Open-Label, Multicenter, Phase 3 Extension Study of the Safety and Efficacy of Donepezil in Patients With Alzheimer Disease

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**Background:** Donepezil hydrochloride is a selective acetylcholinesterase inhibitor approved for the symptomatic treatment of mild to moderately severe Alzheimer disease (AD). Controlled clinical trials of up to 24 weeks have demonstrated that donepezil treatment (5 and 10 mg/d) significantly improves cognition and global function.

**Objective:** To investigate the long-term benefits of donepezil treatment in patients with AD.

**Design:** Multicenter, open-label, 144-week extension of 2 US phase 3, double-blind, placebo-controlled clinical trials: a 15-week study (12 weeks of treatment followed by a 3-week placebo washout) and a 30-week study (24 weeks of treatment followed by a 6-week placebo washout).

**Interventions:** All patients (N=763) initially received donepezil, 5 mg/d, for 6 weeks, after which an increase to 10 mg/d was encouraged.

**Measures:** Primary efficacy measures were the Alzheimer's Disease Assessment Scale–cognitive subscale and the Clinical Dementia Rating–Sum of the Boxes.

**Results:** After the shorter 3-week placebo washout, donepezil-associated benefits remained above original baseline values for an additional 24 weeks of open-label treatment. Benefits on Alzheimer’s Disease Assessment Scale–cognitive subscale scores for patients who received 10 mg/d in the double-blind study were evident compared with the other groups for 108 weeks of open-label treatment. In contrast, donepezil-associated benefits were lost after the 6-week placebo washout, and scores decreased below original baseline values for all patient groups. Although scores improved relative to the new open-label study baseline scores after drug use was restarted, patients remained below original baseline values. The most common adverse events were associated with the nervous and digestive systems and were generally mild and transient; 17% of patient discontinuations were associated with adverse events.

**Conclusions:** Donepezil is an effective and safe drug for the long-term symptomatic treatment of mild to moderately severe AD for up to 144 weeks (2.8 years), and sustained treatment may confer some advantages.

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To date, the most successful agents developed for the treatment of Alzheimer disease (AD) are the acetylcholinesterase inhibitors,1-4 of which donepezil hydrochloride is currently the most widely used. The clinical benefits of donepezil treatment have been demonstrated in 4 clinical trials,3,5-7 in which significant improvements in cognition and global function have been observed in studies of up to 24 weeks’ duration. However, the optimal time for continuing donepezil treatment beyond 24 weeks to maintain benefits remains an important clinical question.

Results of an open-label phase 2 extension trial8 suggest that donepezil-associated benefits can be maintained for up to 1 year, but these results might have underestimated the true effect of donepezil treatment for 2 reasons. First, during the 12 weeks of the initial double-blind study, most patients were treated with donepezil, 1 and 3 mg/d; these dosages are now known to be subtherapeutic. Second, because of previous protocol restrictions, most patients did not receive the most beneficial dosage of donepezil (10 mg/d) until 60 weeks after initiation of open-label treatment.8

Long-term use of donepezil is also supported by a favorable safety profile. Preclinical trials have shown that donepezil preferentially inhibits brain acetylcholinesterase, with little effect on cholinesterase of cardiac or smooth intestinal muscles.9 This observation provides a possible advantage for long-term use.
PATIENTS AND METHODS

PATIENTS

Men and women aged 50 years and older who had successfully completed 1 of 2 US phase 3, double-blind clinical trials were eligible for this extension study. Patients were required by the double-blind study protocol to have an established diagnosis of AD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, category 290.00 or 290.10 and by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association guidelines. Patients were also required to have mild to moderately severe AD at baseline of the double-blind trials, as defined by Mini-Mental State Examination scores of 10 to 26 and Clinical Dementia Rating (CDR) scores of 1 (mild) or 2 (moderate). Patients were otherwise generally healthy and ambulatory or ambulatory aided. Women were surgically sterile or at least 2 years past menopause.

Patients were excluded if they had evidence of other psychiatric or neurological disease, other serious diseases that were not clinically stable, type 1 or type 2 diabetes mellitus, alcoholism or drug misuse, a history of a hematologic or oncologic disorder in the past 2 years, or known sensitivity to acetylcholinesterase inhibitors. Most concomitant medications were allowed, except investigational agents, cholinomimetic agents, and cholinergic antagonists. Patients were excluded from this open-label study if they had withdrawn prematurely from the initial double-blind studies.

This trial was conducted in compliance with the US Code of Federal Regulations and the principles stated in the Declaration of Helsinki.

STUDY DESIGN

This multicenter, open-label extension study was a continuation of 2 US phase 3, randomized, double-blind, placebo-controlled, clinical trials: a 15-week study (study 301) comprising 12 weeks of treatment followed by a 3-week placebo washout and a 30-week study (study 302) comprising 24 weeks of treatment followed by a 6-week placebo washout. Study duration was 152 weeks: 144 weeks of treatment followed by an intended 8-week placebo washout period and subsequent evaluation were not routinely performed. At the start of the extension trial, all patients received single daily doses of 5 mg of donepezil for the first 6 weeks, irrespective of the daily dosage received during the initial double-blind studies. The dosage of donepezil could be increased to single daily doses of 10 mg after the week 6 visit based on the decision of the clinician and the overall drug tolerability of the patient. Up to week 120, the dosage of donepezil could be reduced or increased to 5 or 10 mg/d at the discretion of the investigator. Between weeks 120 and 144 (end of study), no dosage adjustments were permitted.

Safety and efficacy evaluations were undertaken at termination of the double-blind study, after the placebo washout (cumulative week 15 or 30), at weeks 6 and 12 of the open-label study, and at 12-week intervals thereafter. Patients had to remain 80% compliant with the donepezil regimen to continue in the open-label study.

EFFICACY EVALUATION

The primary efficacy measures were the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-Cog), an extensively validated scale for the assessment of cognitive performance, and the CDR-Sum of the Boxes (CDR-SB), a global measure of dementia severity. The baseline for all efficacy measures was the original baseline from study 301 or 302.

SAFETY EVALUATIONS

Safety was assessed by physical examination (including vital signs), clinical laboratory tests (including hematology analysis, clinical chemistry analysis, and urinalysis), electrocardiography, monitoring of AEs, and evaluation of general health and well-being. The baseline for all safety evaluations was the week 0 visit of study 303, which, with few exceptions, was the termination visit of study 301 (week 15) or study 302 (week 30).

All AEs, reported or observed, were recorded at each office visit and classified in terms of severity, date of onset, duration, and investigator’s rating of relation to drug. Events were grouped by body system and assigned preferred terms using the modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Medications were coded using a modified World Health Organization preferred drug name dictionary.

DATA ANALYSIS

The primary analysis of efficacy and safety included all patients who received at least the first dose of study drug and provided at least 1 postbaseline assessment. In the open-label phase, mean total scores (on the ADAS-Cog, CDR-SB, and Mini-Mental State Examination) for observed cases at each office visit were used to calculate mean changes from baseline scores. Standard errors and 95% confidence intervals were also calculated to assess the separation between the groups. Because of the open-label study design, using no comparator placebo group, no statistical analyses were performed. A subanalysis of the data was performed (mean and mean change from baseline) after stratifying patients into groups based on the original double-blind treatment received.

For the safety analysis, AEs were defined as an AE that started with or after administration of the first dose of study medication or a preexisting condition that was exacerbated after initiation of treatment. Similarly, abnormal laboratory values were defined as values that were within reference ranges before but outside reference ranges after administration of the first dose or preexisting abnormalities that deteriorated after the start of treatment. Adverse events and abnormal laboratory values were also included if they occurred within 30 days of discontinuing treatment.
PATIENT CHARACTERISTICS AND DISPOSITION

A total of 763 patients enrolled in this extension study (398 [85%] of 468 patients from study 301 and 365 [77%] of 473 from study 302 (Figure 1). Demographic characteristics (age, sex, and race), Mini-Mental State Examination scores, and CDR scores collected at baseline in the double-blind studies were similar for both patient cohorts. Overall, 96% of patients were taking concomitant medications; at least 20% of patients took analgesics (54%), systemic antibacterials (43%), vitamins (37%), psycholeptics (36%), and anti-inflammatory compounds (26%). Overall, 76% of patients were still receiving donepezil after 48 weeks of open-label treatment, and 49% were still being treated with donepezil after 2 years (week 108; a high number of withdrawals took place at this stage due to donepezil’s commercial availability, leading to prescriptive use of the drug) (Figure 1). The most common reasons for study discontinuation were study closure on commercialization of donepezil (46%), AEs (17%), and request of patient or investigator (13%).

DOSE INCREASES

By week 12 of the open-label trial, the dosage of donepezil had been increased from 5 mg/d to 10 mg/d for most patients (88%). After this point, the percentage of patients receiving 10 mg/d varied between 92% and 97% for the remainder of the study.

Efficacy

ADAS-Cog Scores

During the double-blind studies (studies 301 and 302), all donepezil-treated groups demonstrated statistically significant clinical benefits compared with placebo-treated patients during the study and at the end point.3,6

At entry into the extension study, patients had completed a placebo washout of 3 or 6 weeks. During the 3-week washout (study 301), patients taking donepezil did not experience a complete loss of treatment benefit before initiation of open-label treatment.3 Consequently, the effects of donepezil treatment on cognitive performance were still apparent at the start of the open-label trial (cumulative week 15) (Figure 2).

In contrast, during the longer, 6-week placebo washout (study 302), donepezil-associated benefits were lost, with mean change in ADAS-Cog scores from baseline for both active treatment groups declining to a level similar to the mean change in the score for the placebo group.6 Thus, at the start of the open-label trial (cumulative week 30), the mean change in ADAS-Cog scores from baseline for this patient cohort had declined to below the initial baseline scores reported from study 302 by +3.06 points for the 5- and 10-mg doses averaged (Figure 3). The mean change in ADAS-Cog scores from baseline did not reach statistical significance compared with placebo (Figure 3).

Overall, donepezil treatment provided important evidence for the sustained efficacy of donepezil treatment.

Explanation for the few peripheral adverse events (AEs) reported with the use of donepezil.9 Preclinical toxicology investigations have shown that donepezil is not associated with hepatotoxicity or unexpected toxic reactions.5 These impressions have been confirmed in phase 2 trials10 and 3 clinical trials,3,6,7 in which donepezil has shown no dose-limiting hepatotoxicity.

To further assess the long-term efficacy and safety of donepezil administration, this phase 3, open-label extension study evaluated treatment of patients with effective dosages of donepezil (5 or 10 mg/d) from day 1 for up to 144 weeks. It is recognized that open-label studies are not optimal; however, given that there are practical and ethical difficulties in maintaining patients with AD in long-term, placebo-controlled trials, this study provides important evidence for the sustained efficacy of donepezil treatment.


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not improve to the original baseline values of the double-blind study at any time throughout the open-label extension study. However, improvements were observed relative to the new baseline of the open-label study, and these improvements were maintained for a further 24 weeks (cumulative week 54).

When patients from study 301 were examined based on the treatment they received during the original double-blind trial, a differential response was observed (Figure 2). The mean change in ADAS-Cog scores from baseline for patients originally randomized to receive 5 mg of donepezil daily and placebo began to decline to below baseline values from week 12 of the open-label study (cumulative week 27). In contrast, patients who had initially received 10 mg of donepezil daily continued to show improvement compared with baseline for 24 weeks, declining to below baseline values by week 36 of the open-label study (cumulative week 51) but showing less decline compared with the other groups until week 108 (cumulative week 123). Because the effects of donepezil therapy

Figure 1. Enrollment and completion of patients through the double-blind and open-label phases of the study. In the open-label phase, patients were encouraged to take 10 mg of donepezil daily, and more than 90% did so.

Figure 2. Mean change in Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores from baseline in the study 301 cohort stratified by treatment originally received in the double-blind study. The double-blind study includes only patients enrolled in the open-label study. In the open-label study, more than 90% of patients received 10 mg of donepezil daily; the remainder received 5 mg of donepezil daily.
were completely washed out in the study 302 cohort, and all patients were starting below their original baseline value, there was no differential response observed with respect to the treatment patients received in the double-blind phase (Figure 3).

Changes in ADAS-Cog scores after 1, 2, and 3 years of donepezil treatment by treatment received in the double-blind studies are shown in the Table. Patients who originally received placebo in the double-blind studies showed a larger decline in ADAS-Cog scores after 1, 2, and 3 years of donepezil treatment than did those who had taken donepezil from the beginning of the double-blind studies, presumably because of the delayed start of treatment.

CDR-SB Scores

After the 3-week placebo washout, the mean change in CDR-SB scores from baseline for patients originally in study 301 were at or improved with respect to the original baseline, irrespective of the treatment received during the double-blind study. Once patients began open-label therapy, their scores remained improved compared with baseline scores for 24 weeks (cumulative week 39), after which time scores gradually declined (data not shown).

After the 6-week placebo washout, the mean change in CDR-SB scores from baseline for all of the study 302 double-blind treatment groups had declined to below the original baseline values. However, once patients began open-label therapy, their scores remained at, or close to, the new baseline value (week 0 of the extension study, cumulative week 30) for 12 weeks (cumulative week 42) (data not shown).

SAFETY

Adverse events were generally mild and transient, resolving without the need for dose modifications; the most common AEs were associated with the nervous and digestive systems. Overall, 92% of patients experienced at least 1 AE; AEs occurring in 10% or more of patients were
urinary tract infection (23%), accident (20%), pain (19%), agitation (19%), diarrhea (14%), insomnia (13%), depression (12%), headache (10%), and nausea (10%). Only 3 of these events were considered by the investigator to be related to donepezil treatment in most patients: diarrhea (62% considered possibly or definitely related), nausea (65%), and headache (62%). Selected AEs (those that occurred more frequently with donepezil use than with placebo use in previous double-blind, placebo-controlled trials\(^3,6,7\)) occurred predominantly during the first 24 weeks of treatment. Two hundred fourteen patients (28%) experienced a serious AE; 203 patients (27%) experienced nonfatal serious AEs, none of which were considered possibly related to donepezil treatment in more than 1% of patients who experienced the serious AE. The incidence of discontinuations related to AEs was low (128 patients [17%]).

There were 37 deaths (5% of patients) during the study or within 4 weeks of discontinuation or completion of the study; cancer (10 patients) and progression of AD (5 patients) were the most common causes of death. For 33 patients, death was considered to be unrelated to donepezil treatment. The role of donepezil treatment could not be ruled out by the investigator in the other 4 deaths (2 myocardial infarctions and 2 unknown causes). Death due to myocardial infarction or other causes has not been associated with donepezil treatment in any previous studies.

No clinically significant, donepezil-related changes were apparent in the results of the clinical laboratory tests, physical examinations, or electrocardiograms. By radial pulse rate, bradycardia (defined as a heart rate \(\leq 50\) bpm) was observed in 138 patients (18%) at some point during the study, although only 9 patients (1%) were reported by the investigator as having bradycardia as an AE. Of these 9 events, 7 were judged to be possibly related to use of the study medication, with 4 resulting in withdrawal from the study and 2 being considered serious AEs. The earliest occurrence of bradycardia as an AE was noted at week 12, with most cases recorded after week 26.

Use of concomitant medications increased during the study from 7% in weeks 0 to 6 to 22% in weeks 85 to 120. Two therapeutic classes, antidepressants and psycholeptics, showed a progressive increase in use through weeks 49 to 84.

**COMMENT**

In this open-label extension study, when patients were examined with respect to original double-blind study group (study 301 or 302), differences in response were observed. After the 6-week placebo washout, the benefits of 24 weeks of treatment with donepezil on cognition and global function were completely lost in the study 302 cohort. Scores on the ADAS-Cog and CDR-SB at the start of the extension trial had declined to below the original baseline values, and although cognitive and functional benefits of donepezil treatment were observed for these patients during open-label treatment, they did not improve to their original baseline levels. These data suggest that interrupting donepezil treatment for as long as 6 weeks might result in patients not returning to the levels of cognition and global function that they had attained before interruption, taking into account the deterioration expected with the passage of time.

Patients from study 301 underwent a shorter, 3-week placebo washout and, as a consequence, the donepezil-associated benefits observed during the double-blind period were not completely lost. The efficacy scores for these patients remained improved from baseline at the end of placebo washout. Patients who received 10 mg of donepezil daily during the double-blind period showed the largest and most sustained response during the open-label period. Mean ADAS-Cog scores remained at or improved with respect to baseline for almost a year (51 weeks) of treatment (mean change from baseline score at week 51, +0.57), exceeding the time above baseline observed for the placebo or 5 mg/d groups (mean change from baseline scores at week 51, +1.92 and +1.93, respectively). This is supported by better outcomes found on all measures for 10 mg/d (after 4-6 weeks at 5 mg/d) vs 5 mg/d in all previous studies\(^3,6,7\). The results of this study suggest that patients who receive 10 mg of donepezil daily without interruption achieve the best long-term outcome.

Furthermore, the results suggest that if initiation of treatment is delayed, patients might not have the opportunity to attain maximal benefits because of more advanced disease. In study 301, although patients treated with placebo for 3 months before starting donepezil treatment had a similar initial treatment response as those who received donepezil, 10 mg/d, for 3 months, they were unable to achieve the same level of cognitive function because they were starting from a lower baseline level.

Donepezil has been shown to have an excellent safety and tolerability profile in patients with AD\(^3,6\) including those with a variety of comorbid conditions and taking concomitant medications\(^19,20\). In this study, donepezil was well tolerated during long-term treatment, with approximately half of the original patient cohort still receiving donepezil after 2 years. This is an excellent result considering not only the unrelenting progression of the disease but also that 46% of patients withdrew to receive donepezil by prescription when it became commercially available. Although 92% of patients experienced at least 1 AE, this slightly higher incidence than in the preceding placebo-controlled trials\(^3,6\) was likely related to the long study duration. The incidence of AEs resulting in discontinuations was low (17%) and was comparable to the rates reported in shorter-term clinical trials\(^3,6\). During the extension trial, use of concomitant medications, in particular psycholeptics and antidepressants, increased. This observation is consistent with the progressive changes in cognitive and behavioral symptoms observed in patients with AD.

In conclusion, the results of this extension trial strongly suggest that donepezil is an effective agent for long-term treatment of mild to moderately severe AD based on clinical data up to 144 weeks (2.8 years). At the very least, conservative interpretations suggest that patients taking 10 mg of donepezil daily, with uninterrupted treatment, can expect to perform better than baseline after 1 year. The data from this study suggest that...
patients do best when taking 10 mg of donepezil daily and when the dosage is maintained at that level without interruption. Donepezil treatment effects that are lost after prolonged discontinuation are not fully recovered when drug treatment is restarted.

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