MS Oral Options Warrant Cautious Optimism

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

HONOLULU – Oral therapies for relapsing-remitting multiple sclerosis that are in development have neurologists feeling both excited and a bit apprehensive.

"There are a whole slew of orals coming," Dr. Mariko Kita said in an interview at the meeting. "It's really exciting, but I think it will be challenging for the clinician" because there will be inadequate guidance on which drug or drugs to prioritize in treatment and how best to combine various therapies.

"I think it's going to be very intimidating, actually," said Dr. Kita, director of the multiple sclerosis center at Virginia Mason Medical Center, Seattle.

She comoderated a session on multiple sclerosis trials that included a report on a pooled analysis of safety data on the only approved oral therapy for multiple sclerosis, fingolimod (Gilenya). (See story on p. 10.) The session also included positive phase III clinical trial results for the experimental oral therapy teriflunomide. Earlier in the meeting, separate investigators reported positive phase III clinical trial results for the experimental oral therapy laquinimod.

Another oral agent under study, BG-12 (dimethyl fumarate), received Fast Track designation from the Food and Drug Administration and is in phase III clinical trials. Cladribine (Leustatin), which is currently marketed as chemotherapy for certain leukemias and lymphomas, initially was rejected by the FDA when it was submitted for approval as an oral therapy for multiple sclerosis. Following resubmission by the manufacturer, the FDA in early 2011 sent a letter to the company acknowledging sufficient data on the drug's efficacy in multiple sclerosis but requiring more data on safety and risk-benefit considerations before it could be approved.

Dr. Kita's comoderator, Dr. Benjamin N. Greenberg, commented after the session that with the expected approvals of several oral agents over the next few years, "I'm getting concerned that there's going to be a little bit of a free-for-all coming." But he added, "It's good to have options. We're all thrilled."

The only head-to-head comparison of an oral therapy against another active treatment for multiple sclerosis so far is a study of fingolimod vs. interferon, he noted. Direct comparisons of the various oral agents will be needed to help clinicians develop treatment strategies, said Dr. Greenberg, a neurologist at the University of Texas Southwestern Medical Center, Dallas.

The challenge of the oral drugs will come from a lack of guidance on which drug or drugs to prioritize in treatment.

DR. KITA

Gilenya may have some superior efficacy, compared with once-weekly interferon dosing, Dr. Kita said, but its potential adverse cardiovascular effects and "downstream consequences in terms of effects on different organ systems makes another oral daily alternative with less toxicity that much more appealing."

Dr. Aaron Miller of Mount Sinai School of Medicine, New York, and Dr. Jerry S. Wolinsky of the University of Texas, Houston, presented results of the Teriflunomide Multiple Sclerosis Oral (TEMSO) trial during the session. The multinational, double-blind study randomized 1,088 patients with relapsing-remitting multiple sclerosis to a single daily dose of 7 mg or 14 mg of teriflunomide or placebo for 2 years.

Both doses reduced the annualized relapse rate by approximately 31%, compared with placebo. The annualized relapse rate was 0.37 in each of the treatment groups and 0.54 in the placebo group. The risk of disability progression also was significantly reduced by 30% in the 14-mg group but was not significantly different in the 7-mg group, compared with placebo.

Both doses showed significant improvements, compared with placebo, in brain disease activity on various MRI tests, although some MRI measures of disease activity were significantly better only in the high-dose group, compared with placebo.

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DR. MILLER

Results of the 2-year, randomized, double-blind study of laquinimod that was presented earlier at the meeting showed an annual relapse rate of 0.304 on laquinimod, a 23% reduction compared with a rate of 0.395 on placebo. The laquinimod group also showed 33% less brain atrophy and significant improvements in brain disease activity on various MRI measures.

Both teriflunomide and laquinimod seemed relatively well tolerated, but among 11 women who became pregnant in the TEMSO study, 3 of 4 spontaneous abortions occurred in the teriflunomide groups. Six of the other pregnant women underwent induced abortions, and one woman successfully delivered a healthy baby.

"I thought that the teriflunomide study was interesting. It was impressive to see that a fairly low dose like that, which seems to be very well tolerated, could have effects on both the MRI and on the clinical end points," Dr. Kita said. "My concern for it is making sure that we understand what the impact is on the female population, on the childbearing years."

Dr. Kita said she has no relevant conflicts of interest. Dr. Greenberg disclosed financial relationships with DioGenix, Biogen Idec (which is developing BG-12), EMD Serono (which is developing cladribine), Teva Neurosciences (which is developing laquinimod), and the Greater Good Foundation.

Sanofi-Aventis, which is developing teriflunomide, funded TEMSO. Dr. Miller, Dr. Wolinsky, and many of their associates in the study disclosed relationships with Sanofi-Aventis and with numerous other companies that make therapies for multiple sclerosis. Three coinvestigators were employees of Sanofi-Aventis. ■

No Improvement in MS With *Ginkgo biloba*, Simvastatin

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

HONOLULU – *Ginkgo biloba* and simvastatin were not helpful in patients with relapsing-remitting multiple sclerosis in separate randomized controlled trials.

Treatment with ginkgo at 120 mg twice a day for 12 weeks produced no significant, short-term improvements in cognitive function in a study of 121 patients. The addition of simvastatin (Zocor) to interferon therapy for multiple sclerosis in a separate study did not significantly reduce the annualized relapse rate after 1-3 years, investigators reported at the meeting.

In the first study, both the ginkgo and placebo groups had improved average scores on a battery of neuropsychological tests. There were no significant differences between groups in scores on the Paced Auditory Serial Addition Test, the California Verbal Learning Test II, the Controlled Oral Word Association Test, or the Stroop Color–Word Test, said Dr. Jesus Lovera of Louisiana State University, New Orleans.

The two groups also did not differ significantly in secondary outcomes (including perceived cognitive deficits, family reports of cognitive deficits, fatigue, or depression) or in rates of adverse events. In the ginkgo group, one patient had an MI and one developed a severe depressive episode requiring hospitalization, but these were not attributed to ginkgo.

While the study found no short-term cognitive benefits from ginkgo, it did not assess any potential long-term benefits, Dr. Lovera said. There are no approved treatments for impairment of cognition in people with multiple sclerosis, which affects 40%-50% of patients.

There was a trend toward more disease activity in the simvastatin group, compared with placebo.

DR. SØRENSEN

Dr. Per Soelberg Sørensen and his associates reported in a separate presentation on a study of 307 treatment-naive patients who were starting treatment with interferon-beta-1a (IFN-beta-1a, Avonex) for relapsing-remitting multiple sclerosis. They were randomized to add-on therapy with either placebo or 80 mg/day of simvastatin (40 mg/day in the first month) for 1-3 years. Patients were followed clinically every 3 months and brain MRIs were conducted at baseline and after 1 year of treatment. At least 1 year of follow-up was completed by 136 patients in the simvastatin group and 132 in the placebo group.

In the study, the annualized documented relapse rate was 31% higher in the simvastatin group (0.19) compared with the placebo group (0.14), but the difference was not statistically significant, said Dr. Sørensen of the Danish Multiple Sclerosis Center in the Rigshospitalet, Copenhagen.

The annualized total rate of documented and undocumented relapses was 15% higher in the simvastatin group (0.44), compared with the placebo group (0.38). Patients who received simvastatin had more new or enlarging T2 lesions on MRI than did those who received placebo (3 vs. 2.5). These and other measures were not statistically significant differences between groups, but suggested a trend toward more disease activity in the simvastatin group compared with placebo, Dr. Sørensen said.

Based on the findings of this multicenter study, simvastatin cannot be recommended as an add-on to IFN-beta-1a therapy for relapsing multiple sclerosis, but patients taking statins for treatment of hypercholesterolemia or to prevent cardiovascular disease should not be discouraged from taking them during IFN-beta-1a therapy, Dr. Sørensen said.

Dr. Lovera and two of his associates disclosed financial relationships with EMD Serono, Teva Pharmaceuticals, Biogen Idec, and/or Pfizer. The ginkgo and placebo were provided by Dr. Willmar Schwabe GmbH, Karlsruhe, Germany. The U.S. Department of Veterans Affairs funded his study.

Dr. Sørensen and multiple associates disclosed financial relationships with Biogen Idec, Merck Serono, Teva Neuroscience, Genmab, Novartis, Bayer Schering, and/or Sanofi-Aventis. The study was funded by Biogen Idec. ■