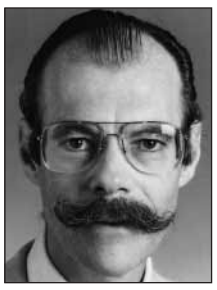
Donepezil's Early AD Benefits Gone for Most by 18 Months

BY DAMIAN McNAMARA
Miami Bureau

MIAMI BEACH — Neither donepezil nor vitamin E significantly prevented more patients with mild cognitive impairment from converting to Alzheimer's disease at 3 years than placebo, according to a study presented at the annual meeting of the American Academy of Neurology.

The randomized, controlled trial included 769 people with mild cognitive impairment (MCI). Researchers compared the number of "conversions" to Alzheimer's disease (AD) among 257 people taking 2,000 IU of vitamin E per day, 253 taking 10 mg of donepezil per day, and 259 taking placebo. The mean age was 72 years, and 46% of participants were women.



Rates of progression from MCI to AD were comparable among patients in the three treatment arms at 36 months. When researchers reassessed the data in 6-month increments, they found that people on donepezil were significantly less likely to have progressed to AD at 6 months and 1 year than those taking placebo. At 18 months, the difference was no longer significant, and then results converged with the placebo group. There were no significant differences at any 6-month measurement between vitamin E and placebo.

"Donepezil appears to reduce the risk of progressing from MCI to Alzheimer's disease up to 12 months," said Leon J. Thal, M.D., professor and chair of the department of neurosciences at the University of California, San Diego, and one of the study authors.

The study is scheduled for publication in the New England Journal of Medicine on June 9. (An online preview was posted at www.nejm.org on April 13.) The National Institute on Aging, Pfizer Inc., Eisai Inc., and DSM Nutritional Products supported the study.

A total of 212 patients converted from MCI to AD during the study. About 16% of patients treated with placebo converted each year, or more than 45% by the study's end. One patient progressed to mixed dementia, and another converted to primary progressive aphasia.

Secondary outcomes included cognition and function. There were very few significant differences between vitamin E and placebo, except in scores for executive, language, and overall cognitive scores; these differences were only significant in the first 18 months. However, "donepezil had a [greater] effect on overall function, memory, and language up to 18 months," Dr. Thal said. Six of seven mental-scoring differences were only significant during the first 18 months of the study.

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DR. THAL

A genetic factor made a significant difference in conversion of MCI to Alzheimer's disease: ε4 allele status for apolipoprotein E (apoE). About 55% of participants tested positive for one or more apoE ε4 alleles. "Positives converted at a higher rate and accounted for 76% of conversions," said Dr. Thal, who is also principal investigator for his university's Alzheimer's disease research center.

Donepezil made a significant difference in participants positive for the allele, compared with placebo, at 12, 24, and 36 months. Most of the treatment effect of donepezil occurred among the apoE ε4 carriers.

David S. Knopman, M.D., discussed the study findings in a subsequent presentation at the meeting. "My thinking is that [apoE ε4] genotyping should not be done prior to initiating therapy with donepezil in people with MCI, he said." Dr. Knopman is professor of neurology at the Mayo Clinic, Rochester, Minn., and had no conflict of interest to report.

"Are we there yet? Should MCI be treated with donepezil?" Dr. Knopman asked. "We need to discuss these results with families and give them both views." On the negative side, treatment with donepezil is not cost effective. On the plus side, the drug provides a 58% 1-year risk reduction "that may be clinically meaningful to some patients and families." ■

Donepezil Safe, Effective In African Americans

SAN DIEGO — Donepezil is safe and effective in African Americans with mild to moderate Alzheimer's disease, a 12-week open-label study showed.

The finding is important because African Americans are underrepresented in clinical trials even though they have a higher risk of developing Alzheimer's disease, compared with whites, Patrick Griffith, M.D., said during a poster session at the annual meeting of the American Association for Geriatric Psychiatry.

In addition, this is the first Alzheimer's trial to use the Fuld Object Memory Evaluation (FOME), which is thought to provide a culturally unbiased evaluation of memory. "The test has been validated in African Americans, and it operates independent of educational level or [social background]."

Dr. Griffith, chief of the division of neurology at Morehouse School of Medicine, Atlanta, said in an interview. "It relies on touch and vision. We may have a measuring tool for future clinical trials that will avoid previous reports of educational or cultural bias." Dr. Griffith and his associates enrolled 125 community-dwelling African Americans aged 51-98 from 30 sites in the United States with a clinical diagnosis of mild to moderate Alzheimer's disease and Mini-Mental State Examination (MMSE) scores of 10-26. The patients received donepezil (Aricept) 5 mg/day at the conclusion of their baseline visit; the dose was increased to 10 mg/day after 4 weeks—according to clinician judgment.

At weeks 4, 8, and 12, the investigators administered the FOME, the MMSE, and the Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC-plus). From baseline to week 12, patients showed significant improvement on the FOME storage and retrieval scores, the MMSE scores, and the CIBIC-plus scores.

The most common treatment-emergent adverse events were diarrhea, hypertension, and urinary tract infection, and the incidences were similar to those reported previously in patients with mild to moderate Alzheimer's. Lab results were unremarkable. Pfizer Inc., which manufactures donepezil, supported the study.

—Doug Brunk

Novel Drug Targets Plaque Formation in Alzheimer's Study

BY HEIDI SPLETE
Senior Writer

A new treatment in the works for Alzheimer's disease is designed to act at the cellular level to reverse plaque formation and prevent development of further disease.

Prana Biotechnology Ltd. has received approval from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom to begin a phase II/phase III study of clioquinol, also known as PBT-1. The investigators maintain that clioquinol will target the formation of amyloid plaques in the brain and thereby slow the progression of Alzheimer's disease (AD).

Ideally, clioquinol will both break up existing plaques and stop new ones from forming by redistributing the buildup of excess metals that are thought to cause plaques. "We believe that this is potentially a disease-modifying agent," Jonas Alsenas, D.V.M., Prana's chief executive officer told this newspaper in an interview.

Currently approved and available AD medications treat the symptoms; Prana is going after the source. Vaccines to prevent AD have fallen short because they target amyloid beta indiscriminately, whereas clioquinol goes after the toxic, aggregated form of the protein, Dr. Alsenas noted.

Known as the Progression Limitation in Alzheimer's: Clioquinol's Efficacy (PLACQUE) trial, the 1-year, randomized, double-blind, placebo-controlled study will include 435 adults with moderate AD, defined as baseline scores between 12 and 20 on the Mini-Mental State Examination (MMSE). Patients will take one pill in the morning and a second in the evening. One-third of them will take two 125-mg pills daily, one-third will take two 250-mg pills daily, and a third group will take a placebo. The researchers are targeting patients at a moderate stage of illness because these patients normally decline most rapidly, allowing the investigators to show an effect within the limits of a 1-year study.

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Researchers will enroll both patients who have taken no other AD medications and those who have taken memantine or similar medications for at least 4 months prior to the study.

In a pilot study of 36 patients, clioquinol effectively slowed cognitive loss in patients who scored greater than 25 on the AD assessment scale cognitive instrument. It was also significantly associated with an increased concentration of zinc in the patients' plasma (Arch. Neurol. 2003;60:1685-91).

The drug was generally well tolerated by the patients. Both folate and vitamin B_{12} were administered to all patients to counteract an observed association between oral clioquinol and myelo-opticoneuropathy that led to the drug's withdrawal from sale in 1970. A vitamin B_{12} deficiency was posited to be the cause of the neuropathy and levels of the vitamin were monitored throughout the trial, the researchers noted.

Many AD patients have slightly lower levels of zinc than would normally be expected. Craig Ritchie, M.B., of the department of psychiatry, University College London, explained that when clioquinol breaks up plaques, it has the added effect of returning zinc levels to normal. "One explanation is that some of the body's zinc is being sequestered into plaques in AD," said Dr. Ritchie, lead investigator on both the pilot study and the upcoming clinical trial.

However, the role of metals in maintaining the body's homeostatic functions is not fully understood, and a buildup of zinc has not been associated with dietary or environmental factors. "We are not saying that people should cut copper and zinc out of their diets," Dr. Ritchie emphasized.

The study will be done at sites in the United Kingdom, Australia, and South Africa. The company's goal is to have results from the study by the end of 2006, Dr. Alsenas said. ■