Donepezil Improves Cognition and Global Function in Alzheimer Disease

A 15-Week, Double-blind, Placebo-Controlled Study

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Background: Donepezil hydrochloride (Aricept) is a selective acetylcholinesterase inhibitor developed for the treatment of Alzheimer disease. This phase 3 study was 1 of 2 pivotal trials undertaken to establish the efficacy and safety of using donepezil in patients with mild to moderately severe Alzheimer disease.

Objectives: To further examine the efficacy and safety of using donepezil in the treatment of patients with mild to moderately severe Alzheimer disease. To examine the relationships between plasma donepezil concentrations, inhibition of red blood cell acetylcholinesterase activity, and clinical response.

Methods: This was a 12-week, double-blind, placebo-controlled, parallel-group trial with a 3-week single-blind washout. Outpatients at 23 centers in the United States were randomized to receive placebo, 5 mg of donepezil hydrochloride, or 10 mg of donepezil hydrochloride (5 mg/d during week 1 then 10 mg/d thereafter) administered once daily at bedtime. Primary efficacy was measured using the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) and Clinician's Interview–Based Impression of Change including caregiver information (CIBIC plus).

Results: A total of 468 patients entered the study, more than 97% of whom were included in the intention-to-treat (end point) analyses. The use of donepezil produced statistically significant improvements in ADAS-cog, CIBIC plus, and Mini-Mental State Examination scores, relative to placebo. The mean drug-placebo differences, at end point, for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride were, respectively, 2.5 and 3.1 units for ADAS-cog ($P<.001$); 0.3 and 0.4 units for CIBIC plus ($P\leq.008$); and 1.0 and 1.3 units for Mini-Mental State Examination ($P\leq.004$). On the CIBIC plus scale, 32% and 38% of patients, respectively, treated with 5 mg/d and 10 mg/d of donepezil hydrochloride demonstrated clinical improvement (a score of 1, 2, or 3) compared with placebo (18%). The mean (± SEM) donepezil plasma concentrations at study end point were 25.9 ± 0.7 ng/mL and 50.6 ± 1.9 ng/mL in the groups receiving dosages of 5 mg/d and 10 mg/d, respectively. Corresponding mean (± SEM) percentages of inhibition of red blood cell acetylcholinesterase activity were 63.9% ± 0.9% and 74.7% ± 1.2% for these 2 dosages, respectively. There was a statistically significant positive correlation between plasma concentrations of donepezil and acetylcholinesterase inhibition; the EC_{50} (50% effect) was obtained at a concentration of 15.6 ng/mL. A plateau of inhibition (80%-90%) was reached at plasma donepezil concentrations higher than 50 ng/mL. The correlations between plasma drug concentrations and both ADAS-cog ($P<.001$) and CIBIC plus ($P = .006$) were also statistically significant, as were the correlations between red blood cell acetylcholinesterase inhibition and change in ADAS-cog ($P<.001$) and CIBIC plus ($P = .005$). The incidence of treatment-emergent adverse events with both dosages of donepezil (68%–78%) was comparable with that observed with placebo (69%). The use of 10 mg/d of donepezil hydrochloride was associated with transient mild nausea, insomnia, and diarrhea. There were no treatment-emergent clinically significant changes in vital signs or clinical laboratory test results. More important, the use of donepezil was not associated with the hepatotoxic effects observed with acridine-based cholinesterase inhibitors.

Conclusion: Donepezil hydrochloride (5 and 10 mg) administered once daily is a well-tolerated and efficacious agent for treating the symptoms of mild to moderately severe Alzheimer disease.

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ALZHEIMER disease (AD) is a progressive dementing disorder that primarily affects the elderly population. Approximately 5% to 10% of the population older than 65 years and as many as 50% of those older than 85 years are estimated to have the disease.[1] Although little is known regarding the cause of AD, it is generally accepted that many of its symptoms are related to a cholinergic deficit in the cerebral cortex and other areas of the brain.[2-4] Indeed, the extent of neuropathological features, eg, cortical atrophy and the presence of amyloid plaques and neurofibrillary

PATIENTS AND METHODS

PATIENT POPULATION

Male and female patients of any race who were 50 years of age or older were recruited into the study by 23 centers in the United States. A diagnosis of probable AD was required to be consistent with the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[16] and the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* categories 290.00 or 290.10.[17] The patients had mild to moderately severe disease as defined by Mini-Mental State Examination (MMSE)[18] scores of 10 to 26, and screening and baseline Clinical Dementia Rating (CDR) scores of 1 or 2.[19] All patients underwent computed tomography or magnetic resonance imaging within 6 months of entry. None of the patients had AD that was complicated by an additional diagnosis of delusions, delirium, or depression, and none had a known or suspected history of alcoholism or drug abuse. The patients were required to be ambulatory, or ambulatory when aided by either a walker or cane, and to have sufficient vision and hearing to enable them to comply with the study procedures.

Patients with any of the following major medical illnesses were specifically excluded from entering the trial: type 1 diabetes, obstructive pulmonary disease, or asthma; hematologic or oncologic disorders in the previous 2 years; or vitamin B_{12} or folate deficiency. Patients were also excluded if they had clinically significant active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease that was not well controlled by diet, pharmacological treatment, or other therapeutic intervention. Patients with evidence of other psychiatric or neurologic disorders (eg, stroke, schizophrenia, or Parkinson disease), and those with a Hachinski ischemia score of 5 or more or known hypersensitivity to cholinesterase inhibitors were also excluded.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles stated in the Declaration of Helsinki. Informed consent was obtained from the patients and also from the caregivers prior to any detailed screening procedures. The study adhered to the institutional review board policies at each site.

STUDY DESIGN

Our study had a randomized, double-blind, placebo-controlled, parallel-group design. Eligibility for inclusion in the trial was assessed during the screening phase that preceded the treatment period by a maximum of 2 weeks.

Patients were randomized to receive 12 weeks of treatment with placebo or 5 mg or 10 mg of donepezil hydrochloride administered once daily at bedtime. Each dose of study medication consisted of 2 tablets: 2 placebo tablets (placebo group); one 5-mg tablet and 1 placebo tablet (5-mg/d donepezil hydrochloride group); or two 5-mg tablets (10-mg/d donepezil hydrochloride group). To minimize the likelihood of reactions to acute extensive inhibition of AChE, a dosage of 10 mg was initiated using a blinded, forced titration scheme in which subjects received a dosage of 5 mg/d of donepezil hydrochloride for the first 7 days and a dosage of 10 mg/d for the remainder of the study. At the end of the double-blind treatment, all patients began a 3-week, single-blind washout period with placebo.

Use of any concomitant medications that could affect functioning of the central nervous system or interfere with efficacy assessments was prohibited. This included the use of any anticholinergic, cholinomimetic, anticonvulsant, antidepressant, antipsychotic, antianxiety, or stimulating agents, as well as anti-Parkinson and certain antihypertensive agents. Occasional use of other medications, such as hypnotics and cold preparations (prescription and over-the-counter sympathomimetic amines and antihistamines) was allowed, but not within 48 to 72 hours of a clinic visit. None of the patients had received investigational medications within 1 month of study entry. Approximately 90% of patients received allowable concomitant medication during the study.

Efficacy and safety assessments were undertaken at 3-week intervals throughout the trial. Treatment compliance was checked at each visit by counting the number of returned tablets and dividing by the number of treatment days. As specified by the protocol, patients were considered compliant when 80% or more of the required medication had been taken. Compliance was used as one of the determinants of the evaluable patient population.

OUTCOME MEASURES

The primary efficacy parameters used were the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog),[20] and a Clinician's Interview-Based Impression of Change scale that included caregiver-supplied information (CIBIC plus).[21]

The ADAS-cog is a sensitive and reliable psychometric scale. It consists of 11 items that evaluate selected aspects of memory, orientation, attention, language, reasoning, and praxis. Scores range from 0 (no impairment) to 70 (very severe impairment). To reduce the potential for practice or carryover effects at subsequent visits, different word lists were used.

The CIBIC is not a specific test instrument, but a technique that uses information obtained during an independent clinical interview to assess disease severity and progression of illness. A variety of CIBIC formats exist, each varying in terms of depth and structure. The format chosen for the donepezil clinical trials was a slightly modified version of the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change.[21] This rating scale assesses patient function in 4 areas—general, cognitive, behavioral, and activities of daily living—through examination of 15 separate domains. Interviews with both the patient and caregiver are conducted by a clinician who is blinded from knowledge of other aspects of the study, including the results of other test procedures, clinical laboratory values, and adverse event reports. Disease severity is rated at baseline (CIBIS plus). Using the baseline interview as the sole source for comparison, patients are reexamined at subsequent visits to determine whether their conditions have changed. The change from baseline at subsequent visits (CIBIC plus) is scored by the same interviewer using a 7-point Likert-type scale, in which 1 represents markedly improved; 4, no change; and 7, markedly worse.

The secondary efficacy variables were the MMSE,[18] the Sum of the Boxes of the Clinical Dementia Rating

(CDR-SB)[22] and a quality of life (QoL) assessment.[23] The MMSE is a brief psychometric test conducted by a trained clinician or psychometrician who evaluates the cognitive state of the patient, including aspects of memory, orientation, language, and praxis. The CDR-SB is a global scale that assesses 6 domains of patient function (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). The CDR-SB was conducted as a consensus assessment by each patient's treatment team, except the CIBIC plus interviewer, and was based on information obtained from all procedures conducted during a clinic visit. The QoL assessment was a 7-item patient-rated scale that evaluated the patients' perceptions of their well-being in terms of relationships, eating and sleeping, and social and leisure activities. The test was conducted through patient interviews by a nurse evaluator or another clinician. The items were scored by marking on an analog scale between 2 anchor points: the extremes were 0 (worst quality) and 50 (best quality). Although this instrument has not been validated in patients with AD, it was selected because no QoL instrument has been validated in this patient population.

THERAPEUTIC DRUG MONITORING

Plasma concentrations of donepezil were measured from blood samples collected at each clinic visit using a sensitive and specific high-performance liquid chromatographic procedure, with UV detection.[24] The AChE activity in RBC membranes was measured from the same blood samples using a radioenzyme method.[25] Standard curves of the percentage of AChE inhibition vs the natural logarithm of the donepezil concentration (nanograms per gram of RBCs) were constructed using a third-order polynomial equation.

SAFETY ASSESSMENTS

Adverse events were elicited at each visit by questioning both the patient and the caregiver generally about the patient's status, and through direct observation by the patient treatment team. All adverse events reported or observed were recorded, along with the date and time of onset and cessation, plus assessments of severity and the likelihood of their being related to treatment.

Supine and standing blood pressures and heart rate were measured at screening and at the end of the washout phase. Sitting measurements were recorded at other visits. Hence, no quantitative data on the potential effects of donepezil on orthostatic hypotension were obtained. A standard 12-lead electrocardiogram was obtained at the start and end of the double-blind treatment.

Clinical laboratory evaluations were conducted at each clinic visit. Hematologic assessments included hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC count, white blood cell count, differential cell count, and platelet count. Clinical chemistry tests included assessment of liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin), renal function (creatinine and serum urea nitrogen), metabolic status (glucose, total protein, albumin, and cholesterol), electrolytes (sodium, potassium, chloride, phosphorus, and calcium), and cardiac enzymes (creatine kinase and lactate dehydrogenase). Routine dipstick urinalysis was performed (pH, glucose, protein, hemoglobin or blood, and ketones), along with specific gravity and microscopic examination of the sediment.

STATISTICAL ASSESSMENTS

The planned study population of 150 patients per group was based on a review of clinical studies of other cholinesterase inhibitors and the results of a previous phase 2 study with donepezil.[11] The sample size was intended to provide 80% power to detect a 0.27-point difference in the mean CIBIC plus scores for donepezil treatment groups compared with the placebo group at the 5% level of significance and assuming a patient completion rate of 80%. It was assumed that the dosages of 5 mg/d and 10 mg/d of donepezil hydrochloride would have equal efficacy. Therefore, this study was not powered to detect a difference between the active treatments but only between placebo and each active treatment group. This assumption was based on the results of a prior study[11] that evaluated dosages up to 5 mg/d and a review of studies of other cholinesterase inhibitors.

The primary analyses of efficacy and safety were performed on the intention-to-treat (ITT) population. For the safety analysis, this included all patients who were randomized to receive treatment, while the analysis of efficacy (that requires calculation of change from baseline scores) included all patients who had at least 1 postbaseline evaluation while undergoing treatment. The primary analysis was conducted on the end point data set. End point was week 12 for patients completing the double-blind portion of the study. For those who did not complete the study, their last observation while undergoing treatment was carried forward (LOCF) and used as the end point value. Secondary analyses were also undertaken in the fully evaluable population to confirm the conclusions of the primary ITT analysis. Fully evaluable patients were those who completed the 12-week period of double-blind treatment and who had at least 80% medication compliance at the week 12 visit and at a minimum of 2 other visits during the trial.

For continuous efficacy variables (ADAS-cog, MMSE, CDR-SB, and QoL), a general linear model was used to construct analysis of covariance models to compare the treatment groups with respect to changes from baseline in efficacy variables.[26] After confirming the assumptions underlying analysis of covariance, the reduced model contained effect for baseline score (covariate), treatment effect, and center effect. Type III sums of squares were used to determine statistical significance among the 3 treatment groups. In cases where differences existed, pairwise comparisons of the groups were undertaken using Fisher 2-tailed least significant difference procedure. The categorical efficacy variable, the CIBIC plus, was analyzed using the Cochran-Mantel-Haenszel test, with RIDITS as the score option.[27,28] The Cochran-Mantel-Haenszel test included adjustment for center.

Nonlinear regression analyses using a maximum-effect (E_{max}) model (AChE inhibition % = $EC_{max} \times$ donepezil/[EC_{50} + donepezil]) were undertaken to correlate plasma donepezil concentrations with inhibition of AChE activity (EC_{50} is the concentration where 50% effect is observed). Similar analyses were performed to investigate the

Continued on next page

association between AChE activity and primary efficacy outcomes (ie, ADAS-cog and CIBIC plus).

Intragroup changes in vital signs (baseline vs end point) were analyzed using paired *t* tests, and between-treatment differences were detected by analysis of variance. The analysis of adverse events was confined to treatment-emergent signs and symptoms (TESS) that began during or after administration of the first dose of study medication, or became more severe during treatment. Events, recorded using investigator terminology, were grouped and coded into common terms using a modified COSTART dictionary.[29]

The incidences of TESS and treatment-emergent laboratory test abnormalities (ie, newly occurring or clinically significant exacerbations of preexisting abnormalities) were compared among treatment groups using the Fisher exact test.

Statistical analyses were undertaken using SAS statistical software version 6 or higher (SAS Institute Inc, Cary, NC). All hypothesis tests were 2-sided, and *P* values of .05 or less were considered to be statistically significant.

tangles, and the severity of memory and cognitive impairments have been found to correlate with cholinergic loss in the central nervous system.[3] These findings suggest that augmentation of cholinergic function might improve clinical symptoms. To this end, various pharmacological agents have been developed.

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To date, perhaps the most widely investigated agents for the treatment of AD are cholinesterase inhibitors, which act by inhibiting acetylcholinesterase (AChE) and butyrylcholinesterase enzymes that reduce the hydrolysis of the neurotransmitter acetylcholine, thereby promoting greater cholinergic activity. In the central nervous system, it is AChE rather than butyrylcholinesterase that is primarily involved in synaptic function, and hence AChE provides the main therapeutic target for drug intervention.

Donepezil (E2020; (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride [Aricept, Eisai Co Ltd, Tokyo, Japan]) is a piperidine-based agent that is chemically unique from other cholinesterase inhibitors.[5-8] It is the product of a specific research program designed to produce an agent for the treatment of AD that was highly selective for AChE as opposed to butyrylcholinesterase, reversible in its activity, and that had a pharmacokinetic and pharmacodynamic profile allowing once-daily dosing. Donepezil is a noncompetitive, reversible antagonist of AChE; however, the spectrum of activity against individual isoforms of AChE is unknown. Donepezil is well absorbed, with a relative oral bioavailability of 100%. After oral administration, peak plasma concentrations are achieved within 3 to 4 hours, with an elimination half-life of approximately 70 hours.

The use of donepezil has been shown to improve performance on memory and learning tests in healthy rats, as well as in rats with experimentally induced cholinergic lesions.[9] Preclinical studies[9] indicate that donepezil has greater specificity for brain tissue and is more selective for AChE than either physostigmine or tacrine hydrochloride. In addition, donepezil also has a longer duration of inhibitory action than either of these agents.[7,10] As a consequence of this high selectivity and specificity, donepezil should produce fewer peripheral cholinomimetic-induced adverse effects at effective doses. Indeed, in a phase 2 clinical trial, 5 mg of donepezil hydrochloride was shown not only to provide significant clinical improvements in cognitive and global function in patients with mild to moderately severe AD, but also these benefits were obtained without peripheral cholinergic adverse events, laboratory test abnormalities, or hepatotoxic effects.[11] These findings contrast with those for tacrine; although this agent displays significant efficacy, its clinical use is limited by a high discontinuation rate[12,13] because of dose-limiting adverse effects, including hepatotoxicity.[14]

Inhibition of AChE in red blood cell (RBC) membranes by donepezil has been shown to correspond closely to its effects in the cerebral cortex of rats ($r = 0.94$),[15] with the inhibition in both tissues showing a similar time course—a rapid onset and a linear decline. In addition, a relationship between inhibition of AChE in RBCs and improvement in cognition has been demonstrated in patients with AD.[11] As a consequence, AChE inhibition in RBC membranes has been used as a surrogate marker to model the clinical effectiveness of using donepezil in patients with AD.

The present phase 3 study was undertaken to establish the efficacy and safety of using donepezil in patients with AD, and to define further the relationships between plasma donepezil concentration, inhibition of AChE in RBCs, and clinical response.

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Table 1. Patient Characteristics at Baseline

Characteristics	Treatment Group		
	Placebo (n = 153)	Donepezil Hydrochloride, 5 mg/d (n = 157)	Donepezil Hydrochloride, 10 mg/d (n = 158)
Sex, No. (%)			
Male	60 (39)	49 (31)	62 (39)
Female	93 (61)	108 (69)	96 (61)
Age, y			
Mean ± SEM	74.0 ± 0.65	73.8 ± 0.67	73.4 ± 0.65
Range	52-93	50-94	50-92
Weight, kg			
Mean ± SEM	66.05 ± 1.01	65.72 ± 0.98	67.8 ± 1.13
Range	43.6-100.5	40.9-99.5	35.5-105.2
Race, No. (%)			
White	147 (96)	149 (95)	152 (96)
Black	6 (4)	6 (4)	1 (1)
Other	0	2 (1)	5 (3)
Clinical Dementia Rating, No. (%)			
0.5*	2 (1)	1 (1)	3 (2)
1.0	121 (79)	121 (77)	120 (76)
2.0	30 (20)	35 (22)	35 (22)
Mini-Mental State Examination score			
Mean ± SEM	19.80 ± 0.35	19.39 ± 0.39	19.35 ± 0.40
Range	10-26	10-28	8-28

**These patients represented protocol violations and were subsequently discontinued from the study.*

Table 2. Summary of Patient Withdrawals

	Treatment Group, No. (%)		
	Placebo (n = 153)	Donepezil Hydrochloride, 5 mg/d (n = 157)	Donepezil Hydrochloride, 10 mg/d (n = 158)
Total No. of patients withdrawn	**11 (7)**	**16 (10)**	**29 (18)**
Reasons			
Adverse event(s)*	2 (1)	7 (4)	14 (9)
Serious adverse events*	1 (1)	0 (0)	2 (1)
Intercurrent illness	0 (0)	0 (0)	0 (0)
Request of patient or investigator	3 (2)	4 (3)	6 (4)
Medication noncompliance	1 (1)	0 (0)	0 (0)
Protocol violation	2 (1)	3 (2)	4 (3)
Other	2 (1)	2 (1)	3 (2)

**These events were not necessarily treatment emergent.*

RESULTS

The demographic data for the 468 patients randomized to receive treatment are shown in **Table 1**. Patient ages ranged from 50 to 94 years (mean, 73.7 years) and their body weights from 35.5 to 105.2 kg. Sixty-one percent of the patients receiving placebo, 69% of those receiving 5 mg/d of donepezil hydrochloride and 61% of those receiving 10 mg/d of donepezil hydrochloride were women, thus accurately reflecting the percentage of women in the population with AD.[30] The 3 treatment groups were found to be comparable with respect to all demographic characteristics.

Only 8 patients had been previously treated with other cholinesterase inhibitors, 5 of whom had been enrolled in other investigative clinical trials. These regimens, as required by the protocol, were discontinued at least 30 days before entry into this study.

A high percentage of patients completed the trial: 93% of the placebo group and 90% and 82% of the patients treated with 5 mg/d and 10 mg/d of donepezil hydrochloride, respectively. In total, 56 patients (12%) withdrew from the trial prematurely. The 2 most frequent reasons were adverse events (6%) and withdrawal of consent (3%). As shown in **Table 2**, the incidence of adverse event–related withdrawals (not all of which were treatment emergent) was low overall, but higher in the group receiving a dosage of 10 mg/d who had received a rapid, forced titration from 5 mg/d to 10 mg/d after 7 days. The frequency of adverse events was similar among patients receiving placebo or 5 mg/d of donepezil hydrochloride. The most common adverse events leading to discontinuation were nausea and diarrhea, although, in general, these adverse events were rated as mild and in most cases did not lead to discontinuation. In the treatment group receiving 10 mg/d of donepezil hydrochloride, 3.8% and 2% withdrew because of nausea and diarrhea, respectively.

EFFICACY ASSESSMENT

As a consequence of the low discontinuation rate recorded in this trial, the ITT analyses and analyses of the evaluable patient population gave essentially the same results (**Table 3** and **Table 4**). Further discussion of these results will report the more conservative ITT analyses using the end point data set (ITT LOCF). To confirm the appropriateness of end point analyses and to test for potential bias in the LOCF procedure (due to differential dropout rates among the treatment groups), analyses of observed cases were conducted at week 12 (based only on patients with week 12 values). Results were found to be consistent, indicating bias did not exist. Indeed, the majority of the 468 patients randomized to treatment were included in the ITT LOCF analyses with, for example, only 7 patients being excluded from the ADAS-cog assessment because they had no evaluations while receiving treatment.

PRIMARY EFFICACY PARAMETERS

Statistically significant improvements in ADAS-cog scores in patients treated with donepezil were present from the third week of treatment and were sustained throughout the 12-week double-blind treatment period (**Figure 1**). Scores at the end of the 3-week placebo washout had begun to return to baseline values for the donepezil groups, with the placebo group showing a similar rate of decline; however, the improvement in both donepezil groups remained statistically significant ($P<.001$) compared with placebo.

Table 3. Primary Efficacy Variables*

	Outcome Measures					
	Intention-to-Treat Analysis (LOCF)			Fully Evaluable Population		
Assessment Score	Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d	Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d
ADAS-cog	(n = 150)	(n = 156)	(n = 155)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM)† baseline score	25.3 (0.87)	26.4 (0.92)	26.4 (0.89)	25.0 (0.90)	26.9 (0.99)	27.2 (0.98)
Range	6.0-51.3	5.7-53.3	4.7-56.7	6.0-51.3	5.7-53.3	4.7-56.3
LS mean (± SEM)‡ change at end point§	0.4 (0.43)	–2.1 (0.43)	–2.7 (0.43)	0.4 (0.47)	–2.2 (0.46)	–2.7 (0.50)
P (treatment vs placebo)‖	. . .	<.001	<.001	. . .	<.001	<.001
95% Confidence intervals	. . .	–3.59 to –1.29	–4.22 to –1.92	. . .	–3.85 to –1.37	–4.38 to –1.82
Favors	. . .	Donepezil	Donepezil	. . .	Donepezil	Donepezil
LS mean (± SEM) change at week 15¶	1.5 (0.47)	–0.7 (0.47)	–1.6 (0.49)	1.7 (0.48)	–0.6 (0.47)	–1.5 (0.50)
CIBIC plus	(n = 150)	(n = 153)	(n = 152)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM)†‡ score at end point§	4.2 (0.07)	3.9 (0.08)	3.8 (0.08)	4.2 (0.08)	3.9 (0.08)	3.8 (0.08)
P (treatment vs placebo)#	. . .	.003	.008	. . .	.001	.02
95% Confidence intervals	. . .	–0.50 to –0.08	–0.55 to –0.13	. . .	–0.55 to –0.11	–0.57 to –0.13
Favors	. . .	Donepezil	Donepezil	. . .	Donepezil	Donepezil
Mean (± SEM)‡ score at week 15¶	4.2 (0.08)	4.0 (0.09)	4.1 (0.09)	4.2 (0.09)	4.0 (0.09)	4.1 (0.10)

**LOCF indicates last observance while receiving treatment was carried forward; ADAS-cog; Alzheimer's Disease Assessment Scale–Cognitive Subscale; CIBIC plus, Clinicians Interview-Based Impression of Change including caregiver information; LS, least squares mean adjusted for baseline covariate; and ellipses, not applicable.*

†*Mean baseline score at randomization.*

‡*Least significant difference method with baseline as covariate.*

§*End point equals week 12 with LOCF.*

‖*P values are based on an analysis of covariance model using the Fisher 2-tailed least significant difference procedure for pairwise comparisons.*

¶*After 3 weeks, single-blind, placebo washout. Values are based on number at week 15.*

#*P values are based on Cochran Mantel-Haenszel test using RIDITS analysis excluding not assessed.*

The mean improvement in ADAS-cog scores at end point, adjusted for baseline severity (least squares mean) was significantly greater for the 5-mg (– 2.1; $P<.001$) and 10-mg donepezil hydrochloride groups (– 2.7; $P<.001$) compared with the decline observed in the placebo group (0.4). The drug-placebo differences were 2.5 and 3.1 ADAS-cog units for the 5-mg/d and 10-mg/d groups, respectively. In general, the magnitude of improvement in mean change in ADAS-cog scores for the 10-mg dosage group appeared to be greater than that for the 5-mg dosage group. However, these differences in magnitude did not reach statistical significance at end point ($P = .28$) by analysis of covariance, although this study was not powered to detect such a difference.

Patients receiving donepezil demonstrated improvements in global function, as measured by the CIBIC plus scale, that were superior to those patients receiving placebo. Overall treatment effects were statistically significant at weeks 9 and 12 and at end point ($P\leq.015$). Pairwise comparisons, using the Cochran-Mantel-Haenszel test, between active treatment groups and placebo were statistically significantly different at weeks 9 and 12 and at end point, except for the comparison between placebo vs the 10-mg/d group at week 9 ($P = .098$; **Figure 2**). The improvement in mean CIBIC plus score at end point was slightly greater for the 10-mg (3.8; $P = .008$) vs the 5-mg (3.9; $P = .003$) dosage group ; (Table 3). The drug-placebo differences in mean CIBIC plus scores at end point were 0.3 for the group receiving 5 mg/d of donepezil hydrochloride and 0.4 for the group receiving 10 mg/d of donepezil hydrochloride. The percentages of patients demonstrating clinical improvement at end point (a score of 1, 2, or 3 on the CIBIC plus) were the following: placebo group, 18%; 5 mg/d of donepezil hydrochloride group, 32%; and 10 mg/d of donepezil hydrochloride group, 38%: an approximate doubling for the active drug groups in comparison with placebo.

SECONDARY EFFICACY PARAMETERS

Overall treatment effects indicating improvement (reflected as a positive change score) in MMSE were found at weeks 3 and 12 and at end point ($P\leq.004$, analysis of covariance) for patients receiving donepezil. The 10-mg/d dosage group exhibited significantly greater improvement than the placebo group at weeks 3, 6, and 12 and at end point, while the 5-mg/d dosage group achieved significance at weeks 3 and 12 and at end point. At week 15 (following 3 weeks of placebo washout) the change scores for both the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride remained significantly improved (**Figure 3**). The mean drug–placebo differences at end point were 1.0 and 1.3 for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride during the double-blind phase, respectively (Table 4).

All 3 treatment groups exhibited consistent trends for improvement in CDR-SB scores from week 9 onward (**Figure 4**). The overall treatment effect was sta-

Table 4. Secondary Efficacy Variables*

Assessment Score	Outcome Measures: Intention-to-Treat Analysis (LOCF) Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d	Fully Evaluable Population Placebo	Donepezil Hydrochloride, 5 mg/d	Donepezil Hydrochloride, 10 mg/d
MMSE	(n = 150)	(n = 156)	(n = 156)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM) baseline score†	19.8 (0.35)	19.4 (0.39)	19.3 (0.40)	19.8 (0.37)	19.1 (0.41)	19.1 (0.43)
Range	10-26	10-28	8-28	10-26	10-26	10-26
LS mean (± SEM)‡ change at end point§	0.04 (0.25)	1.0 (0.25)	1.3 (0.24)	0.1 (0.27)	1.1 (0.27)	1.2 (0.29)
P (treatment vs placebo)‖	. . .	<.004	<.001	. . .	.01	.004
95% Confidence intervals	. . .	0.33 to 1.65	0.65 to 1.97	. . .	0.22 to 1.64	0.38 to 1.86
Favors	. . .	Donepezil	Donepezil	. . .	Donepezil	Donepezil
LS mean (± SEM)‡ change at week 15¶	−0.03 (0.27)	0.7 (0.27)	0.8 (0.28)	−0.02 (0.28)	0.8 (0.27)	0.8 (0.29)
CDR-SB	(n = 150)	(n = 156)	(n = 154)	(n = 135)	(n = 139)	(n = 120)
Mean (± SEM) baseline score†	6.81 (0.18)	6.85 (0.18)	7.18 (0.20)	6.82 (0.20)	6.95 (0.19)	7.22 (0.22)
LS mean (± SEM)‡ change at end point§	−0.14 (0.11)	−0.10 (0.11)	−0.31 (0.11)	−0.09 (0.12)	−0.06 (0.12)	−0.33 (0.13)
P (overall treatment effect)‖	. . .	.32 (NS)	. . .	. . .	.22 (NS)	. . .
95% Confidence intervals	. . .	−0.25 to 0.33	−0.46 to 0.12		−0.29 to 0.35	−0.57 to 0.09
Adjusted mean (± SEM)‡ change at week 15¶	0.03 (0.13)	0.03 (0.13)	−0.27 (0.13)	0.07 (0.13)	0.06 (0.13)	−0.26 (0.14)
QoL	(n = 150)	(n = 155)	(n = 156)	(n = 135)	(n = 138)	(n = 120)
Mean (± SEM) baseline score†	289.4 (3.4)	292.3 (3.6)	283.5 (3.5)	290.8 (3.4)	290.1 (3.8)	284.5 (4.0)
LS mean (± SEM)‡ change at end point§	4.0 (2.7)	5.7 (2.7)	−4.3 (2.7)	3.6 (2.9)	6.6 (2.9)	−3.2 (3.1)
P (treatment vs placebo)‖	. . .	.65	.02	. . .	.45	<.10
95% Confidence intervals	. . .	−5.58 to 8.92	−15.55 to −1.07	. . .	−4.72 to 10.66	−14.79 to 1.19
Favors	. . .	. . .	Placebo	. . .	. . .	. . .
LS mean (± SEM)‡ change at week 15¶	5.6 (2.9)	2.0 (2.8)	−3.9 (3.0)	5.5 (2.9)	3.5 (2.9)	−3.1 (3.0)

**LOCF indicates last observation while receiving treatment was carried forward; MMSE, Mini-Mental State Examination; CDR-SB, Sum of the Boxes of the Clinical Dementia Rating; LS, least squares mean adjusted for baseline covariate; ellipses, not applicable; NS, not significant; and QoL, quality of life.*

†*Mean baseline score at randomization.*

‡*Least significant difference method with baseline as covariate.*

§*End point equals week 12 with LOCF.*

‖*P values are based on an analysis of covariance model using the Fisher 2-tailed least significant difference procedure for pairwise comparisons (also used for the overall treatment effect for CDR-SB).*

¶*After 3 weeks single-blind placebo washout. Values are based on number at week 15.*

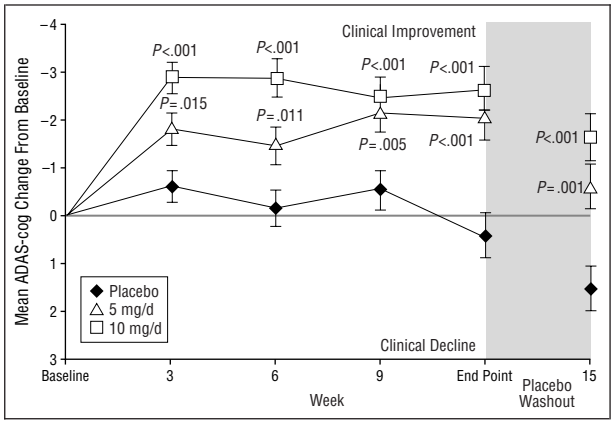

Figure 1. *Least squares mean (± SEM) change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 457 were included in the intention-to-treat analysis at end point.*

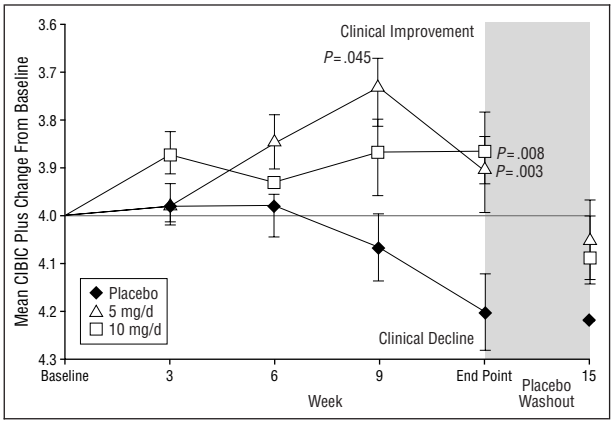

Figure 2. *Mean (± SEM) Clinician's Interview–Based Impression of Change including caregiver information (CIBIC plus) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 455 were included in the intention-to-treat analysis at end point.*

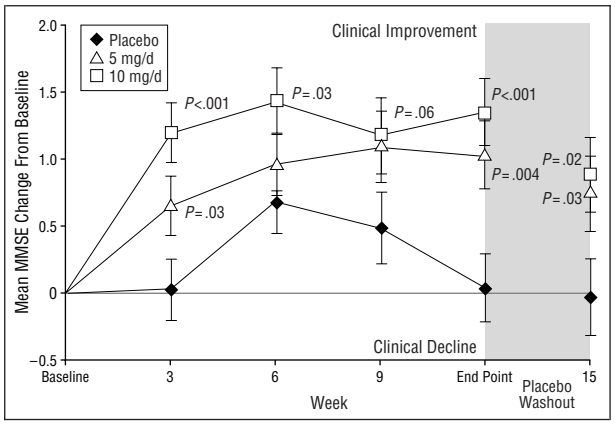

Figure 3. *Least squares mean (± SEM) change from baseline in Mini-Mental State Examination (MMSE) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 460 were included in the intention-to-treat analysis at end point.*

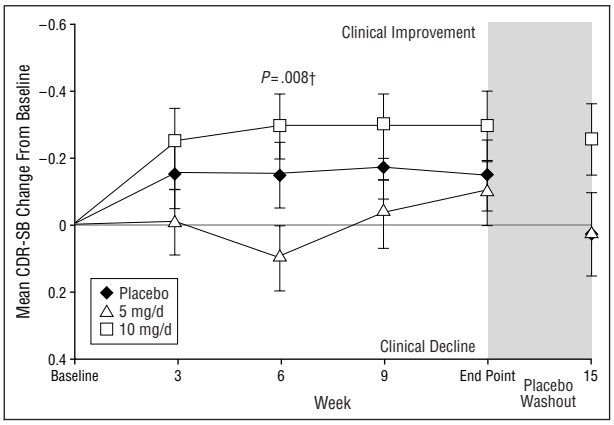

Figure 4. *Least squares mean (± SEM) change from baseline in the Sum of the Boxes of the Clinical Dementia Rating (CDR-SB) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 459 were included in the intention-to-treat analysis at end point. Dagger indicates overall treatment effect.*

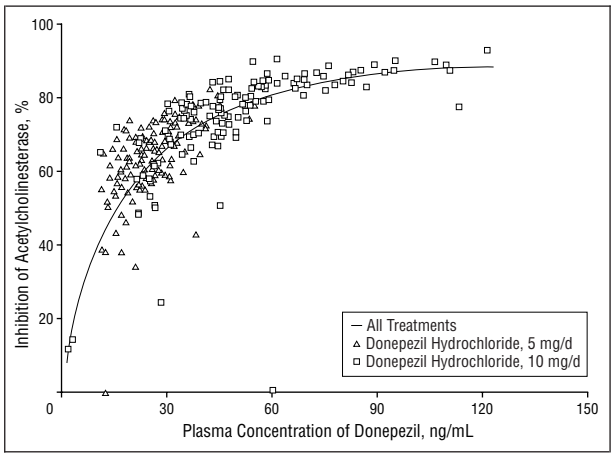

Figure 5. *Correlation between plasma concentrations of donepezil and percentage of acetylcholinesterase inhibition in red blood cells.*

tistically significant at week 6 (P = .008); however, pairwise analysis failed to show any significant difference among the treatment groups at any visit (Table 4), even though the mean changes from baseline for the group receiving 10 mg/d of donepezil hydrochloride were lower (showing greatest improvement) than the corresponding placebo values at all visits.

The results from the QoL assessment were highly variable, both between and within patient groups. Overall treatment effects in the ITT sample were statistically significant at week 12 ($P<.05$) and at end point (P = .02), with the groups receiving placebo and 5 mg/d of donepezil hydrochloride showing improvement, and the group receiving 10 mg/d of donepezil hydrochloride demonstrating worsening. Results for the fully evaluable population were similar except that there was no significant difference at the end point (P = .04).

THERAPEUTIC DRUG MONITORING

The mean (± SEM) donepezil plasma concentrations at study end point were 25.9 ± 0.7 ng/mL (n = 142) and 50.6 ± 1.9 ng/mL (n = 139) in the 5-mg/d and 10-mg/d dosage groups, respectively. Corresponding mean (± SEM) percentages of inhibition of AChE in RBCs were 63.9% ± 0.9% (n = 142) and 74.7% ± 1.2% (n=139) for the 2 donepezil groups, respectively. The relationship between plasma concentrations of donepezil and percentage of AChE inhibition is shown in **Figure 5**. A plateau of inhibition was reached at plasma concentrations higher than 50 ng/mL, and corresponded to 80% to 90% enzyme inhibition. The E_{max} for AChE inhibition in RBCs was 100.8% and the EC_{50} was 15.6 ng/mL.

Correlations between plasma concentrations of donepezil and changes in ADAS-cog ($P<.001$) and CIBIC plus (P = .006) were statistically significant, as was the correlation between AChE inhibition and change in ADAS-cog ($P<.001$) and CIBIC plus (P = .005).

SAFETY

Donepezil was generally well tolerated. As expected in an elderly population, a high number of adverse events were reported for both the drug-treated and placebo-treated groups. The incidences of TESS for both dosages of donepezil hydrochloride (68% at 5 mg/d and 78% at 10 mg/d) were comparable with the incidences observed with placebo (69%). In the majority of cases (92%) these TESS were judged to be mild.

As shown in **Table 5**, the only adverse events significantly more common with donepezil use were nausea, insomnia, and diarrhea ($P<.001$), which also appeared to be dose related. These are the types of adverse events expected from treatment with AChE inhibitors. Many events were mild and transient (lasting 1 or 2 days), and resolved with continued donepezil treatment without the need for adjunct antidiarrheal and/or antiemetic treatment.

Seven patients treated with placebo and 6 in each of the donepezil groups suffered serious adverse events during the trial. Three patients had events that were considered possibly related to treatment with donepezil. These included stomach ulcer with hemorrhage (5 mg/d); syncope and transient ischemic attack (5 mg/d); and nau-

Table 5. Summary of Treatment-Emergent Signs and Symptoms (TESS)*

Preferred Term‡	No. (%) of Patients With TESS†, Treatment Group: Placebo (n = 153)	Donepezil Hydrochloride, 5 mg/d (n = 157)	Donepezil Hydrochloride, 10 mg/d (n = 158)	P§
No. of patients with ≥1 TESS	106 (69)	106 (68)	124 (78)	
Nausea	12 (8)	11 (7)	34 (22)	<.001‖
Insomnia	8 (5)	13 (8)	28 (18)	.001‖
Diarrhea	4 (3)	10 (6)	21 (13)	.001‖
Pain	11 (7)	14 (9)	21 (13)	.20
Headache	13 (8)	21 (13)	19 (12)	.37
Dizziness	10 (7)	14 (9)	14 (9)	.69
Muscle cramp	6 (4)	9 (6)	12 (8)	.37
Fatigue	8 (5)	5 (3)	12 (8)	.22
Accident	11 (7)	9 (6)	10 (6)	.87
Agitation	11 (7)	7 (4)	10 (6)	.59
Vomiting	7 (5)	5 (3)	10 (6)	.41
Anorexia	4 (3)	6 (4)	10 (6)	. . .
Weight loss	3 (2)	3 (2)	8 (5)	. . .
Common cold	10 (7)	8 (5)	7 (4)	.69
Abdominal disturbance	6 (4)	9 (6)	6 (4)	. . .
Urinary tract infection	20 (13)	10 (6)	6 (4)	.009¶
Stomach upset	1 (1)	8 (5)	5 (3)	. . .
Rhinitis	6 (4)	8 (5)	5 (3)	. . .
Upper respiratory tract infection	6 (4)	8 (5)	5 (3)	. . .
Edema in extremities	8 (5)	1 (1)	4 (3)	. . .
Cough	8 (5)	2 (1)	3 (2)	. . .

**Ellipses indicate not applicable.*
†*Incidence of TESS of 5% or more in any randomized group.*
‡*Derived from COSTART dictionary.*[28]
§P *value comparing the 3 treatment groups using Fisher exact tests.*
‖*More frequent with the use of donepezil.*
¶*More frequent with placebo.*

sea, aphasia, tremor, and diaphoresis (10 mg/d). One patient in the placebo group died as a result of renal failure.

Both groups of patients treated with donepezil had group mean decreases in heart rate relative to baseline (mean, 2.65/min in the 5-mg/d group and 2.26/min in the 10-mg/d group). These reductions were significantly larger than those observed in the placebo group (0.09/min reduction; $P<.03$). However, the incidence of bradycardia in individual patients (heart rate <50/min) was not significantly different among the treatment groups. These changes in mean group heart rate are considered small and clinically unimportant.

Two patients treated with donepezil hydrochloride, both in the 5-mg/d dosage group, had notable electrocardiographic changes. One patient developed varying degrees of intraventricular conduction defect and premature ventricular contractions; however, this patient exhibited nonspecific ST abnormalities at screening. The other patient was reported to have sinus arrhythmia, left axis deviation, and increased QRS voltage possibly secondary to left ventricular enlargement. Neither patient reported cardiovascular adverse events. Two patients in the placebo group had abnormalities shown on the electrocardiograms: one with left bundle-branch block, the other with sinus bradycardia with premature ventricular contractions.

There were no clinically significant treatment-related effects on vital signs, hematologic examination findings or clinical biochemistry test results. More important, the use of donepezil was not associated with any hepatotoxic effects.

COMMENT

The results reported herein demonstrate that once-daily administration of donepezil enhances cognition, measured by standardized psychometric testing, and improves clinician-rated global function, measured by CIBIC plus, in patients with mild to moderately severe AD. The cognitive improvements began during the initial 3 weeks of treatment, and by the first visit during the double-blind phase the improvements measured by ADAS-cog were maximal and statistically significant (Figure 1). This improvement was sustained throughout the study. At end point (week 12 LOCF, the end of the double-blind phase), the adjusted mean treatment effect of donepezil hydrochloride relative to placebo was 2.5 points at the 5-mg/d dosage, and 3.1 points at the 10-mg/d dosage, with a higher proportion of the patients receiving 10 mg/d having the larger reductions in ADAS-cog scores. During the 3-week placebo washout phase, scores demonstrated a trend toward a return to baseline values, although the treatment effect at week 15 remained statistically significant ($P<.001$) relative to baseline for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride. In contrast, no significant effect was seen for the placebo group.

During the 12-week active treatment period, approximately 60% of patients receiving 10 mg/d of donepezil achieved a best change score of 4 points or more on the ADAS-cog, as opposed to approximately 30% of the placebo controls. An improvement of 4 or more points on the ADAS-cog is considered by regulatory authorities to be clinically meaningful. The withdrawal rate was 7% in the placebo group, 10% in the 5-mg/d dosage group, and 18% in the 10-mg/d dosage group. A conservative measure, adjusting for these withdrawals (ITT analysis), shows that between 48% and 57% of patients randomized to receive drug treatment achieved a 4-point or more reduction in ADAS-cog compared with 29% for placebo. These data are consistent with a 24-week study that showed a greater effect on ADAS-cog with 10 mg/d than with 5 mg/d of donepezil hydrochloride.[31] These improvements in ADAS-cog were accompanied by mean drug–placebo differences at end point in MMSE scores of 1.0 and 1.3 for the groups receiving 5 mg/d and 10 mg/d of donepezil hydrochloride, respectively. In general, the magnitude of improvement in mean change in ADAS-cog and MMSE scores appeared to be greater for the group receiving 10 mg/d than for the group receiving 5 mg/d of donepezil hydrochloride, although the results did not reach statistical significance.

It should be mentioned that the ADAS-cog, although one of the most recognized and widely used scales for the measurement of cognitive function, lacks linearity and possesses floor and ceiling effects. Thus, the rate of disease progression, when expressed as point increases in ADAS-cog per year, for patients with mild (floor) and severe (ceiling) dementia appears slower than that for patients with moderate dementia. This difference represents a limitation in the ability of the tool to discriminate changes in cognitive capabilities at the mild and severe ends of the spectrum of disease, rather than any true differences in the rate of progression of neuropathologic conditions. Due to this limitation, effect sizes in populations dominated by patients with mild or severe dementia whose annualized rate of decline may be 5 points or lower (baseline ADAS-cog scores of 15, mild; and of 55, severe) will appear numerically smaller than those from a population dominated by patients with moderate dementia whose annualized rate of decline may be as much as 12 or more points (baseline ADAS-cog score of 35). The range normally reported for untreated patients with moderate disease is between 7 and 11 points per year.[32,33] Hence, when examining treatment effect sizes between and within clinical studies, it is essential that effect size as a proportion of the annualized rate of change in the placebo cohort be considered. In this study, the mean baseline ADAS-cog score was 26 and approximately 80% of patients had a CDR rating score of 1.0, indicating a population dominated by patients with mild dementia.

Improvements in CIBIC plus scores were also observed in patients treated with donepezil. Although not apparent until week 9, the donepezil hydrochloride groups were rated higher than the placebo group (3.9 for the 5-mg/d group, 3.8 for 10-mg/d group vs 4.2 for the placebo group) at end point, and this difference failed to dissipate completely after donepezil use was discontinued during the 3-week washout period. There was no statistically significant improvement ($P>.05$) in CDR-SB scores, probably because of the short duration of the study. Nonetheless, a trend for improvement was clearly and consistently evident. However, attempts at QoL measurement were unsuccessful in this study, and it is unclear why no treatment effect was observed. These results are inconsistent with those obtained in a 24-week pivotal trial in which the use of donepezil hydrochloride (5 and 10 mg/d) showed trends for improvement in QoL assessment.[31]

Plasma concentrations of donepezil were directly related to AChE inhibition in RBCs (Figure 5) and to improvements in cognitive and global function (ADAS-cog and CIBIC plus). There was also a statistically significant correlation between inhibition of AChE in RBCs and improvement in ADAS-cog ($P<.001$) and CIBIC plus ($P<.005$) scores. Other researchers have described an inverted U-shaped dose response curve for drugs such as physostigmine and metrifonate, reporting that maximum clinical efficacy corresponded to 40% cholinesterase inhibition (plasma butyrylcholinesterase measurements).[34,35] In our study, 50% inhibition of AChE in RBCs was seen at a plasma donepezil concentration of 15.6 ng/mL, and a plateau of enzyme inhibition (80%-90%) was attained at higher plasma concentrations. Statistically significant improvement in ADAS-cog scores was correlated with AChE inhibition in RBCs of 65% or more as opposed to the 40% inhibition value for plasma cholinesterase that has been reported for the other agents. There appears to be a close relationship between percentage of inhibition and drug effect for donepezil.

The rate of patient withdrawal from treatment was much lower with the use of donepezil than with the rates reported for other cholinesterase inhibitors, such as physostigmine, rivastigmine (ENA-713), velnacrine maleate, and tacrine.[12,36-38] All these cholinesterase inhibitors are associated with a higher incidence of peripheral cholinergic adverse effects than the use of donepezil, with some (tacrine and velnacrine) being associated with hepatotoxic effects.[12,36-38] One of several factors contributing to this low rate of patient withdrawal is that the long half-life of donepezil (approximately 70 hours) combined with the once-daily administration produced AChE inhibition with little diurnal variation and a slow and gradual rise to steady state levels of activity. Once-daily dosage also aids medication compliance. Indeed, 95% of patients were more than 80% compliant at each postbaseline visit during the treatment phase of the study.

Analysis of the reported incidences of TESS and treatment-emergent laboratory abnormalities demonstrated that donepezil is well tolerated. There were no unexpected adverse events, and TESS observed were consistent with those reported in other donepezil clinical trials of 12- and 24-week durations.[11,31] The only dose-related adverse events in this study were anticipated cholinergic effects, including mild nausea, diarrhea, and insomnia, which occurred primarily in the group receiving 10 mg/d of donepezil hydrochloride at the time of the forced dosage increase from 5 mg/d to 10 mg/d. These events were generally self-limiting, resolving in 1 to 2 days without the need for interruption or adjustment of the donepezil dosage. Subsequent analysis from an open-label extension study of the use of donepezil in 269 patients who had received placebo in the double-blind pivotal trial phase demonstrated that the occurrence of these

events is minimized when a longer dosage titration period is used. When these patients entered into the open-label extension study, escalation to 10 mg/d of donepezil hydrochloride was undertaken after 4 to 6 weeks at 5 mg/d. As a consequence, the incidence of these adverse events was reduced and was comparable with that experienced with both 5 mg/d of donepezil hydrochloride and placebo. Donepezil produced no statistically significant treatment-emergent laboratory abnormalities, including liver function tests.

The results of this study indicate that donepezil is a well-tolerated and efficacious agent for the symptomatic treatment of mild to moderately severe AD. Statistically significant improvements in scores on tests of cognition are present as early as 3 weeks after starting treatment with donepezil, and statistically significant global improvement was observed after 9 to 12 weeks. Based on ADAS-cog and CIBIC plus results, clinicians should recognize significant improvement in cognitive and global functioning in about 35% to 60% of patients with AD treated with donepezil, while observing stabilization of cognitive function (compared with the decline typically observed in untreated patients) in an additional 20% to 45%. Thus, improvement of cognitive function, or no change in cognitive function, is likely to be seen in approximately 80% of patients with AD treated with donepezil. Further studies are needed to define the role of donepezil in treating patients more severely affected with AD and to determine its long-term efficacy and tolerability.

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