Alzheimer's Treatment Strategies Fail in Trials

BY MICHELE G. SULLIVAN

VIENNA — Alzheimer's drug researchers served up a string of bad news at the International Conference on Alzheimer's Disease, presenting one failed trial after another.

None of these strategies tested—blocking amyloid, improving insulin sensitivity in the brain, or even doubling up on agents that improve synaptic signaling—was able to alter the steady rate of cognitive and functional decline in patients with mild to moderate Alzheimer's.

The disappointments, combined with the failed omega-3 fatty acid studies that were also presented at the meeting, left researchers wondering where to best focus their efforts.

"We are again left to wonder whether clues from epidemiology are more related to delaying or protective factors rather than factors related to progression of established disease," said Dr. Samuel Gandy, Mount Sinai Professor of Alzheimer's Disease Research at Mount Sinai Medical Center in New York.

Instead of searching for the compound that will alter the so-far inevitable decline seen in Alzheimer's, the key will probably be preventing the disease from taking hold in the first place, Dr. Gandy said in an interview. Unfortunately, those studies require very large cohorts and years of follow-up, making them logistically and financially intimidating.

"The major barrier to primary prevention studies in Alzheimer's is cost," Dr. Gandy said.

No Effect With Rosiglitazone

Although researchers around the world are busy exploring the pathologic links between Alzheimer's and diabetes, a phase II placebo-controlled trial of rosiglitazone failed to show any benefit on cognition in a group of 553 patients with mild to moderate Alzheimer's.

The 24-week trial, sponsored by GlaxoSmithKline, randomized the patients (mean age 72 years) to placebo, a positive control group of donepezil 10 mg/day, or one of two rosiglitazone doses (2 mg or 8 mg daily). The extended-release formulation was an experimental one, and not the Food and Drug Administration–approved Avandia, Dr. Michael Gold said at the meeting.

The study examined each treatment's effect in the overall cohort, on those who were apolipoprotein E e4 (APOE e4) negative, and all subjects except those homozygous for the high-risk gene. The primary end points were changes in the Alzheimer's Disease Assessment Scale–cognitive domain (ADAS-cog) and Clinicians' Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus).

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DR. GANDY

At 24 weeks, neither of the rosiglitazone doses was significantly different from placebo in either cognitive assessment for any of the populations. However, in the overall population and in the group that included everyone except the APOE e4 homozygous carriers, CIBIC-plus scores were significantly better for those taking donepezil than for those taking placebo.

But since that finding had not been adjusted for covariates, "I don't think it's anything we can hang our hats on," said Dr. Gold, global clinical vice president of neurology at GlaxoSmithKline.

End of the Road for Tarenflurbil

Dr. Gordon Wilcock announced the final nail in the coffin for tarenflurbil: another failed phase III trial, this one conducted in the United States, Canada, and Western Europe.

In 2008, tarenflurbil, a selective amyloid-lowering agent, failed its very highly anticipated phase III U.S. trial. The results of this second trial, which was unblinded in February, confirm last year's disappointment, said Dr. Wilcock of the University of Oxford (England).

"The results really mirror the failed U.S. trial very much," Dr. Wilcock said at the meeting. "I'm afraid with two failed phase III trials, tarenflurbil has killed itself off completely."

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 beta (AB_{42}) in the brain by changing the point at which the enzyme gamma secretase cuts the amyloid precursor protein, shifting the ratio to less of the toxic AB_{42} and more of the less-toxic AB_{40}.

However, the most recent trial failed to show any statistically significant or clinically meaningful changes in any of the three outcomes it assessed: ADAS-cog, ADAS-activities of daily living (ADAS-ADL), or the Clinical Dementia Rating–sum of boxes (CDR-sb).

Patients were randomized to placebo or to 800 mg tarenflurbil twice a day. After 18 months, the mean placebo decline rates were 6 points on the ADAS-cog, 11 points on the ADAS-ADL, and 2.7 points on the CDR-sb. "The picture with tarenflurbil was absolutely the same," Dr. Wilcock said. "You can virtually superimpose the decline" on tarenflurbil over that on placebo.

"We also included a neuropsychiatric test battery, thinking it might be more sensitive to early changes, but this produced a similarly disappointing picture," he said.

Adverse events were reported in 88% of the placebo patients and 85% of the tarenflurbil patients—again, not a significant difference. However, compared with placebo, the drug was associated with significantly more anemia (14% vs. 4%), infections (4% vs. 1%), and gastrointestinal ulcers (2% vs. 0%).

"This was a well-powered, well-designed, and well-conducted trial," that would have identified any benefit that existed, Dr. Wilcock said. Instead, its message seems to be that researchers would do well to investigate non–amyloid-centered therapies.

"It's one of three different strategic approaches to deal with amyloid in the brain that have proved negative," Dr. Wilcock said. "Whether that is due to the study design, or means we need to be rethinking what is going on with the amyloid cascade hypothesis is an interesting question."

The trial was sponsored by Myriad Pharmaceuticals Inc. of Salt Lake City. Dr. Wilcock is a consultant with the company.

Drug Combo No Better Than One Drug

Finally, a combination of two drugs already proven effective in Alzheimer's disease worked no better than a single agent to slow the disorder's cognitive and functional decline, Dr. Oliver Peters said.

Dr. Peters of Charité University Hospital Berlin, presented the results of a trial of a combination of galantamine and memantine, compared with galantamine alone, in 233 patients with mild to moderate Alzheimer's.

The patients (mean age 72 years) were randomized to 24 mg of galantamine daily plus a placebo, or a combination of 24 mg galantamine and 20 mg memantine for 1 year. The primary end points were the ADAS-cog, ADAS-ADL, and CDR-sb.

The combination was well tolerated, but the addition of memantine did not significantly affect any of the clinical end points.

"At 16 weeks, we saw a little better effect in the combination group," on all three measures, although none of the differences were statistically significant, Dr. Peters said. After 16 weeks, patients in both treatment arms experienced steady declines which, by week 52, were significantly worse than their baseline scores.

Janssen-Cilag sponsored the trial. Dr. Peters said he had no financial relationship with the company. ■

Midlife Brain MRI Markers Predict Later Stroke, Dementia

BY MICHELE G. SULLIVAN

VIENNA — The presence of brain infarcts at age 60 strongly predicts later stroke and dementia, while the presence of white matter hyperintensities is related to a wider variety of outcomes, including stroke, cognitive decline, dementia, and death.

The relationships suggest that each imaging abnormality could be used as a risk marker for the various disorders, Dr. Stephanie Debette said at the International Conference on Alzheimer's Disease.

"The association of large-volume white matter hyperintensities with incident dementia and amnestic MCI [mild cognitive impairment] suggests that it could be a useful quantitative intermediate marker for risk factors of early-stage cognitive impairment and dementia, whereas brain infarcts may be a more appropriate intermediate marker for stroke," said Dr. Debette of Boston University. "These imaging measures could potentially serve as intermediate end points in prevention trials."

The study cohort consisted of 2,229 subjects (mean age 62 years) in the Framingham Heart Study Offspring Cohort who underwent brain MRI and neuropsychological testing between 1999 and 2005. Of these, 1,694 returned for a second neuropsychological assessment an average of 6 years later.

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DR. DEBETTE

At baseline, 2% had evidence of an ischemic stroke and 0.3% had clinical dementia. Excess white matter hyperintensity volume was present in 14%, and 11% showed at least one brain infarct.

After 6 years, 7 subjects had developed dementia; 32 had experienced an ischemic stroke; and 187 had developed new-onset MCI, 94 cases of which were amnestic. During follow-up, 97 of the subjects died.

Two multivariate analyses that controlled for age, sex, and vascular risk factors revealed significant associations between the MRI markers, neurocognitive outcomes, stroke, and death.

Subjects with a large volume of white matter hyperintensities at baseline were significantly more likely than were those without a large volume of lesions to experience stroke and dementia (hazard ratio 2.0), amnestic mild MCI (HR 1.75), and death (HR 1.77). This association was particularly strong with cardiovascular death (HR 3.5).

Subjects with at least one brain infarct at baseline were significantly more likely to develop MCI of the executive function type (HR 2.3). Baseline brain infarcts also significantly predicted stroke (HR 3.0) and dementia (HR 9.0). ■