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 in 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 morbidity and mortality due to con- trolling disease. The corticosteroid typically must be administered for at least 1-2 years, however, which places patients at risk for adverse ef- fects 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 ad- verse event, said Dr. Marco A. Cimmino of the University of Genoa (Italy).

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possible explanations for the negative result were the very narrow difference in cumulative prednisone dose between patients and controls, the overall low in- cidence of adverse events that were seen in the relatively healthy patients who were selected for inclusion in clinical tri- als, and the short duration of follow-up. For this last reason, we decided to re- view the charts of participating patients and revisit them 5 years after completion of the study,” Dr. Cimmino said.

In all, 29 methotrexate-treated pa- tients and 28 placebo-treated patients were available for evaluation. At the time of reevaluation, there were no differences in clinical and labo- ratory findings between the two groups,

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.’

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).

‘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-re- lated adverse events between treated pa- tients and controls.

‘Our conclusion was that we have many unanswered or incorrectly an- swered 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 ini- tiate 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 vas- culitis. 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 spon- sored by the Hospital for Special Surgery.

Clinical experience with methotrexate in GCA also was reviewed at the meet- ing by Dr. Alfred D. Mahr of Hôpital St. Louis, Paris.

As with PMR, studies of adjunctive methotrexate in GCA have yielded con- flicting and inconclusive results. Num- bers have been small, so a meta-analysis was undertaken to pool the data, ac- cording to Dr. Mahr.

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

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

To address these 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 ad- verse events,’ Dr. Mahr said.

This conclusion has recently been af- firmed in a recommendation from the European League Against Rheuma- tosis: ‘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 glucocorti- coid therapy. … We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjuvative therapy’ (Ann. Rheum. Dis. 2008 April 15 [doi:10.1136/ard.2008.088351]).

Following the presentation, Dr. Gary Hunder, professor of medicine at Case West- ern Reserve University, Cleveland, said that he did not agree with the conclu- sions 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 va- lidity of the meta-analysis, you are still left with patients with no differences in corticosteroid-related or methotrexate- related adverse events,’ said Dr. Hoff- man, who is Harold C. Schott Chair of Rheumatic and Immunological Diseases and professor of medicine at Case West- ern Reserve University, Cleveland.

He went on to say, ‘Given that we know methotrexate can cause problems such as pneumonitis, which can some- times be a fatal disease, and that pneu- monitis 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 methotrex- ate group, your 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 unequiv- ocal signal for efficacy, and if you have to treat 11 or 12 patients to pre- vent 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.

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

At present there are no specific sero- logic 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 con- trolled trials in PMR,’ he said at the confer- ence, which was sponsored by the Hospital for Special Surgery.

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