Trial Drug Shows Hints of Efficacy in Alzheimer's

BY MITCHEL L. ZOLER
Philadelphia Bureau

PHILADELPHIA — Alzhemed, an investigational drug believed to prevent formation of amyloid fibrils in Alzheimer's patients, was safe and showed hints of efficacy in a phase II study, Paul A. Aisen, M.D., said at the Ninth International Conference on Alzheimer's Disease and Related Disorders.

The results were encouraging enough to warrant the launch of a phase III efficacy study in 950 patients with Alzheimer's disease, said Dr. Aisen, director of the memory disorders program at Georgetown University, Washington.

In the open-label phase of the current study, in which patients were treated for as long as 20 months, the results were "consistent with a stabilization effect on cognitive function, particularly in patients with mild Alzheimer's disease," he said at the conference, presented by the Alzheimer's Association.

The study was sponsored by Neurochem Inc., the manufacturer of Alzhemed. Alzhemed is a small molecule that is administered orally and binds to soluble β-amyloid and thereby prevents it from forming amyloid fibrils.

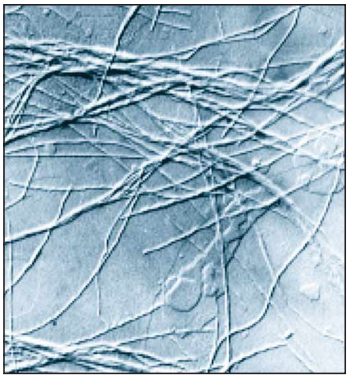
Deposition of amyloid fibrils in the brain is a hallmark of Alzheimer's disease.

The study enrolled 58 patients with mild to moderate Alzheimer's disease. Their average age was about 75 years old, and their average score on the Mini-Mental State Examination was about 20. Patients could be enrolled if they were already on stable treatment with an acetylcholinesterase inhibitor, and about 70% of the patients fell in this category, said Dr. Aisen, who is on Neurochem's clinical advisory board.

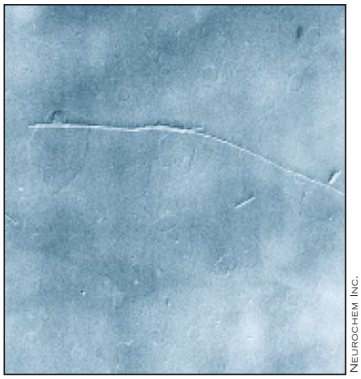
Patients were randomized to receive placebo or 50 mg, 100 mg, or 150 mg of Alzhemed b.i.d. The study was designed to continue blinded treatment for 12 weeks, and 52 patients completed this phase. Four of the six dropouts were from the Alzhemed groups, and three of these patients dropped out because of adverse effects (two because of nausea and one due to weakness and weight loss).

After 12 weeks of treatment, the patients who received 100 mg or 150 mg of the drug b.i.d. had a significant drop in the level of β-amyloid in their cerebral spinal fluid, a surrogate marker for what might have happened to the β-amyloid in their brains, Dr. Aisen said.

Patients treated with placebo or the lowest dosage of Alzhemed had no measurable change in their β-amyloid levels.



Formation of amyloid fibril is aggressive in this incubated in vitro model.



NEUROCHEM INC.

After administration of Alzhemed, the amyloid fibril formation is inhibited.

No patients in the study showed a measurable change in cognition during this relatively brief period.

Forty-two of the 52 patients who finished the blinded phase agreed to participate in an open-label treatment phase in which all patients received 150 mg b.i.d. Of the 16 patients who eventually stopped their treatment, two did so as a result of adverse effects, with one patient stopping because of nausea and vomiting and the other because of agitation and delusion.

Among the 19 patients who completed 20 months of treatment, their Alzheimer's Disease Assessment Scale cognitive score rose by an average of 6.2 points (the higher a patient's score, the worse the dementia), compared with an average rise of 11.9 points in historic controls, Dr. Aisen said.

Of the 10 patients from this group who entered the study with mild disease, the average rise in their score from baseline was 2.4 points, compared with an average 8.6-point rise among historic controls. ■

High-Dose Atorvastatin May Slow the Progression of Alzheimer's Disease

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — High-dose atorvastatin in Alzheimer's disease patients slowed progressive cognitive deterioration and improved depressive symptoms in a first-of-its-kind small, randomized, double-blind trial, D. Larry Sparks, Ph.D., said at the annual scientific sessions of the American Heart Association.

The definitive word on the efficacy of high-dose statin therapy for the cognitive and behavioral manifestations of Alzheimer's dementia must await completion of two ongoing large multicenter clinical trials, but the results of this single-center 1-year pilot study are certainly promising, said Dr. Sparks, senior scientist and head of the Ralph and Muriel Roberts Laboratory for Neurodegenerative Research at the Sun Health Research Institute, Sun City, Ariz.

He reported on 46 patients with mild-to-moderate Alzheimer's disease who completed 1 year on 80 mg/day of atorvastatin or placebo in addition to whatever cholinesterase inhibitors they were already on at randomization.

Primary outcomes in the study, were change in the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), both administered quarterly. The study was sponsored by the Institute for the Study of Aging and Pfizer Inc.

From a mean baseline score of 20 on the ADAS-cog, both the atorvastatin and placebo groups showed deterioration at 3 months. Thereafter, scores in the statin group stabilized, but the placebo group continued to deteriorate by about 1 point per quarter, so that at 1 year the atorvastatin group had a mean 3.5-point superior score on this instrument.

Mean ADCS-CGIC scores declined with time in both groups. However, the rate of decline was consistently steeper in the placebo arm, with the between-group differences missing statistical significance by the barest of margins at both 9 and 12 months, Dr. Sparks continued.

Mean scores on the Geriatric Depression Scale improved from 6 to 4 over the course of the year in the atorvastatin group while deteriorating to 8 in the placebo arm—a significant between-group difference.

Scores on the 10-item Neuropsychiatric Inventory declined from a baseline of 7.5 to 9 in the atorvastatin group and to 16 in the placebo group at 1 year.

Mean scores on the Mini-Mental State Examination remained stable in the atorvastatin group—20.8 at baseline and 20.4 at 1 year—while declining to 18 in the placebo group.

Performance on the ADCS Activities of Daily Living scale at 6 and 12 months didn't show any strong between-group differences.

Serum levels of superoxide dismutase and glutathione peroxidase activity were unchanged by high-dose atorvastatin; however, mean circulating ceruloplasmin levels were reduced 10%-15% at various time points, compared with placebo.

Dr. Sparks noted that animal studies suggest cholesterol in the brain plays a key role in production of β-amyloid, the putative neurotoxin believed to precipitate Alzheimer's disease. But while the marked reductions in circulating total, LDL, and VLDL cholesterol achieved with high-dose atorvastatin in the study are consistent with a lipid-lowering mechanism for the apparent cognitive and affective benefits, statins also improve vascular endothelial function and have antiinflammatory effects that might be relevant.

The impetus for this pilot randomized trial as well as the ongoing far larger ones stems in large part from multiple hypothesis-generating epidemiologic studies that have reported an association between lipid-lowering drug therapy and reduced rates and/or slower progression of Alzheimer's disease. ■

Rosiglitazone Slows Alzheimer's and MCI

BY MIRIAM E. TUCKER
Senior Writer

PHILADELPHIA — The diabetes drug rosiglitazone appears to preserve cognitive function in patients with mild cognitive impairment and Alzheimer's disease, G. Stennis Watson, Ph.D., reported at the Ninth International Conference on Alzheimer's Disease and Related Disorders.

The finding, from a small randomized clinical trial funded by GlaxoSmithKline, suggest that "there may be a therapeutic window … a novel approach to treating cognitive dysfunction," study coauthor Dr. Suzanne Craft said at a press briefing.

Twenty subjects with either mild cognitive impairment or Alzheimer's disease were randomized to receive 4 mg/day of rosiglitazone for 24 weeks, while another 10 subjects with similar degrees of cognitive impairment were randomized to receive placebo. Tests of cognition were performed at 2, 4, and 6 months, said Dr. Watson of the University of Washington, Seattle.

On the eight-word delayed recall part of the Buschke Selective Reminding Test, subjects on rosiglitazone remembered significantly more words than did the placebo subjects at 4 months (5.7 vs. 5.4) and 6 months (5.4 vs. 4.9), after adjustment for baseline performance. Similarly, the rosiglitazone group made fewer errors on the Stroop Color-Word Interference test, which measures selective attention. At 6 months, the rosiglitazone subjects made an average of 1.9 errors, compared with the expected 3.2 in the placebo group.

The effects are likely due to the drug's insulin-sensitizing and anti-inflammatory properties, and perhaps also to the amyloid-processing modulation action of rosiglitazone and other agents of the same class, Dr. Watson said at the conference, presented by the Alzheimer's Association. ■