

Atorvastatin May Slow Alzheimer's Disease

High-dose statin therapy slowed cognitive deterioration, improved depressive symptoms.

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 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 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 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.

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

Galantamine Shows Mixed Results For Vascular Dementia Patients

BY BRUCE JANCIN
Denver Bureau

SAN FRANCISCO — The widely used anti-Alzheimer's disease drug galantamine also is effective in the treatment of patients with vascular dementia, Dr. Alexander P. Auchus said at the annual meeting of the American Academy of Neurology.

Galantamine proved significantly more effective than placebo at improving cognition and executive function in a phase III randomized clinical trial unique in that it was the first ever to employ expert MRI evaluators at a central radiology laboratory to confirm that participants indeed had vascular dementia, said Dr. Auchus of Case Western Reserve University, Cleveland.

There is at present no Food and Drug Administration-approved therapy for vascular dementia. Johnson & Johnson, sponsor of the phase III trial, doesn't intend to apply for a separate indication for galantamine in the treatment of vascular dementia, because only one of the study's two primary end points achieved statistical significance. But there is clear evidence of efficacy based upon multiple other study end points, and physicians will want to examine the data and decide for themselves whether this ther-

apy is worth considering for their patients, the physician told this newspaper.

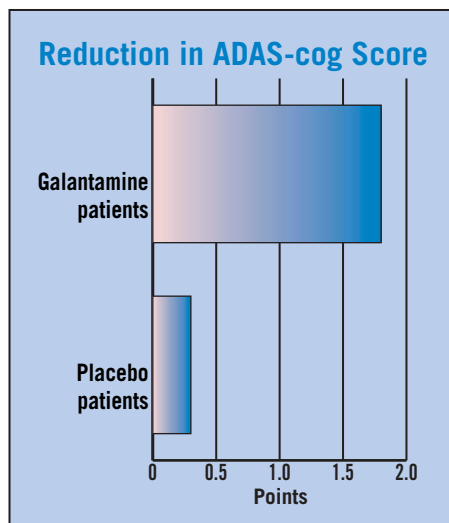
He reported on 788 patients diagnosed with vascular dementia by National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria with

Disease Assessment Scale-cognitive subscale (ADAS-cog). Galantamine-treated patients had significantly greater improvement in this domain, with a mean 1.8-point reduction at week 26, compared with a 0.3-point decrease in the placebo arm.

The other primary study end point—the one that didn't reach statistical significance—was improvement in a patient's ability to perform activities of daily living as assessed by the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL). Scores improved from baseline in both the galantamine and placebo groups. This was the dealbreaker in terms of a new indication for the drug, according to Dr. Auchus.

But the galantamine-treated patients did experience significantly greater improvement in executive function, a secondary study end point, than did the placebo group. Galantamine-treated patients had a mean 2.4-point reduction in the 25-item Executive Interview (EXIT-25) score at week 26, compared with a 1.4-point decline in the placebo group.

The only side effects that were significantly more common in the galantamine group were insomnia and cholinergic GI symptoms. ■



MRI confirmation who were randomized to galantamine or placebo in a double-blind 26-week trial conducted at 146 sites in 21 countries. Galantamine-treated patients received either 8 or 12 mg b.i.d. at the investigator's discretion.

One primary outcome measure was improvement in cognitive-related performance as assessed by the 11-item Alzheimer's

Signs of Alzheimer's Evident In Iris Murdoch's Final Novel

BY ROBERT FINN
San Francisco Bureau

Famed British author Iris Murdoch suffered from Alzheimer's disease before her death in 1999, and her final novel contains evidence of her increasing disability, according to an analysis by Peter Garrard, M.D., of University College, London, and his colleagues.

The last final work, "Jackson's Dilemma," published in 1995, was characterized by simplified language and a dwindling vocabulary, at least compared with "Under the Net," her first novel, published in 1954, and "The Sea, the Sea," the Booker Prize-winning novel published in 1978 at the height of her creative powers, wrote Dr. Garrard of the college's Institute of Cognitive Neuroscience (Brain [online] 2004;www.brain.oupjournals.org/cgi/reprint/awh341v1).

Critics' reaction to "Jackson's Dilemma" proved lukewarm, and the author later revealed that she had struggled with "writer's block" while writing it.

The investigators digitized portions of the three books and used specialized software to analyze, among other things, the frequency of words by word type. Of the three books, "Jackson's Dilemma" used the fewest word types, "The Sea, the Sea" used the most, and "Under the Net" used an intermediate

number of word types. This suggests that her vocabulary was enriched between 1954 and 1978, and impoverished between 1978 and 1995.

In contrast to the relatively impoverished lexical characteristics of "Jackson's Dilemma," the investigators found no difference in its syntactic characteristics—its grammar and structure. This is consistent with other studies of early Alzheimer's disease, in which many sufferers have trouble finding words while producing perfectly well-formed sentences.

Dr. Garrard and his colleagues wrote that their findings have clinical and theoretical implications. "From a clinical point of view, the results support the idea that the occurrence in the brain of Alzheimer's disease pathology may predate the onset of the earliest overt symptoms by years, or even decades," they wrote. "This in turn raises the possibility that an intellect of exceptional premorbid quality and/or a lifetime's engagement with intellectual work may either protect against cognitive deterioration or enable it to be masked."

Soon after the publication of "Jackson's Dilemma," Ms. Murdoch was diagnosed with Alzheimer's disease at the age of 76. She died 3 years later, and the Alzheimer's diagnosis was confirmed post mortem. ■