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Effectiveness and Safety of Donepezil in Hispanic Patients with Alzheimer's Disease: A 12-Week Open-Label Study

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Abstract

Background—Hispanics represent 10% of the U.S. population and are the fastest growing group. Studies show a higher prevalence and incidence of Alzheimer's disease (AD) in Hispanics than in the non-Hispanic white population, with an earlier age of onset. Among the currently estimated 200,000 Hispanics with AD, a significant number remain undiagnosed and untreated, and Hispanic participation in AD clinical trials has been historically low. This study evaluated the efficacy and safety of donepezil hydrochloride (donepezil) in Hispanics with mild-to-moderate AD.

Methods—In this multicenter, open-label, 12-week study conducted in the United States, subjects were Hispanic men or women aged ≥ 50 years with a diagnosis of mild-to-moderate AD (DSMV-IV and NINCDS/ADRDA criteria), with Mini-Mental State Examination (MMSE) scores of 10–26 (inclusive) at screening. Subjects were treated with donepezil 5 mg/day for 6 weeks followed by 10 mg/day for 6 weeks. Clinical evaluation was performed at baseline, week 6 and week 12. Cognitive improvement was measured using the MMSE, Fuld Object Memory Evaluation (FOME) and Symbol Digit Modality Test (SDMT). Behavioral symptoms and associated caregiver distress were assessed with the Neuropsychiatric Inventory (NPI).

Results—One-hundred-six patients with mild-to-moderate AD (mean age 68.6 years) were enrolled (intent to treat, $n=97$); most chose to have assessments conducted in Spanish. With 12 weeks of treatment, subjects showed statistically significant improvement from baseline on MMSE ($P<0.0001$), FOME retrieval ($P=0.0042$), FOME repeated retrieval ($P=0.0020$) and SDMT correct scores ($P<0.0001$). The NPI subdomain "apathy/indifference" showed statistically significant improvement ($P=0.0010$). The NPI Caregiver Distress scale (NPI-D) total score was statistically significantly improved ($P=0.0500$), suggesting a positive impact on relieving caregivers' burden associated with patient behavior. Most patients tolerated the treatment well, with only 2 discontinuing because of adverse events. The most common ($>5\%$) adverse events were insomnia (9.5%), dizziness (7.6%), diarrhea (5.7%) and nausea (5.7%).

Conclusion—The cognitive improvement and safety results from this study were consistent with those reported for donepezil in the general population. Increased awareness of AD in the Hispanic population will help more Hispanics with AD to benefit from early diagnosis and effective treatment.

Keywords

Alzheimer's disease; drugs; Latinos

INTRODUCTION

The term “Hispanic” means “relating to or derived from people, speech or culture of Spain,”¹ and it is used in the United States to characterize individuals from Latin-American countries. This group includes people with direct roots in Spain or other European countries, as well as those with a mixture of European, American-Indian or African ancestors. While they are diverse in terms of racial and national origins, American Hispanics share common cultural characteristics that appear to affect their experience of Alzheimer’s disease (AD).

Hispanics are the most rapidly growing minority in the United States. Currently, 1 of every 8 people in the United States is Hispanic, and by 2050 they will comprise nearly one-fourth of the U.S. population.² In addition, the 2000 Census identified 1.7 million Hispanic/Latinos age >65, a number which is projected to increase to >13 million by 2050.²

It has been estimated that 24–30 million people worldwide have dementia, with 4–6 million new cases per year.³ AD is the most common form of dementia in the elderly.⁴ There are approximately 5 million people in the United States with AD,⁵ and the prevalence of this disease is expected to reach 11–13 million by 2050.⁶ Interestingly, population studies have shown a higher prevalence and incidence of AD in Hispanic populations versus non-Hispanic white populations.^{7–9} It also appears that AD symptoms appear earlier in Hispanics than in non-Hispanic whites. Results from a cross-sectional study carried out at 5 centers indicated that Hispanic patients had a mean age of symptom onset 6.8 years younger than non-Hispanic white patients after adjusting for factors including education.¹⁰ In another epidemiologic study, the onset of AD was 7–8 years earlier in Hispanics than in non-Hispanics.⁸ Studies from referral clinics have shown further that up to 40% of Hispanic patients had an undiagnosed cognitive syndrome for ≥3 years.¹¹ The reason(s) for the apparently higher risk for and earlier onset of AD in Hispanics is not known but may be related to higher prevalence of cerebrovascular risk factors (e.g., hypertension, diabetes mellitus)⁸ or other metabolic abnormalities (e.g., low erythrocyte folate levels, high homocysteine levels).^{12,13}

One of the most important advances in the care of patients with dementia has been the introduction of symptomatic treatments for AD, including donepezil hydrochloride (donepezil) for all stages of the disease,^{14–16} rivastigmine¹⁷ and galantamine¹⁸ for mild-to-moderate AD and memantine for moderate-to-severe AD.¹⁹ The present study, Evaluating Aricept® Treatment in Hispanics (EARTH), is the first sponsor-initiated donepezil clinical trial conducted solely in the Hispanic AD population, and it was aimed at providing additional information about the safety and efficacy of donepezil in this population.

MATERIALS AND METHODS

Subjects

Subjects age ≥50 were self-identified as Hispanic living in the community in the United States and had a reliable caregiver, had a diagnosis of AD according to *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria and with a consistent computed tomography (CT)/magnetic resonance imaging (MRI) finding within 12 months prior to or at the screening visit, and had Mini-Mental State Examination (MMSE) scores of 10–26 (inclusive). Subjects with AD who may also have cerebrovascular disease as evidenced by risk factors such as hypertension, diabetes, elevated cholesterol levels and smoking, but in stable conditions, were also eligible to enroll in the study; subjects must have been naïve to donepezil or had a previous AD treatment with rivastigmine, galantamine, memantine or tacrine, provided that such

medications were discontinued ≥ 3 months prior to screening and that such discontinuation was not solely for the purpose of study enrollment. Subjects with any of the following conditions were not qualified for the study: known hypersensitivity to piperidine derivatives or cholinesterase inhibitors; active and uncontrolled disease conditions (diabetes, thyroid disease, hypertension, obstructive pulmonary disease, hematologic/oncologic disorders within past 2 years, active gastrointestinal, renal, hepatic, endocrine or cardiovascular disease); a current *DSM-IV* diagnosis of major depressive disorder or any current primary psychiatric diagnosis other than AD and dementia complicated by delirium; or subjects with a history of drug or alcohol abuse within the past 5 years. Subjects with microinfarcts on CT or MRI that did not affect presentation or prognosis of dementia were allowed.

Study Design

This was a multicenter, open-label 12-week study. Because the safety and efficacy of donepezil have been demonstrated in multiple double-blind, placebo-controlled clinical trials, an open-label study was considered adequate to confirm safety and effectiveness in a Hispanic population. After written informed consent was obtained, subjects entered a screening phase that lasted up to 4 weeks and included assessment of medical history, physical and neurologic examinations, electrocardiograms, laboratory testing, and a CT or MRI scan if one had not been performed within the past 12 months or if warranted by new symptoms since the last scan. Following the screening phase, donepezil was given at a dose of 5 mg/day (15-mg tablet) for the first 6 weeks, after which the dose was increased to 10 mg/day. If the subject could not tolerate the 10-mg dose, it was reduced temporarily to 5 mg/day. The subject was rechallenged with 10 mg/day donepezil after 7–10 days. If the subject could not tolerate the higher dose after rechallenge, he/she was allowed to remain in the study with a 5-mg/day dose. Subjects were evaluated in the clinic at weeks 6 and 12 for efficacy and safety, and had a phone contact at week 8.

The study was conducted in compliance with the U.S. Food Drug Administration Code of Federal Regulations, Good Clinical Practice and the Declaration of Helsinki. The protocol and consent form were reviewed and approved by the institutional review board for each site.

Efficacy Measures

The cognitive evaluations were conducted in the language (either English or Spanish) with which the subject felt more comfortable. All subjects were instructed to complete the test in the language in which they started. Efficacy was examined with the following measures:

- MMSE: a 30-point test assessing orientation to time and place, immediate and delayed recall, attention, language and visuoconstructional praxis. Lower scores indicate greater cognitive impairment.²⁰
- Fuld Object Memory Evaluation (FOME): an assessment of explicit memory (storage and retrieval) using a selective reminding procedure that is based on multiple sensory modalities (sight, touch and hearing), which reduces dependence on spoken English.²¹ In addition, it is relatively insensitive to the confounding effect of education and literacy.²² The scores range from 0–50, with lower scores indicating greater impairment. The FOME has been shown to be effective in detecting cognitive impairment in Spanish-speaking individuals²² and in the diagnosis of AD.²³
- Symbol Digit Modality Test (SDMT): a measure of speed of mental processing, attention and concentration functions. It involves filling nonsense symbol blanks with matching numbers to specific code. The scoring ranges from 0–110, with higher scores representing better performance.²⁴ The SDMT is extremely sensitive for detecting dementia²⁵ and has minimal educational, language or cultural bias.

- Neuropsychiatric Inventory (NPI): a 12-item scale that assesses behavioral disturbances commonly occurring in patients with dementia. Information about frequency and severity of behavioral disturbances is provided by the caregiver. The scoring ranges from 0–144, with higher scores indicating greater behavioral disturbance.²⁶ The NPI includes a Caregiver Distress Scale (NPI-D), which assesses the level of caregiver distress associated with the subjects' behavioral disturbances. The scoring of the NPI-D ranges from 0–60, with higher scores indicating greater caregiver distress associated with behavioral disturbances.²⁶

Both English and Spanish versions of MMSE, FOME and NPI were used in the study. Subjects/caregivers were asked to choose either English or Spanish as the language they wanted to be tested in, and the appropriate version of the instruments was used. It was emphasized at the screening visit that the preferred language version must be used throughout the study. The SDMT form was provided from Western Psychological Services, Los Angeles, CA, and the instructions for the SDMT were either in English or translated into Spanish (certified translation).

Safety Measures

Physical and neurologic examinations, recording of vital signs, clinical laboratory tests and electrocardiograms were conducted at each clinic visit. Adverse events were defined as any untoward medical issue that was reported by the subject or by the investigator, including any abnormal laboratory value or abnormal medical symptomatology. The severity and potential relationship to treatment of each adverse event were assessed by the investigator. Serious adverse events were defined as any adverse event that resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or was a congenital/birth defect.

Statistical Analysis

The intent-to-treat (ITT) cohort consisted of all subjects who took ≥ 1 dose of donepezil, and had baseline and ≥ 1 postbaseline efficacy evaluation. For the ITT subjects, missing data were imputed by the last observation carried forward method (ITT-LOCF). The statistical analysis was performed using SAS[®] version 8.2 (SAS Institute, Cary, NC). Efficacy variables were analyzed by paired t tests comparing week 6, week 12, and endpoint versus baseline or screening (MMSE). All tests were 2 tailed at the 5% significance level. The safety population was defined as all subjects who received ≥ 1 dose of donepezil. Safety variables were summarized by descriptive statistics, but no statistical comparisons were performed.

RESULTS

Subjects

A total of 173 subjects were screened for the study, and 106 were enrolled. The safety population consisted of 105 subjects, the ITT population of 97, and a total of 89 completed the study. The reasons for discontinuation included adverse events, medication noncompliance, lost to follow-up and withdrawn consent (Table 1). The demographic and clinical characteristics and national origins (15 countries) of the safety population are summarized in Table 2. The mean age was 68.6 years, with a mean education level of 10.8 years. 35.2% of subjects were <65 years old, 34.3% were aged 65–74 years and 27.6% were aged 75–84. Most subjects (85.7%) used Spanish as their primary language and were tested in Spanish. Baseline scores on the cognitive and behavioral assessments are summarized in Table 3.

Cognitive and Behavioral Performance

Cognitive performance, as measured with the MMSE, showed statistically significant improvement from baseline at weeks 6 and 12 and in the ITT-LOCF analysis at endpoint (Figure 1). The mean improvement was approximately 2 points from screening [mean $\pm$ standard deviation (SD) = 22.0 $\pm$ 3.4] to the endpoint (mean 24.1 $\pm$ 4.1) ($P < 0.0001$).

Memory function, as measured with the FOME, showed statistically significant improvement with donepezil treatment. The FOME retrieval scores were significantly improved from baseline at week 12 and in the ITT-LOCF analysis at endpoint (Figure 2). The mean improvement at endpoint was 2.1 points ($P = 0.0042$), and the FOME repeated retrieval scores showed a similar pattern of improvement ($P = 0.002$) (Figure 2). However, the FOME storage scores did not show statistically significant improvement from baseline.

Speed of mental processing, attention and concentration functions, as measured by the SDMT, showed statistically significant improvement from baseline at weeks 6 and 12 and at endpoint in the ITT-LOCF analysis, with a mean improvement at endpoint of 3.2 points (Figure 3) ($P = 0.0254$ for week 6 and $P < 0.0001$ for week 12 and endpoint).

NPI mean total score showed statistically significant improvement from baseline at week 6 (-3.2 points; $P = 0.0018$) but not at week 12 or in the ITT-LOCF analysis (Figure 4). The NPI subdomain of apathy/indifference showed statistically significant improvement from baseline to endpoint in the ITT-LOCF analysis ($P = 0.001$). The NPI-D (caregiver distress) score showed statistically significant improvement at endpoint in the ITT-LOCF analysis (-1.25 points, $P = 0.050$).

Safety

Of the 105 subjects included in the safety analyses, 49 (46.7%) experienced ≥ 1 treatment-emergent adverse events during the study. The most frequent adverse events that occurred in $>5\%$ of subjects were diarrhea (5.7%), nausea (5.7%), dizziness (7.6%) and insomnia (9.5%) (Table 4). Most adverse events were mild in severity. Two subjects (1.9%) discontinued from the study due to treatment-emergent adverse events. Three additional subjects (2.6%) discontinued donepezil due to adverse events but remained in the study; 2 of these subjects had a final evaluation and completed the study. Two subjects reduced their donepezil dose due to treatment-emergent adverse events. Of 7 subjects experiencing serious adverse events, 1 was considered to be possibly related to donepezil and 1 other was considered to be probably related to donepezil. There were no deaths during the study; however, 1 subject died 36 days after the last dose of donepezil, which was 2 days after the study termination visit. The death was not considered to be related to donepezil. There were no notable clinically significant changes in laboratory parameters, electrocardiograms, vital signs or physical examinations observed and reported by investigators throughout the study.

DISCUSSION

This is the first study to evaluate donepezil in an exclusively Hispanic population. Donepezil was well tolerated and significantly improved global cognition, memory retrieval and attention/concentration from baseline. All of these results are consistent with those reported for donepezil in studies of predominantly non-Hispanic white subjects^{14–16} and those of a study in African Americans with AD (the Treating African-American Alzheimer's Patients, or TAAAP, study).²⁷ In addition, there was also a numeric improvement in 9 of 12 NPI domains, with that for apathy/indifference achieving statistical significance. There was also a significant improvement from baseline in caregiver stress associated with patient behavior as measured by NPI-D scores.

Hispanics are the largest minority population in the United States, and epidemiologic studies have shown that they are more vulnerable to the development of AD than whites. Hispanics with dementia tend to be younger than non-Hispanics.^{8,9} The results of this study are consistent with these epidemiologic observations: 35% of Hispanic subjects in this study were <65 years of age. The mean age of Hispanics with AD in the present study is 6–10 years less than that of a predominantly white study population,²⁸ and 8 years less than a study population of African Americans with AD.²⁷ In a retrospective database analysis carried out at 5 AD centers, the mean age at symptom onset for 366 Hispanic patients with a clinical diagnosis of AD was 68.8 years, compared with 73.5 years for 2,823 white patients.¹⁰ Particularly in clinical samples such as ours (as opposed to population-based screening), this observation may reflect a cultural bias toward diagnosis and treatment in younger persons, whereas Hispanic families often accept dementia as normal in the oldest old.

Many factors may contribute to the high incidence and prevalence of dementia in Hispanics. Cerebrovascular risk factors such as hypertension, diabetes mellitus and heart disease are more common in Hispanics than in non-Hispanic whites.²⁹ Vascular disease has been found to be an important risk factor for AD as well as for other dementias.^{30,31} Pathologic studies have shown that midlife hypertension is correlated with the presence of neurofibrillary tangles in the elderly,³² and patients with concomitant vascular disease on neuropathologic examination have symptoms of dementia with lower levels of AD-related neuropathology.³³ This suggests that vascular disease can modulate the onset of AD and perhaps also its severity. Education level and acculturation can also influence the diagnosis of dementia, especially in patients who are most probably not educated in English. Regardless of the multiple factors that may moderate and modulate the development and diagnosis of dementia in Hispanics, results from the present study show that Hispanic subjects benefit from cholinesterase inhibitor treatment as do other racial and ethnic groups in the United States.²⁷

The cognitive outcome measures employed in this trial deserve comment. The assessment of dementia in Hispanic populations may be challenging since social/education level and cultural issues can affect cognitive performance on tests that have been designed for non-Hispanic groups.^{11,34–36} Although education may influence some cognitive tests, it is unlikely that such effects influenced results from the present trial for several reasons. First, the education level for subjects in this study was 10.8 years on average. Second, performance on the efficacy measures used in this study is not strongly affected by educational level; and third, patient results during treatment were compared with their own baseline performance. All of these considerations strongly support the validity of the conclusion that donepezil significantly improved cognitive performance in the study population.

The FOME²¹ and SDMT²⁴ were both selected because they are useful for assessment of memory and speed of mental processing/attention and are not substantially impacted by language barriers. Spanish versions of the FOME,³⁷ MMSE⁸ and NPI³⁸ have been validated in U.S. Hispanic populations. The SDMT itself does not require translation, but the instructions were provided in Spanish via certified translation. As noted above, 86% of the subjects enrolled used Spanish as their primary language, and they showed improvements in all cognitive outcome measures selected for the study. Interestingly, results from the FOME showed dissociation between storage and retrieval, with no improvement in the former measure but significant benefit of donepezil on both retrieval and repeated retrieval. It is not clear whether this difference is due to educational factors³⁹ or a specific effect of donepezil. In contrast with the present results, those from the TAAAP study indicate that donepezil treatment improved all FOME memory subscales in African-American subjects with AD.²⁷

Neuropsychiatric symptoms are common in AD patients,^{40,41} and they occur more frequently as the disease progresses.⁴⁰ Importantly, recent studies have shown that Hispanics tend to

manifest more psychiatric symptoms than whites.³⁷ A meta-analysis of the efficacy of cholinesterase inhibitors in the treatment of psychiatric symptoms in patients with AD showed that these compounds had a modest beneficial effect,⁴² suggesting that cholinesterase inhibition improves not only cognition but also behavioral symptoms in mild-to-moderate AD. A very clear demonstration of the beneficial effect of cholinesterase inhibitors on behavior in mild or moderate AD was provided by Holmes and colleagues.⁴³ These investigators treated subjects with mild-to-moderate AD with donepezil for 6 weeks, and subsequently randomized them to either placebo or donepezil. Subjects who continued on donepezil showed an improvement in NPI and NPI-D scores, compared with those in the placebo arm. In the present study, donepezil improved global NPI scores, although the difference from baseline was significant only at week 6. Although the study population was small and the duration of treatment relatively short, the apathy subscale showed a statistically significant improvement in the week-12 ITT-LOCF analysis. The global NPI-D score was significantly improved with donepezil, suggesting a positive effect of treatment on caregiver's quality of life.

A potential weakness of the study is that practice effects cannot be ruled out as a source of cognitive improvement in an open-label study. However, the overwhelming evidence from double-blind, placebo-controlled studies is that practice effects contribute minimally to the cognitive improvement seen with donepezil treatment. Although this was an open-label design with approximately 100 subjects examined, the efficacy and safety results were consistent with those that have been reported for donepezil in the general population and in a similarly designed study of African Americans (TAAAP).^{14–16,27} These results also support earlier findings of a greater prevalence of AD at earlier ages in Hispanics.^{7–10} Taken together, the results of this study suggest that aggressive screening and diagnosis of AD in the Hispanic community are warranted given the high risk, relatively young age of onset and availability of effective treatment options for diagnosed patients. Primary care physicians serving largely Hispanic populations should be encouraged to start screening for signs of dementia at a younger age, potentially 55 or 60 years. This study also demonstrates the feasibility of Spanish-language testing in clinical trials and supports the need for including more Hispanic subjects in clinical trials.

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Figure 1.

Mean change from baseline in Mini-Mental State Examination (MMSE) total score [intent-to-treat population, endpoint using last observation carried forward (ITT-LOCF)]

Figure 2. Mean change from baseline in Fuld Object Memory Evaluation (FOME) retrieval and repeated retrieval scores [intent-to-treat population, endpoint using last observation carried forward (ITT-LOCF)]

Figure 3. Mean change from baseline in Symbol Digit Modality Test (SDMT) scores [intent-to-treat population, endpoint using last observation carried forward (ITT-LOCF)]

Figure 4. Mean change from baseline in Neuropsychiatric Inventory (NPI) and NPI Caregiver Distress (NPI-D) scores [intent-to-treat population, endpoint using last observation carried forward (ITT-LOCF)]

Table 1

Subject disposition

Screened	173
Eligible	106 (61.3%)
Enrolled	106
Discontinued	17 (16.0%)
Lost to follow-up	6 (5.7%)
Patient/caregiver withdrew consent	5 (4.7%)
Medication noncompliance	3 (2.8%)
Adverse event	2 (1.9%)
Other	1 (0.9%)
Completed	89 (84.0%)

Table 2
Demographic and clinical characteristics (safety population)

Age, Years [Mean (SD)]	68.6 (9.4)
Gender (n [%])	
Male	32 (30.5%)
Female	73 (69.5%)
Country of Heritage (n [%])	
Cuba	33 (31.4%)
Mexico	19 (18.1%)
Colombia	16 (15.2%)
Puerto Rico	12 (11.4%)
Other *	25 (23.8%)
Language [n (%)]	
Spanish only with no understanding of English	24 (22.9%)
Spanish only but may recognize a few simple English words	44 (41.9%)
Both Spanish and English, with Spanish as primary language	22 (21.0%)
Both Spanish and English, with English as primary language	15 (14.3%)
English only	0
Time since Onset of Alzheimer's Disease, Years [Mean (SD)]	2.9 (2.3)
Time since Diagnosis of Alzheimer's Disease, Years [Mean (SD)]	0.9 (1.3)
Education, Years [Mean (SD)]	10.8 (4.0)

SD: standard deviation;

* Other countries included Dominican Republic (3 subjects; 2.9%), Ecuador (5 subjects; 4.8%), Peru (4 subjects; 3.8%), Spain (3 subjects; 2.9%), Argentina, Chile and United States (2 subjects each; 1.9% each), and El Salvador, Honduras, Nicaragua and Panama (1 subject each; 1.0% each).

Table 3

Baseline scores on clinical assessment scales

	Mean (SD)
MMSE	22.0 (3.4)
FOME storage	39.2 (11.0)
FOME retrieval	32.8 (12.2)
FOME repeated retrieval	21.5 (10.3)
SDMT	18.9 (10.8)
NPI	11.5 (14.3)
NPI-D	6.6 (7.3)

MMSE: Mini-Mental State Examination; FOME: Fuld Object Memory Evaluation; SDMT: Symbol Digit Modality Test; NPI: Neuropsychiatric Inventory;
NPI-D: NPI Caregiver Distress Scale

Table 4

Adverse events occurring in >5% of the safety population

Adverse Event	N (%)
Insomnia	10 (9.5%)
Dizziness	8 (7.6%)
Diarrhea	6 (5.7%)
Nausea	6 (5.7%)