Alzheimer's Therapeutic 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 disease (AD). The disappointments, combined with the failed omega-3 fatty acid study that was also presented at the meeting, left researchers wondering where to best focus their efforts.

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

Dr. Michael Gold presented the results of a phase II placebo-controlled trial of rosiglitazone that failed to show any benefit on cognition in a group of 553 patients with mild to moderate AD.

The 24-week trial, sponsored by GlaxoSmithKline, randomized the patients to placebo, a positive control group of donepezil 10 mg/day, or 2 mg or 8 mg daily of an experimental extended-release formulation of rosiglitazone.

At the 24-week end point, neither of the rosiglitazone doses was significantly different than placebo in either the AD Assessment Scale-cognitive domain (ADAS-cog) or the Clinicians' Interview-Based Impression of Change plus Caregiver Input, said Dr. Gold, global clinical vice president of neurology at GlaxoSmithKline, Durham, N.C.

Dr. Gordon Wilcock announced negative results in a second phase III trial with tarenflurbil, a selective amyloid-lowering agent. The results confirm those first seen in a phase III trial of the drug in 2008.

The results of the most recent trial, which randomized patients to placebo or to 800 mg tarenflurbil twice a day for 18 months, 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), said Dr. Wilcock of the University of Oxford (England). He is a consultant to Myriad Pharmaceuticals Inc., which sponsored the trial

A combination of two drugs already proven effective in AD worked no better than a single agent to slow the disorder's cognitive and functional decline, said Dr. Oliver Peters of Charité University Hospital Berlin.

Dr. Peters presented the results of a 1-year, randomized, controlled trial of a combination of 24 mg of galantamine daily and 20 mg memantine daily compared to 24 mg of galantamine alone in 233 patients with mild-moderate AD.

"At 16 weeks, we saw a little better effect in the combination group," on the ADAS-cog, ADAS-ADL, and CDR-sb, although none of the differences were statistically significant, said Dr. Peters, who has no financial relationship with the trial sponsor, Janssen-Cilag of Buckinghamshire, England.

The negative results of an 18-month, randomized, placebo-controlled trial in 402 patients with mild-moderate AD may have sealed the fate of docosahexaenoic acid (DHA) as a treatment for AD, but a second study, which examined DHA's effect on memory performance in 485 normal subjects with mild, age-related memory difficulties, concluded that the supplement did significantly improve performance on a memory test.

"The data suggest that DHA may serve to reduce risk by perhaps facilitating neuronal health," Dr. Marwan Sabbagh, director of clinical research at the Sun Health Research Institute, Sun City, Ariz., said in an interview. "However, it appears that once symptomatic Alzheimer's is present, the critical mass of pathology may be too much for even DHA to offset." ■