Is MTX Best for Giant Cell Arteritis And Polymyalgia Rheumatica?

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NEW YORK — More questions than answers remain regarding the use of methotrexate for giant cell arteritis and polymyalgia rheumatica, despite international efforts to identify a therapeutic approach that could avoid the adverse consequences of long-term corticosteroid use in the vulnerable population afflicted by these conditions.

Prednisone has long been the mainstay of treatment for patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR), disorders that are seen almost exclusively in patients older than 50 years, and it is clearly effective in reducing inflammation and controlling disease. The corticosteroid typically must be administered for at least 1-2 years, however, which places patients at risk for adverse effects such as osteoporosis, cataracts, hypertension, and hyperglycemia.

In one series of 124 PMR patients who were treated with an average daily dose of 9.6 mg prednisone for 1.6 years, 65% experienced at least one adverse event, said Dr. Marco A. Cimmino of the University of Genoa (Italy).

Methotrexate has been widely used in PMR, although early experience, which was largely uncontrolled, provided inconclusive results, Dr. Cimmino said at the Fourth International Conference on Giant Cell Arteritis and Polymyalgia Rheumatica.

In order to more clearly establish an evidence base for the use of methotrexate in PMR, a double-blind trial was done by the systemic vasculitis study group of the Italian Society for Rheumatology. The trial randomized 72 patients with newly diagnosed PMR to prednisone in initial dosages of 25 mg/day, plus either methotrexate (10 mg/week) or placebo for 48 weeks. Prednisone was tapered within 24 weeks and resumed if flare occurred.

The mean age was 72 years, two-thirds were women, and 62 patients completed the study (Ann. Intern. Med. 2004;141:493-500).

At 76 weeks, the proportion of patients who were steroid free was higher in the methotrexate group than in the placebo group, with 28 of 32 patients on methotrexate having discontinued prednisone, compared with 16 of 30 patients on placebo.

The effect of treatment also was positive: Patients receiving methotrexate also had fewer relapses, the duration of prednisone therapy was shorter, and the total dose of prednisone was significantly lower, Dr. Cimmino said.

"However, when we looked at adverse events, there was no difference between treated patients and controls, and because steroid-sparing agents are used primarily to avoid steroid-related toxicity, in this sense the study was not successful," he said.

Possible explanations for the negative result were the very narrow difference in cumulative prednisone dose between patients and controls, the overall low incidence of adverse events that were seen in the relatively healthy patients who were selected for inclusion in clinical trials, and the short duration of follow-up.

"For this last reason, we decided to review the charts of participating patients and revisit them 5 years after completion of the study," Dr. Cimmino said.

In all, 29 methotrexate-treated patients and 28 placebo-treated patients were available for evaluation.

At the time of reevaluation, there were no differences in clinical and laboratory findings between the two groups, except for levels of C-reactive protein, which were higher in the placebo group (10.2 mg/dL), compared with those of the methotrexate group (2.7 mg/dL) (Clin. Exp. Rheum. 2008;26:395-400).

There was no difference between groups in adverse events; steroid-sparing agents were used primarily to avoid toxicity, so 'in this sense the study was not successful.'

"This suggested that perhaps there was more residual disease activity and more inflammation in patients who did not receive methotrexate," he said.

However, once again there were no differences in the incidence of steroid-related adverse events between treated patients and controls.

"Our conclusion was that we have many unanswered or incompletely answered questions," he said. "What dosage of methotrexate to use? We used 10 mg, but many of you have suggested that 20 mg would be more appropriate," Dr. Cimmino said.

Other questions include when to initiate methotrexate—at the same time as steroids are begun, or later, if response is inadequate?—and whether it may be more useful in certain subsets of PMR patients, such as those who also have vasculitis. Finally, more studies are needed if efficacy is to be demonstrated in real-life experience with sicker patients, he said at the meeting, which was sponsored by the Hospital for Special Surgery.

Clinical experience with methotrexate in GCA also was reviewed at the meeting by Dr. Alfred D. Mahr of Hôpital Cochin, Paris.

As with PMR, studies of adjunctive methotrexate in GCA have yielded conflicting and inconclusive results. Numbers have been small, so a meta-analysis was undertaken to pool the data, according to Dr. Mahr.

Three randomized trials that included 161 patients were included in the meta-analysis, which found that methotrexate in dosages of 7.5-15 mg/week reduced first and second relapses by 35% and 51%, respectively.

Adjunctive methotrexate also cut cumulative steroid exposure and increased the probability of achieving a sustained 24-week discontinuation of steroids (Arthritis Rheum. 2007;56:2789-97).

The meta-analysis had limitations, Dr. Mahr said, including small numbers of patients and short follow-ups. As with the PMR trial, there were no differences in adverse events between the treatment and control groups.

"Methotrexate could be considered as a therapeutic option for patients with GCA, particularly for those who are at high risk for corticosteroid-related adverse events," Dr. Mahr said.

This conclusion has recently been affirmed in a recommendation from the European League Against Rheumatism: "A meta-analysis of these three trials demonstrates a modest role for methotrexate (10-15 mg/week) in reducing relapse rate and lowering the cumulative dose of glucocorticoid therapy. … We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy" (Ann. Rheum. Dis. 2008 April 15 [doi:10.1136/ard.2008.088351]).

Following the presentation, Dr. Gary Hoffman of the Cleveland Clinic stated that he did not agree with the conclusions of the study, noting that there was "enormous heterogeneity" in terms of study design, and significant differences in methotrexate doses and in the timing of the addition of methotrexate. "And ultimately, even if you buy into the validity of the meta-analysis, you are still left with patients with no differences in corticosteroid-related or methotrexate-related adverse events," said Dr. Hoffman, who is Harold C. Schott Chair of Rheumatic and Immunological Diseases and professor of medicine at Case Western Reserve University, Cleveland.

He went on to say, "Given that we know methotrexate can cause problems such as pneumonitis, which can sometimes be a fatal disease, and that pneumonitis can occur in 1%-5% of patients who are treated with methotrexate, there may not have been enough patients in the individual studies to identify those one or two who might be affected. With just one such patient in the methotrexate group, our view of the outcome would be considerably different," he said.

In a subsequent interview, session cochair Dr. Robert F. Spiera of Cornell University, New York, said that although there may be some justification for the use of methotrexate in these conditions, "it clearly is not the standard of care."

"There has never been an unequivocally powerful signal for efficacy, and if you have to treat 11 or 12 patients to prevent one relapse, you are giving methotrexate to a lot of older patients who could have adverse events," said Dr. Spiera, also director of the scleroderma and vasculitis program at the Hospital for Special Surgery, New York. ■

Validation Planned

PMR *from page 1*

many clinicians regard a rapid response to steroids as the primary defining feature of PMR, an assumption that can result in diagnostic error because steroids are potent anti-inflammatory drugs that can mask symptoms from serious conditions, including cancer and infections (Clin. Exp. Rheumatol. 2007;25[Suppl. 47]:S130-6).

To address these uncertainties, Dr. Dasgupta and other members of the American College of Rheumatology's work group for the development of classification criteria for PMR have undertaken a Delphi exercise to rate inclusion criteria for the diagnosis, as well as to evaluate response to treatment.

From a broad range of candidate criteria collected from the literature and reviewed by experts and a wider clinical audience of nonrheumatologists, the following core inclusion criteria for the diagnosis of PMR have been identified:

- ► Age 50 years or older.
- ► Symptom duration of at least 2 weeks.
- ► Aching in bilateral shoulder and/or pelvic girdle.
- ► Morning stiffness lasting more than 45 minutes.
- ► Elevated erythrocyte sedimentation rate or C-reactive protein.
- ► Rapid steroid response, with a 75% global response within 1 week to 15-20 mg/day prednisone.

These criteria are now being validated in a prospective study that will enroll 120 cases and 240 controls, all with bilateral shoulder pain.

Cases will be patients with presumptive diagnoses of PMR, whereas controls will be patients whose shoulder pain is thought to be caused by inflammatory conditions, such as new-onset rheumatoid arthritis, seronegative arthritis, or vasculitis; noninflammatory causes, such as rotator cuff disorders; and other conditions, such as endocrinopathies and neurologic disorders.

Evaluations will include demographics, vital signs, and clinical features, as well as physician- and patient-based measures at baseline and at fixed intervals thereafter.

Patients will be followed for 6 months, at which time the investigators are planning to compare the presence of disease features to see which can best distinguish PMR from its mimics, and which can predict evolution to other diagnoses.

Additional goals of the prospective study include the development of a reliable and valid composite disease activity score, a definition for response to therapy, and criteria for remission—all of which are lacking for PMR.

At present there also are no specific serologic markers for PMR, so another important aim is to develop an infrastructure for the storage of biospecimens for future work in identifying biomarkers.

"Ultimately, all this should help us develop standardized protocols for randomized controlled trials in PMR," he said at the conference, which was sponsored by the Hospital for Special Surgery.

Currently some 70 cases have been enrolled, and Dr. Dasgupta said that he expects to complete enrollment of cases by the end of the year and enrollment of controls shortly thereafter. He hopes to have preliminary data available for the 2009 annual meeting of the American College of Rheumatology. ■