A randomized, placebo-controlled study of donepezil in poststroke aphasia

Abstract—We studied 26 patients in a randomized, placebo-controlled, double-blind parallel trial to evaluate the efficacy and safety of donepezil in chronic poststroke aphasia. Donepezil (10 mg/day) improved aphasia severity at endpoint (week 16) relative to placebo ($p = 0.037$).

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Donepezil has been shown to improve the severity of aphasia, motor aspects of speech, input-output phonology, and lexical-semantic processing.[1,2] Moreover, a 6-month extension phase of an open-label trial of donepezil in poststroke aphasia (PSA) has demonstrated the persistence of beneficial effects.[2] We report the results of a randomized controlled trial (RCT) of donepezil as an adjunctive treatment to standard speech-language therapy (SLT) in patients with chronic PSA.

Methods. We performed a double-blind, randomized, placebo-controlled, parallel-group study in which eligible patients had to be younger than 70 years with a chronic aphasia (≥1 year since onset) and a unilateral stroke lesion. We obtained written informed consent from all patients or caregivers. This RCT was conducted as an independent research grant funded by Pfizer Spain and Eisai and it was designed, conducted, and controlled by principal investigators. Pfizer Spain provided the donepezil and placebo. The study was performed according to the Declaration of Helsinki and the protocol was approved by the Local Community Ethics Committee for Clinical Trials and by the Spanish Medical Agency. Patients enrolled in our previous open-label trial were not included.[1]

After baseline evaluation, the patients were randomized in a 1:1 fashion, using a computer-generated random procedure, into donepezil (5 mg/day) or placebo during a 4-week titration phase, followed by a 12-week maintenance phase (10 mg/day of donepezil or placebo) with the possibility of dose adjustment to improve tolerability, and a 4-week washout phase. The procedures of allocation sequence, participant enrollment, and assignment of participants to trial groups were performed by different groups of people. Blinding was established with identical film-coated capsules containing 5 mg of either donepezil or placebo. Permitted concomitant medications included those agents that were clinically required before study recruitment to maintain and stabilize clinical status. Testing was performed at weeks 0, 4, 16 (endpoint), and 20 (washout). Standard SLT was provided for 2 hours per week and consisted of a syndrome-specific standard approach.[3]

Primary efficacy measures were the mean score change from baseline to endpoint (week 16) on Aphasia Quotient of the Western Aphasia Battery (WAB)[4] and Communicative Activity Log (CAL) (a scale that assesses the patient's communicative behavior in everyday life).[3] Secondary efficacy measures were subtests of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA)[5,6] and the Stroke Aphasic Depression Questionnaire (SADQ).[7]

Sample size and statistic analysis. The sample size was determined using the treatment effect size from our previous open-label trial of donepezil in PSA.[1] A two group t test with a 0.050 two-sided significance level will have 80% power to detect a difference in means of 5,000 in AQ of the WAB, assuming that the common SD is 4,000 when the sample size in each group is 12. The χ^2 test was used for categorical variables and the independent sample t test (two-tailed) for continuous variables. Since this was a pilot study, multiple testing corrections (e.g., Bonferroni) were not performed. The data were analyzed by Euroclin Institute (Spain).

Results. The flow chart diagram of participants is represented in the figure. A total sample of 26 patients was recruited from February 2003 to November 2004. The completion rates for the study were 85% in each group. The donepezil and placebo groups were well-matched regarding baseline variables (table 1) and they did not differ in the use of concomitant medications.

The severity of aphasia (AQ of the WAB) improved more in the donepezil group than in the placebo group at endpoint (week 16) (donepezil: 6.4 ± 3.8; 95% CI, 4.13 to 8.81; placebo: 3.5 ± 2.7; 95% CI, 1.93 to 5.22; $p = 0.037$) (table 2). These differences correspond to large effect sizes (Cohen's d = 0.87). Comparison of the CAL did not reveal significant differences between baseline and endpoint. At post-washout testing, the donepezil group decreased its performance on the CAL relative to the placebo group when these scores were compared with those obtained at endpoint (donepezil: −4.6 ± 8.6; 95% CI, −2.10 to 11.7; placebo: 4.8 ± 4.5; 95% CI, 1.27 to 12.55, $p = 0.008$).

The scores in the picture naming subtest of the PALPA improved more with donepezil at endpoint (4.6 ± 5.8; 95% CI, 0.1 to 5.0) than with placebo (−1.0 ± 6.3; 95% CI, −0.3 to 5.0) ($p = 0.025$), a difference that corresponds to a large effect size (Cohen's d = 0.92) (table 2). There were no between-group differences in other PALPA subtests nor in the SDAQ at endpoint.

Adverse events were higher in the donepezil group (8 patients, 61%) than in the placebo group (3 patients, 23%) (χ^2: 2.42, df: 1, $p = 0.119$). Irritability (4 patients [30%]) and insomnia and tiredness (2 patients [15%]) were seen only during donepezil titration. Recurrence of poststroke seizures (2 patients [15%]) was seen during donepezil maintenance without relapsing after dose reduction. Adverse events in the placebo group included headache (n = 1), abnormal dreams (n = 1), and anorexia (n = 1).

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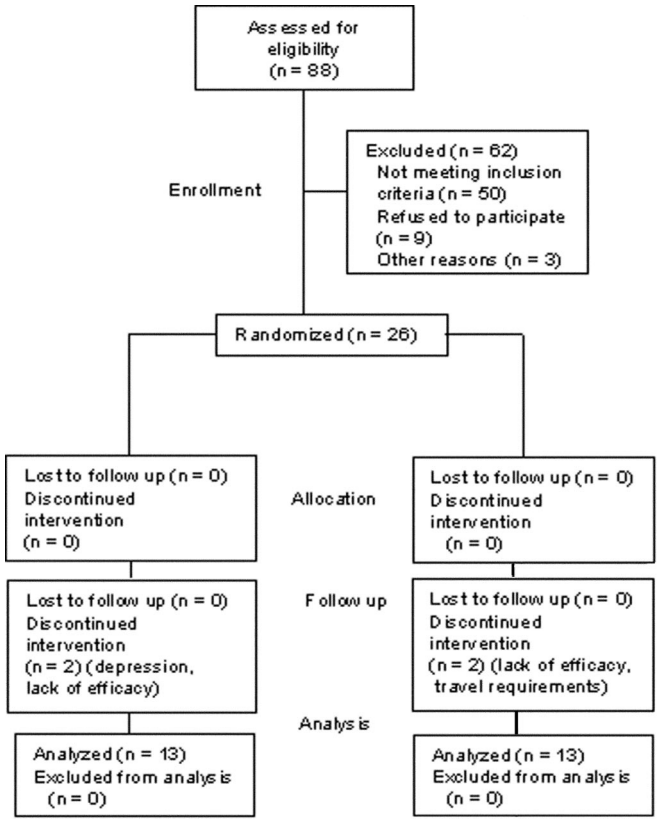

Figure. The revised CONSORT diagram showing the flow of participants. Four patients did not complete the week 20 evaluation (post-washout testing).

Discussion. In this study, donepezil significantly improved the AQ of the WAB and the picture naming subtest of the PALPA compared to placebo at endpoint. The CAL did not show significant donepezil-placebo differences between baseline and endpoint, but these between-group differences reached statistical significance when scores at 10 mg/day of donepezil (endpoint) were compared with lower doses (5 mg/day), suggesting that the beneficial effect of cholinergic therapy may be appreciable on measures of everyday communication.

Between-group differences were no longer significant at week 20 for most outcome measures, thus suggesting that donepezil enhances language and communication performance only when it is being taken. However, scores on outcome measures in post-washout testing for the donepezil group remained well above baseline scores and the attenuation of donepezil/placebo differences may have resulted from a good placebo response. Future studies should examine outcome variables using longer post-washout periods to detect whether the benefits of donepezil persist in a more durable fashion.

Acetylcholine acts as a cortical modulator playing a role in task-related plasticity and long-term potentiation necessary for learning, memory, language, and attention.[1,2] Cholinergic pathways are vulnerable to vascular damage.[8,9] Localized left hemisphere strokes involving the insulo-opercular cortex, white matter tracts, or the mesial frontoparietal cortex in our patients presumably interrupted cholinergic projections en route to remote cortical sites necessary for language processing.[8,9]

Since neuronal activity is tightly coupled to vascular brain perfusion, it seems possible that the beneficial effect of donepezil in PSA outcome may be attributed to the improvement of neurovascular coupling.[9] A recent study found reduced levels of acetylcholinesterase in the CSF of anomic patients and that abnormalities in naming and the cholinergic marker were reversed by the cholinergic agent, bifemelane.[10] Additionally, preliminary evidence indicates that donepezil improves the regulation of regional cerebral blood flow in patients with vascular

Table 1 *Baseline demographic and clinical information of donepezil and placebo groups*

Variable	Donepezil-treated group (n = 13)	Placebo-treated group (n = 13)	Whole sample (n = 26)
Age, y, mean ± SD	48.0 ± 10.6	48.3 ± 9.2	48.1 ± 9.7
Male sex, n (%)	8 (61.5)	10 (76.9)	18 (69.2)
Right handedness, n (%)	12 (92.3)	13 (100)	25 (96.1)
Education, y, mean ± SD	9.7 ± 3.7	10.0 ± 3.2	9.9 ± 3.4
Time since stroke onset, mo, mean ± SD	33.9 ± 27.6	38, 2 ± 34.2	36.0 ± 30.5
Aphasia Quotient, mean ± SD (range) (max = 100)	62.6 ± 23.8 (13.6–90.4)	59.5 ± 15.2 (33.4–77.8)	61.0 ± 19.7 (13.6–90.4)
Communicative Aphasia Log, mean ± SD (max = 108)	70.3 ± 13.7	69.0 ± 7.1	69.6 ± 10.7
Stroke Aphasia Depression Questionnaire, mean ± SD (max = 84)	36.9 ± 8.4	40.3 ± 5.8	38.6 ± 7.3

According to the WAB classification criteria 10 patients had Broca's aphasia (4 in the donepezil group and 6 in the placebo group), 9 patients had anomic aphasia (7 in the donepezil group and 2 in the placebo group), 4 patients had conduction aphasia (1 in the donepezil group and 3 in the placebo group), and 3 patients had Wernicke's aphasia (1 in the donepezil group and 2 in the placebo group). All but one patient had strokes in the left middle cerebral artery territory.

Table 2 *Mean change from baseline scores on primary and secondary efficacy measures of the donepezil and placebo groups*

	Donepezil (10 mg)* (n = 13), mean ± SD		Placebo (n = 13), mean ± SD	
Test	Baseline	Endpoint	Baseline	Endpoint
Aphasia Quotient (max = 100)	62.6 ± 23.8	6.4 ± 3.8†	59.5 ± 5.2	3.5 ± 2.7
Communicative Activity Log (max = 108)	70.3 ± 13.7	8.2 ± 9.3‡	69.0 ± 7.1	2.4 ± 9.0
Stroke Aphasia Depression Questionnaire (max = 84)	36.9 ± 8.4	−1.6 ± 4.0	40.3 ± 5.8	−2.5 ± 4.3
Auditory phonemic discrimination-word pairs (n = 56)	45.0 ± 8.8	3.4 ± 6.6	45.8 ± 8.1	3.0 ± 7.3
Auditory lexical decision (n = 160)	138.5 ± 21.9	8.0 ± 15.5	149.0 ± 5.5	1.5 ± 4.5
Word repetition (n = 24)	18.1 ± 7.6	0.7 ± 1.8	17.3 ± 7.5	1.0 ± 2.9
Nonword repetition (n = 24)	12.2 ± 7.0	−0.2 ± 5.2	10.3 ± 6.5	2.4 ± 2.3
Picture naming (by frequency) (n = 60)	32.5 ± 22.2	4.6 ± 5.8§	40.3 ± 17.7	−1.0 ± 6.3
Spoken word-picture matching (n = 40)	34.9 ± 4.7	2.6 ± 4.4	37.6 ± 2.9	0.1 ± 3.9
Spoken sentence-picture matching (n = 60)	42.1 ± 11.1	2.6 ± 3.4	43.6 ± 8.4	1.6 ± 3.5

Endpoint was at week 16.

* The last observation carried forward (LOCF) was used where there were missing values during the active phase of treatment.
† Week 16 vs baseline, $p = 0.037$; ‡week 16 vs week 4, $p = 0.007$; §week 16 vs baseline, $p = 0.025$.

dementia.[9] Therefore, donepezil might restore the brain mechanisms for recovery from PSA, presumably by promoting both a reorganization of cortical networks[1,2] and a better control of regional cerebral blood flow regulation.[9]

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