Donepezil Misses Primary End Point in CADASIL Treatment Trial

Susan Jeffrey

February 26, 2008 (New Orleans, Louisiana) — A randomized trial of donepezil (Aricept, Eisai/Pfizer) in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) has found no effect of treatment on the study's primary end point, change from baseline in the vascular Alzheimer's disease (AD) assessment scale cognitive subscale (V-ADAS-cog).

Improvements were seen on several secondary measures of executive function, the researchers, with first author Martin Dichgans, MD, from Ludwig Maximilian University, in Munich, Germany, note, "but the clinical relevance of these findings is not clear."

Results of the trial, funded by Esai Medical Research, were published online February 22 in Lancet Neurology, to coincide with their presentation here at the American Stroke Association International Stroke Conference 2008.

Although the results were negative, the researchers feel this trial has some lessons for how to proceed in the study of vascular dementia, Dr. Dichgans told a press conference here. "First, we feel our results emphasize the need to focus on specific etiologic subgroups in future interventional trials in vascular dementia," he said, as well as the importance of using dedicated neuropsychological test batteries developed for vascular dementia, not Alzheimer's disease.

Finally, he added, "we feel that CADASIL is a good model to assess novel therapeutic approaches in future trials."

Heterogeneous Disease

Cholinesterase inhibitors, including donepezil, have been shown to benefit patients with mild to moderate Alzheimer's disease, with improvements seen in cognition, global functioning, and activities of daily living (ADL), the authors write.

The picture is less clear in vascular dementia. These patients do have cholinergic deficits caused by disruption of cholinergic pathways by subcortical ischemic lesions, and trials of cholesterase inhibitors in vascular dementia have shown some benefit on cognition. "However, effects on global functioning and ADL have been inconsistent, and regulatory approval for this class of drugs has so far not been granted for use in this condition," they write.

Dr. Dichgans said that the conduct and interpretation of trials in vascular dementia have been difficult; vascular dementia is a heterogeneous group of disorders, he explained, and there is frequent overlap with AD pathology. In addition, many of the assessment tools used in these trials were developed in the field of AD.

"We set out to perform a dedicated trial in a more narrowly defined type of vascular dementia, subcortical vascular dementia," Dr. Dichgans said. They focused on a specific disorder, CADASIL, a genetic disorder with an early age of onset that causes subcortical vascular ischemic dementia. "These patients, because of the very early age of onset, are unlikely to have AD pathology, so this seemed a very clean system, a clear model, to study vascular dementia, specifically subcortical vascular dementia," he said.

The current study was an 18-week, double-blind, placebo-controlled, parallel-group trial carried out in 10 countries. A total of 168 patients with a diagnosis of CADASIL and cognitive impairment, defined as a Mini-Mental State Examination (MMSE) score of 10 to 27 or a trail-making test (TMT) B time score of at least 1.5 standard deviations below the mean, after adjustment for age and education.

They were randomized to receive either donepezil, 5 mg per day for the first 6 weeks, increasing to 10 mg until 18 weeks, or placebo. The primary efficacy measure was the change from baseline on the V-ADAS-cog at 18 weeks.

Of 168 patients randomized, 82 were assigned to placebo and 86 to donepezil. Of these, 5 in the placebo group and 2 in the donepezil group discontinued the trial either because they did not receive at least 1 dose of the study medication or did not have a baseline and postbaseline assessment on the V-ADAS-cog available for analysis. The intention-to-treat analysis therefore included 77 placebo and 84 donepezil patients.

Results at 18 weeks showed no significant difference between the donepezil and placebo groups on the primary end point.

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<th>End Point</th>
<th>Placebo</th>
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<tr>
<td>Least-squares mean change from baseline score (SE)</td>
<td>-0.81 (0.59)</td>
<td>-0.85 (0.57)</td>
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Similar results were seen on the V-ADAS-cog and the MMSE assessments of a range of cognitive functions, both secondary end points. They did see a significant treatment effect, though, on several measures of executive function, specifically the TMT B time ($P = .023$), TMT A time ($P = .015$), and the executive interview-25 ($P = .022$).

This finding is "of great interest because it emphasizes the involvement of cholinergic deficits in executive function," the authors note, adding, however, that the clinical relevance of these improvements is not clear.

The rate of adverse events was slightly higher with donepezil, as was expected, Dr. Dichgans said, but the rate and spectrum of events was similar to known effects seen in previous trials with donepezil. There were no serious adverse events with donepezil; 1 such event in the placebo group was probably unrelated to study medication, he noted.

Questions on Sample Selection

In a Reflection and Reaction commentary accompanying the paper, Lon S. Schneider, MD, from the University of Southern California Keck School of Medicine, in Los Angeles, lays out several issues with the design of the trial that he suggests may limit how the effect of donepezil can be interpreted.

For example, inclusion criteria required "poor — but not necessarily abnormal — performance" on cognitive tests, he writes. "The consideration that this sample included patients with dementia and possibly even patients who had normal scores on psychometric tests but with cognitive symptoms might imply that the investigators did not have the sample of patients with CADASIL that they were seeking or did not have a sample that was best suited to test the effects of donepezil," Dr. Schneider writes.

He suggests that half of the outcomes measured were more appropriate for patients with mild to moderate dementia who have orientation, memory, and comprehensive deficits. Further, randomization did not achieve balance between treatment groups on the basis of sex, antidepressant use, and TMT B time, which was longer in the placebo group, with a mean difference of about 22 seconds, he points out.

"Dichgans and colleagues showed the feasibility of multicenter trials with patients with CADASIL and the therapeutic potential of cholinesterase inhibitors," Dr. Schneider concludes. "In future trials, the sample selection should be reconsidered to better define the cognitive impairment syndrome to be treated, choose outcomes that reflect the deficits to be treated, and identify the individual patients who benefit from treatment."

"Slain by the Data"

Commenting on the findings for Medscape Neurology & Neurosurgery, session moderator and American Stroke Association program committee chair Philip Gorelick, MD, from the University of Illinois College of Medicine, in Chicago, said the negative findings in this trial are disappointing but perhaps not surprising.

"Unfortunately, this is the story of all the cholinesterase inhibitors that have been tested in vascular dementia, all of them," he said. "If you look at the studies, some of the subtests are positive, but the primary end point they choose, the most important one, doesn't come out to be positive."

The present study was well-designed, and the primary end point was the correct one, in his opinion, but the study was nevertheless negative. "We were all hoping it would work, and it just didn't." Although there was a "very strong scientific rationale" for testing cholinesterase inhibitors in CADASIL because of the disruption of cholinergic pathways in the white matter of these patients, he said during the press conference here, "this hypothesis has been slain by the data."

The study was funded by Esai Medical Research. Dr. Dichgans participated as an investigator and received consultancy fees and research grant support from Esai Medical Research. Disclosures for coauthors are listed in the paper. Dr. Snyder reports he has received honoraria for educational presentations from or has acted as a consultant for Forest Pharmaceuticals, Johnson & Johnson, Lundbeck, Merz GmbH, Novartis, and Pfizer.

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