderate, as exemplified by the fact that 4, 5, or 11 individuals would have to be treated to prevent one first relapse, one second relapse, or one first relapse of cranial symptoms up to 48 weeks. Although a main goal of prescribing MTX is to reduce the occurrence of corticosteroid-related adverse events, our findings did not demonstrate a significant difference in therapy-related side effects, presumably because none of the trials included in this meta-analysis had been specifically designed to study this issue. The followup periods in the original studies were likely too short to demonstrate such a difference in effect, given that the mean interval up to the occurrence of the first corticosteroid-related adverse events after initiation of therapy for GCA has been shown to be 2.7 years (4). Nonetheless, there is evidence that the occurrence of corticosteroid-associated morbidity in GCA is directly related to the cumulative dose of corticosteroids (4).

Therefore, the question arises whether an 800-mg decrease in the cumulative dose of prednisone by week 48 is a clinical outcome sufficiently meaningful to justify the additional risk of MTX-induced side effects. Indeed, whereas low-dose MTX has been proven to have a favorable toxicity profile even in populations of elderly patients (17,18), other observations indicate that increasing age is a risk factor for severe side effects, including myelosuppression (19–21) and liver disease (22). On the other hand, the true corticosteroid-sparing effect of MTX was perhaps underestimated in our study, because one of the original trials did not extend the followup of participants beyond the occurrence of a first or second relapse (7), thereby overlooking the period in which the greatest corticosteroid-sparing potential of MTX could be observed.

The present study has some limitations. Although this is the largest effort made to address this topic thus far, the number of individuals included in the meta-

analysis was relatively small and the mean observation time did not exceed 55 weeks. Therefore, our study might have lacked statistical power to adequately assess the benefit of MTX in specific subgroups. Similarly, the small number of studies assembled in this meta-analysis prevented us from more in-depth investigation of further sources of heterogeneity, such as the potential effects of the differing corticosteroid-tapering schemes as well as the influence of corticosteroid treatment prior to initiation of MTX. Because the MTX regimen used in the trials fell within a small dose range, we could not evaluate a potential dose-response effect, and it remains unknown whether increased MTX dosages, such as 20–25 mg/week, as has been routinely used in treatment of other vasculitides (23–25), might be both more efficacious and acceptably safe in this elderly population.

Our study results lead to questions of how MTX should be incorporated in the therapeutic armamentarium for GCA. MTX had a favorable impact on almost all of the investigated outcomes. Whereas our findings may not provide sufficient evidence to establish MTX plus prednisone as the current standard of care for patients with GCA, this treatment could be considered as an option at the time of diagnosis. MTX might be particularly useful in treating individuals at highest risk of experiencing corticosteroid-related side effects because of comorbid conditions such as diabetes mellitus, severe hypertension, and severe osteoporosis or because of older age (4,6). The results of our study also imply, but do not directly demonstrate, that MTX may be a reasonable choice for treatment of the subset of individuals who have a prolonged GCA course.

To summarize, this individual patient data meta-analysis supports low-dose MTX as an effective corticosteroid-sparing agent, which should be considered as a therapeutic option for patients with GCA. Further studies are warranted to clarify the benefits conferred by MTX in terms of reductions in side effects, and to assess the efficacy and safety of higher doses of MTX for GCA.

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AUTHOR CONTRIBUTIONS

Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Mahr, Jover, Hernández-García, Fernández-Gutiérrez, Merkel.

Acquisition of data. Mahr, Jover, Spiera, Hernández-García, Fernández-Gutiérrez, Merkel.

Analysis and interpretation of data. Mahr, Jover, Spiera, Hernández-García, Fernández-Gutiérrez, LaValley, Merkel.

Manuscript preparation. Mahr, Jover, Fernández-Gutiérrez, LaValley, Merkel.

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