Tarenflurbil Shows 'No Efficacy' for Alzheimer's

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CHICAGO — Tarenflurbil, a drug designed to reduce toxic amyloid β levels in the brains of Alzheimer's disease patients, has failed its large phase III trial, Dr. Robert Green reported at the International Conference on Alzheimer's Disease.

Patients who received the drug (800 mg twice daily) exhibited virtually the same declines in cognition and function as did those who received placebo, said Dr. Green of the Boston University. "I think the results are definitive. There was no efficacy of the compound in this trial."

In the wake of these results, Myriad Genetics Inc. of Salt Lake City, has decided to scrap its research on the drug, Dr. Green said at the meeting presented by the Alzheimer's Association.

Tarenflurbil had a somewhat encouraging phase II trial. In that study of 207 patients, those taking tarenflurbil experienced significant improvements in global functioning and activities of daily living, and near-significant improvements in cognition.

No such benefits occurred in the phase III trial, which comprised 1,653 patients with mild Alzheimer's. It was conducted at 133 sites across the United States.

Patients were randomized to equal groups to the study drug or placebo for 18 months; the treatment period was followed by a 30-day washout. Primary end points were the Alzheimer's Disease Assessment Scale–cognition (ADAS-Cog) and the Alzheimer's Disease Assessment Scale–activities of daily living (ADAS-ADL). Patients were evaluated every 3 months.

The groups were well matched at baseline, with an average age of 74 years and an average Mini-Mental State Exam score of 23; 51% were female. Most of the patients were on concomitant antidementia drugs: 33% were taking only cholinesterase inhibitors, 6% were on memantine alone, 19% were taking no antidementia drugs, and the rest were on combination therapy.

After 18 months of treatment, both the active and placebo groups showed a steady and almost identical decline in cognition. Both groups lost 7 points on the ADAS-Cog scale by the end of the study. In a secondary cognitive measure, the Clinical Dementia Rating sum of boxes, both groups lost 2.5 points by the end of the study.

The drug had a somewhat encouraging phase II trial. But the phase III results fell short.

DR. GREEN

A similar pattern appeared on the ADAS-ADL scale. Both groups followed an almost identical pattern of decline, each losing 10 points on the scale by 18 months.

Overall adverse events were similar in the tarenflurbil and placebo arms (88% vs. 86%). More patients taking the study drug discontinued because of adverse events (18% vs. 12%). Serious adverse events occurred in 23% of the active group and 20% of the placebo group.

The most common adverse event was anemia (10% tarenflurbil vs. 4% placebo—a significant difference). Infection was also significantly more common among the active group (7% vs. 3%), as was gastrointestinal ulcer (2% vs. 0.4%). There was no difference in the incidence of gastrointestinal bleeding.

Although the trial was a failure in terms of tarenflurbil efficacy, it did confirm an important observation—one that will be greatly helpful in future AD drug trials, Dr. Green said. "This study, which was well designed and well powered, proved that patients with mild Alzheimer's disease do decline enough over 18 months to actually look for a signal of efficacy."

Tarenflurbil was the first gamma secretase modulator to be tested in a phase III trial. This class of drug is thought to reduce the levels of toxic amyloid β ($A\beta_{42}$) in the brain by changing the point at which the enzyme gamma secretase cuts the amyloid precursor protein. "This shifts the ratio to less of the toxic $A\beta_{42}$ and more of the less-toxic $A\beta_{40}$," Dr. Green said.

Dr. Green said he did not receive compensation from Myriad Genetics for his role as a primary investigator on the study. ■