Efficacy of Donepezil in Early-Stage Alzheimer Disease

A Randomized Placebo-Controlled Trial

Ben Seltzer, MD; Parvaneh Zolnouni, MD; Margarita Nunez, MD; Robert Goldman, PhD; Dinesh Kumar, MA; John Ieni, PhD; Sharon Richardson, PhD; for the Donepezil “402” Study Group

Objective: To evaluate the efficacy of donepezil in patients with early-stage Alzheimer disease.

Design: Multicenter, randomized, double-blind, 24-week, placebo-controlled study that enrolled patients with early-stage Alzheimer disease. Patients were randomized in an approximately 2:1 ratio to donepezil, 5 mg/d, for the first 6 weeks, with a forced escalation to 10 mg/d thereafter (n=96), or placebo (n=57). The primary efficacy measure was the modified Alzheimer Disease Assessment Scale–cognitive subscale. Secondary efficacy measures included the Mini-Mental State Examination, the Computerized Memory Battery Test, the Clinical Dementia Rating Scale–Sum of the Boxes, the Patient Global Assessment Scale, and the Apathy Scale.

Results: Improvements favoring donepezil on the Alzheimer Disease Assessment Scale–cognitive subscale were found at weeks 12 and 24 and at the end point (last observation carried forward); treatment differences were 1.9 (P = .03), 2.3 (P = .008), and 2.3 (P = .001) points, respectively. Improvements favoring donepezil on the Mini-Mental State Examination were found at weeks 6, 12, and 24 and at the end point (last observation carried forward); treatment differences were 1.4 (P = .02), 1.2 (P = .04), 1.4 (P = .03), and 1.8 (P = .002) points, respectively. Donepezil-treated patients showed greater mean improvement compared with placebo-treated patients on the following Computerized Memory Battery Test subscales: facial recognition (P = .007 in the intent-to-treat population and P = .04 in the fully evaluable population), first and last name total acquisition (P = .02), and name-face association delayed recall (P = .04). Donepezil was safe and well tolerated in this population; serious adverse events occurred in similar numbers of donepezil- and placebo-treated patients.

Conclusion: These data suggest significant treatment benefits of donepezil in early-stage Alzheimer disease, supporting the initiation of therapy early in the disease course to improve daily cognitive functioning.

Arch Neurol. 2004;61:1852-1856

Pivotal clinical trials of cholinesterase inhibitors such as donepezil have focused on patients with mild to moderate Alzheimer disease (AD) and have demonstrated the treatment benefits of cholinesterase inhibitors in this patient population.1,2

The diagnosis of AD is often delayed until 2 to 3.5 years after the initial complaints of cognitive impairment,3 by which time patients have well-entrenched cognitive symptoms. Little prospective research has been conducted to evaluate the benefit of initiating treatment in the earliest phase of the disease, when cognitive symptoms are only mild and patients’ activities of daily living are preserved. Yet, improving symptoms and delaying progression of the disease at this stage might be expected to be particularly beneficial because these individuals have the highest level of functioning to preserve.

To our knowledge, this is the first clinical trial to prospectively evaluate donepezil’s effects on patients with early-stage AD. These patients do meet the criteria for probable AD and have crossed the threshold from mild cognitive impairment. Standardized psychometric tests, including the modified Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE), were used to evaluate donepezil’s treatment effects. The Computerized Memory Battery Test (CMBT)4—initially developed for age-associated memory impairment—was used to assess donepezil’s effects on critical cognitive tasks of everyday life.
PATIENTS

Generally healthy ambulatory patients, aged 50 to 92 years, diagnosed as having probable AD within the past 12 months were enrolled. Inclusion criteria included a modified Hachinski Ischemia Scale score of 4 or less; a global Clinical Dementia Rating Scale (CDR) score of 0.5 or 1.0; an MMSE score of 21 to 26 (inclusive); and only mild impairment in activities of daily living, defined by a summed score of 2 to 4 on the 3 functional domains (home and hobbies, community affairs, and personal care) of the CDR, with no more than 1 functional domain with a score of 2 or more. Patients were excluded if the decline in memory was possibly attributable to a psychiatric or neurologic disorder (eg, stroke or Parkinson disease) or to cognitive deficits following head trauma. Previous treatment with cholinesterase inhibitors, whether approved or in development, was not permitted.

The study was conducted in accordance with the principles stated in the Declaration of Helsinki, and was approved by institutional review boards at each site. Written informed consent was obtained from patients and their caregivers before screening.

STUDY DESIGN

This 24-week, randomized, double-blind, placebo-controlled study was conducted at 17 sites in the United States. Patients were randomized in an approximately 2:1 ratio to donepezil, 5 mg/d, for the first 6 weeks, with a forced escalation to 10 mg/d thereafter, or placebo. Patients unable to tolerate 10 mg of donepezil were discontinued from the study. Assessments were conducted at screening, at baseline, and at 6-week intervals thereafter through week 24 (final study visit) or at unscheduled termination visits.

OUTCOME MEASURES

The primary efficacy measure was the least squares means change from baseline to end point on the modified ADAS-cog total score. Secondary efficacy measures included change from baseline to end point on the MMSE, the CDR-Sum of the Boxes, the CMBT, and the Apathy Scale. Patients were asked to rate their impression of change using the Patient Global Assessment Scale at the end point visit.

SAFETY EVALUATIONS

Safety assessments were conducted at screening and at the final visit. Adverse events (AEs) were elicited at each visit by questioning the patient throughout the study by telephone and through direct observation by the patient treatment team.

DATA ANALYSIS

Efficacy analyses were performed on the intent-to-treat and fully evaluable (FE) populations, whereas safety analyses were performed on the safety population. Study end point was the final visit observation (ie, if a patient was missing a week 24 observation, then the last observed value was carried forward and used as the end point visit observation).

The intent-to-treat population included all patients randomized to treatment regardless of follow-up evaluations or compliance with treatments. The FE population comprised patients who completed 24 weeks of treatment with 80% or more compliance at the week 24 visit and at 2 other clinic visits, with no significant protocol violations.

RESULTS

PATIENT DISPOSITION AND DEMOGRAPHIC CHARACTERISTICS

A total of 153 patients were randomized to treatment, 96 receiving donepezil and 57 placebo (Figure 1). Patient characteristics are summarized in Table 1. The mean±SD time to onset of dementia symptoms, as determined by interview of patient and caregiver, was 2.8±1.9 years before enrollment. The treatment groups were similar with respect to scores on screening and baseline neuropsychologic and cognitive tests (Table 1). The proportions of patients with comorbid illnesses and concomitant medication use were similar in the 2 groups.

PRIMARY EFFICACY MEASURE

Improvements favored donepezil on the modified ADAS-cog 13-item scores as early as week 12 (P=.03) (Figure 2). The drug-placebo difference was approximately 2.3 points at week 24 (P=.008) and at the end point (P=.001). Improvement of 4 points or more was seen in 16% of placebo-treated patients and in 37% of donepezil-treated patients; improvement of 7 points or more was noted in 7% of the placebo- and 10% of the donepezil-treated patients. In addition, improvements favored donepezil in the FE population at the end point (P=.02) (data not shown).

Figure 1. Patient enrollment and completion through the study. The asterisk indicates that percentages sum to more than 19% because of rounding.

Statistical analyses of efficacy variables were performed on the change from baseline scores at weeks 6, 12, 18, and 24 and at the end point (last observation carried forward). The overall treatment effect was assessed using type III sums of squares performed at the 5% level to determine statistical significance. Ordinal variables were analyzed using the Cochran-Mantel-Haenszel chi² test with MODRIDITS scores. Treatment differences in the incidence rates for AEs were tested using the Fisher exact test.

Table 1. Patient Global Assessment Scale (GAS) scores at end point (last observation carried forward). The mean±SD indicates that percentages sum to more than 19% because of rounding.

Figure 2. Improvements in the modified ADAS-cog 13-item total score from baseline to end point (last observation carried forward). The drug-placebo difference was approximately 2.3 points at week 24 (P=.008) and at the end point (P=.001).
Table 1. Demographic Characteristics of Patients Randomized to Study Treatments

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donepezil Group (n = 96)</th>
<th>Placebo Group (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td>73.3 ± 9.6 (50-90)</td>
<td>75.1 ± 8.8 (52-92)</td>
</tr>
<tr>
<td>Female sex</td>
<td>48 (50)</td>
<td>34 (60)</td>
</tr>
<tr>
<td>Onset of cognitive</td>
<td>2.9 ± 2.0</td>
<td>2.5 ± 1.8</td>
</tr>
<tr>
<td>symptoms, y‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening CDR score</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>30 (31)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>61 (64)</td>
</tr>
<tr>
<td>Memory Box</td>
<td>0.5</td>
<td>20 (21)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>66 (69)</td>
</tr>
<tr>
<td>Score at screening†</td>
<td>MMSE</td>
<td>24.1 ± 1.7 (20-27)</td>
</tr>
<tr>
<td></td>
<td>Modified ADAS-cog total</td>
<td>21.0 ± 7.9 (5.7-40.7)</td>
</tr>
<tr>
<td></td>
<td>(13 items)</td>
<td>21.3 ± 6.8 (8.0-41.3)</td>
</tr>
<tr>
<td></td>
<td>Hachinski</td>
<td>0.6 ± 0.7 (0-4)</td>
</tr>
<tr>
<td></td>
<td>Ischemia Scale</td>
<td>0.7 ± 0.8 (0-3)</td>
</tr>
<tr>
<td></td>
<td>HAM-D total</td>
<td>2.9 ± 2.8 (0-12)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog, Alzheimer Disease Assessment Scale–cognitive subscale; CDR, Clinical Dementia Rating Scale; HAM-D, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

At least 70% of the patients with early-stage AD receiving donepezil did not experience cognitive worsening vs 47% of the placebo patients, during the 24 weeks of treatment.

SECONDARY EFFICACY MEASURES

Improvements in MMSE scores favoring donepezil were observed as early as week 6 (P = .02), and were sustained through week 24 (P = .03) (Figure 3). The drug-placebo difference at the end point was 1.8 points in favor of donepezil (P = .002). In the FE population, improvements favored donepezil in MMSE scores at the end point (P = .04) (data not shown).

Improvements favoring donepezil were seen on CMBT tasks testing verbal and visual memory. Donepezil improved performance of the intent-to-treat population on name-face association delayed recall (mean±SD scores: donepezil group, 0.1±0.1; placebo group, −0.1±0.1; P = .04) and facial recognition (First Miss) (mean±SD scores: donepezil group, 0.8±0.6; placebo group, −1.6±0.8; P = .007). In addition, donepezil improved performance on first and last name total acquisition (mean±SD scores: donepezil group, 0.7±0.2; placebo group, 0.2±0.3; P = .02) and facial recognition (First Miss) (mean±SD scores: donepezil group, −0.1±0.8; placebo group, −2.3±0.9; P = .04) in the FE population. No significant improvements were seen on other CMBT tasks (P ≥ .07).

On the Apathy Scale, the donepezil group tended to score higher than the placebo group; however, the difference was not significant. No significant differences on CDR–Sum of the Boxes or Patient Global Assessment Scale scores were observed between treatment groups.

SAFETY

Donepezil was well tolerated in this study; 15 (16%) of the 96 patients receiving donepezil withdrew because of AEs compared with 5 (9%) of the 57 patients receiving placebo. The incidence rates of common AEs are presented in Table 2. Most AEs were mild to moderate in severity and transient. Serious AEs were experienced by 5 (5%) donepezil-treated patients and by 3 (5%) placebo-treated patients. Serious AEs in donepezil-treated patients included colon cancer, dizziness, fall and cerebral hemorrhage, syncope, and right-sided carotid stenosis. Only 1 serious AE (fall and cerebral hemorrhage) for 1 donepezil-treated patient was considered possibly related to treatment. Serious AEs in placebo-treated patients included pancreatic cancer, bradycardia, and prostate cancer.
This trial demonstrates that donepezil treatment resulted in significant improvements in cognitive function over 24 weeks in patients with early-stage AD. The modified ADAS-cog and MMSE scores improved significantly during the treatment period in the donepezil group. In contrast, the placebo group failed to improve on both assessments.

The rate of cognitive decline seems to vary during the course of AD.13,15 The present study found, on average, little or no decline in the ADAS-cog or MMSE scores of the patients with early-stage AD in the placebo group during the 24-week period. This is in contrast to earlier clinical studies enrolling patients with mild to moderate AD, who showed significant decline (1-1.8 points in ADAS-cog scores) within this time frame.2,15 Thus, data from this study suggest that treatment response of patients with early-stage AD may be different from the response of patients with advanced stages of AD.

Significant differences in cognitive function favoring donepezil were also observed for the following components of the CMBT: facial recognition (First Miss), name-face association delayed recall, and first and last name total acquisition. These tests assess verbal and visual memory, which are impaired in the early stages of AD.10

Given the minimal functional impairment of patients at enrollment, the lack of a drug-placebo difference on the CDR–Sum of the Boxes was not unexpected. The CDR–Sum of the Boxes may have limited ability to detect functional differences over a 6-month period in minimally impaired patients and, thus, may not be the best assessment tool for this population. A similar argument can be made for the Apathy Scale and Patient Global Assessment Scale scores. Patients enrolled in the trial had only mild apathy at study enrollment, consistent with the notion that apathy is a symptom with a later onset.17 Thus, the absence of drug-placebo differences may not be an unexpected outcome. The lack of significant improvement in Patient Global Assessment Scale scores may reflect a limited sensitivity of the measure in this population because the reliability of the self-assessment by the patients may not adequately reflect the actual treatment benefits.

Donepezil was safe in this population; serious AEs occurred in similar numbers of donepezil- and placebo-treated patients. Good tolerability was demonstrated overall. Discontinuations due to AEs were higher in the donepezil than in the placebo group, but similar to those in donepezil trials of patients with mild to moderate AD.2,18

The use of cholinesterase inhibitors such as donepezil has been shown to impact long-term outcomes, such as maintaining patients at a higher level of functioning19 and keeping them in the community longer.20,21 Thus, initiating treatment early may preserve cognitive function and maintain patient independence longer, thereby reducing the pharmacoeconomic impact of the disease.

While clinical studies such as this one provide further evidence for the symptomatic benefits of donepezil treatment, imaging studies suggest additional neuroprotective effects with donepezil, compared with placebo, causing significantly smaller decreases in hippocampal volumes in patients with AD.22 Suggested mechanisms of action include an antagonist effect on N-methyl-D-aspartate receptor sites,23 induction of neuroprotective factors by stimulation of nicotinic acetylcholine receptors,24 and modulation of gene expression.24,25

The robust effect of donepezil on cognitive performance provides further evidence of the benefit of early initiation of donepezil therapy in the treatment of AD. Longer-term studies are required to further evaluate the potential benefits to the patient, family, caregivers, and society by early initiation of donepezil therapy.

Accepted for Publication: May 12, 2004.

Author Affiliations: Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, La (Dr Seltzer); California Clinical Trials Medical Group, Beverly Hills.

Table 2. Adverse Events Occurring in 5% or More of Patients Receiving Donepezil and at Least Twice the Rate of Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Donepezil Group (n = 96)*</th>
<th>Placebo Group (n = 57)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal dreams</td>
<td>9 (9)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (8)</td>
<td>1 (2)</td>
<td>.16</td>
</tr>
<tr>
<td>Injury</td>
<td>6 (6)</td>
<td>0</td>
<td>.08</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (5)</td>
<td>0</td>
<td>.16</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (10)</td>
<td>2 (4)</td>
<td>.21</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>9 (9)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (8)</td>
<td>1 (2)</td>
<td>.16</td>
</tr>
<tr>
<td>Injury</td>
<td>6 (6)</td>
<td>0</td>
<td>.08</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (5)</td>
<td>0</td>
<td>.16</td>
</tr>
<tr>
<td>Any</td>
<td>67 (70)</td>
<td>37 (65)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not applicable.
*Data are given as number (percentage) of each group.
Group, Beverly Hills (Dr Zolnouni); ICSL Clinical Studies, St Petersburg, Fla (Dr Nunez); Pfizer Inc, New York, NY (Dr Goldman); and Eisai Inc, Teaneck, NJ (Mr Kumar and Drs Ieni and Richardson).

Correspondence: Ben Seltzer, MD, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112-2699 (seltzer@tulane.edu).

Author Contributions: Study concept and design: Ieni and Richardson. Acquisition of data: Seltzer, Zolnouni, Nunez, and Richardson. Analysis and interpretation of data: Seltzer, Goldman, Kumar, Ieni, and Richardson. Drafting of the manuscript: Seltzer, Goldman, and Richardson. Critical revision of the manuscript for important intellectual content: Seltzer, Zolnouni, Nunez, Goldman, Kumar, Ieni, and Richardson. Statistical analysis: Kumar. Obtained funding: Goldman and Ieni. Administrative, technical, and material support: Seltzer and Goldman. Study supervision: Seltzer, Ieni, and Richardson. Funding/Support: This study was supported by Eisai Inc and Pfizer Inc.

Acknowledgment: We thank Yvonne Noble, RN, clinical study manager, Eisai Inc, for her commitment and hard work; and Teresa Griesing, PhD, Pfizer Inc, for her role in the early phases of this study.

REFERENCES