Atorvastatin May Slow Alzheimer's Progression

BY BRUCE JANCIN
Denver Bureau

New Orleans — High-dose atorvastatin in patients with Alzheimer's disease 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.

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 at 1 year on the Geriatric Depression Scale improved from 6 to 4 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 over time 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 did not 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 anti-inflammatory effects that might be relevant

During a press conference, he said that serum cholesterol is the culprit contributing to Alzheimer's. By choosing a drug that does not cross the blood-brain barrier, he showed that lowering serum cholesterol slowed Alzheimer's progression.

Dr. Sparks' study was funded by the Institute for the Study of Aging and by Pfizer Inc. ■

CIs Underused in Moderate Alzheimer's

BY SALLY KOCH KUBETIN
Publication Editor

Toronto — Neurologists are more likely than are primary care physicians or psychiatrists to prescribe a cholinesterase inhibitor for a patient with mild to moderate Alzheimer's disease, but even neurologists fall short of meeting goals in clinical guidelines, Daniel L. Murman, M.D., said at the annual meeting of the American Neurological Association.

The ANA's evidence-based guidelines on management of patients with dementia call for physicians caring for ambulatory patients with mild to moderate dementia to consider using a cholinesterase inhibitor (CI) where appropriate, said Dr. Murman of the University of Nebraska, Omaha.

Dr. Murman and his associates reviewed office visit data from the National Ambulatory Medical Care Survey of office-based non–federally employed physicians. They focused on office visits made in 1993-2001 with the ICD-9 codes 331.0 (Alzheimer's disease), 290.2 (senile dementia with delusion or dementia), and 290.3 (senile dementia with delirium). Because the patients were ambulatory, their dementia was presumed to be mild to moderate.

A total of 700,000 office visits were made by the study population for Alzheimer's disease and senile dementia during the years of the study.

About 34% of the office visits for these categories of dementia were made to internists, 27% were made to family physicians, 12% were made to neurologists, and 11% to psychiatrists. Only 10% of the office visits were by new patients. Overall, 17% of the office visits were by patients referred by other physicians.

On average, physicians spent 34 minutes with a new patient and 20 minutes with an established patient. Neurologists spent the longest time with new patients (40 minutes during that first office visit), compared with 22 minutes for family physicians, 32 minutes for internists, and 37 minutes for psychiatrists.

Cholinesterase inhibitors, the only drugs with an indication for Alzheimer's disease, were prescribed for 29% of the patients with Alzheimer's disease. A CI was prescribed in 48% of office visits to neurologists, 29% of those to family physicians, and 27% of those to internists and psychiatrists.

Women accounted for 65% of the office visits, and 95% of the visits were made by whites; mean age was 79 years. Women and whites were more likely than were other demographic groups to be prescribed a CI.

This study was funded by a grant from the National Institute on Aging of the National Institutes of Health. ■

Alzheimer's Cognitive, Behavioral Symptoms May Respond Differentially to Donepezil

BY BRUCE JANCIN
Denver Bureau

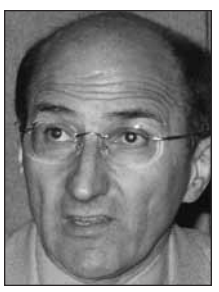
Orlando, Fla. — Alzheimer's disease patients who don't obtain clear-cut cognitive benefits with donepezil nonetheless often experience significant improvement in behavioral symptoms of the dementia, Ralf Ihl, M.D., said at Wonca 2004, the conference of the World Organization of Family Doctors.

"Behavioral symptoms should be considered an evaluable treatment response in patients with mild to moderate Alzheimer's disease. It may require the need for more than one visit to find out if the outcome is positive," added Dr. Ihl, a psychiatrist at the University of Düsseldorf (Germany) and president of the European Association of Geriatric Psychiatry.

The often-divergent cognitive and behavioral responses to donepezil therapy were highlighted in the Aricept Washout and Rechallenge (AWARE) study, a Pfizer-sponsored randomized clinical trial conducted in eight European nations and the United States.

AWARE had a three-phase design. In phase I, 1,812 patients with mild to moderate Alzheimer's disease received 24 weeks of open-label donepezil at 10 mg/day. During this phase, 193 patients withdrew from the study due to side effects and various other reasons.

Of the 619 patients who completed phase I, 68.8% showed clear benefit in cognitive symptoms as defined by improvement on the Mini-Mental State Examination (MMSE) or physician global assessment. At that point their participation in the trial was over. Phases II and III of AWARE were reserved for the 31.2% of patients who didn't show cognitive improvement in phase I.



Donepezil lessened behavior problems in patients with stable or declining cognition.

DR. IHL

Phase II was a double-blind study in which patients were randomized to receive either donepezil or placebo for 12 weeks. In phase III, everyone who participated in phase II was placed on donepezil for 12 weeks of single-blind therapy.

Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI). At the close of the double-blind phase II of AWARE, patients in the donepezil arm showed a significant 2.4-point mean improvement on the NPI, while those assigned to placebo displayed a 0.76-point worsening. The greatest improvement with the cholinesterase inhibitor was seen on the depression/dysphoria section of the NPI.

The improvement in behavioral symptoms seen with donepezil in phase II occurred in patients who simultaneously experienced cognitive decline as well as in those who remained cognitively stable or showed cognitive improvement.

"This shows those parameters are not really parallel during the course of the disease," the psychiatrist observed.

In phase III, patients who had been on donepezil throughout the AWARE trial showed continued behavioral improvement. However, patients who had been on placebo in phase II showed an attenuated improvement in behavioral symptoms in phase III.

"This shows something that many general practitioners already feel: If you interrupt treatment with a drug against dementia you lose something—and you can't win it back later even if you bring in the drug once more," Dr. Ihl said.

He noted that in 1906 when Alois Alzheimer first described the disease that bears his name, the physician stressed that the symptoms of the dementia include not only cognitive but also behavioral and functional problems that worsen with time.

"Relevant outcomes in Alzheimer's disease include all these dimensions: functional abilities, behavioral problems, quality of life, resource utilization. They all relate to an increased burden. It's not sufficient to look only at cognitive decline. You also have to look at other symptoms where there could be significant benefit," he said. ■