Methotrexate plus prednisone was more effective than prednisone monotherapy in giant-cell arteritis

Jover JA, Hernández-García C, Morado IC, et al. **Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial.** Ann Intern Med. 2001 Jan 16;134:106-14.

QUESTION

What are the safety and effectiveness of methotrexate plus prednisone in giant-cell arteritis?

DESIGN

Randomized (unclear allocation concealment*), double-blind (physicians and patients),* placebo-controlled trial with 24-month follow-up.

SETTING

University-based clinic in Madrid, Spain.

PATIENTS

42 patients (mean age 78 y, 69% women) with newly diagnosed, biopsy-confirmed, active giant-cell arteritis who had had < 2 weeks of treatment with a high-dose corticosteroid. Exclusion criteria were contraindications to methotrexate, renal failure, alcohol abuse, chronic infection, history of neoplasm or another condition that might hinder follow-up, history of poor compliance with other treatments, use of low-dose steroids for > 3 months before the study, or previous immunosuppressive drug use. Follow-up was 93%.

INTERVENTION

Patients were allocated to receive oral methotrexate, 10 mg/wk (n = 21), or placebo (n = 21) for 24 months. All patients received oral prednisone at an initial dose of 60 mg/d, which was tapered over about 6 months until it was completely withdrawn. Prednisone tapering could be adjusted if response to initial therapy was not complete or if relapse occurred or was suspected. In addition, all patients received oral calcium, 1000 mg/d; oral vitamin D_3, 600 IU/d; and oral folic acid, 5 mg/d. Patients with a history of tuberculosis received oral isoniazid, 600 mg/d, during the first 6 months.

MAIN OUTCOME MEASURES

Disease relapse, defined as recurrent symptoms of giant-cell arteritis, that improved with reversal of symptoms on prednisone; cumulative dose of prednisone during follow-up; and number of adverse events (including complications from corticosteroid use).

MAIN RESULTS

Fewer patients who received methotrexate plus prednisone had ≥ 1 relapse (P = 0.02), ≥ 2 relapses (P < 0.01), or cranial relapse {P = 0.04}† than did those who received placebo plus prednisone (Table). More patients who received methotrexate plus prednisone had no relapse than did those who received placebo plus prednisone (P = 0.004) (Table). Patients who received methotrexate plus prednisone used a lower cumulative dose of prednisone during follow-up than did those who received placebo plus prednisone (4187 vs 5490 mg, P < 0.01). Groups did not differ for rate or severity of adverse events (including complications from corticosteroid use).

CONCLUSION

Methotrexate-plus-prednisone therapy was safe and more effective than prednisone monotherapy in lowering the rate of disease relapse in patients with giant-cell arteritis.

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*See Glossary.

†P value provided by author.

Methotrexate plus prednisone (combination therapy) vs prednisone monotherapy for rate of disease relapse in giant-cell arteritis at 24 months‡

Outcomes	Combination	Prednisone	RRR (95% CI)	NNT (CI)
≥ 1 relapse	45%	84%	47% (14 to 70)	3 (2 to 11)
≥ 2 relapses	10%	47%	79% (27 to 94)	3 (2 to 11)
Cranial relapse	10%	37%	73% (2 to 93)	4 (2 to 2242)
			RBI (CI)	
No relapse	55%	16%	248 (29 to 952)	3 (2 to 11)

‡Abbreviations defined in Glossary; RRR, RBI, NNT, and CI calculated from data in article.

COMMENTARY

Giant-cell arteritis is a common, curable condition whose treatment, corticosteroids, has substantial side effects. Thus, the quest in giant-cell arteritis has been for an equally efficacious and less toxic alternative. Jover and colleagues have provided the first important study in the search for the desired steroid-sparing therapy. Was it a success? Patients who received combined methotrexate plus prednisone had 47% fewer relapses and used a cumulative steroid dose that was 1300 mg lower over 2 years than those who received prednisone alone. However, no statistical difference existed in steroid side effects, and 2 patients (10%) developed pancytopenia while receiving methotrexate.

Should we commit patients with giant-cell arteritis to initial therapy with methotrexate? Although methotrexate may become the standard of care, 1 small, albeit insightful, trial does not provide a basis for such a change. First, study patients may have had more severe disease. The relapse rate and proportion of patients with visual impairment were at the upper end of that reported previously (1). Second, the benefit of methotrexate did not appear for 5 to 6 months; therefore, waiting may be an option. Third, the risk-to-benefit ratio is uncertain. A clinician would need to treat 3 to 4 patients with methotrexate plus steroids to see fewer relapses than with steroids alone; however, 1 of 10 patients would have pancytopenia with methotrexate, and steroid side effects would not be lessened.

Until a larger confirmatory trial is available, clinicians should consider treating giant-cell arteritis initially with prednisone alone. For those patients who have a relapse with cranial symptoms (e.g., vision loss, jaw claudication, abnormal temporal artery, and headache), however, methotrexate may be an effective steroid-sparing alternative.

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Reference

1. **Duhaut P, Pinede L, Bornet H, et al.** Ann Rheum Dis. 1999;58:335-41.