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# A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis

1. Gary S. Hoffman<sup>1,\*</sup>,
2. Maria C. Cid<sup>2</sup>,
3. David B. Hellmann<sup>3</sup>,
4. Loic Guillevin<sup>4</sup>,
5. John H. Stone<sup>3</sup>,
6. John Schousboe<sup>5</sup>,
7. Pascal Cohen<sup>4</sup>,
8. Leonard H. Calabrese<sup>1</sup>,
9. Howard Dickler<sup>6</sup>,
10. Peter A. Merkel<sup>7</sup>,
11. Paul Fortin<sup>8</sup>,
12. John A. Flynn<sup>3</sup>,
13. Geri A. Locker<sup>1</sup>,
14. Kirk A. Easley<sup>1</sup>,
15. Eric Schned<sup>5</sup>,
16. Gene G. Hunder<sup>9</sup>,
17. Michael C. Sneller<sup>6</sup>,
18. Carol Tuggle<sup>1</sup>,
19. Howard Swanson<sup>10</sup>,
20. J. Hernández-Rodríguez<sup>2</sup>,
21. Alfons Lopez-Soto<sup>2</sup>,
22. Debora Bork<sup>1</sup>,
23. Diane B. Hoffman<sup>1</sup>,
24. Kenneth Kalunian<sup>11</sup>,
25. David Klashman<sup>11</sup>,
26. William S. Wilke<sup>1</sup>,
27. Raymond J. Scheetz<sup>1</sup>,
28. Brian F. Mandell<sup>1</sup>,
29. Barri J. Fessler<sup>1</sup>,
30. Gregory Kosmorsky<sup>1</sup>,
31. Richard Prayson<sup>1</sup>,
32. Raashid A. Luqmani<sup>12</sup>,

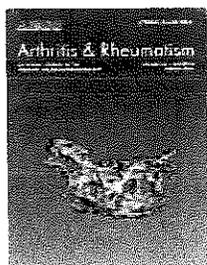
33. George Nuki,<sup>1</sup>  
34. Euan McRorie<sup>12</sup>,  
35. Yvonne Sherrer<sup>13</sup>,  
36. Shawn Baca<sup>14</sup>,  
37. Bridgit Walsh<sup>15</sup>,  
38. Diane Ferland<sup>7</sup>,  
39. Martin Soubrier<sup>4</sup>,  
40. Hyon K. Choi<sup>7</sup>,  
41. Wolfgang Gross<sup>16</sup>,  
42. Allen M. Segal<sup>1</sup>,  
43. Charles Ludivico<sup>17</sup>,  
44. Xavier Puechal<sup>4</sup>,  
45. International Network for the Study of Systematic Vasculitides (INSSYS)

Article first published online: 8 MAY 2002

DOI: 10.1002/art.10262

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Issue



## Arthritis & Rheumatism

Volume 46, Issue 5, ([/doi/10.1002/art.v46:5/issuetoc](https://doi.org/10.1002/art.v46:5/issuetoc)) pages 1309–1318, May 2002

Additional Information

### How to Cite

Hoffman, G. S., Cid, M. C., Hellmann, D. B., Guillevin, L., Stone, J. H., Schousboe, J., Cohen, P., Calabrese, L. H., Dickler, H., Merkel, P. A., Fortin, P., Flynn, J. A., Locker, G. A., Easley, K. A., Schned, E., Hunder, G. G., Sneller, M. C., Tuggle, C., Swanson, H., Hernández-Rodríguez, J., Lopez-Soto, A., Bork, D., Hoffman, D. B., Kalunian, K., Klashman, D., Wilke, W. S., Scheetz, R. J., Mandell, B. F., Fessler, B. J., Kosmorsky, G., Prayson, R., Luqmani, R. A., Nuki, G., McRorie, E., Sherrer, Y., Baca, S., Walsh, B., Ferland, D., Soubrier, M., Choi, H. K., Gross, W., Segal, A. M., Ludivico, C., Puechal, X. and International Network for the Study of Systematic Vasculitides (INSSYS) (2002), A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis & Rheumatism*, 46: 1309–1318. doi: 10.1002/art.10262

### Author Information

<sup>1</sup> Cleveland Clinic Foundation, Cleveland, Ohio

<sup>2</sup> Hospital Clinic í Provincial, Barcelona, Spain

- 3 Johns Hopkins University School of Medicine, Baltimore, Maryland
- 4 Universite Paris XIII, Paris, France
- 5 Park Nicollet Medical Foundation, St. Louis Park, Minnesota
- 6 NIH, Bethesda, Maryland
- 7 Massachusetts General Hospital, Boston
- 8 Montreal General Hospital/McGill University, Montreal, Quebec, Canada
- 9 Mayo Clinic, Rochester, Minnesota
- 10 Marshfield Clinic, Marshfield, Wisconsin
- 11 University of California, Los Angeles
- 12 Western General Hospital, Edinburgh, Scotland
- 13 Center for Rheumatology, Immunology & Arthritis, Fort Lauderdale, Florida, and Rheumatology Association of South Florida, Delray Beach
- 14 Center for Rheumatology, Immunology & Arthritis, Fort Lauderdale, Florida
- 15 University of Arizona, Tucson
- 16 Medizinische Universität zu Lubeck, Lubeck, Germany
- 17 Bethlehem, Pennsylvania

Email: Gary S. Hoffman (hoffmag@ccf.org)

\*Harold C. Schott Chair of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation A50, 9500 Euclid Avenue, Cleveland, OH 44915

### Publication History

1. Issue published online: 8 MAY 2002
2. Article first published online: 8 MAY 2002
3. Manuscript Accepted: 11 JAN 2002
4. Manuscript Received: 25 SEP 2001

### Funded by

- Food and Drug Administration and the Office of Orphan Products Development. Grant Number: FD-R 001040
- George B. Storer Foundation
- Ayhan Sahenk Foundation
- Fondo de Investigación Sanitaria. Grant Number: FIS 98/0443

- [Abstract \(/doi/10.1002/art.10262/abstract\)](http://doi/10.1002/art.10262/abstract)
- [Article](#)
- [References \(/doi/10.1002/art.10262/references\)](http://doi/10.1002/art.10262/references)
- [Cited By \(/doi/10.1002/art.10262/citedby\)](http://doi/10.1002/art.10262/citedby)

## Abstract

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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 ( $\leq 60$  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 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

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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

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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  $\geq 40$  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  $\geq 2.0$  mg/dl), white blood cell count  $< 4,000/\text{mm}^3$ , platelet count  $< 120,000/\text{mm}^3$ , 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  $\leq 72$  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 folic 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.

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  $\geq 3$  times the upper limits of normal, that did not diminish to  $< 1\frac{1}{2}$  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.