Cognitive Improvement in Mild to Moderate Alzheimer's Dementia After Treatment with the Acetylcholine Precursor Choline Alfoscerate: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

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ABSTRACT

Background: Parallel with the development of hypotheses regarding cholinergic involvement in geriatric memory dysfunction, the first attempts to treat patients with Alzheimer's disease (AD) involved the cholinergic-precursor loading approach. Despite encouraging early results, well-controlled clinical trials did not confirm a clinical utility of cholinergic precursors such as choline and lecithin (phosphatidylcholine) in AD.

Objective: This study assessed the efficacy and tolerability of the cholinergic precursor choline alfoscerate (CA) in the treatment of cognitive impairment due to mild to moderate AD.

Methods: In this multicenter, double-blind, randomized, placebo-controlled trial, patients affected by mild to moderate dementia of the Alzheimer type were treated with CA (400-mg capsules) or placebo capsules, 3 times daily, for 180 days. Efficacy outcome measures that were assessed at the beginning of the investigation and after 90 and 180 days of treatment included scores of the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), the Mini-Mental State Examination™ (MMSE), the Global Deterioration Scale (GDS), the Alzheimer's Disease Assessment Scale–Behavioral Subscale (ADAS-Behav), all items of the Alzheimer's Disease Assessment Scale (ADAS-Total), and the Clinical Global Impression (CGI) scale. The Global Improvement Scale (GIS) score was assessed after 90 and 180 days of treatment.

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Results: A total of 261 patients (132 in the CA group, 129 in the placebo group) were enrolled in the study. The mean (SD) age in the CA group was 72.2 (7.5) years (range, 60–80 years), and in the placebo group it was 71.7 (7.4) years (range, 60–80 years). The CA group comprised 105 women and 27 men; the placebo group, 94 women and 35 men. The mean decrease in ADAS-Cog score in patients treated with CA was 2.42 points after 90 days of treatment and 3.20 points at the end of the study (day 180) ($P < 0.001$ vs baseline for both), whereas in patients receiving placebo the mean increase in ADAS-Cog score was 0.36 point ≤1 after 90 days of treatment and 2.90 points after 180 days of treatment ($P < 0.001$ vs baseline). In the CA group, all other assessed parameters (MMSE, GDS, ADAS-Behav, ADAS-Total, and CGI) consistently improved after 90 and 180 days versus baseline, whereas in the placebo group they remained unchanged or worsened. Statistically significant differences were observed between treatments after 90 and 180 days in ADAS-Cog, MMSE, GDS, ADAS-Total, and CGI scores and after 180 days of treatment in ADAS-Behav and GIS scores.

Conclusion: The results of this study suggest the clinical usefulness and tolerability of CA in the treatment of the cognitive symptoms of dementia disorders of the Alzheimer type. (*Clin Ther.* 2003;25:178–193)

Key words: Alzheimer's disease, cognitive impairment, choline alfoscerate, clinical trial.

INTRODUCTION

A range of disorders involving brain metabolism, regional blood supply, and neurotransmitter availability occur in the later decades of adult life. These changes are characterized clinically by impaired motor function, memory, and ability to learn.[1] Problems with memory and learning represent a main trait of Alzheimer's disease (AD), the most common adult-onset cognitive disorder.[2] Age is the main risk factor for AD. The incidence of AD is estimated to be from 1% to 4% in the population aged 65 to 70 years and is >20% in the population aged 85 to 90 years.[3]

From a neuropathologic point of view, AD is characterized by brain atrophy accompanied by neuronal loss primarily in cerebrocortical areas involved in learning and memory functions and by hallmarks such as neurofibrillary tangles, beta-amyloid plaques, and amyloid angiopathy.[4]

AD represents a major public health problem.[5] In addition to severe disabilities in patients and the emotional burden on family members, the societal costs of AD are substantial, and the impact of the disease is expected to increase significantly in the future.[5]

Deficits in several neurotransmitter systems in various brain regions have been reported in AD, but the cerebrocortical cholinergic system and the somatostatin-

containing neuronal systems are the most affected. A primary trait of AD is the degeneration of basal forebrain cholinergic neurons, which causes a remarkable deficit of avenues of cortical cholinergic neurotransmission, such as acetylcholine (ACh) synthesis, release, and uptake, and choline acetyltransferase and acetylcholinesterase (AChE) activities.[6,7]

Observations of the loss of cholinergic function in the neocortex and hippocampus of AD patients provided the rationale for developing cholinergic replacement therapy.[1] Among the possible approaches to enhance impaired cerebrocortical cholinergic neurotransmission, inhibition of endogenous ACh degradation through inhibition of AChE or of cholinesterase (ChE) and precursor loading have been the most largely investigated in clinical trials.[8,9] The rationale for the use of AChE or ChE inhibitors in the treatment of patients with adult-onset dementia disorders is their capability to increase the synaptic availability of ACh by retarding its catabolism.[8,9] Treatment with these inhibitors is an important step in the treatment of AD. However, a retrospective analysis[8] of the available clinical trials of these drugs did not confirm a significant benefit in all 4 key symptom domains of AD—cognition, behavioral disturbances, activities of daily living, and global function.

Parallel with the development of hypotheses regarding cholinergic involvement in geriatric memory dysfunction,[1] and based on the positive results obtained with the administration of a neurotransmitter precursor (L-dopa) in the treatment of Parkinson's disease, the first attempts to treat patients with AD involved the cholinergic-precursor loading approach. Despite encouraging early results obtained in a double-blind, placebo-controlled study,[10] well-controlled clinical trials did not confirm a clinical utility of cholinergic precursors such as choline and lecithin (phosphatidylcholine) in AD.[11] A problem with these precursors is that they are probably not suitable to enhance brain levels of ACh.[12]

Choline alfoscerate (L-alpha-glycerylphosphorylcholine; CA) is a semisynthetic derivative of phosphatidylcholine that, in preclinical studies, has been shown to increase the release of ACh in rat hippocampus[13] and to facilitate learning and memory,[14] improve cognitive deficit in experimental models of the aging brain,[15] and reverse mnemonic deficits induced by scopolamine administration.[14] Clinical studies to assess the efficacy of CA in dementia disorders have been reviewed in an independent, nonsponsored review[16] that included 1570 patients, 854 in controlled trials. Clinical results obtained with CA, as measured with relevant, different psychometric tests, were superior or equivalent to those observed in control groups receiving active treatment and were superior to the results observed in placebo groups. The clinical efficacy of CA, as assessed mainly with use of the Sandoz Clinical Assessment–Geriatric scale,[17] was superior to that displayed by other choline donors such as cytidine diphosphocholine in cognitive impairment occurring in vascular dementia.[18–20]

The current multicenter, double-blind, randomized, placebo-controlled clinical trial was undertaken to assess the efficacy and tolerability of the cholinergic precursor CA in the treatment of cognitive impairment due to mild to moderate AD.

PATIENTS AND METHODS

Patients

Outpatients with a history of cognitive decline that was consistent with the diagnosis of degenerative mild to moderate Alzheimer's dementia, gradual in onset and progressive, were examined. Inclusion criteria were age ≤80 years; clinical history of progressive impairment from 60 to 80 years of age; diagnosis of probable or possible AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[21] and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria[22]; Mini-Mental State Examination™[23] (MMSE) score between 12 and 26 (indicating cognitive impairment); Modified Hachinski Score[24] (M-HIS) <4 (consistent with degenerative dementia); Hamilton Rating Scale for Depression[25,26] (HAM-D) score <22 (indicating absence of depressive illness); school education of at least 5 years; good general clinical conditions as assessed using clinical history, clinical/neurologic examinations, and laboratory tests; and a cerebral computed tomography scan performed in the previous 6 months showing compatible atrophy or no abnormalities. Exclusion criteria were concomitant neurologic disorders; severe anemia (hemoglobin <9 g/dL); history of nutritional deficiency; deficiency of B vitamins or folates (serum vitamin B_{12} concentration <199 pg/mL; serum folate concentration <3 ng/dL); psychiatric disorders, including primary depression; systemic diseases (eg, cancer, acquired immunodeficiency syndrome, organ failure [heart, liver, kidney, lung]); clinical signs of endocrine abnormalities; stroke in the previous 6 months; alcoholism or drug addiction; treatment (concomitant or in the previous 30 days) with neuroleptic agents (excluding thioridazine), antidepressants, nootropics, any other cognitive enhancer, or alpha-methyldopa; and treatment (concomitant or in the previous 3 months) with reserpine or clonidine. Use of insulin, angiotensin-converting enzyme (ACE) inhibitors, calcium entry blockers (other than nimodipine), and coronary vasodilators was allowed, provided the treatment had been stable for >3 months before the beginning of the study.

Study Design

The study was a double-blind, randomized, placebo-controlled clinical trial carried out in 5 centers in Mexico and was conducted in accordance with the Good Clinical Practice guidelines, the Declaration of Helsinki and its Amendments, and local and international regulatory requirements, and with the ap-

proval of the Mexican Board of Health and of each center's ethics committees. All enrolled patients provided written informed consent to participate.

Before undergoing treatment, patients underwent a screening examination that included assessment of general and neurologic history, physical and neurologic examinations (including administration of the M-HIS and HAM-D), and administration of the following psychometric or behavioral tests: the Alzheimer's Disease Assessment Scale[27]–Cognitive Subscale (ADAS-Cog), the MMSE, the Global Deterioration Scale[28] (GDS), and the Alzheimer's Disease Assessment Scale–Behavioral Subscale (ADAS-Behav), all items on the Alzheimer's Disease Assessment Scale (ADAS-Total), and the Clinical Global Impression (CGI) scale.[29]

Patients were randomized to receive CA or placebo. Randomization was done in blocks of 4 patients, and allocation to the active-treatment or the placebo group was done according to tables of random numbers. The test medications were CA capsules* 400 mg per unit dose or placebo capsules that were identical in appearance. In all patients, capsules were given orally 3 times a day for 180 days; patients received 1 capsule in the morning, 1 at lunch, and 1 before dinner.

Placebo was chosen as the reference treatment because, at the time the study was designed (1995), no reference drug (including ChE inhibitors) was adequately documented as being active in the treatment of dementia.

Treatment efficacy was assessed after 90 and 180 days of treatment. The primary study efficacy end point was a slowing of cognitive decline, as measured with the ADAS-Cog score; a difference versus placebo of at least 2.20 points at the end of the study period was considered to be clinically relevant. Secondary end points were improvements in scores on the MMSE, GDS, ADAS-Behav, ADAS-Total, and CGI scale. Global Improvement Scale (GIS) score was assessed after 90 and 180 days of treatment.

During the course of the study, efficacy assessments generally were performed by the same investigator under the same conditions.

Tolerability assessments throughout the study comprised monthly physical examinations and monitoring for adverse events (AEs).

In a post hoc analysis, a criterion to count patients who were responsive to treatment was introduced. In this complementary assessment of drug efficacy, patients who had an improvement of at least 4 points on the ADAS-Cog at the end of treatment were considered *responders*, and patients with an improvement of at least 7 points in the same subscale were considered *complete responders*.[30,31]

Statistical Analysis

Statistical analyses were carried out using SAS version 6.12 (SAS Institute, Inc., Cary, North Carolina). Sample size was calculated to detect a mean difference in

*Trademark: Gliatilin® (Italfarmaco SpA, Milan, Italy).

ADAS-Cog score of 2.20 points between the CA and placebo groups at the end of treatment, on the basis that this result was obtained in a trial with a ChE inhibitor.[32] The SD of this difference was estimated to be 6.0 points.[32] It was calculated that a sample size of 95 patients per group was required to detect a significant difference between the 2 groups, assuming 1-tailed $\alpha = 0.05$ and $ß = 0.20$, with a potency of 80%. Considering a dropout rate of ~10%, it was estimated that at least 190 patients (that is, 95 + 95) + 10% = 209 patients would have to be enrolled.

Baseline demographic variables, risk factors, and relevant clinical variables were summarized descriptively to characterize the study population. Efficacy data were fitted with a proper mixed linear model with treatment, visit, and treatment × visit interaction as fixed effects, and a nonparametric covariance matrix (unstructured) as nuisance parameters.[33] Statistical hypotheses for primary and secondary efficacy end points were tested using mixed-model estimates of the following contrasts on treatment × visit interaction:

Placebo versus CA × 90 days versus baseline
Placebo versus CA × 180 days versus baseline

The estimates of later contrast are considered the primary study results.

RESULTS

A total of 261 patients (132 in the CA group, 129 in the placebo group) were enrolled in the study. The CA group comprised 105 women and 27 men; the mean (SD) age was 72.2 (7.5) years (range, 60–80 years), the mean (SD) height was 154.9 (9.3) cm (range, 132–182 cm), and the mean (SD) body weight was 63 (11.2) kg (range, 37–97 kg). Most of the patients in the CA group were Hispanic (n = 129 [97.7%]), and the remaining patients were black (1 [0.8%]), Asian (1 [0.8%]), or of a nonspecified race (1 [0.8%]). The placebo group comprised 94 women and 35 men; the mean (SD) age was 71.7 (7.4) years (range, 60–80 years), the mean (SD) height was 155.8 (8.8) cm (range, 139–176 cm), and the mean (SD) body weight was 63.2 (11.2) kg (range, 43–89 kg). Most of the patients in the placebo group were Hispanic (n = 126 [97.7%]), and the remaining patients were black (1 [0.8%]), Asian (1 [0.8%]), or of a nonspecified race (1 [0.8%]).

Twenty-three concomitant diseases were recorded in 20 (15.2%) patients of the CA group: metabolic (7 [35%]); musculoskeletal (6 [30%]); respiratory (4 [20%]); cardiovascular (2 [10%]); central nervous system (CNS; 2 [10%]); ear, nose, and throat (ENT; 1 [5%]); and peripheral vascular (1 [5%]) disease. Twenty-nine concomitant diseases were recorded in 23 (17.8%) patients of the placebo group: musculoskeletal (10 [43.5%]); metabolic (4 [17.4%]); respiratory (4 [17.4%]);

CNS (4 [17.4%]); cardiovascular (3 [13.0%]); gastrointestinal (2 [8.7%]); ENT (1 [4.3%]); and whole-body (1 [4.3%]) disease. No concomitant disease constituted a violation of any of the inclusion criteria of the study protocol.

Forty-three (16.5%) patients were receiving 67 concomitant medications at baseline or at any of the study visits, 20 (15.2%) patients in the CA group were receiving 1 or more of 32 medicinal products, and 23 (17.8%) patients in the placebo group were receiving 1 or more of 35 medicinal products. These products were nonsteroidal anti-inflammatory drugs in 27 (10.3%) patients (14 [10.6%] in the CA group, 13 [10.1%] in the placebo group), antibiotics in 9 (3.4%) patients (5 [3.8%] in the CA group, 4 [3.1%] in the placebo group), oral antihypoglycemic agents in 10 (3.8%) patients (7 [5.3%] in the CA group, 3 [2.3%] in the placebo group), ACE inhibitors in 4 (1.5%) patients (2 [1.5%] in the CA group, 2 [1.6%] in the placebo group), ranitidine in 2 (0.8%) patients (both [1.6%] in the placebo group), and other permitted medications in 15 (5.7%) patients (4 [3.0%] in the CA group, 11 [8.5%] in the placebo group).

A total of 229 (87.7%) patients (115 [87.1%] in the CA group, 114 [88.4%] in the placebo group) completed the study, whereas 32 (12.3%) patients were withdrawn because of protocol violations (30 [11.5%] patients; 16 [12.1%] in the CA group, 14 [10.9%] in the placebo group) or because they were lost to follow-up (2 [0.8%] patients; 1 [0.8%] in the CA group and 1 [0.8%] in the placebo group). Most of the protocol violations (15 [11.4%] in the CA group, 14 [10.9%] in the placebo group) were school education <5 years.

All 261 (100.0%) enrolled patients were considered for intent-to-treat (ITT) analysis, and 229 (87.7%) were considered for per-protocol (PP) analysis (ADAS-Cog score only).

The baseline values of the neuropsychological tests (ADAS-Cog, MMSE, GDS, ADAS-Behav, ADAS-Total, and CGI) were similar between treatment groups, and no statistically significant differences between groups were observed for these psychometric assessments carried out at baseline (ITT analysis except PP and ITT analyses for the ADAS-Cog).

Primary Efficacy End Point: ADAS-Cog Score

The table and figure (A) show that, in the CA group, the raw mean of the ADAS-Cog score decreased after 90 days versus baseline and that this decrease continued during the 180 days of the study, whereas in the placebo group, an increase in ADAS-Cog score was found after both 90 and 180 days.

The mean decrease from baseline in the ADAS-Cog score in patients treated with CA (in both ITT and PP populations) after 90 days of treatment was 2.42 points ($P < 0.001$ vs baseline), whereas at the end of the study it was 3.20 points ($P < 0.001$ vs baseline). In the patients given placebo, the mean increase in ADAS-Cog score was 0.36 point after 90 days of treatment and 2.90 points after

Table. Efficacy end points. (Values are expressed as mean [SD] points.)

Instrument	Choline Alfoscerate Group (n = 132)	Placebo Group (n = 129)
ADAS-Cog*		
Baseline	35.52 (6.59)	36.74 (7.27)
90 days	33.10†‡ (6.86)	37.10 (6.66)
180 days	32.32†‡ (8.19)	39.64† (7.47)
MMSE§		
Baseline	18.19 (3.38)	17.62 (3.43)
90 days	21.37†‡ (4.17)	17.62 (3.60)
180 days	24.52†‡ (3.82)	17.12 (4.04)
GDS‖		
Baseline	3.73 (0.62)	3.72 (0.65)
90 days	3.23†‡ (0.63)	3.75 (0.70)
180 days	2.78†‡ (0.76)	3.91¶ (0.78)
ADAS-Behav#		
Baseline	19.62 (5.49)	18.37 (6.43)
90 days	18.12** (3.31)	17.93 (5.46)
180 days	17.37†‡ (2.07)	19.79¶ (6.51)
ADAS-Total††		
Baseline	55.14 (9.31)	55.12 (10.92)
90 days	51.22†‡‡ (9.00)	55.03 (9.64)
180 days	49.68†‡ (9.17)	59.43† (11.93)
CGI‖‖		
Baseline	3.92 (0.65)	3.77 (0.62)
90 days	3.39†‡ (0.58)	3.74 (0.63)
180 days	2.90†‡ (0.66)	3.93¶ (0.69)

ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE = Mini-Mental State Examination™; GDS = Global Deterioration Scale; ADAS-Behav = ADAS–Behavioral Subscale; ADAS-Total = all items of the ADAS; CGI = Clinical Global Impression scale.

*Scores range from 0 to 70, with higher scores indicating more severe impairment.

†$P < 0.001$ versus baseline.

‡$P < 0.001$ versus placebo (intent-to-treat [ITT] analysis except per-protocol and ITT analyses for ADAS-Cog).

§A score >24 indicates probable cognitive impairment. A score >17 indicates definite cognitive impairment.

‖Scale: 1 = no cognitive decline; 2 = very mild cognitive decline; 3 = mild cognitive decline; 4 = moderate cognitive decline; 5 = moderately severe cognitive decline; 6 = severe cognitive decline; 7 = very severe cognitive decline.

¶$P < 0.05$ versus baseline.

#Scores range from 0 to 99, with higher scores indicating more severe impairment.

**$P < 0.002$ versus baseline.

††Scores range from 0 to 169, with higher scores indicating more severe impairment.

‡‡$P < 0.002$ versus placebo.

‖‖Scale: 1 = very much improved; 2 = much improved; 3 = slightly improved; 4 = unchanged; 5 = slightly worse; 6 = much worse; 7 = very much worse.

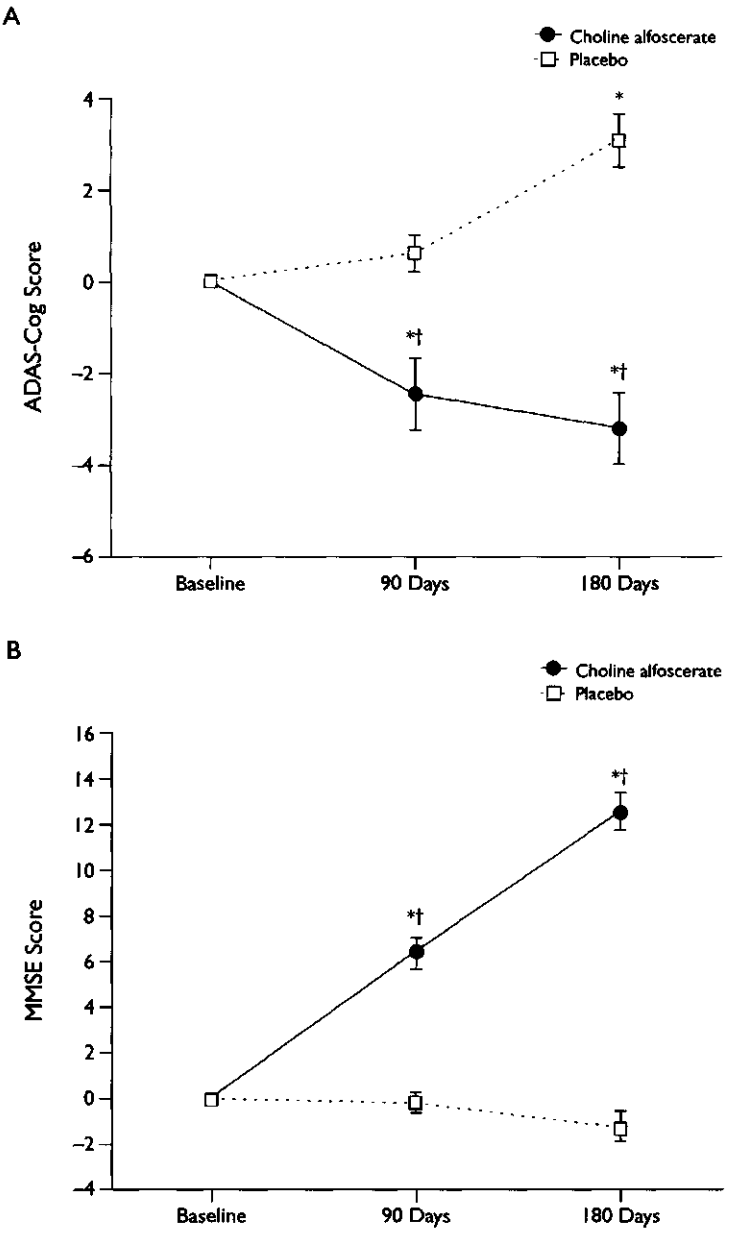

Figure. Mean changes (SEM) from baseline to day 90 and to the end of treatment (day 180) in the 2 treatment groups. (A) The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog); (B) Mini-Mental State Examination™ (MMSE).

(continued)

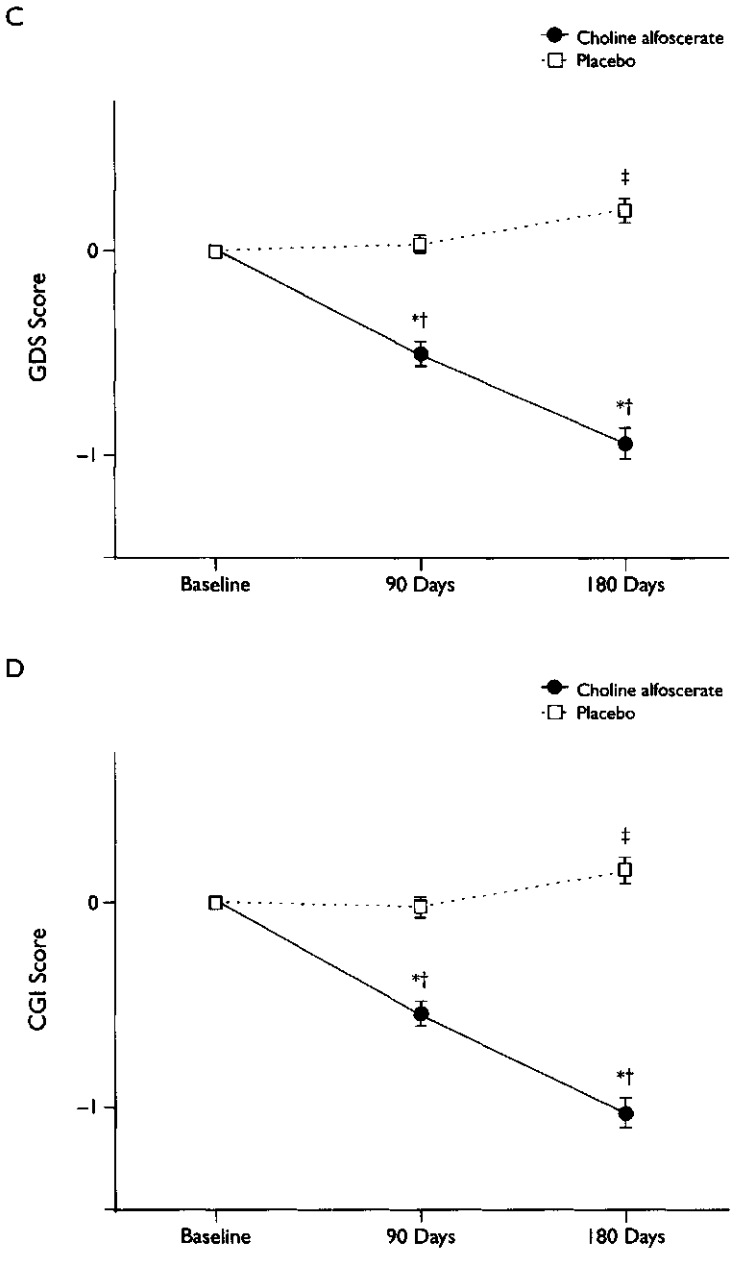

Figure. (Continued) (C) Global Deterioration Scale (GDS); (D) Clinical Global Impression (CGI) scale. $^{*}P < 0.001$ versus baseline. $^{\dagger}P < 0.001$ versus placebo. $^{\ddagger}P < 0.05$ versus baseline. (Intent-to-treat [ITT] analysis except per-protocol and ITT analyses for ADAS-Cog.) See table for definitions of scales/points.

180 days of treatment ($P < 0.001$ vs baseline). A statistically significant difference between treatments was observed after both 90 and 180 days of treatment ($P < 0.001$). According to these results, the primary end point of this study (ie, to slow cognitive decline enough for a mean difference in ADAS-Cog score of at least 2.20 points between the 2 groups at the end of treatment) was reached.

Sixty-one (46.2%) patients in the CA group and 13 (10.1%) patients in the placebo group were considered to be responders ($P < 0.001$), with an improvement of at least 4 points on the ADAS-Cog scale at the end of treatment, whereas 47 of the responders in the CA group (35.6% of all patients in this group) and 5 of the responders in the placebo group (3.9% of all patients in this group) were considered to be complete responders ($P < 0.001$), with an improvement in score of at least 7 points.

Secondary Efficacy End Points: Psychometric Assessments

The table shows the raw mean and SD of the psychometric assessments and details the results from the mixed linear model analysis for differences within and between treatments in the ITT population.

The MMSE score improved by 3.18 points after 90 days and by 6.33 points after 180 days versus baseline in the CA group ($P < 0.001$ for both), whereas in the placebo group it was unchanged at day 90 and had decreased by 0.50 point after 180 days of treatment (Figure [B]). The between-group differences reached statistical significance at both 90 and 180 days ($P < 0.001$ for both).

In the CA group, the GDS score improved by 0.50 point and 0.95 point after 90 and 180 days, respectively, versus baseline ($P < 0.001$ for both), whereas in the placebo group the increases were 0.03 point after 90 days and 0.19 point after 180 days of treatment ($P < 0.05$ for 180 days vs baseline) (Figure [C]). The between-group differences reached statistical significance at both 90 and 180 days ($P < 0.001$ for both).

In the CA group, the ADAS-Behav score improved by 1.50 points after 90 days and by 2.25 points after 180 days versus baseline ($P < 0.002$ and $P < 0.001$, respectively), whereas in the placebo group a decrease of 0.44 point occurred after 90 days of treatment and an increase of 1.42 points occurred at the end of the study period ($P < 0.05$ for 180 days vs baseline). The between-group differences reached statistical significance at 180 days ($P < 0.001$).

The ADAS-Total score improved by 3.92 points after 90 days and by 5.46 after 180 days versus baseline in the CA group ($P < 0.001$ for both), whereas in the placebo group a decrease of 0.09 point was found at day 90 and an increase of 4.31 points was found after 180 days of treatment ($P < 0.001$ for 180 days vs baseline). The between-group differences reached statistical significance at both 90 and 180 days ($P < 0.002$ and $P < 0.001$, respectively).

The CGI score improved by 0.53 point after 90 days and by 1.02 points after 180 days versus baseline in the CA group ($P < 0.001$ for both), whereas in the placebo group a decrease of 0.03 point was found after 90 days and an increase of 0.16 point was found after 180 days of treatment ($P < 0.05$ for 180 days vs baseline) (Figure [D]). The between-group differences reached statistical significance at both 90 and 180 days ($P < 0.001$ for both).

Global Improvement Scale Score

In the CA group, the mean (SD) GIS score was 2.21 (1.01) after 90 days and 1.90 (1.04) at day 180, with a decrease of 0.31 point after 180 days versus after 90 days ($P < 0.001$). In the placebo group, the mean score was 3.93 (0.67) after 90 days and 4.21 (0.86) after 180 days ($P < 0.001$). A statistically significant difference between treatments was observed after 180 days of treatment ($P < 0.001$).

Tolerability Assessment

Fifteen drug-related AEs (10 episodes of constipation, 5 episodes of nervousness) were reported in 11 (8.3%) patients treated with CA; 6 AEs (1 nausea, 1 dizziness, 1 hostility, 3 headache) were related to treatment in 3 (2.3%) patients given placebo (11 vs 3 patients with AEs; $P = 0.030$).

In most patients, drug-related AEs were mild, and no patient was withdrawn early from the study because of a drug-related AE.

DISCUSSION

Our study shows that, compared with placebo, treatment with oral CA significantly improved cognition and global function in our relatively small group of patients selected according to the enrollment criteria of the study protocol from the population affected with mild to moderate dementia of the Alzheimer type.

Based on the results of different tests examined, the following points should be considered. The ADAS-Cog score, the primary end point of efficacy, showed a statistically significant improvement after 90 and 180 days of treatment with CA, demonstrating a comprehensive improvement of cognitive measures compared with the worsening observed in the placebo group.

The analysis of patients responding to treatment was implemented only post hoc (by classification of each patient according to the improvement observed on this scale at the end of treatment) and therefore cannot be acknowledged as a major study finding. Nevertheless, this analysis allows us to classify 46.2% of total patients in the CA group as *responders*, and 35.6% as *complete responders* to treatment.

Based on published data, mean ADAS-Cog score deteriorates up to 3.5 points over a 180-day period in untreated patients.[27,34] In the current study, patients treated with CA had a mean improvement in ADAS-Cog score of 3.20 points,

compared with a decrease in score of 2.90 points in patients treated with placebo for 180 days; this suggests that the response to CA treatment, as assessed using the mean ADAS-Cog score, counteracts symptom progression.

During the first 90 days in this investigation, treatment with CA improved the ADAS-Cog score by 2.42 points, a result similar to those obtained with the AChE inhibitor donepezil in randomized clinical trials, in which 3-month decreases of 2.5[35] and 2.7[36] points were recorded in treated patients. Moreover, ADAS-Cog results obtained in this investigation of CA are superior to those obtained in published trials[37,38] of the AChE rivastigmine.

Results of the secondary outcome measures contributed to a better assessment of the effects of pharmacologic treatment: MMSE, GDS, ADAS-Behav, and ADAS-Total indicated that patient improvement was not only in the cognitive domain but also involved behavior and activities of daily living, possibly improving patients' and caregivers' quality of life.

In randomized, controlled trials of CA in patients with dementia disorders, treatment with CA for 3 to 6 months improved patient clinical conditions, especially regarding memory and attention.[16]

Direct comparison of our results with the clinical results of previous CA trials[16] is not feasible because in those trials, different scales were used. Also, the results of this trial cannot be generalized because the enrollment criteria in our study protocol restrict the ability to extrapolate results to the general population of patients with AD. However, the results of this study are consistent with and extend those of previous trials.[16] Overall, positive clinical results gained with CA may be ascribed to both its effects on neurotransmission[13] and its activity in slowing the age-related loss of neuronal cells.[39] Also, in this study, the administered formulation of CA was well tolerated on the whole. Additional studies are needed to determine whether enhancement of impaired cholinergic neurotransmission with a combination of an effective ACh precursor, such as CA, and AChE inhibitors might be an approach to more satisfactory clinical results in controlling the symptoms of AD.

CONCLUSION

The results of this study suggest the clinical usefulness and tolerability of CA in the treatment of the cognitive symptoms of dementia disorders of the Alzheimer type.

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