Clinical Review

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 1999;10:237–244

Accepted: March 7, 1999

The Effects of Donepezil in Alzheimer's Disease – Results from a Multinational Trial[1]

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Key Words
Donepezil · Acetylcholinesterase inhibitor · Alzheimer's disease · Efficacy · Safety

Abstract
Donepezil has been shown to be well tolerated and to improve cognition and global function in patients with mild to moderately severe Alzheimer's disease (AD). The current trial was undertaken to investigate further the efficacy and safety of donepezil, in a multinational setting, in patients with mild to moderately severe AD. This 30-week, placebo-controlled, parallel-group study consisted of a 24-week, double-blind treatment phase followed by a 6-week, single-blind, placebo washout. Eight hundred and eighteen patients with mild to moderately severe AD were randomly allocated to treatment with single, daily doses of 5 or 10 mg donepezil, or placebo. The two primary efficacy measures were: a cognitive performance test, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and a global evaluation, the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC plus). Secondary outcome measures included the Sum of the Boxes of the Clinical Dementia Rating Scale (CDR-SB), a modified Interview for Deterioration in Daily living activities in Dementia (IDDD) and a patient-rated quality of life assessment. Statistically significant improvements in cognitive and global function were observed, as evaluated by ADAS-cog and CIBIC plus, respectively, in both the 5 and 10 mg/day donepezil groups, compared with placebo. Treatment-associated changes were also observed in functional skills, as shown by improved scores on the CDR-SB and the complex-tasks component of the IDDD. A dose–response effect was evident, with the 10 mg/day donepezil group demonstrating greater benefits in all outcome measures than the 5 mg/day group. Donepezil was well tolerated by this patient population and did not produce any clinically significant laboratory test abnormalities. The results of this study confirm that donepezil is effective and well tolerated in treating the symptoms of mild to moderately severe AD.

Introduction

Alzheimer's disease (AD) is a progressive disease, characterised by disorders of cognitive function, deficits in activities of daily living and the presence of psychiatric symptoms and behavioral disturbances. It is primarily a condition of elderly people, affecting 3% of 70-year-olds, rising to 10% in people over 80 [1]. The pathogenesis of AD is not understood. There is, however, widespread loss of cholinergic innervation to the cerebral cortex, which

[1] This study was supported by Eisai Inc., Teaneck, N.J., USA and Eisai Co. Ltd., Tokyo, Japan.
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forms the basis for memory impairment, a hallmark of the disease [2]. Theoretically, increasing the levels of brain acetylcholine may improve clinical symptoms in AD. Most successful therapeutic strategies have focused on blocking the breakdown of acetylcholine by inhibiting its enzymatic hydrolysis.

Donepezil hydrochloride (Aricept®)[4] is a potent and specific inhibitor of acetylcholinesterase with minimal effects on butyrylcholinesterase [3] and, as a piperidine-based molecule, is chemically distinct from other cholinesterase inhibitors. It has a long duration of action, with a half-life of approximately 70 h [4–6], which allows once-daily administration. Preclinical [7] and clinical studies in Japan [8] and the USA [9] have shown that donepezil is devoid of unexpected toxicity, particularly the hepatotoxicity characteristic of acridine-based cholinesterase inhibitors.

Phase II and Phase III [10, 11] double-blind, placebo-controlled clinical trials conducted in the USA have shown that donepezil significantly improves cognitive and global function, with these benefits being maintained during open-label, long-term donepezil administration [12]. Donepezil was studied in a population where 95% of patients had prior medical or co-morbid conditions, and was shown to be well tolerated, producing no clinically significant changes in metabolic, cardiovascular, hepatic or renal function. In addition, no clinically significant drug-drug interactions were observed, even though over 80% of the patients in these trials were taking one or more concomitant medications. Importantly, the cytochrome P450 isoenzyme inhibitors cimetidine [13] and ketoconazole [14] produce no clinically significant changes in the pharmacokinetics of donepezil, suggesting that dose modification is not necessary when donepezil is co-administered with such compounds.

The objectives of the current study were to evaluate further the safety and efficacy of once-daily administration of donepezil at doses of 5 and 10 mg, versus placebo, in a large, multinational cohort of patients with mild to moderately severe AD.

Materials and Methods

Patient Population

Men and women, ≥50 years of age, with probable AD were recruited at 82 sites in Australia, Belgium, Canada, France, Germany, Ireland, New Zealand, South Africa and the UK. For the diagnosis of AD, patients satisfied both the criteria defined by the DSM-III-R for primary degenerative dementia of the Alzheimer type [15] and by the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD [16].

Patients were required to have mild to moderately severe AD, at screening and baseline, as defined by Mini-Mental State Examination [17] scores between 10 and 26 inclusive, and Clinical Dementia Rating (CDR) [18] scores of 1 (mild) or 2 (moderate). All patients had a computerised tomography or magnetic resonance imaging scan within the previous 6 months, and patients with structural lesions or significant vascular changes were excluded. Women were required to be 2 years post-menopausal or surgically sterile. In addition, patients had to be generally healthy, with vision and hearing sufficient for compliance with the testing procedures. Patients with other neurological or psychiatric disorders, asthma, significant uncontrolled gastrointestinal, renal, hepatic, endocrine or oncological disorders, or who were taking prohibited study medications, were excluded.

The study was conducted in accordance with the principles stated in the revised Declaration of Helsinki (1989) and the European Community GCP Guidelines (1990). All centres had local ethics committee approval. Prior to screening, the nature and purpose of the investigation was explained to the patient and caregiver, and written, informed consent was obtained from both.

Study Design

This was a 30-week, randomised, multinational, multicentre, placebo-controlled, parallel-group study with a 24-week, double-blind treatment phase followed by a 6-week, single-blind, placebo washout. Patients were screened within 2 weeks of entry and randomly assigned to receive 5 or 10 mg/day donepezil, or placebo. Study medication was administered orally, once-daily, in the evening. A blinded schedule was used for the 10 mg/day donepezil group, where patients initially received 5 mg/day for the first 7 days, then 10 mg/day for the remainder of the study. Efficacy and safety evaluations were conducted at baseline and at Weeks 6, 12, 18, 24 and 30.

Outcome Measures

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [19], and a Clinician's Interview-Based Impression of Change with caregiver input (CIBIC plus) [20], were the two primary outcome measures used, reflecting cognition and global function, respectively.

The secondary efficacy variables used were the Sum of the Boxes of the Clinical Dementia Rating scale (CDR-SB) which sums the ratings from six domains ('boxes') of the CDR to provide a consensus-based, global clinical measure [21], a modified Interview for Deterioration in Daily living activities in Dementia (IDDD) [22] and a patient-rated quality of life (QoL) assessment [23]. Descriptions of ADAS-cog, CIBIC plus, CDR-SB and QoL assessment tools have been reported previously [10, 11].

The IDDD was designed originally as a severity instrument for quantifying impairment in activities of daily living of dementia patients. It consists of 33 items and the severity of impairment is rated on a 7-point scale, where 1–2 = no or slight impairment, 3–4 = mild impairment, 5–6 = moderate impairment and 7 = severe impairment, giving a total score range of 33–231 points. The IDDD provides a self care tasks rating (16 items) and complex tasks rating (17 items). Both initiation of tasks and their performance by the patient are quantified during a structured interview of the caregiver. At baseline, severity of disability was scored for each item of the IDDD. To assess change at subsequent visits, the severity scale was modified to measure change from baseline, where the evaluator rated

[4] Aricept® is a registered trademark of Eisai Co. Ltd., Tokyo, Japan.

improvement, no change or deterioration in comparison to the baseline performance level. In assessment of change, a 7-point Likert-type scale was used, where 1 = marked improvement from baseline, 4 = no change from baseline and 7 = marked deterioration from baseline. Hence, a patient exhibiting no change in complex task functioning, for example, would receive a total score of 68 (17 × 4) on the IDDD complex tasks. Thus, it follows that a score below 68 would represent improvement and a score above 68 would denote deterioration. This trial represents the first use of this modification of the IDDD scale. Unlike the ADAS-cog and CIBIC plus assessment tools, which are widely accepted in research settings, there are no instruments to measure change in the patients' ability to perform both complex and basic daily tasks that are in common use in clinical trials for AD.

Safety Measures

Adverse events were monitored at each visit by questioning both the patient and the caregiver, as well as through direct observation. All adverse events, whether reported or observed, were recorded, together with the time and date of onset and cessation, severity of condition and whether, in the opinion of the investigator, the event was related to donepezil treatment. Serious adverse events (SAE) included fatal or life-threatening situations, permanently disabling conditions or incidents that required or prolonged hospitalisation.

Blood pressure and pulse were measured at all clinic visits, with temperature and respiration also measured at baseline and Week 30. A standard 12-lead ECG was performed at the start and end of the double-blind treatment. In addition, clinical laboratory assessments including haematology, clinical chemistry and urinalysis were conducted at each clinic visit.

Statistical Assessments

An original sample size of 150 patients/treatment group was estimated, based on the results obtained from an earlier Phase II study of donepezil and from published results from US tacrine trials. The sample size had 80% power to detect a difference of 0.27 points in mean CIBIC plus scores for each donepezil treatment group when compared to placebo, at a 0.05 significance level. The patient completion rate was estimated to be 80%. During the study, a blinded examination of the ADAS-cog test data indicated a larger variance in the multinational data than projected from the US data. This was not unexpected given the multinational nature of this patient cohort. However, to ensure a valid representation of the patient cohort it was thus necessary that the sample size be increased to 250 patients per treatment group. The final sample size of 818 was a result of additional patients already in screening at the time of termination of recruitment.

Three populations were used in the analyses of efficacy: fully evaluable, retrieved drop-out and intention-to-treat (ITT). The ITT population was analysed on both observed cases and traditional last observation carried forward (LOCF; endpoint, as outlined by the US FDA [24]). As specified a priori, the primary population was the ITT, and the primary endpoint was the Week 24 LOCF. Since the results of all analyses were similar, only the primary analysis is presented in this report.

For the continuous variables (ADAS-cog, modified IDDD, CDR-SB and QoL), an analysis of covariance (ANCOVA) model was used to compare treatment groups. The models for efficacy contained factors for baseline score, treatment effect and centre effect. The assumptions of the covariance were tested before using the reduced model. Fisher's least significant difference procedure was used to control for multiple comparisons to placebo.

Table 1. Patient demographics

	Placebo	Donepezil	
		5 mg/day	10 mg/day
Patients	274	271	273
Age, years			
Mean ± SE	71 ± 0.5	72 ± 0.5	72 ± 0.5
Range	50–90	51–91	53–93
Gender			
Male	123 (45)	107 (39)	118 (43)
Female	151 (55)	164 (61)	155 (57)
Race			
Caucasian	272 (99)	270 (100)	271 (99)
Other	2 (1)	1 (<1)	2 (1)
Weight, kg			
Mean ± SE	66 ± 0.8	65 ± 0.8	66 ± 0.7
Range	37–107	38–108	38–99
Screening MMSE			
Mean ± SE	20 ± 0.3	20 ± 0.3	20 ± 0.2
Range	10–26	10–26	9–26
Screening CDR			
0.5	0	2 (1)	2 (1)
1.0	230 (84)	222 (82)	236 (86)
2.0	44 (16)	47 (17)	35 (13)

Figures in parentheses are percentages. MMSE = Mini-Mental State Examination.

For the categorical efficacy variable (CIBIC plus), the Cochran-Mantel-Haenszel test was employed, with RIDITS as the score option and stratified for centre [25, 26].

Demographic variables of age, weight and height were investigated utilising ANOVA models with factors for treatment and centre. Sex was assessed by the Cochran-Mantel-Haenszel test with centres as strata.

Within-group changes in vital signs were analysed using paired *t*-tests. Between-group differences were investigated by ANCOVA models. As in previous studies, the analysis of adverse events was restricted to signs and symptoms that either began, or became more severe, after administration of the first dose of study medication. Events were coded using a modified COSTART dictionary [27], and the assessment of relationship to treatment for all adverse events was conducted blind to treatment assignment. The incidence of adverse events and laboratory test abnormalities were compared between treatment groups using Fisher's exact test.

All statistical analyses were undertaken by an independent clinical research organization using SAS version 6 or higher (SAS Institute, Cary, N.C., USA). All hypothesis tests were two-sided and statistical significance was achieved if $p \leq 0.05$.

Results

Description of the Sample

A total of 818 patients were randomised to treatment. The treatment groups were comparable with respect to all the demographic variables examined (table 1). The com-

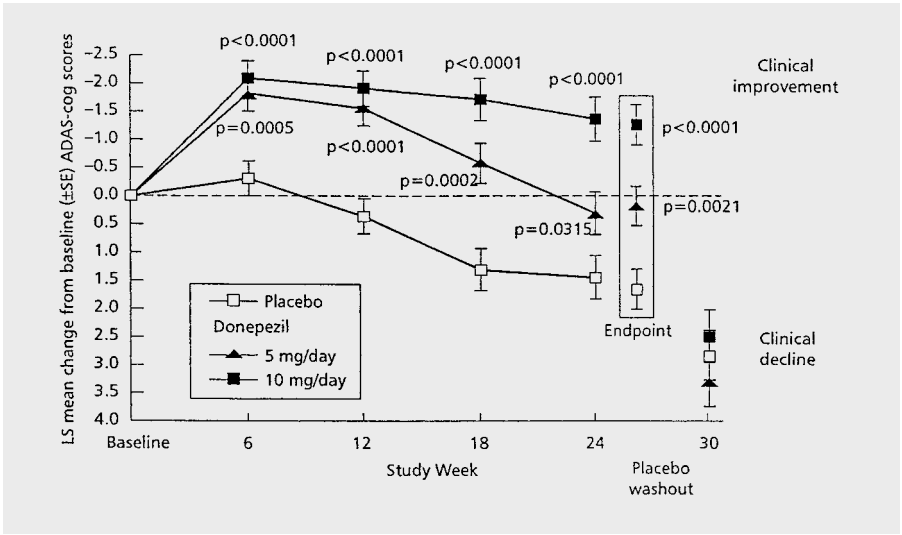

Fig. 1. LS mean (± SE) change from baseline in ADAS-cog scores for 5 and 10 mg/day donepezil and placebo groups.

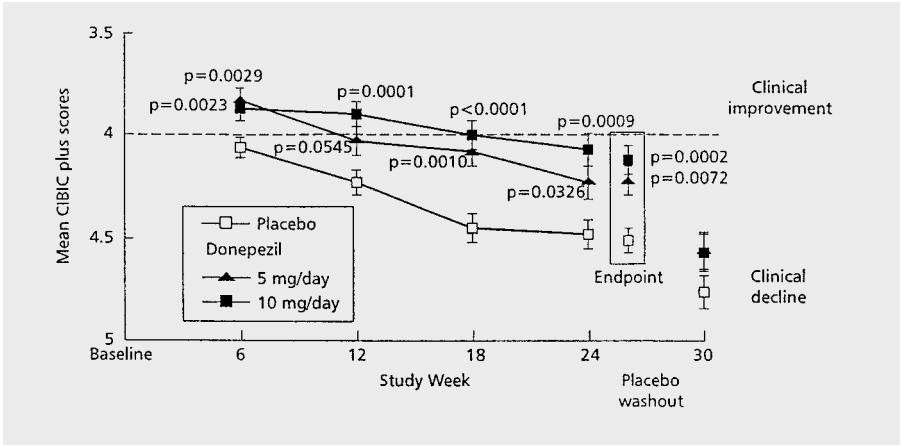

Fig. 2. Mean (± SE) CIBIC plus scores for 5 and 10 mg/day donepezil and placebo groups; p values were calculated using the Cochran-Mantel-Haenszel test.

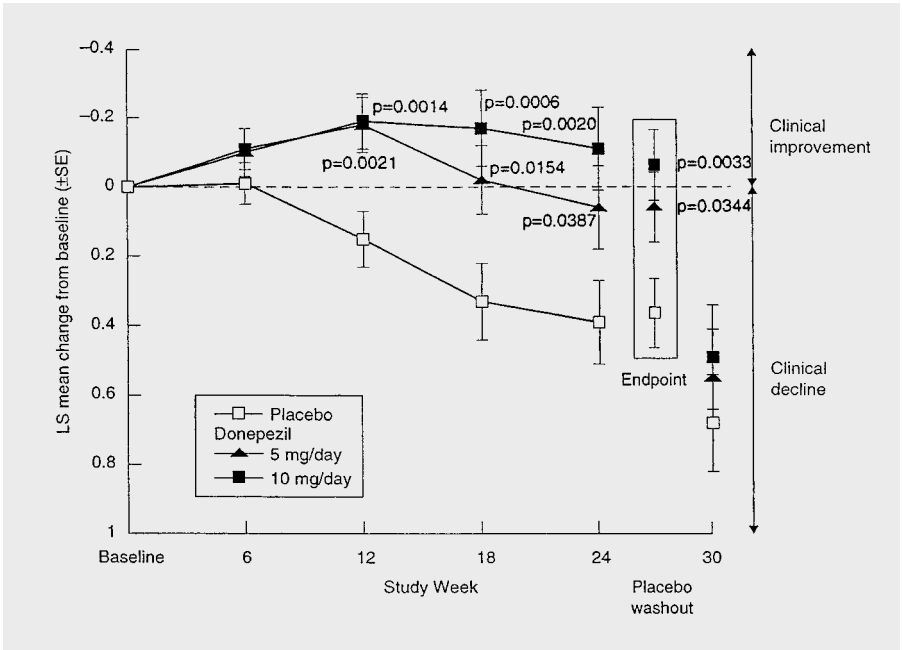

Fig. 3. LS mean (± SE) change from baseline in CDR-SB scores for 5 and 10 mg/day donepezil and placebo groups.

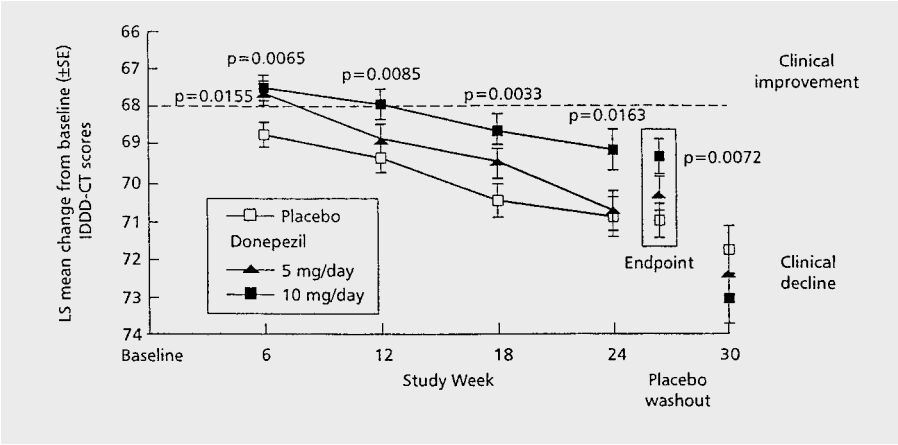

Fig. 4. LS mean (± SE) change from baseline in IDDD-complex tasks scores for 5 and 10 mg/day donepezil and placebo groups.

pletion rates for this study were high at 78, 74 and 80% for the 5 and 10 mg/day donepezil and placebo groups, respectively.

Primary Outcome Measures

ADAS-cog. There was a statistically significant improvement in ADAS-cog scores for the two donepezil-treated groups compared with placebo. This was observed at Week 6 and maintained throughout the active treatment phase (fig. 1). At endpoint, the donepezil versus placebo differences in least-squares (LS) means for change from baseline ADAS-cog scores were 1.5 and 2.9 points for the 5 and 10 mg/day donepezil groups, respectively.

CIBIC plus. Statistically significantly greater numbers of donepezil-treated patients were judged clinically improved, by comparison with placebo. This beneficial drug treatment effect was observed from Week 6 and was maintained at all subsequent visits (fig. 2) and at endpoint. Donepezil increased the percentage of patients rated as improved (CIBIC plus scores ≤ 3 at endpoint): 21 and 25% for the 5 and 10 mg/day donepezil-treated groups, respectively, compared with 14% for the placebo group. In addition, donepezil reduced the percentage of treatment failures (CIBIC plus scores ≥ 5 at endpoint: 43 and 37% for the 5 and 10 mg/day donepezil-treated groups, respectively, compared with 51% for the placebo group.

Secondary Outcome Measures

CDR-SB. Statistically significant improvements in LS mean change CDR-SB scores were observed for both donepezil-treated groups, versus placebo, at Weeks 12, 18, 24 and endpoint ($p < 0.05$; fig. 3). At endpoint, the mean drug–placebo differences for the 5 and 10 mg/day donepezil groups were 0.3 and 0.4, respectively.

Table 2. IDDD baseline severity scores – ITT population

	Placebo	Donepezil	
		5 mg/day	10 mg/day
IDDD-total score			
Total baseline severity (possible range 33–231)	69.84 ± 1.68	67.78 ± 1.61	69.85 ± 1.71
Mean severity per item	2.10	2.04	2.09
IDDD-self care			
Total baseline severity (possible range 16–112)	24.31 ± 0.72	23.14 ± 0.61	23.72 ± 0.66
Mean severity per item	1.52	1.45	1.48
IDDD-complex tasks			
Total baseline severity (possible range 17–119)	45.53 ± 1.17	44.64 ± 1.13	46.12 ± 1.21
Mean severity per item	2.68	2.63	2.71

Means ± SE. The severity scale per item: 1–2 = no or slight impairment; 3–4 = mild impairment; 5–6 = moderate impairment; 7 = severe impairment.

IDDD. The mean total baseline IDDD severity scores were low (~70 out of a total of 231), with a mean score of 2.1 points per item, indicating that patients entering this study had very mild functional impairment on this scale (table 2). The mean IDDD-self care and IDDD-complex task scores per item at baseline were 1.5 and 2.7, respectively, demonstrating that patients had little or no impairment of self-care abilities and only mild impairment in the execution of complex tasks.

From Week 6, through the active treatment phase, IDDD-complex task scores for both the 5 and 10 mg/day donepezil groups were improved when compared with placebo, with statistical significance for the 10 mg/day donepezil dose at all assessments (fig. 4). As IDDD-self care scores in this patient population were not impaired at

Table 3. Patient disposition

	Placebo	Donepezil		All donepezil treatments
		5 mg/day	10 mg/day	
Patients randomised	274	271	273	544
Patients discontinued	55 (20)	60 (22)	72 (26)	132 (24)
Withdrawn due to:				
Adverse events[1,2]	27 (10)	24 (9)	50 (18)	74 (14)
Body as a whole	6 (2)	4 (1)	12 (4)	16 (3)
Cardiovascular	3 (1)	1 (<1)	5 (2)	6 (1)
Digestive	2 (<1)	4 (1)	27 (10)	31 (6)
Nervous	14 (5)	13 (5)	21 (10)	34 (6)
Intercurrent illness	3 (1)	0	0	0
Request of patient or investigator	6 (2)	12 (4)	6 (2)	18 (3)
Non-compliance	2 (1)	3 (1)	2 (1)	5 (1)
Protocol violation	13 (5)	13 (5)	8 (3)	21 (4)
Other	4 (1)	8 (3)	6 (2)	14 (3)

Figures in parentheses are percentages.
[1] There may be more than one adverse event that led to withdrawal.
[2] Adverse events and symptoms were not necessarily treatment related or treatment emergent.

Table 4. Adverse events experienced by at least 5% of all donepezil patients

	Placebo	Donepezil		All donepezil treatments
		5 mg/day	10 mg/day	
Total patients with any adverse events	207 (76)	213 (79)	234 (86)	447 (82)
Digestive system[1]	65 (24)	70 (26)	127 (47)	197 (36)
Nausea[1]	7%	7%	24%	16%
Diarrhoea[1]	4%	10%	16%	13%
Vomiting[1]	4%	4%	16%	10%
Anorexia	1%	4%	8%	6%
Nervous system[1]	80 (29)	98 (36)	109 (40)	207 (38)
Dizziness	5%	5%	9%	7%
Confusion	6%	7%	6%	7%
Insomnia	4%	7%	8%	8%
Total patients with SAE	25 (9)	19 (7)	29 (11)	73 (9)

Figures in parentheses are percentages.
[1] Donepezil groups significantly differed from placebo, $p \leq 0.05$ employing Fisher's exact test.

baseline, no improvements could be measured during the study.

QoL. The mean change from baseline at each evaluation of this patient-rated measure was associated with a large standard error, indicating the high variability of responses from patients. As such, no clear trends among the treatment groups were evident during the active phase of this trial and no overall treatment effects were observed at any assessment visit. This reflects the difficulties inherent in using patient-rated instruments in populations with cognitive impairment.

Treatment Washout. Following the 6-week, single-blind, placebo washout phase, patient scores for efficacy measures (ADAS-cog, CIBIC plus, CDR-SB and IDDD) reverted to levels similar to placebo, indicating that the beneficial effects of donepezil were lost when treatment was discontinued (figs. 1–4).

Safety Measures

Donepezil was well tolerated: 76% of donepezil-treated patients, compared with 80% of the placebo group, completed the study (table 3). A low incidence of patients withdrew due to adverse events: only 9 and 18% for the 5 and 10 mg/day donepezil groups, respectively, as compared with 10% in the placebo group (table 3), and not all events were treatment-emergent or treatment-relevant. The most frequently experienced adverse events were digestive system related (nausea, vomiting and diarrhoea; tables 3 and 4), which are predictable effects of cholinergic drugs. The percentage of patients experiencing cholinergic-induced side-effects was higher in the 10 mg/day donepezil group and was likely to be due to the rapid increase to the 10 mg/day dose after only 1 week on 5 mg/day [28, 29].

Overall, the proportion of patients with at least one reported adverse event within the donepezil groups was only slightly higher than in the placebo group (table 4). The majority of these events were mild and transient in nature, typically lasting 1–2 days and resolving during continued donepezil use, without dosage adjustment. Most adverse events, other than those clearly cholinergic in nature, were judged by the investigators not to be related to donepezil treatment.

Of the 818 patients enrolled in the study, 73 (9%) experienced at least one SAE either during the study or within 1 month of study termination; the incidence of SAEs was similar for all treatment groups and unrelated to study medication (table 4). Five patients (two receiving placebo, one receiving 5 mg/day donepezil and two receiving 10 mg/day donepezil) died during the study or within 1 month of stopping medication. All 5 deaths were determined to be unrelated to donepezil treatment.

No clinically significant abnormal test values, for any laboratory parameter, were observed at a greater frequency in the donepezil-treated patients as compared with the placebo group. In particular, donepezil was not associated with evidence of hepatotoxicity.

Discussion

The results of this Phase III, multinational, clinical trial confirm previously published findings that the daily doses of both 5 and 10 mg donepezil significantly improve cognitive and global functioning in patients with mild to moderately severe AD, with an effect size similar to those reported in the US 30-week, Phase III trial of donepezil. Hence, these improvements in cognitive and global function were consistent and independent of the populations studied (US versus multinational).

In addition to cognition and global function, this study assessed the effects of donepezil treatment on activities of daily living (IDDD-complex tasks and IDDD-self care). These subscores measure aspects of early- and late-stage AD progression, respectively [30]. In the early stages of the disease, patients primarily experience difficulty with relatively complex activities, such as handling finances or preparing meals (complex tasks). It is not until later in the disease course that basic activities of daily living (self care) become affected, e.g. dressing, bathing, etc. Consistent with this premise, the mildly to moderately demented patient population in this study had well-preserved basic skills, but mildly impaired complex task performance.

Thus, as might be expected, donepezil administration did not improve the well-preserved, self care task performance scores of this patient population. By contrast, improvements relative to placebo, in complex task performance scores, were observed for both the 5 and 10 mg/day donepezil groups, at all treatment visits, with statistically significant differences obtained for the 10 mg/day donepezil group versus placebo.

Consistent with earlier trials, this study confirms that the 5 mg/day dose of donepezil is clinically effective, as assessed by the ADAS-cog and CIBIC plus. In addition, and in agreement with previous study findings, a dose–response effect is evident, with patients receiving 10 mg/day donepezil demonstrating greater sustained benefits.

Both doses of donepezil were well tolerated. The higher incidence of cholinergic adverse events experienced in the 10 mg/day donepezil group, as compared with the 5 mg/day donepezil and placebo groups, has been shown in a separate study to be a direct result of the rapid dose increase used (5 mg/day for the first 7 days, then 10 mg/day thereafter). When the patients' dosage had been increased to 10 mg/day donepezil after 4–6 weeks of treatment at 5 mg/day, the adverse event profile for 10 mg/day donepezil was similar to that of both the 5 mg/day donepezil- and placebo-treated groups. However, despite the rapid dose increase used in this study, the discontinuation rates related to adverse events are substantially lower than those reported for other cholinesterase inhibitors, such as tacrine [31] and physostigmine. Common side-effects experienced in this study ($\geq 5\%$) included nausea, vomiting, diarrhoea, anorexia, dizziness, confusion and insomnia, and are consistent with adverse events reported in previous studies.

Results of this multinational trial confirm previous findings that donepezil is well tolerated and efficacious in treating the symptoms of cognitive loss and in improving global functioning in patients with mild to moderately severe AD. The improvement in IDDD-complex tasks also indicates that the benefits of donepezil may translate into an effect on complex activities of daily living. Thus, despite variations in local diagnostic and treatment practices, this multinational study demonstrates that donepezil therapy is an effective and well tolerated symptomatic treatment for patients with mild to moderately severe AD.

Acknowledgments

We thank Dr. Rachelle Doody, Baylor College of Medicine, Houston, Tex., USA, for her contribution in training investigators on the CIBIC plus assessment tool and PPS International, Worthing, UK, for their assistance in developing this manuscript.

Appendix

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