Methotrexate Holds Promise for Progressive MS

BY BETSY BATES
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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 continued relapses, worsening Expanded Disability Status Scale (EDSS) scores, or increased disease burden seen on MRI.

Exclusion criteria included known allergy to methotrexate, pregnancy, active infection, or a significant associated medical condition such as heart disease. Patients ranged in age from 30 to 74 years. Females outnumbered males, 87 to 39. There were 91 patients with secondary progressive MS and 35 patients with primary progressive MS. Their baseline EDSS scores ranged 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 (57 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, 15 patients remained the same, and 6 patients had decreased quality of life scores.

The course of MS in these patients is inexorably progressive. Stability is very exciting.

DR. SADIQ

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 astroglial 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 leucopenia 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. ■

Data From Multiple Sclerosis Study Point to Locus on Chromosome 6

SAN DIEGO — A very large genetic linkage study has pinpointed the major histocompatibility complex on the short arm of chromosome 6 as the key genetic player in multiple sclerosis.

The study is not the first to implicate the major histocompatibility complex (MHC), a cluster of genes critical to the recognition of the body's own cells as "self."

However, this study is the largest and most definitive to date, and its findings call into question data from smaller studies that suggested critical roles for other genetic regions.

Jonathan Haines, Ph.D., of Vanderbilt University, Nashville, Tenn., presented the findings on behalf of the International Multiple Sclerosis Genetics Consortium.

The team typed 4,506 single nucleotide polymorphism markers in 730 families who had more than one family member with multiple sclerosis.

Subjects were from Australia, Scandinavia, the United Kingdom, and the United States. Genes from 945 pairs of relatives were studied for genetic linkages.

"Highly significant linkage is observed in the region of the MJC ([linkage analysis] logarithm of the odds score 11.7), and suggestive linkage is found on chromosomes 17 and 5," Dr. Haines stated in a poster presented at the annual meeting of the American Neurological Association.

An ordered subset analysis identified a further locus on chromosome 19.

The mean information extraction from the marker panel is 80%, with a range of 42%-91%, Dr. Haines reported.

Observed Mendelian inconsistencies suggest that within the data set, the genotyping error rate was just 0.002%.

"Our results confirm the strong role of the major histocompatibility complex genes in MS, and provide a definitive statement that no other region of the genome harbors a gene with a similar overall influence on MS genetics," Dr. Haines said in a statement released at the meeting.

"Other genes may still play an important role in MS but finding them will require using new genomic techniques," he added.

Dr. Haines said the findings have "profound implications for the future directions of multiple sclerosis genetics research and suggest that previous efforts in this area are almost all substantially underpowered."

Future association studies should include at least 500-1,000 cases of multiple sclerosis to be considered reliable, he said.

—Betsy Bates