Methotrexate Holds Promise for Progressive MS

BY BETSY BATES

SAN DIEGO — Pulsed, intrathecal methotrexate was safe and well-tolerated in patients with primary progressive or secondary progressive multiple sclerosis, and appears to have stabilized their disease in a small, open-label, phase I tolerability and safety study that followed patients only 2 years, Saud A. Sadiq, M.D., reported at the annual meeting of the American Neurological Association.

Dr. Sadiq, director of the Multiple Sclerosis Research and Treatment Center at St. Luke’s Roosevelt Hospital Center in New York, said that a larger, longer study would be needed to confirm the usefulness of intrathecal methotrexate in this notoriously difficult-to-treat population.

Nonetheless, his poster detailing the treatment in 126 patients drew considerable interest at the meeting, where clinicians expressed hope that the therapy might represent an alternative for these two groups of patients who currently have very few treatment options.

To be eligible for the study, patients had to have undergone treatment with at least three FDA-approved, disease-modifying drugs for multiple sclerosis (MS) for at least 1 year. Despite this therapy, eligible patients still had active disease with EDSS scores ranging from 3.0 to 9.0.

Preservative-free methotrexate was administered at a dose of 12 mg every 2 months, either via lumbar puncture with a 24- or 25-gauge needle (91 patients), or through the access port of a surgically implanted Medtronic pump that patients had received for spasticity control (35 patients). Each injection was followed by injection of 3 cc of the patient’s previously drawn cerebrospinal fluid (CSF) to ensure that the drug entered the CSF and there was no dead-space loss.

Brain MRI studies were performed in 50 randomly selected patients both before and after at least four treatment cycles. After methotrexate treatment, disease stabilized in 32 of 39 patients with secondary progressive MS and 9 of 11 patients with primary progressive MS.

In the total cohort, improved or stabilized EDSS scores were noted in 85 of 91 patients with secondary progressive MS and 32 of 35 patients with primary progressive MS. Quality of life scores improved (37 patients) or remained unchanged (23 patients) in patients with secondary progressive MS, while just 11 reported a decreased quality of life at the end of the 2-year study.

Among patients with primary progressive MS, 14 patients improved, 11 patients remained the same, and 6 patients had decreased quality of life scores.

Laboratory studies using mouse stem cells and CSF from a study patient and an MS patient not receiving methotrexate showed that the drug appeared to have no effect on oligodendroglial or neuronal cell development, but that it inhibited astrogial proliferation, key to sclerosis formation.

Dr. Sadiq said the findings suggest a possible mechanism of action.

Patients generally tolerated the drug well. No drug-related deaths occurred (a 74-year-old patient died of a myocardial infarction). There were no cases of meningitis or serious infection, CNS tumors, or lymphomas.

Patients reported transient fatigue after 34 of a total of 489 treatments. Mild leukocytopenia was seen in two patients. Post-spinal headache was reported after nine treatments, and vomiting was reported after one. One patient had shingles.

A total of 21 patients discontinued treatment, most citing a lack of effect after two or three treatments. No patient dropped out of the trial due to adverse effects.

“In patients that we selected for this study . . . disease course is inexorably progressive, with definite decline in function every few months. Stability in this population is very exciting,” said Dr. Sadiq following the meeting.

“Obviously, the longer this can go on, the better. To date, no patients who appeared to have an initial favorable response appear to have subsequently declined.”

To be sure, “other studies verifying efficacy for a longer term are needed,” he said.

A randomized, controlled study is planned that will compare intrathecal methotrexate with intravenous pulsed Cytoxan, according to Dr. Sadiq, who serves on the neurology faculty at the Albert Einstein College of Medicine, New York.

No pharmaceutical company support was used to fund Dr. Sadiq’s study.