Failed Alzheimer's Trials Shift Focus to Prevention

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 signalling—was able to alter the steady rate of cognitive and functional decline in patients with mild to moderate Alzheimer's. also among the failures were the omega-3 fatty acid studies.

"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, he said in an interview.

Among the failures was a phase II placebo-controlled trial of rosiglitazone that showed no 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).

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

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, Durham, N.C.

Dr. Gordon Wilcock reported another failed phase III trial for tarenflurbil, this one conducted in the United States, Canada, and Western Europe. In 2008, tarenflurbil, a selective amyloid-lowering agent, failed its highly anticipated phase III U.S. trial.

"With two failed phase III trials, tarenflurbil has killed itself off completely," Dr. Wilcock, of the University of Oxford (England), said at the meeting.

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}.

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

"This was a well-powered, well-designed, and well-conducted trial," that would have identified any benefit that existed, Dr. Wilcock said. Its message seems to be that researchers should investigate non–amyloid-centered therapies. The trial was sponsored by Myriad Pharmaceuticals Inc. of Salt Lake City, for which Dr. Wilcock is a consultant.

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, reported Dr. Oliver Peters of Charité University Hospital Berlin.

He presented results of a randomized, controlled trial of a combination of galantamine and memantine compared to galantamine alone in 233 patients with mild-moderate Alzheimer's. The patients (mean age 72 years) were naive to cholinesterase inhibitors and memantine. They 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 arms experienced steady declines which, by week 52, were significantly worse than their baseline scores. APOE e4 status had no significant impact on the results.

Dr. Peters acknowledged that a larger group would have been preferable. Janssen-Cilag of Buckinghamshire, England, which sponsored the trial, thought that the study was sufficiently powered, he said, adding that he had no financial relationship with the company. ■