Phase III Study Finds Oral MS Drug Safe, Effective

BY HEIDI SPLETE

TORONTO — The investigational drug fingolimod at doses of 0.5 mg and 1.25 mg appears to be a safe and effective treatment for adults with multiple sclerosis, based on data from more than 1,000 patients.

In previous studies, fingolimod had "a clear-cut effect on inflammatory outcomes," in relapsing-remitting multiple sclerosis patients, said Dr. Ludwig Kappos of University Hospital in Basel, Switzerland.

The current phase III study addressed whether the effects of fingolimod (FTY720) persisted over time, and whether a 0.5-mg dose is as effective as the previously studied 1.25-mg dose. The main outcome was relapse rate per year over a 2-year follow-up period.

The Food and Drug Administration has scheduled a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to review the safety and efficacy data for fingolimod in June.

The Fingolimod (FTY720) vs. Placebo in Relapsing-Remitting Multiple Sclerosis (FREEDOMS) study included 1,272 patients aged 18-55 years.

The average age of the patients was 37 years, and the average duration of MS was 8 years. Patients with systemic or immune system disease were excluded, and 1,033 patients completed the study.

Patients were randomized to receive a daily dose of 1.25 mg fingolimod, 0.5 mg fingolimod, or a placebo.

The annualized relapse rate was reduced by 54% in patients who took 0.5 mg of fingolimod and by 60% in those who took 1.25 mg of fingolimod. There was no significant difference in effectiveness between the doses, and both doses were significantly more effective than was placebo.

VITALS

Major Finding: The annualized relapse rate was reduced by 54% in multiple sclerosis patients who took 0.5 mg of fingolimod and by 60% in those who took 1.25 mg of fingolimod. After 24 months, around 70% of patients given fingolimod were relapse free, compared with 46% of the placebo group.

Data Source: A randomized, double-blind, placebo-controlled phase III study of 1,272 adults with MS.

Disclosures: The study was supported by Novartis Pharma AG. Dr. Kappos has received research support from multiple pharmaceutical companies, including Novartis. Dr. O'Connor has served as a consultant and received research support for multiple pharmaceutical companies, including Novartis.

After 24 months, significantly more patients in either fingolimod group (70%-75%) were relapse free, compared with 46% of the placebo group.

In addition, both the 1.25-mg and 0.5-mg doses of fingolimod were associated with reductions of 32% and 30%, respectively, in the risk of 3-month confirmed disability progression.

Both reductions were significant, compared with placebo. Similarly, both the 1.25-mg and 0.5-mg doses were associated with reductions in risk of 6-month confirmed disability progression of 40% and 37%, also significant compared with placebo.

The study results were presented at the annual meeting of the American Academy of Neurology.

Safety and tolerability data for the study population were presented separately in a poster by Dr. Paul O'Connor of St. Michael's Hospital in Toronto, and colleagues.

In the safety analysis, the researchers evaluated all patients at baseline screening, week 2, and months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24.

Overall, the incidence of any adverse event was 94% in both fingolimod groups and 93% in the placebo group. The incidence of an adverse event that caused a patient to stop treatment was 14% in the 1.25-mg group, and 8% in both the 0.5-mg and placebo groups.

Serious adverse events were reported in 51 patients (12%) in the 1.25-mg group, 42 patients (10%) in the 0.5-mg group, and 56 patients (13%) in the placebo group. Serious adverse events included cardiovascular disorders, neoplasms, nervous system disorders, macular edema, and abnormal liver function test results.

Sinus bradycardia, the most common ECG finding, occurred in 47 patients (11%) in the 1.25-mg group, 20 patients (5%) in the 0.5-mg group, and 6 patients (2%) in the placebo group. In addition, first- and second-degree atrioventricular blocks were reported in 20 patients (5%) and 1 patient (0.2%), respectively, in the 0.5-mg group, compared with 37 patients (9%) and 4 patients (1%), respectively, in the 1.25-mg group.

Malignant neoplasms were reported in 4 patients in each of the fingolimod groups, and in 10 patients in the placebo group. All 11 cases of skin cancer reported in the study were successfully treated with excision.

Abnormal liver function tests were reported more than twice as frequently in the fingolimod 1.25-mg and 0.5-mg groups, compared with placebo (19%, 16%, and 5%, respectively). But "liver enzyme elevations were asymptomatic and improved once therapy was discontinued; no patient developed liver failure," the researchers wrote.

In the 1.25-mg group, one case of ischemic stroke occurred during the study period, and a transient ischemic attack occurred 8 months after the discontinuation of treatment. No clinically relevant pulmonary function changes were observed in any of the groups.

All seven reported cases of macular edema occurred in the 1.25-mg group, and all cases resolved after treatment was discontinued.

The overall incidence of infections was similar (69%-72%) for all three groups, and included herpesvirus infections, lower respiratory tract infections, and urinary tract infections.

The results support safety data from previous studies and suggest that most patients with MS tolerate oral fingolimod, the researchers said. Also consistent with previous studies, "the overall safety profile of fingolimod 0.5 mg appears to be more favorable than that of the 1.25-mg dose," they added. ■

MS Patients Get 4-Year Remission in Alemtuzumab Follow-up

BY HEIDI SPLETE

TORONTO — Data further gleaned from a phase II study of low or high dose alemtuzumab indicate that the drug kept nearly three-fourths of multiple sclerosis patients clinically disease free for 4 years and was effective in halting disease activity even in patients who suffered autoimmune adverse events.

VITALS

Major Finding: Significantly more patients who took 12 mg/day or 24 mg/day of alemtuzumab were clinically disease-free after 4 years, compared with patients who received subcutaneous interferon beta-1a (71% vs. 35%).

Data Source: A subset of patients from a phase II trial of 334 patients with relapsing-remitting MS.

Disclosures: The trial was sponsored by Genzyme. Dr. Khan has received research support and personal compensation from Teva Neuroscience, Biogen Idec, EMD Serono, and Bayer Healthcare. He also has received personal compensation from Novartis. Dr. Brinar has received research support from Genzyme.

Dr. Omar Khan of Wayne State University, Detroit, and his colleagues reported 4-year follow-up results for a subset of patients in the CAMMS223 trial, an assessor-blinded study that randomized 334 patients to either 12 mg/day or 24 mg/day of alemtuzumab (Campath) against 44 mcg of subcutaneous interferon beta 1-a (IFN beta-1a, Rebif) 3 times a week.

Campath already is approved as a single agent for the treatment of B-cell chronic lymphocytic leukemia.

Data on follow-up at 4 years were available for 42 patients who received IFN beta-1a, 63 patients who received 12 mg/day of alemtuzumab, and 71 patients who received 24 mg/day of alemtuzumab. Treatment with alemtuzumab consisted of two to three cycles each year that each lasted 3-5 days. A total of 110 patients received only two cycles of alemtuzumab annually. The demographics of this subset of patients were similar to those in the original study group, Dr. Khan and his associates reported in a poster session at the annual meeting of the American Academy of Neurology.

After 4 years, no clinical disease activity had occurred in 71% of all patients treated with alemtuzumab and in 72% of those who received only two cycles of alemtuzumab. In comparison, significantly fewer patients in the IFN beta-1a group (35%) were free from clinical disease activity. Alemtuzumab-treated patients also had significantly higher rates of freedom from sustained accumulation of disability, compared with patients treated with IFN beta-1a (91% vs. 68%).

In addition, significantly more patients in the alemtuzumab groups (77%) were relapse-free than were those in the IFN beta-1a group (49%).

Comparisons between the IFN beta-1a group and each of the two alemtuzumab groups drew similar efficacy conclusions, Dr. Khan wrote.

Another analysis of the trial suggested that alemtuzumab may halt disease progression in the subset of MS patients who experienced autoimmune adverse events. In a poster at the meeting, Dr. Vesna Brinar of University Hospital Center in Zagreb, Croatia, and her colleagues reviewed 3-year follow-up data from 216 patients treated with alemtuzumab and 107 patients treated with IFN beta-1a in the phase II trial.

After 3 years, autoimmune adverse events had occurred in 47 patients who received alemtuzumab and in 3 patients who received IFN beta-1a. The most common events in alemtuzumab-treated patients included hyperthyroidism (21 patients), hypothyroidism (13 patients), and autoimmune thyroiditis (8 patients).

By 36 months, 12% of alemtuzumab-treated patients had experienced sustained accumulation of disability, compared with 26% of patients treated with IFN beta-1a.

The annualized relapse rate was significantly lower among the alemtuzumab-treated patients with autoimmune problems, compared with patients treated with IFN beta-1a (0.09 vs. 0.36), according to Dr. Brinar.

In addition, those who experienced autoimmune problems on alemtuzumab had a significant mean improvement on the Expanded Disability Status Scale of -0.44 points from baseline.

Ongoing phase III studies are in place to confirm and further expand the results, the researchers said. ■