Teriflunomide Reduced MS Relapse Rate by 31%

BY SHARON WORCESTER

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS)

Teriflunomide, a novel oral disease-modifying drug, significantly reduced the annualized relapse rate and the risk of disability progression in relapsing multiple sclerosis by about 31% in a 2-year, phase III trial.

The study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients with Multiple Sclerosis (TEMSO), which was sponsored by Sanofi-Aventis, randomized 1,088 patients to receive a single daily dose of 7 mg or 14 mg of teriflunomide or placebo.

VITALS

Major Finding: Compared with the placebo group, those in both the 7-mg and 14-mg teriflunomide groups experienced a statistically significant 31% reduction in the annualized relapse rate, which was the primary end point.

Data Source: A randomized, placebo-controlled phase III study (TEMSO) involving 1,088 patients with relapsing MS.

Disclosures: Sanofi-Aventis sponsored the trial. Dr. O'Connor, Dr. Comi, and Dr. Freedman disclosed financial relationships with many companies that manufacture drugs for MS, including Sanofi-Aventis.

The primary end point – the annualized relapse rate – was significantly lower in the 7-mg and 14-mg groups (0.370 and 0.369, respectively) than it was in placebo-treated patients (0.539). These rates represented a statistically significant reduction of 31% compared with placebo. Patients in the 14-mg group also experienced a significant 30% reduction in the risk of disability progression, Dr. Paul O'Connor reported at the congress.

Teriflunomide is the active metabolite of leflunomide, a synthetic, low-molecular-weight drug that was approved by the Food and Drug Administration in 1998 for the treatment of rheumatoid arthritis. The metabolite is a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) that exerts anti-inflammatory, antiproliferative, and immunosuppressive effects, but the mechanisms by which it does so are not yet completely understood. Inhibition of pyrimidine biosynthesis (via suppression of DHODH) and interference with tyrosine kinase activity both appear to be involved.

The treatment groups also experienced a significant reduction in brain disease activity as measured by magnetic resonance imaging (MRI). The burden of disease as determined by total lesion volume, for example, was reduced by 39% and 67% in the 7-mg and 14-mg dose groups, respectively, compared with placebo, said Dr. O'Connor of St. Michael's Hospital, Toronto. He is the principal investigator for TEMSO.

"In my view, teriflunomide is a safe and effective new monotherapy, and it represents a potential first-line treatment for patients with relapsing MS," he said during a press briefing on the TEMSO findings.

The safety profile of teriflunomide in this study was a particularly strong, positive point, he added. The overall adverse event rates were the same in the placebo and treatment groups, as were the rates of adverse events leading to permanent discontinuation of treatment. Patients in the teriflunomide group experienced more nausea, diarrhea, increases in alanine transferase, and hair thinning than did those in the placebo group, but these effects were mild. Treatment was generally very well tolerated, and no opportunistic infections occurred, he said.

TEMSO participants were adults aged 18-55 years with relapsing MS and a score of 5.5 or lower on the Expanded Disability Status Scale, and had experienced at least one relapse in the year prior to enrollment, or two relapses in the prior 2 years.

The availability of an oral agent for the treatment of this complex and progressively disabling disease is very good news for MS patients, Dr. Giancarlo Comi said during the press briefing.

"Of course it is central in the management of these patients to have available drugs to modify the disease course … we are literally entering a period where we can provide patients with much better support than ever before," said Dr. Comi of Clinica Neurologica, Ospedale San Raffaele, Milan, Italy.

Indeed, other ongoing research is also demonstrating the safety and efficacy of teriflunomide, both as monotherapy and in combination with other treatments, said Dr. Mark Freedman of the Multiple Sclerosis Research Clinic at Ottawa (Canada) Hospital. Dr. Freedman and Dr. Comi are investigators in the TEMSO trial.

For example, an open-label extension of a phase II trial of teriflunomide, which was also reported at the ECTRIMS congress, showed that teriflunomide was well tolerated during 8 years of continuous use following a 36-week double-blind portion of the study. Also, teriflunomide in combination with subcutaneous injection of interferon beta-1a has been shown to improve MRI outcomes in MS patients to a significantly greater extent than does interferon beta-1a and placebo.

Dr. Freedman said that the results from a second phase III study of teriflunomide are expected to be reported in 2012. ■

Inhaled Drug Relieved Migraine Even if Taken Long After Onset

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN HEADACHE SOCIETY

LOS ANGELES – An experimental inhaled form of dihydroergotamine appears to be effective in reducing migraine pain even if taken as late as 8 hours or more after the start of the headache, a post hoc analysis of a phase III clinical trial suggests.

Investigators analyzed data from the randomized, double-blind, placebo-controlled trial known as the FREEDOM 301 study. Among 771 patients who treated a moderate to severe migraine and recorded both efficacy and the time from onset of headache to treatment, patients randomized to inhaled dihydroergotamine were significantly more likely than those given placebo to report being pain free 2 hours after treatment if they initiated treatment within an hour of migraine onset, 1-4 hours after onset, or 4-8 hours after migraine onset, Dr. Stewart J. Tepper and his associates reported.

Rates of freedom from pain were not significantly higher with the drug, compared with placebo, in patients who took treatment more than 8 hours after the migraine started. Reports of pain relief, however, were significantly higher in the inhaled dihydroergotamine subgroups regardless of how long after headache onset they took treatment, he said at the meeting.

In the real world, patients give a number of reasons for delaying treatment for migraines, noted Dr. Tepper of the Cleveland Clinic. Some want to be sure they have a migraine, or that they need triptan therapy. Some patients hoard medicine for cost reasons. Others just don't want to take a strong medicine if it's not needed.

Inhaled dihydroergotamine may offer an alternative for patients who delay starting migraine treatment, if the formulation wins approval, he said.

Freedom from pain at 2 hours after treatment was reported by 34% of 112 patients randomized to inhaled dihydroergotamine and 11% of 118 on placebo who took treatment within an hour of headache onset. In those who took treatment after an hour but within 4 hours of migraine onset, 18% of 152 patients on inhaled dihydroergotamine and 6% of 169 on placebo were pain free 2 hours later. Among patients who treated their migraine after 4 hours but within 8 hours of onset, 22 of 68 (32%) on inhaled dihydroergotamine and 8 of 53 (15%) on placebo were pain free 2 hours later.

For patients who started treatment more than 8 hours after migraine onset, 19 of 53 (36%) on inhaled dihydroergotamine and 9 of 46 (20%) on placebo were pain free 2 hours later. Although those rates were not significantly different, pain relief 2 hours after treatment was reported by 49 on inhaled dihydroergotamine (92%) and 24 on placebo (52%), a significant difference between groups.

VITALS

Major Finding: An investigational, inhaled form of dihydroergotamine was significantly more likely than placebo to relieve pain within 2 hours in patients who took treatment more than 8 hours after headache onset (92% vs. 52%, respectively) and in patients who took treatment earlier.

Data Source: Post hoc analysis of data from a randomized, double-blind trial of 771 patients who treated a single moderate to severe migraine.

Disclosures: Dr. Tepper and each of his associates in the study has been a speaker or consultant for, or received funding from, MAP Pharmaceuticals Inc., which hopes to market the inhaled formulation of dihydroergotamine.

"That's a very dramatic finding," Dr. Tepper said.

Pain relief rates in patients who started treatment within an hour of migraine onset were 60% with inhaled dihydroergotamine and 35% with placebo. Among those who started treatment after an hour but within 4 hours of migraine onset, 37% on inhaled dihydroergotamine and 21% on placebo reported pain relief 2 hours later. Pain relief also occurred in 53 patients on inhaled dihydroergotamine (78%) and 30 on placebo (57%) who took treatment after 4 hours but within 8 hours of migraine onset.

Data on adverse events in 404 patients in the inhaled dihydroergotamine group and 401 in the placebo group suggest that the drug is well tolerated, Dr. Tepper said. Symptoms typically associated with triptan use, such as chest discomfort or chest pain, occurred rarely and at similar rates in both groups. There were no drug-related serious adverse events and no clinically meaningful change in lung function in this single-dose study. The most common adverse events that occurred more often with inhaled dihydroergotamine than with placebo were bad taste (in 6% and 2%, respectively), nausea (in 4% and 2%, respectively), and cough or vomiting (both in 2% and 1%, respectively).

The main FREEDOM 301 trial included 792 patients in an intent-to-treat analysis, and showed significantly increased likelihood of pain relief 2 hours after treatment in all patients on inhaled dihydroergotamine (59%), compared with patients on placebo (35%). Pain relief rates were significantly different between groups within an hour of treatment and remained significantly different after 24 and 48 hours.

"I can think of many clinical situations where this will be useful," he said. "We hope this device will be able to be used at home." ■