Amyloid β–Lowering Agent Fails in Phase III

Patients who received 800 mg of the drug saw the same cognitive decline as patients taking placebo.

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

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.

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.

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DR. GREEN

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 being a primary investigator on the study. ■

Tau-Targeting Drug May Aid Memory in Mild Dementia

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

CHICAGO — An experimental drug that attacks neurofibrillary tau tangles significantly improved some measures of memory in mild cognitive impairment, but failed to meet its primary cognitive end point.

Because of its effects on visual and verbal memory, AL-108 will move on to phase II, Dr. Donald E. Schmechel said at the International Conference on Alzheimer's Disease.

"Twelve weeks of AL-108 resulted in statistically significant, dose-dependent, and durable improvement on measures of short-term memory, including visual, verbal, and auditory working memory, which is a type of memory function that deteriorates throughout the progression of Alzheimer's," said Dr. Schmechel. "This makes AL-108 the first drug to validate in humans the importance of the tangle, or tau, pathway in the disease."

Neurofibrillary tau tangles, a diagnostic hallmark of Alzheimer's, are composed of hyperphosphorylated tau, a protein that normally occurs in neurons. In its hyperphosphorylated state, tau forms tangled fibrils that interfere with neuronal function. AL-108, developed by Allon Therapeutics Inc. of Vancouver, is the first drug in development to exert action on those tangles.

Many more Alzheimer's drugs under investigation target the amyloid pathway of neurodegeneration. Dr. Schmechel, whose research was funded by Allon, said AL-108's success shows that tangles also can be a target. " 'Tangles' may be as important—or perhaps more important—than 'plaques.' "

The phase IIa study comprised 144 patients (mean age 69) with amnestic mild cognitive impairment. Patients had a Mini-Mental State Examination of at least 24. They were divided into three groups: placebo, 5 mg AL-108 daily, and 15 mg AL-108 twice daily. The drug was administered for 12 weeks; cognition was tested at baseline and at weeks 4, 8, 12, and 16.

The drug was safe and well tolerated, Dr. Schmechel said at the meeting presented by the Alzheimer's Association. The dropout rate was 13% and not different between the active and placebo groups. Compliance was high (98%). The most common adverse event was headache, but there was no difference in incidence between the active and placebo groups.

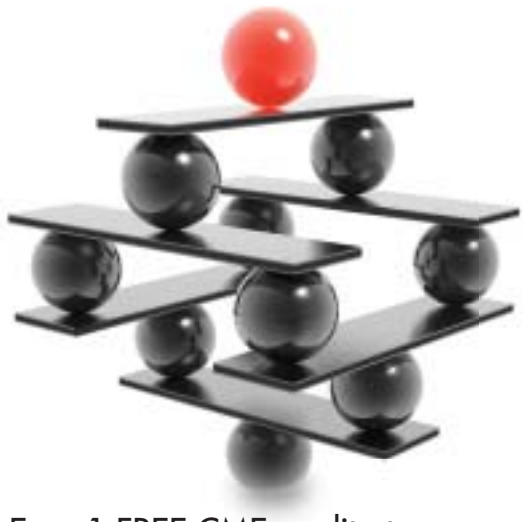
The primary end point was a composite of memory component scores from four cognitive tests. By 16 weeks, neither of the active groups scored significantly better than the placebo group on this measure. However, those taking the higher dose showed a trend toward better performance, noted Dr. Schmechel, professor of neurology at Duke University, Durham, N.C.

On the digit span forward test—a measure of verbal recall and short-term memory—the high-dose group performed significantly better than the low-dose or placebo groups, with a 12% increase over baseline. The high-dose group also performed significantly better than the others on the delayed match-to-sample test, a measure of visual working memory. By week 16, these patients had a 62% improvement over baseline. ■

Parkinson's Disease:

Reevaluating Treatment Strategies for Maximizing Patient Benefit

Redefining Treatment Success in Patients With Parkinson's Disease



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Online Program Overview

Parkinson's disease (PD) is a chronic, progressive, neurologic disorder with an estimated prevalence of 4.1 million worldwide and 340,000 in the United States in individuals >50 years of age. Early diagnosis of PD and treatment with disease-modifying therapies may provide improved long-term patient outcomes by potentially slowing the progression of PD. Overall, effective management of the motor and nonmotor symptoms of PD through an individualized, patient-focused perspective is crucial to minimize disability, improve health-related quality of life, and achieve therapeutic success. The objective of this program is to present healthcare providers with information necessary to develop and implement a routine comprehensive assessment of patient needs and to facilitate the development of an appropriate individualized treatment strategy for patients with PD.

Faculty

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