A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA)

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Abstract

Objective

To determine if methotrexate has disease-controlling and corticosteriod (cs)-sparing effects in the treatment of giant cell arteritis (GCA).

Methods

This was a randomized, controlled, double-blind trial comparing methotrexate versus placebo in addition to corticosteroid therapy in patients with newly diagnosed giant cell arteritis. Patients with giant cell arteritis were enrolled and treated with high dose corticosteroids as well as methotrexate starting at 7.5 mg/week or placebo. Corticosteroids were tapered by the treating physician as guided by the clinical picture, with methotrexate or placebo dose increased by 2.5 mg/week for disease flare with a maximum allowable dose of 20 mg/week. After a clinically-defined remission and steroid discontinuation, methotrexate or placebo was tapered monthly to zero by 2.5 mg/week.

Results

Twenty-one patients were enrolled, 12 randomized to methotrexate, 9 to placebo. Baseline characteristics (age, height, weight, sedimentation rate, bone mineral density, total corticosteroid dose prior to randomization, and quality of life as measured by SF-36 and function as measured by AIMS) were comparable between groups. At completion, there was no significant difference between methotrexate-and placebo-treated patients with regard to the cumulative corticosteroid dose (6469 mg and 5908 mg respectively, p=0.6), number of weeks to completion of steroids (68 and 60 respectively, p=0.5), time (weeks) to taper prednisone to less than 10 mg prednisone/day (23 and 25 respectively, p=0.5), bone mineral density in lumbar spine (p=0.2) or hip (p=0.4) at one year, or functional status as measured by AIMS and quality of life as measured by SF36. There was no late vision loss in either group, and only one major treatment-responsive relapse in a methotrexate-treated patient. There were few major corticosteroid-related side effects and these did not significantly differ between groups.

Conclusion

With this study design, no corticosteroid-sparing benefit could be attributed to the combination of methotrexate with corticosteroid therapy for the treatment of patients with giant cell arteritis. Both groups did well, with few major corticosteroid-related side effects, and most patients were safely tapered off corticosteroids sooner than reported in many series. The shorter overall duration of steroid treatment in this study probably contributed to the remarkably low frequency of side effects, without increased ischemic risk for the patient.

Key words

Giant cell arteritis, methotrexate, vasculitis.

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Introduction

Giant cell arteritis is a systemic disease characterized by granulomatous inflammation of medium and large arteries with a predilection for those arising from the aortic arch (1). Vision loss, which is often permanent, is the major feared complication, and occurs most commonly secondary to vasculitic involvement of the central retinal artery and posterior ciliary branches of the ophthalmic artery (2-5). Therapy with corticosteroids, generally used in high doses, is effective in controlling the inflammatory process and preventing further ischemic complications. The duration of corticosteroid therapy, however, is often prolonged, up to two years in most series (6-11). The morbidity of lengthy corticosteroid use is substantial, particularly in this older population in whom co-morbid medical conditions make them particularly susceptible to corticosteroid-induced complications. Most studies have found a greater than 50% incidence of major steroid-related complications in treated patients (8, 12-14). A number of potential corticosteroid-sparing agents have been examined, including azathioprine(15), dapsone (16-17), cyclophosphamide (18), and more recently methotrexate(19-21). Its relatively rapid onset of action and a more acceptable safety profile than some of the other immunosuppressives have stimulated the use of methotrexate therapy in a variety of vasculitides and inflammatory arthropathies. Open studies have suggested a possible steroid-sparing benefit due to the addition of methotrexate to the treatment regimen patients with of giant cell arteritis (19-20). We report here the results of a double blind, randomized, placebo-controlled trial assessing whether the addition of methotrexate to corticosteroid therapy has disease-controlling and steroid-sparing benefits and results in fewer steroid-related complications in patients with giant cell arteritis.

Materials and methods

Patient selection

Patients with newly-diagnosed giant cell arteritis (Table I) were enrolled within one month of diagnosis. Patients were excluded if they had active infectious or neoplastic disease, concomitant connective tissue disease, prior immunosuppressive therapy within the past year, and co-morbid disease that would preclude the use of methotrexate including: a history of adverse effects from methotrexate, including hypersensitivity pneumonitis, pulmonary fibrosis or insufficiency; creatinine > 2; elevated baseline transaminase measurements exceeding 2 times the upper limits of normal; acute or chronic liver disease; ongoing alcohol consumption; leukopenia or thrombocytopenia.

Treatment protocol

The study protocol was approved by the Hospital for Special Surgery institutional review board and informed consent was obtained. The patients were treated with corticosteroid therapy (range 40-1000 mgs daily) at diagnosis as determined by their treating physicians and based on their clinical

Table I. Diagnostic criteria.

Positive temporal artery biopsy consistent with active arteritis
Negative temporal artery biopsy with one of the following inclusion criteria:
Ischemic optic neuropathy with ESR > 50 mm/hour and the presence of polymyalgia rheumatica (PMR)
Stenotic disease of the aorta or its major branches (not attributable to atherosclerosis or cholesterol emboli) plus the presence of: PMR and ESR > 50, other clinical manifestations of GCA such as onset of headaches, scalp tenderness, and/or abnormal temporal arteries, unexplained tongue or jaw pain, or visual loss due to retinal ischemia.
An elevated ESR > 50 in the presence of 3 of the following symptoms: - severe headache, PMR, tender temporal arteries, jaw claudication, or visual disturbance - plus the absence of clinical evidence of other connective tissue disease, infection, or neoplasm - plus a favorable clinical response to high dose steroids

manifestations. Pulse steroids (1 gram of Solumedrol intravenously per day x 1-3 days) was employed in 3 patients with ophthalmologic signs or symptoms. Steroids were then tapered by the primary treating physician based upon clinical evidence of disease control. When the daily corticosteroid dose reached 30 mgs of prednisone, patients were randomly assigned to receive either methotrexate starting at 7.5 mgs weekly or placebo. A recommended treatment protocol suggested initial treatment with oral prednisone 1 mg/kg/day, then to be tapered by 10 mg per week to 40 mg daily once clinical and laboratory abnormalities resolved, then tapered by 5 mg/week to 20 mg by the end of the second month then by 2.5 mg/week until drug withdrawal. The prednisone taper would be curtailed for persistence or increased activity of the underlying disease. Although corticosteroid dosing was done in consultation and close communication with study physicians, the treating physician was ultimately responsible for decisions regarding corticosteroid dosing.

This was a double-blind trial with treatment assignment known only to the statistician and pharmacist; all others were blinded including patients, treating physicians, study physicians, and nurses. However, close monitoring of clinical and laboratory parameters assured safety. When a clinically-defined flare of disease was recognized, the steroid dose was increased as guided by the treating physician and the study drug (methotrexate or placebo) was increased by 2.5 mgs/week to a maximum allowable dose of 20 mg per week. A relapse was defined as a recurrence of prior or the development of new giant cell arteritis symptoms following a clear and sustained objective improvement, and symptom reversal upon resumption of or increase in steroid dosage. When corticosteroids were discontinued, methotrexate or placebo were tapered monthly by 2.5 mg/week to zero. All patients received folic acid 1 mg daily, 1500/mgm of calcium carbonate and 800 I.U. of vitamin D3 supplements. The treating physicians guided the use of adjunctive anti-resorptive medications.

Measurements

The patients were evaluated by the study physician at entry, at randomization to methotrexate or placebo (when the steroid dose reached 30 mgs daily prednisone equivalent), then at a minimum of every third month until the patient was off prednisone and methotrexate for one year. Treating physicians saw the patients more frequently, as guided by clinical necessity. On a daily basis, patients recorded their glucocorticoid dosage and concurrent medications and medication changes in diaries that were reviewed by the study coordinator at each visit. Laboratory studies obtained included complete blood counts, liver function profiles, glucose, and sedimentation rate. Anteroposterior and lateral radiographs of the lumbar spine as well as bone mineral density measurements of the lumbar spine and hip measured by dual energy X-ray absorptometry were obtained at baseline, 1 year, and 2 year follow-ups. The presence of fractures at baseline and of new fractures at follow-up examinations were determined by measurement of vertebral dimensions (14). Quality of life measurements were obtained at baseline and at 1 year using the SF-36 and functional assessment using AIMS patient questionnaires. Formal detailed ophthalmologic evaluations were also obtained at baseline, and then every third month during the study.

Primary outcome: Cumulative corticosteroid dose.

Secondary outcomes: Total duration of corticosteroid treatment, length of time to reach a 10mg daily prednisone dose, numbers of disease flares.

Data analysis and power

We had based our study and power calculations on previous data from Hernandez *et al.* (20), who found a total prednisone dose of 3400 ± 1030 mg in eleven GCA patients who had been treated with methotrexate in addition to prednisone. Our previous study had resulted in a cumulative steroid dose of 5033 mg over a mean of 22 months with a standard deviation of approximately 800 mg (14). Therefore, a 1500 mg dose difference was assumed with a standard deviation of 1000. Alpha was set at 0.05. Ten patients per group would give a power of 0.9 to detect this dose difference. All variables were examined at baseline using univariate statistics. All variables were examined for their association both with the treatment group and the prednisone dose. Differences between groups were analyzed using t-tests or non-parametric tests as appropriate. The time to complete therapy was analyzed using survival techniques.

The change in SF-36 data was compared between groups using the baseline as a covariate. The AIMS-2 data was analyzed in a comparable manner.

Results

Of 171 patients approached for the study, only 21 were ultimately enrolled. Sixty three patients refused to participate (39 did not want to be in any study, 17 cited difficulties with travel to study centers, 7 gave no reasons), 85 patients did not meet criteria, the majority having already been tapered below 30 mg daily prednisone prior to referral to the study. Two patients were randomized, but excluded prior to starting study drug (one found to be PPD positive and started on isoniazid, precluding in her treating physician's opinion exposure to further potential hepatotoxic agents, and one was hospitalized with congestive heart failure). Twenty-one patients enrolled from 1994 through 1996, 12 randomized to methotrexate and 9 to placebo. The characteristics of the patients are shown in Table II. All patients fulfilled the ACR criteria for classification as GCA (22). There was no significant difference at baseline in age, height, weight, blood pressure, sedimentation rate, or length of time on steroids prior to randomization. Bone density in the hip and lumbar spine, as well the number of fractures at baseline in the lumbar spine, were comparable. Seventeen patients had positive temporal artery biopsies. The total dose of prednisone prior to institution of the study drug was comparable and the two groups were similar clinically in terms of presenting signs and symptoms (Table III).

There were two dropouts in the methotrexate-treated group, both late in the

Table II. Baseline characteristics.

	Methotrexate group	Placebo group	P-value
Number of patients	12	9	
Average age	72 ± 7 (range 57 - 84 yr)	74 ± 6 (range 57 - 84 yr)	0.4
Female (percent of total)	9 (75%)	4 (56%)	0.3
Height	159.8 ± 11 cm	165.1 ± 9 cm	0.3
Weight	65.3 ± 19 kg	66.7 ± 11 kg	0.9
Positive temporal artery biopsy (percent positive)	10 (83%)	7 (78%)	0.7
Sedimentation rate at diagnosis (mm/hour Westergren)	70 ± 33	72 ± 36	0.4
BMD hip (femoral neck)	0.694/cm^2 ± 0.2	0.833 ± 0.2 g/cm^2	0.3
BMD spine (L2 - L4)	1.00/cm^2 ± 0.3	1.217 ± 0.4 g/cm^2	0.7
Total corticosteroid dose at randomization	2,826 ± 1300 mg	2,743 ± 1345 mg	0.9

course of treatment, and while on less than 10 mg of daily prednisone: one was diagnosed with colon cancer requiring surgical intervention at week 48, and a second dropped out at week 62 when she was hospitalized with congestive heart failure felt to be unrelated to GCA or its therapy. There was one late major flare of disease in the methotrexate treated group. This patient developed a pulseless left upper extremity with a concomitant rise in her sedimentation rate, both of which responded to resumption of corticosteroid therapy, with eventual return of the pulse. Minor flares occurred in 5 methotrexate treated patients (2 polymyalgia, 2 increased headache, and 1 with jaw claudication) and in 3 placebo treated patients (2 polymyalgia and 1 increased headache). Adverse effects were comparable between groups (Table IV). No patients in either group developed visual loss or worsening of vision more than 5 days after the initiation of corticosteroid therapy. No significant cataractous or glaucomatous changes developed in either group during the course of the study. Details of ophthalmologic measurements in the group are reported elsewhere (23).

Table III. Presenting signs and symptoms.

	Methotrexate group	Placebo group
Temporal artery biopsy		
Positive	10 positive	7 positive
Negative	2 negative	2 negative
Visual loss due to:		
- Central retinal artery occlusion	1	2
- Ischemic optic neuropathy	0	3
Headache	11	6
Scalp tenderness	8	6
Ear pain	5	3
Jaw pain	8	6
Tongue pain	2	0
Weight loss	10	8
General malaise	11	7
Fever	3	1
Pulse loss	2	0
Polymyalgia rheumatica	7	5

There were no statistically significant differences between methotrexate- and placebo-treated patients with regard to the cumulative corticosteroid dose (6469 mgs±2024 and 5908 mgs ±2131 respectively, p=0.6) (Fig. 1). Moreover, the number of weeks to corticosteroid completion (68 and 60 weeks respectively, p=0.5) (Fig. 2), time to reach a corticosteroid dose of less than 10 mg of prednisone (23 and 25 weeks respectively, p=0.6), average dose of study (methotrexate or placebo) drug (8.4 mg and 7.8 mg respectively, p=0.6), bone mineral density measurements in the lumbar spine (p=0.2) or hip (p=0.4) at one year, or quality of life as measured by SF-36 or functional status as measured by AIMS were not statistically significantly different between groups. The power of the study to detect a 30% difference in cumulative corticosteroid dose between groups was 0.6 and the power to detect a 50% difference in the cumulative corticosteroid dose was 0.92.

Using analysis of variance, we examined the effect of the ESR measurement, as a covariate, on the prescribed prednisone dose. The effect of the measured ESR was not statistically significant p=0.5.

Discussion

Using our study design, we could not demonstrate a corticosteroid-sparing or improved disease-controlling effect by the addition of methotrexate to conventional corticosteroid therapy in the treatment of giant cell arteritis. Prior studies of methotrexate in polymyalgia rheumatica have led to conflicting results regarding its efficacy (19-21). In Vander Veen's study (21), 40 patients with polymyalgia rheumatica were treated with methotrexate 7.5 mg weekly or placebo in addition to prednisone starting at 20 mg daily. Thirty seven patients also underwent temporal artery biopsy, and of those 6 were positive. Overall, no benefit was found in methotrexate-treated patients in terms of time to remission, duration of remission, number of relapses, or cumulative

Table IV. Adverse effects.

	Methotrexate	Placebo
Musculoskeletal		
Muscle weakness (subjective)	12	8
Back pain	5	3
Vertebral fracture	1	3
Neuropsychiatric		
Mood changes	12	9
Tired and/or insomnia	10	7
Tremors	6	2
Loss of balance/dizzy	3	5
Memory loss	3	0
Gastrointestinal		
Gastric discomfort	10	6
Diarrhea	1	0
Dermatologic		
Skin fragility	4	1
Alopecia	6	5
Hirsuitism	1	1
Rash	1	2
Acne	0	1
Endocrine		
Cushingoid	3	3
Hyperglycemia	1	1
Infectious		
Cellulitis	1	1
Herpes Zoster	2	1
Fungal (skin)	2	0
Urinary tract infection	1	1
Pneumonia	0	1
Malignancy		
Adenocarcinoma (colon)	1	0
Squamous cell carcinoma	0	1
Basal cell	1	0

prednisone dose. The data however was not explicitly presented for that subgroup of patients with giant cell arteritis. In a multi-center international study by Hoffman *et al*. of 98 patients with GCA (24), methotrexate (median dose of 15 mg) did not permit more effective disease control, nor did it afford a steroid-sparing benefit. In contrast, Jover *et al*. found a combination of methotrexate and corticosteroids to be superior to corticosteroids alone in a study of 42 patients with GCA (25). Our study included 21 patients with giant cell arteritis and although the power to detect a small difference in cumulative corticosteroid dose was limited, there was reasonable power to exclude a large and clinically- meaningful steroid-sparing benefit.

One possible reason for the lack of efficacy in our study could be related to the fact that our starting methotrexate dose was lower than might be effective in this type of vasculitis. The reason for choosing the 7.5 mg/weekly oral dose included the fact that it was a fairly standard initial dose used in the treatment of inflammatory arthopathies at the time of design development and also our attempt to carefully balance the cumulative toxicities of prednisone and methotrexate in an elderly population. Actually, the optimal dosing regimen for the treatment of a broad range of vasculitides is unknown. Studies in Wegener's granulomatosis, for example, have demonstrated efficacy at a weekly methotrexate dose of 15 mg or more (26-28). Despite the fact that giant cell arteritis and Wegener's granulomatosis are both granulomatous disorders, it is not at all clear that the experience gained with Wegener's granulomatosis can be extended to patients with giant cell arteritis. This is supported by the fact that while the use of cytotoxic agents plus steroids are mandatory for the successful treatment of Wegener's granulomatosis, steroids alone are generally quite effective in the treatment of giant cell arteritis. Further, giant cell arteritis is generally a self-limited inflammatory disorder and Wegener's granulomatosis tends to be chronic.

Another consideration is whether the delayed addition of methotrexate contributed to its apparent lack of efficacy in this study. The consensus among the participating investigators was that adding methotrexate to high dose corticosteroids (>30 mg daily prednisone) would confer an unacceptably high risk in this elderly population. It seems likely, however, that if methotrexate had a substantial corticosteroid-sparing benefit in this type of vasculitis, it would have been demonstrable in the period of taper studied.

Our study design did not call for a uniform corticosteroid dosing regimen, although one was suggested to the participating physicians. This was done to facilitate patient accrual and with the recognition that there is no single, uniformly-accepted correct dosing schedule for corticosteroids in this disease. This limitation, however, led to greater variability and therefore detracted from the power of the study. Nevertheless, if addition of methotrexate to conventional therapy had a powerful corticosteroid-sparing effect, we would have expected this to result in a recognition of earlier and more complete disease control in the active treatment group, resulting in a more rapid corticosteroid taper. No such effect was observed.

Our cohort of patients did well in general. Late vision loss did not occur, and only one patient suffered a major relapse (pulseless upper extremity) which responded to resumption of corticosteroid therapy. Interestingly, that

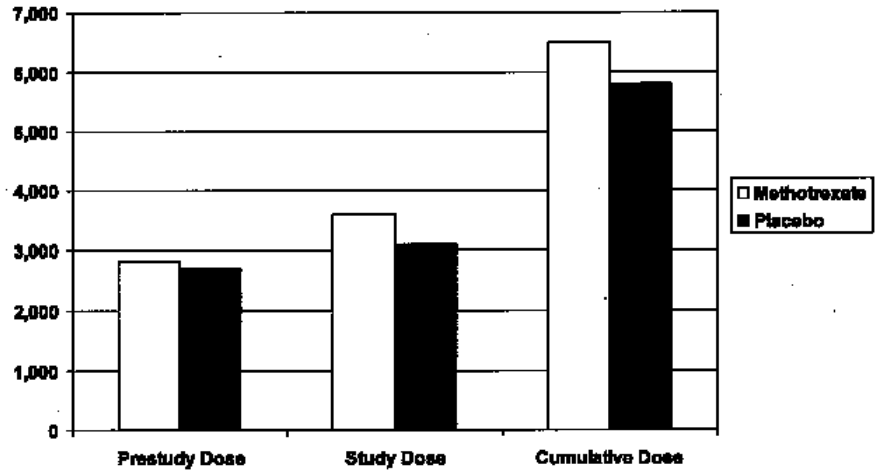

Fig. 1. Profile of corticorsteroid dosing.

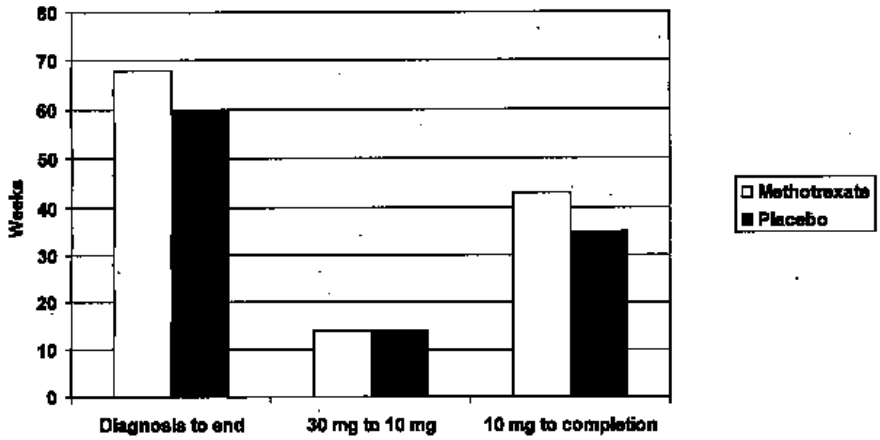

Fig. 2. Average number of weeks on corticosteroids.

patient was off of corticosteroids but still on 7.5 mg of weekly methotrexate at the time of her relapse. The mean duration of corticosteroid therapy was just over 1 year, which is considerably shorter than what is often reported in the literature and other series where a duration of therapy of two to five years has been described (6-11). In general, steroid tapering was guided by symptoms and not by fluctuations in the sedimentation rate, resulting in the shorter yet safe duration of treatment. We retrospectively attempted to correlate an increase in sedimentation rate with changes in dose of steroids in 7 patients, and correlations were low and not statistically significant. This shorter duration of treatment is the likely reason for the paucity of serious steroid-related side effects, even compared with a prior study by the same group of referring and treating physicians assessing patients with giant cell arteritis and polymyalgia rheumatica(14). In that study, the total duration of steroid therapy was longer (mean 88 weeks), and our suspicion is that even with similar cumulative steroid doses, the duration of therapy has more to do with steroid-related morbidity than the cumulative dose of corticosteroids *per se*. Another likely contributing factor is our enhanced sensitivity to bone density issues, and the efficacy of our available antiresorptive medications along with rigorous attention to adequate calcium and vitamin D supplementation. It has been shown that calcium and vitamin D supplements are helpful in preventing steroid-induced bone loss in patients with rheumatic diseases treated with low dose steroids (14, 29, 30). Fifty percent of our patients were also on antiresorptive medications, which similarly have been shown to prevent corticosteriod-induced osteoporosis (31, 32)

Our data supports the concept that by adopting an aggressive steroid tapering schedule after an initial period of optimal disease control, along with attending closely to co-morbidities and prevention and treatment of corticosteriods complications, the issue of a need for steriod-sparing therapy in this vasculitis is less relevant in many patients.

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