Donepezil in Vascular Dementia: Combined Analysis of Two Large-Scale Clinical Trials

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Key Words

Vascular dementia · Cholinesterase inhibitors ·
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Abstract

Background and Objective: There are currently no drugs approved to treat vascular dementia (VaD). The objective of this study was to determine if treatment with donepezil, an acetylcholinesterase inhibitor, may provide benefit for VaD patients. **Methods:** Combined analysis of 2 identical randomized, double-blind, placebo-controlled, 24-week studies involving 1,219 patients enrolled at 109 investigational sites in the USA, Europe, Canada and Australia. Patients were randomized to receive donepezil 5 mg/day (n = 406) or 10 mg/day (after brief titration; n = 421) or placebo (n = 392). Patients were assessed on cognition [Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE)], global function [Clinician's Interview-Based Impression of Change plus (CIBIC-plus), Clinical Dementia Rating – Sum of the Boxes (CDR-SB)] and function [Alzheimer's Disease Functional Assessment and

Change Scale (ADFACS); instrumental activities of daily living (ADFACS-IADL)]. **Results:** Both donepezil groups showed significant improvements in cognition compared with placebo (ADAS-cog, MMSE, $p < 0.01$). Significant global function benefits were seen on the CIBIC-plus in the 5 mg/day group (placebo vs. 5 mg/day, $p < 0.001$; vs. 10 mg/day, $p = 0.006$) and on the CDR-SB in the 10 mg/day group (placebo vs. 5 mg/day, $p = 0.09$; vs. 10 mg/day, $p < 0.01$). Significant functional benefits were also seen (ADFACS, placebo vs. 5 mg/day, $p = 0.08$; vs. 10 mg/day, $p = 0.02$; ADFACS-IADL, $p < 0.05$ for both donepezil groups). Donepezil was well tolerated, with low withdrawal rates due to adverse events. **Conclusions:** This combined analysis of the largest trial on VaD to date showed that donepezil-treated patients had significant benefits in cognition, global function and ability to perform IADL. Based on these findings and reported tolerability, donepezil should be considered as an important therapeutic element in the overall management of patients with VaD.

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Introduction

Vascular dementia (VaD) is an increasing and often unrecognized health problem that currently may affect more than 1 million people in the USA [1]. As many as 25% of patients aged 65 and older may develop VaD after ischemic stroke [1]. Since there are no approved treatments, affected patients are usually treated by managing their cardiovascular risk factors [1].

VaD may be recognized by the presence of cerebrovascular disease (CVD) together with a characteristic symptom profile, particularly impairment in executive function [2], which is associated with a decreased ability to perform instrumental activities of daily living (IADL) [3]. Impairment in memory and other cognitive abilities is also observed. Special attention is required to distinguish VaD from Alzheimer's disease (AD) coexisting with CVD [1]. The importance of diagnosing and treating VaD is emphasized by the increased mortality risk in VaD patients [4].

In patients with AD, the acetylcholinesterase inhibitor donepezil has demonstrated benefits in cognition, behavior and activities of daily living (ADL) [5, 6]. Accumulating evidence shows that VaD patients also have cholinergic deficits independent of AD [7, 8] and may similarly benefit from donepezil treatment [9, 10].

We report the results of a combined analysis of 2 placebo-controlled, 24-week studies of donepezil in patients with VaD with identical protocols, totaling 1,219 patients. This constitutes the largest trial to date in VaD. Donepezil treatment resulted in significant improvements in cognition and global function versus placebo in both studies. However, the observed stabilization in cognitive and global function in the placebo group in both studies reduced the likelihood of detecting the full treatment effect. Identical study protocols enabled combined analysis in this larger patient population, thereby reducing the impact of the placebo group stabilization.

Patients and Methods

Design

We performed a combined analysis of 2 randomized, double-blind, placebo-controlled, 24-week studies conducted at 109 sites in the USA, Europe, Canada and Australia [9, 10]. Detailed methods have been reported previously [9, 10].

Patient Population

Patients with mild to moderate [Mini-Mental State Examination (MMSE) score 10–26] VaD were diagnosed according to modified National Institute of Neurological Disorders and Stroke and

the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [9–11]. Patients with AD or other dementias were excluded. Studies were conducted according to the Declaration of Helsinki [12].

Protocol

Patients were randomized using a computer-generated randomization protocol to receive once daily doses of placebo, donepezil 5 mg or donepezil 10 mg (after 5 mg/day for 28 days) for 6 months. Screening occurred within 3 weeks prior to baseline.

Outcome Measures

Cognition was assessed using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) [13] and the MMSE [14]. The Clinician's Interview-Based Impression of Severity was used to rate baseline disease severity. Global function was assessed using a modified Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) [15] and the Clinical Dementia Rating – Sum of the Boxes (CDR-SB) [16]. The Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) [17] was used to measure change in ADL and IADL.

Efficacy was assessed at screening (except CIBIC-plus), baseline and weeks 6, 12, 18 and 24. Safety and tolerability were assessed by physical examination, vital signs, laboratory tests, electrocardiograms and by monitoring adverse events (AEs) throughout the studies.

Statistical Analysis

Pooled data were analyzed using analysis of covariance to test for between-group differences in efficacy based on least squares mean change from baseline scores for all measures except the CIBIC-plus, for which scores were analyzed using the Cochran-Mantel-Haenszel test. Numerical values for CIBIC-plus categories were used to calculate mean scores that were analyzed by analysis of variance. All tests were 2-tailed and conducted at the 0.05 significance level. Analyses were conducted for observed cases at each visit and the last observation carried forward (LOCF) at end point for the intent-to-treat population (all randomized patients taking at least 1 dose of study medication, and providing a baseline assessment and at least 1 postbaseline efficacy assessment). The primary efficacy end point was defined as week 24 LOCF on the ADAS-cog and the CIBIC-plus.

Effect size (Cohen's *d*) was calculated as the difference between treatment and placebo groups divided by the baseline pooled standard deviation in the LOCF analysis [18]. The numbers needed to treat (NNTs) were based on the proportion (*p*) of responders (patients improved ≥ 4 points on ADAS-cog and stabilized or improved on CIBIC-plus and CDR-SB functional subscale) for each treatment group [19] (p_{Placebo} , $p_{5 \text{ mg}}$, $p_{10 \text{ mg}}$). Briefly, the NNT formula used for 5 mg and 10 mg donepezil treatment groups is:

5 mg group:

$$\text{NNT} = \frac{1}{(p_{5 \text{ mg}} - p_{\text{Placebo}})}$$

10 mg group:

$$\text{NNT} = \frac{1}{(p_{10 \text{ mg}} - p_{\text{Placebo}})}$$

Table 1. Patient demographics and baseline characteristics

	Placebo (n = 392)	Donepezil		Total (n = 1,219)
		5 mg/day (n = 406)	10 mg/day (n = 421)	
Male/female	220/172	241/165	241/180	702/517
Age (mean $\pm$ SE), years	74.3 $\pm$ 0.4	74.2 $\pm$ 0.4	74.8 $\pm$ 0.4	74.5 $\pm$ 0.2
CVD	356 (91)	359 (88)	380 (90)	1,095 (90)
Hypertension	284 (72)	288 (71)	285 (68)	857 (70)
HIS scores	9.8	9.6	9.7	9.7
Abnormal neuroimaging	388 (99)	402 (99)	418 (99)	1,208 (99)
≥ 1 stroke	270 (69)	270 (67)	284 (67)	824 (68)
≥ 1 TIA	118 (30)	111 (27)	115 (27)	344 (28)
Executive dysfunction	354 (90)	360 (89)	376 (89)	1,090 (89)
Screening score (mean $\pm$ SD)				
ADAS-cog	22.3 $\pm$ 11.1	23.1 $\pm$ 11.7	23.2 $\pm$ 11.4	22.9 $\pm$ 11.4
MMSE	21.6 $\pm$ 4.2	21.6 $\pm$ 4.1	21.4 $\pm$ 4.1	21.5 $\pm$ 4.2
CDR-SB	6.0 $\pm$ 2.6	6.3 $\pm$ 3.0	6.1 $\pm$ 2.7	6.1 $\pm$ 2.8
ADFACS	15.5 $\pm$ 9.6	16.4 $\pm$ 10.2	15.4 $\pm$ 10.1	15.8 $\pm$ 10.0

Figures in parentheses are percentages. HIS = Hachinski ischemic score; TIA = transient ischemic attack.

Least squares mean differences between each of the 2 treatment groups and placebo and reported 95% confidence intervals were used for pairwise comparison.

Results

Demographic characteristics of patients in all groups were similar at baseline (table 1). Seventy-nine percent of patients (969 of 1,219) completed the studies (fig. 1). Thirty-nine patients were excluded from the efficacy analyses because of missing evaluations. All 1,219 patients were included in the safety analyses.

All patients met NINDS-AIREN criteria for probable (73%) or possible (27%) VaD. Neuroimaging revealed that 11% had only cortical lesions, 51% had only subcortical lesions and the remainder had mixed lesions. Most patients (95%) had ≥ 1 comorbid medical illness, with 5 ± 3 (mean $\pm$ SD) comorbidities per patient. Most patients (99%) were receiving concomitant medications, with 8 ± 5 medications per patient.

Cognitive Function

ADAS-cog and MMSE scores improved from baseline in both donepezil groups, while scores of placebo-treated patients remained close to baseline (table 2, fig. 2a, b),

demonstrating statistically significant benefits on cognition for donepezil versus placebo at end point. Statistically significant benefits in favor of donepezil were apparent from week 6 onward (data not shown).

Global Function

Statistically significant benefits in favor of 5 mg/day donepezil over placebo on the CIBIC-plus (table 2, fig. 2c) were observed at end point; statistically significant differences were observed from week 6 onward (data not shown). A similar trend was seen for the donepezil 10 mg/day group. Overall, donepezil-treated patients improved from baseline, whereas placebo-treated patients remained stable; the proportion showing marked, moderate or minimal improvement at end point was 27% for placebo, 37% for donepezil 5 mg/day ($p = 0.0007$ vs. placebo) and 30% for donepezil 10 mg/day ($p = 0.06$ vs. placebo). Improvements from baseline in both donepezil treatment groups were also apparent on the CDR-SB, including a statistically significant difference for the 10 mg/day group compared with placebo (table 2, fig. 2d).

Ability to Perform ADL

Ability to perform ADL, as measured by the ADFACS, was maintained above baseline at end point for both donepezil-treated groups (table 2), reaching significance

Fig. 1. Subject disposition. A total of 1,219 patients were randomized to treatment, 969 (79%) completed and 250 (21%) discontinued, with 17 reported deaths (5 in the placebo group, 4 in the donepezil 5 mg/day group and 8 in the donepezil 10 mg/day group). Other reasons for discontinued treatment include: caregiver no longer available, caregiver request, medication noncompliance, nursing home placement, patient moved, patient or investigator request, patient withdrew consent and protocol violation. ITT = Intention to treat.

Table 2. Efficacy measure outcomes in placebo- and donepezil-treated patients at week 24 LOCF and week 24 observed cases (OCs)

	Week 24 LOCF			Week 24 OCs		
	placebo (n = 383)	donepezil 5 mg/day (n = 399)	10 mg/day (n = 398)	placebo (n = 306)	donepezil 5 mg/day (n = 306)	10 mg/day (n = 297)
CIBIC-plus score (least squares mean $\pm$ SE)	4.0 $\pm$ 0.1	3.8 $\pm$ 0.1**	3.9 $\pm$ 0.1	4.0 $\pm$ 0.1	3.7 $\pm$ 0.1***	3.8 $\pm$ 0.1
Change from baseline (least squares mean $\pm$ SE)						
ADAS-cog	0.2 $\pm$ 0.3	-1.6 $\pm$ 0.3***	-2.0 $\pm$ 0.3***	-0.1 $\pm$ 0.3	-1.9 $\pm$ 0.3***	-2.4 $\pm$ 0.3***
MMSE	0.4 $\pm$ 0.2	1.3 $\pm$ 0.1***	1.5 $\pm$ 0.2***	0.6 $\pm$ 0.2	1.4 $\pm$ 0.2**	1.6 $\pm$ 0.2***
CDR-SB	0.14 $\pm$ 0.09	-0.06 $\pm$ 0.08	-0.19 $\pm$ 0.08**	0.10 $\pm$ 0.10	-0.11 $\pm$ 0.09	-0.33 $\pm$ 0.09**
ADFACS	0.95 $\pm$ 0.28	0.24 $\pm$ 0.29	0.03 $\pm$ 0.27*	0.82 $\pm$ 0.30	-0.19 $\pm$ 0.31*	-0.19 $\pm$ 0.31*
IADL	0.60 $\pm$ 0.21	-0.09 $\pm$ 0.21*	-0.18 $\pm$ 0.20**	0.54 $\pm$ 0.23	-0.30 $\pm$ 0.23*	-0.34 $\pm$ 0.23**

SE = Standard error. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. placebo.

compared with placebo for the 10 mg/day group. Similar results were observed on the ADFACS-IADL subscale, with improvement from baseline for both donepezil groups from week 18 onwards, and a decline from baseline in the placebo group (table 2, fig. 2e).

Effect Size and NNT

Cohen's d effect sizes for cognition were 0.17 (ADAS-cog, donepezil 5 mg/day), 0.22 (ADAS-cog, donepezil 10 mg/day), 0.22 (MMSE, 5 mg/day) and 0.26 (MMSE, 10 mg/day). For function (ADFACS-IADL), the Cohen's

Fig. 2a-e. Pairwise treatment differences and 95% confidence interval (CI) at week 24 (LOCF) for donepezil 5 mg/day and 10 mg/day versus placebo.

d effect sizes were 0.10 (5 mg/day) and 0.11 (10 mg/day). The NNTs in this study (based on clinically improved cognition and stable/improved global function) were 19 for donepezil 5 mg/day and 11 for donepezil 10 mg/day.

Safety

There were no statistically significant differences between groups in the proportion of reported AEs or AE-related withdrawals (fig. 1, table 3), but there were numerically more withdrawals and AEs in the 10 mg/day

Table 3. AEs including cardiovascular and cerebrovascular AEs

	Placebo (n = 392)	Donepezil	
		5 mg/day (n = 406)	10 mg/day (n = 421)
≥ 1 AE	343 (88)	364 (90)	392 (93)
Nausea	29 (7)	40 (10)	69 (16)
Anorexia	14 (4)	28 (7)	36 (9)
Leg cramps	2 (1)	22 (5)	35 (8)
Rhinitis	7 (2)	15 (4)	25 (6)
Abnormal dreams	5 (1)	11 (3)	24 (6)
≥ 1 cardiovascular AE	78 (20)	80 (20)	84 (20)
Hypertension	20 (5)	21 (5)	24 (6)
Stroke	17 (4)	15 (4)	20 (5)
TIA	16 (4)	14 (3)	11 (3)
Syncope	10 (3)	7 (2)	19 (5)
Bradycardia	7 (2)	9 (2)	9 (2)

Figures in parentheses are percentages. AEs occurring in >5% of donepezil-treated patients and greater than or equal to twice the incidence in the placebo group. Cardiovascular and cerebrovascular AEs are presented if they occurred in >2% of patients.

group than in the 5 mg/day or placebo groups. Most AEs were mild to moderate, transient and usually considered unrelated to the study drug.

Reported deaths did not differ significantly among treatment groups. No deaths were considered by the investigators to be related to the study drug. The frequency of cardiovascular and cerebrovascular AEs was low and was similar in each treatment group (table 3).

Discussion

This combined analysis provides important information regarding the treatment of VaD. Use of identical protocol designs in the two 24-week studies enabled combined analysis and empowered greater detection of clinically significant benefits of donepezil treatment in VaD. This analysis indicates that treatment of this patient population with donepezil provides clinical benefits for their cognition, global function and ability to perform ADL.

In these clinical trials, VaD was rigorously defined, mixed cases of AD + CVD were excluded, and imaging evidence of CVD was required. This resulted in the selection of a relatively large sample of patients with probable VaD [20] and distinct from populations in previous trials of cholinesterase inhibitors in AD or AD + CVD [21, 22].

In contrast to AD trials, the placebo-treated VaD patients in these and other studies that used NINDS-AIREN criteria over 24–48 weeks [21, 22] exhibited little decline in cognition and global function. Over longer periods, however, untreated patients typically deteriorate [23]. The decline of IADL observed in the placebo group is consistent with deterioration of executive function, perhaps reflecting functional impairment resulting from cerebrovascular events, and underscoring the importance of the management of risk factors. Taken together, these observations suggest that short-term treatment expectations in VaD should be focused on actual improvement in cognition and global function as well as stabilization or improvement in IADL. Thus, it is important to differentiate whether a dementia is due to VaD, AD or AD + CVD, in order to manage treatment expectations.

NNT is a widely used method of describing the benefit of an active treatment over a control that is often more clinically meaningful, and easily interpreted, than outcomes on complex assessment scales such as the ADAS-cog. NNT is defined as the number of patients who must be exposed to an intervention to achieve the desired clinical outcome in 1 patient. We used a clinically relevant response of improved cognition and stable or improved global function. The NNTs for donepezil in VaD appeared to be dose responsive and were comparable to those seen with donepezil in AD [6]. The effect sizes in this VaD population were somewhat smaller than those found in an overview analysis of cholinesterase inhibitors in AD [24]; this is likely to be a result of the stabilization seen in the placebo group and the nature of disease progression in VaD (i.e. stepwise rather than progressive deterioration), over a relatively short trial duration [9]. Nonetheless, effect sizes were detectable, reproducible, dose responsive and likely to be clinically meaningful in VaD patients, with an effect size of ≥ 0.20 conventionally held as clinically detectable [24].

Treatment with another cholinesterase inhibitor, galantamine, provided cognitive and global function benefits in a population composed of patients with AD + CVD and VaD [21], although that may have been driven by the underlying AD pathology in this mixed group. In studies involving only VaD patients, treatment with the *N*-methyl-D-aspartate antagonist memantine failed to show benefits in global function but did show some cognitive stabilization [25, 26].

VaD patients represent a more frail population than patients with AD as a result of their comorbid conditions and concomitant medication use, with associated higher morbidity and mortality than age-matched AD patients

[1]. This population is at increased risk for cardiovascular and cerebrovascular events, and so tolerability and a lack of drug interactions with concomitant medications are important considerations when choosing a pharmacological treatment. Donepezil is well tolerated in VaD patients, as it is in AD patients [6]. Most treatment-emergent AEs reported here were mild to moderate in intensity, transient in effect and related to expected cholinergic effects [9, 10]. No increase in cardiovascular events was observed in the donepezil groups. These results demonstrate that donepezil treatment is efficacious across the domains of dementia symptoms in VaD patients and is

well tolerated in this very sick patient population. Therefore, donepezil may offer an effective and safe treatment for the symptomatic management of VaD.

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