American Journal of Alzheimer's Disease & Other Dementias®
Volume 23 Number 2
April/May 2008 167-176

10.1177/1533317507312558
http://ajadd.sagepub.com
hosted at
http://online.sagepub.com

Different Responses to Rivastigmine in Subcortical Vascular Dementia and Multi-Infarct Dementia

Rita Moretti, MD, Paola Torre, MD, Rodolfo M. Antonello, MD, Giuseppe Cazzato, MD, and Gilberto Pizzolato, MD

Vascular dementia (VaD) is associated with a large amount of heterogeneity, as it groups together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebrovascular or cardiovascular disease. Thus, a study was designed to determine the effects of rivastigmine on cognitive function, global daily living performance, and behavioral disorders in VaD patients versus an active control (nimodipine), stratifying patients according to the type of VaD, subcortical vascular dementia (sVAD), and multi-infarct dementia (MID). The trial was a prospective study. This study shows that long-term treatment with rivastigmine, at dosages approved for therapeutic use in Alzheimer's disease, produces significant improvement in all behavioral symptoms in 2 forms of VaD, MID and sVaD, except delusions. It also suggests that rivastigmine may enable a reduction in concomitant neuroleptics and benzodiazepines in VaD, especially in MID. The results are discussed with an overview of the literature.

Keywords: multi-infarct dementia; subcortical vascular dementia; rivastigmine; vascular dementia

Introduction

Vascular dementia (VaD) is associated with a large amount of heterogeneity, as it groups together a broad category of patients in whom various manifestations of cognitive decline are attributed to cerebrovascular or cardiovascular disease. The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN) consensus criteria help in defining it.[1] Furthermore, the NINDS–AIREN criteria[2] list different disorders that help in identifying patients with different subtypes of VaD: multi-infarct dementia (MID; multiple large and complete infarcts, hypoperfusion), strategic infarct VaD (single strategically placed infarcts), and subcortical VaD (sVAD; small-vessel disease, hypoperfusion). The International Classification of Diseases, 10th revision, criteria only recently identified sVaD as a major subtype.[3] sVaD relates to small-vessel disease and hypoperfusion resulting in focal and diffuse ischemic white matter lesions and incomplete ischemic injury.[4]

In patients with sVaD, ischemic lesions are particularly apparent in the prefrontal subcortical circuit, including the prefrontal cortex.[5] sVaD occurs mainly because of lacunar infarct, occurring in the distribution of small arterioles, usually in the white matter, basal ganglia, thalamus, and pons, or because of microinfarct—small area of cystic or noncystic necrosis surrounded by astrocytes (not seen on macroscopic examination). Incomplete infarcts may also be present, as a result of a selective loss of neurons, myelin, and oligodendrocytes, without cystic necrosis, occurring in the periphery of major artery distribution infarcts (eg, penumbra) or in deep white matter. Incomplete white matter infarcts are associated with myelin pallor, astrocytosis, and a variable degree of axonal loss. sVaD now incorporates the old entities "lacunar state" and "Binswanger disease" and relates to small-vessel disease and hypoperfusion, resulting

From the Department of Medicine and Neurology, University of Trieste, Trieste, Italy.

Professor Giuseppe Cazzato died while the article was being written.

Address correspondence to: Rita Moretti, MD, Department of Neurology, University of Trieste, Gattinara Hospital 34149, Trieste, Italy; e-mail: moretti@univ.trieste.it.

in focal and diffuse ischemic white matter lesions and incomplete ischemic injury.[6] This deterioration of the frontal lobe is reflected by the core feature of sVaD—dysexecutive syndrome.[7,8] Memory impairment and attention deficits are also apparent, and patients often experience mood changes, such as apathy, abulia, personality changes, and emotional lability. These behavioral symptoms can be a major cause of stress, anxiety, and concern for caregivers and frequently lead to the institutionalization of patients.

MID is defined by cognitive and behavioral alterations; among these alterations, depression is frequent and has been defined as poststroke depression.[9] Apathy, depression, and loss of awareness are, in our experience, what caregivers mostly stress among the behavioral changes in MID patients. The complaints are reported to be constantly associated with somatic pain and discomfort, which are more evident than memory loss or verbal defects.[10]

A host of medications have been tried but with limited success, including alkaloid derivatives, hemorheologics, metabolic enhances, and GABA antagonists.[6]

There is currently no approved symptomatic treatment for VaD, although daily aspirin treatment may improve or stabilize cognitive decline when compared with placebo,[6,11] but the report of the Quality Standards Subcommittee of the American Academy of Neurology[12] stated that there are no adequately controlled trials demonstrating pharmacologic efficacy for any agent in ischemic vascular dementia.

Thus, what has clearly emerged in the past years is the deep conviction that in VaD there is a depauperation of acetylcholine as in Alzheimer's disease. However, successful trials in patients with VaD are limited. One post hoc subgroup analysis of the 6-month Scandinavian Multi-Infarct Dementia Trial has shown that although a treatment effect was not observed in the total trial population, the subgroup of sVaD patients receiving nimodipine performed better on the majority of tests and functional scales compared with patients given placebo.[13] Even considering that the Cochrane Database Systematic Review[14] concludes that nimodipine can be of some benefit, the short-term benefits do not justify its long-term use as an antidementia agent. However, nimodipine remains one of the most used therapies for VaD.

A growing body of evidence suggests that cholinesterase (ChE) inhibitors may be of use in VaD.[6,10] Significant reductions in acetylcholine levels have been found in the cortex, hippocampus, and cerebrospinal fluid in rat models of VaD and in the cerebrospinal fluid of VaD patients, which were correlated to cognitive impairment. Postmortem studies in humans have shown that choline acetyltransferase activity is lower in VaD patients than in controls, and it has been proved that acetylcholine plays an important role in the autoregulation of cerebral blood flow. The objective of a recent work was to determine if treatment with donepezil, an acetylcholinesterase inhibitor, may provide benefits for VaD patients.[14] In this study, a combined analysis of 2 identical randomized, double-blind, placebo-controlled, 24-week studies involving 1219 patients enrolled at 109 investigational sites in the United States, Europe, Canada, and Australia was done. 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 and Mini-Mental State Examination [MMSE]), global function (Clinician's Interview-Based Impression of Change plus [CIBIC-plus] and Clinical Dementia Rating–Sum of the Boxes [CDR-SB]), and function (Alzheimer's Disease Functional Assessment and Change Scale [ADFACS] and Instrumental Activities of Daily Living [ADFACS-IADL]). Both donepezil groups showed significant improvements in cognition compared with the placebo group. Significant global function benefits were seen on the CIBIC-plus in the 5 mg/day group and on the CDR-SB in the 10 mg/day group. Significant functional benefits were also seen for both donepezil groups. 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.

The most recent Cochrane review on the topic states that evidence from the available studies supports the benefit of donepezil in improving cognition function, clinical global impression, and activities of daily living in patients with probable or possible mild to moderate vascular cognitive impairment after 6 months of treatment. Extending studies for longer periods would be desirable to establish the efficacy of donepezil in patients with advanced stages of cognitive impairment. Moreover, there is an urgent need for establishing specific clinical diagnostic criteria and rating scales for vascular cognitive impairment.[15]

Rivastigmine is a ChE inhibitor approved for therapeutic use in Alzheimer's disease and is characterized by dual inhibition, that is, inhibition of both acetylcholinesterase and butyrylcholinesterase. The drug has been proved to be an effective therapeutic agent for the amelioration of cognitive and behavioral symptoms in Alzheimer's disease, and a recent Cochrane review suggests that it may be effective also in vascular cognitive impairment.[16,17] It appears to be particularly suitable for sVaD, because imaging studies have shown that the drug improves blood flow significantly in cerebral frontal areas known to be associated with executive function and behavior.[6,17-20]

Cerebrovascular disease is common in the elderly. The potential role of ChE inhibitors is closely related to the concept of the particular vulnerability of specific brain regions in VaD. For example, lacunes correlate with metabolic rates in the dorsolateral frontal cortex. In fact, white matter lesions substantially reduce metabolic rates throughout the cortex, most strongly so in the dorsolateral frontal cortex. Regional cerebral glucose metabolism and normalized activity in the dorsolateral frontal regions correlated with executive function, memory, and global executive function. There is no clear reason for the particular vulnerability of this selectivity, whose significance might be important for the development of specific therapeutic strategies, at least for sVaD.

Our suggestion is that VaD is not a univocal and unique pathology: the etio-pathogeneses of MID and sVaD are quite different.

Based on the considerations mentioned above and evidence in the literature,[9,16,17] we designed a study to determine the effects of rivastigmine on cognitive function, global daily living performance, and behavioral disorders in VaD patients when compared with an active control (nimodipine), stratifying patients according to the type of VaD (sVAD or MID).

Methods

The trial was a prospective study that began on January 1, 2003, and lasted up to March 1, 2004. A total of 245 outpatients of both sexes were screened; their ages ranged from 65 to 85 years, they had an MMSE[18] score ≥ 12, and they met the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* for dementia[3] and the NINDS–AIREN criteria for probable VaD.[1] Patients were excluded if they showed signs of normal pressure hydrocephalus, cortical hemispheric large vessel strokes, or lobar hemorrhage; had a history of psychiatric or central nervous system disorders or alcoholism; did not have a reliable caregiver; had an important aphasic syndrome that could impair comprehension and compliance; or had already been enrolled in a clinical trial.

Forty-five patients were not enrolled: 5 because of very low compliance, 15 because of a diagnosis of major aphasia syndrome (global aphasia or fluent sensorial aphasia), and 8 because of poor general condition; 17 patients did not accept the study conditions.

VaD was diagnosed when the computed tomography (CT) scan showed moderate to severe ischemic white matter changes and at least 1 lacunar infarct.[4] Multi-infarct VaD was diagnosed when the CT scan showed 2 cortical infarcts, excluding by definition the so-called strategic infarct.[9] Brain CT scans were assessed independently by 2 neurologists (RM and PT). In the event of disagreement, the scans were reassessed together with an experienced neuroradiologist, blind to the study, who took the final decision.

Patients were stratified into 2 groups according to the type of VaD: 100 patients had MID and the remaining 100 had sVAD. In the MID group, 45 patients had 1 large ischemic or hemorrhagic stroke and at least 2 lacunar strokes, 35 had 2 major ischemic or hemorrhagic events and other lacunar infarcts, and 20 had 3 major ischemic or hemorrhagic events.

All patients were given background therapy with 100 mg acetylsalicylic acid (ASA) daily. The patients in each stratum were then randomly allocated either to rivastigmine (starting dose, 3 mg daily with titration up to 6 mg over 8 weeks according to response) or to 60 mg daily nimodipine (30 mg daily with titration up to 60 mg over 8 weeks) according to a randomization list prepared by the investigator. Examiners (RM and PT) were blinded to treatment, which was administered by 2 other doctors (RMA and GC). Patients and caregivers were blinded to treatment. Blinding was ensured by dispensing study drug in anonymous white envelopes; the drug intake was twice a day. Fifty patients in each stratum took rivastigmine plus ASA and 50 nimodipine plus ASA.

Patients were allowed to continue any previous therapy, such as antihypertensive, antidyslipidemic, or antidiabetic agents; previous or concomitant anticholinergic therapy was not permitted.

The follow-up lasted 14 months. Visits were scheduled to take place after 1, 4, 7, and 14 months.

All patients underwent a standardized baseline assessment that included a detailed history, a physical examination, routine laboratory tests, and a series of neurological and psychiatric evaluations. The physical examination, which was repeated at every visit, focused on the cardiovascular system and included the recording of body weight; evaluations of heart rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessels, and carotid arteries; and chest X-rays. Laboratory tests, which were repeated at the end of the study after 14 months, included measurements of urea nitrogen, creatinine, hemoglobin, glucose, glycosylated hemoglobin, thyroid-stimulating hormone, thyroid hormones T3 and T4, vitamin B_{12} and folate levels, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, urinalysis, and electrocardiogram. Global performance was assessed using the CDR,[21] and global cognitive function was assessed using the MMSE.[22] In addition, phonological and semantic fluency[23] was assessed by counting the number of nouns provided during a 3-minute task; as dysexecutive syndrome is the core feature of VaD,[7,8] executive function was assessed using the 10-point clock drawing test.[24] A functional rating scale was also used, the Tinetti gait scale.[25]

Behavioral symptoms were assessed using the Behavioral Pathology in AD Rating Scale (BEHAVE-AD).[26] In addition to the total BEHAVE-AD score, 7 items from the scale were assessed individually: delirium (maximum score 21), hallucinations (maximum score 15), activity disorders (maximum score 9), aggressiveness (maximum score 9), sleep disturbances (maximum score 3), affective disorders (maximum score 6), and anxiety and phobias (maximum score 12). The Ryden Aggression Scale[27] total score was used to assess aggressive behavior further, and the Geriatric Depression Scale[28] was used to assess depression.

In addition, new prescriptions of neuroleptics and/or benzodiazepines were recorded and compared between the 2 treatment groups (indicated by a binomial scale, where 1 = intake and 0 = no intake).

Adverse events were recorded throughout the study. They were elicited by putting specific questions to detect the presence of nausea, muscle contractions, and postural hypotension, plus a general, nonleading question to elicit any other unexpected adverse events.

Safety and tolerability were also assessed by administering the Cumulative Illness Rating Scale.[29,30]

Table 1. Timing of Study Assessments

	Visit (months)				
Assessment	0	1	4	7	14
Medical history	X				
Physical examination	X	X	X	X	X
BEHAVE-AD	X				X
Ryden scale	X				X
Geriatric Depression Scale	X			X	X
Clinical Dementia Rating Scale	X	X	X	X	X
MMSE	X			X	X
Ten-point clock drawing test	X			X	X
Phonological fluency	X			X	X
Semantic fluency, 3-minute task	X			X	X
Tinetti Gait Scale	X				X
New prescriptions, neuroleptics/ benzodiazepines	X			X	X
Cumulative Illness Rating Scale	X	X	X	X	X
Adverse events	X				
ECG	X				X
Laboratory tests	X				X

Abbreviations: BEHAVE-AD, Behavioral Pathology in AD Rating Scale; MMSE, Mini-Mental Status Examination; ECG, electrocardiogram.

The timings of the various assessments are shown in Table 1. The primary endpoint was the total BEHAVE-AD score.

The study was conducted following the Declaration of Helsinki and the ethical guidelines of our institute. Informed consent was obtained in writing, duly signed by the patients and their caregivers.

Statistical Analyses

A sample size of approximately 50 patients per group was required to achieve 85% power to detect a difference between treatment groups of at least 5 points in the last observation carried forward mean change on the BEHAVE score at a 2-tailed level of $\alpha = .05$.

The demographic and baseline characteristics were summarized by subtype of VaD and treatment group. Distributions of continuous variables were expressed as means and standard deviation. Categorical variables were described as frequency distributions. To assess baseline comparability of treatment groups, the distributions of baseline characteristics were inspected, but no statistical test was applied.[31] The efficacy variables were compared between treatment groups in each stratum (MID and sVAD) in terms of the change in scores from baseline at month 14 using the nonparametric analysis

Table 2. Baseline Characteristics of Patients in the 2 Treatment Groups

	MID		sVAD	
	Rivastigmine	Nimodipine	Rivastigmine	Nimodipine
Number of patients	50	50	50	50
Gender (male/female)	19/31	23/27	24/26	20/30
Age, years (mean ± SD)	74.23 ± 2.23	73.45 ± 2.21	73.23 ± 2.46	72.45 ± 3.11
Education level, years (mean ± SD)	8.39 ± 2.21	8.19 ± 1.23	7.99 ± 2.11	8.02 ± 1.1
Handedness	Right	Right	Right	Right
Hachinski score	13.7 ± 1.3	14.1 ± 1.4	8.7 ± 1.9	8.71 ± 1.45
Concomitant illnesses (% patients)				
Essential hypertension	21.87%	23.1%	19.78%	20.1%
Diabetes mellitus, type 2	19.56%	18.34%	17.64%	19.2%
Chronic bronchitis	21.43%	18.76%	19.23%	21.34%
Ischemic cardiopathy/valvular failure	21.1%	19.1%	19.6%	17.89%
Chronic renal failure	6.25%	4.58%	6.78%	3.12%

Abbreviations: MID, multi-infarct dementia; sVAD, subcortical vascular dementia; SD, standard deviation.

of covariance,[32] adjusting for the baseline scores. A significant level of .05 was used, and all the tests were 2-sided. All statistical analyses were performed using SAS System for Windows XP, version 8.02 (SAS Institute Inc; Cary, NC).

Results

The demographic and other baseline features of the treatment groups in the 2 strata are shown in Tables 2 and 3. There were no important differences between the 4 treatment groups in terms of demographic features and concomitant diseases. Also, concomitant treatment, which consisted mainly of angiotensin converting enzyme inhibitors, calcium antagonists, oral antidiabetic agents, diuretics, and bronchodilators, was similar and so were baseline BEHAVE-AD scores (total and individual items).

The 2 groups of patients, those with MID and sVAD, presented different aspects in their profiles, either under cognitive or under behavioral aspects. Table 4 reports these differences, underlying some peculiarities that emerge from a Wilcoxon signed rank test.

At baseline, MID patients presented more behavioral alterations, such as delusions and hallucinations. In contrast, sVAD patients presented more affective disorders and anxiety. They obtained higher scores in the Tinetti Gait Scale and had less problems in deambualtion than MID patients, and the aggressiveness levels of the patients in the sVAD group was lower than those in the MID group.

The results related to the primary endpoint—the BEHAVE-AD total score—and its individual items are shown in Figures 1 and 2. After 14 months of treatment, rivastigmine significantly improved behavioral symptoms, whereas patients allocated to nimodipine significantly deteriorated, with highly significant differences between the 2 treatments both in terms of change from baseline in total score and in single-item scores ($P < .0001$), except for aggressiveness, affective disturbances, and delusions in MID.

Affective disturbances in MID were stabilized by rivastigmine but deteriorated with nimodipine ($P = .003$). Delusions improved slightly with both drugs in MID ($P = .43$) and remained stable with both drugs in sVaD ($P = .20$).

Aggression, as measured by the Ryden Aggression Scale, was modified in MID by rivastigmine treatment, showing a significant decrease when compared with the nimodipine group ($P < .0001$; Table 5). Even depression (as measured by the Geriatric Depression Scale) was reduced in the rivastigmine group. On the contrary, all the other parameters (such as general status, cognitive performance, and gait) did not differ in the 2 groups. In particular, clinical dementia, MMSE, and 10-point clock drawing scores deteriorated slightly with both drugs in MID and sVaD, with no differences between treatments, except for the more pronounced deterioration of the clinical dementia and 10-point clock drawing scores in sVaD with nimodipine ($P < .0001$; Table 5).

The fluency scores deteriorated with both drugs; the deterioration of the phonological fluency score was more pronounced with nimodipine both in the

Table 3. Baseline Scores by Stratum and Treatment[a]

	MID		sVAD	
Parameter Scores	Rivastigmine	Nimodipine	Rivastigmine	Nimodipine
BEHAVE-AD, total score	44.6 ± 7.7	44.2 ± 7.0	40.6 ± 7.5	40.1 ± 7.0
BEHAVE-AD, subscores				
Hallucinations	8.9 ± 2.2	8.7 ± 3.3	6.9 ± 2.3	6.0 ± 2.2
Aberrant activity	3.4 ± 1.1	3.3 ± 1.0	4.2 ± 1.2	4.3 ± 1.3
Aggressiveness	6.0 ± 1.4	6.1 ± 1.7	4.0 ± 0.9	4.9 ± 1.1
Sleep disturbances	2.0 ± 0.3	2.6 ± 0.5	2.0 ± 0.3	2.6 ± 0.5
Affective disorders	2.7 ± 1.3	3.3 ± 1.2	3.6 ± 1.3	4.0 ± 1.5
Anxiety disorders	8.9 ± 1.8	8.9 ± 2.5	10.3 ± 2.0	10.4 ± 1.9
Delusions	10.0 ± 1.6	10.8 ± 2.8	8.5 ± 1.6	8.3 ± 1.6
Ryden Aggression Scale	20.5 ± 7.2	21.1 ± 8.5	8.4 ± 4.5	8.8 ± 4.8
Geriatric Depression Scale	8.2 ± 3.7	7.7 ± 2.4	13.6 ± 2.8	13.7 ± 2.0
Clinical Dementia Rating Scale	1.8 ± 0.2	1.8 ± 0.3	1.6 ± 0.2	1.6 ± 0.2
MMSE	18.6 ± 2.1	18.9 ± 2.0	20.7 ± 2.0	20.0 ± 2.1
Ten-point clock drawing test	4.3 ± 1.4	4.6 ± 1.3	5.1 ± 0.8	5.2 ± 0.7
Phonological fluency	16.5 ± 2.0	16.7 ± 2.4	18.1 ± 1.8	18.4 ± 2.5
Semantic fluency	12.2 ± 1.4	12.6 ± 1.7	13.4 ± 2.7	13.3 ± 2.0
Tinetti Gait Scale	5.9 ± 1.6	5.9 ± 1.2	11.2 ± 0.8	11.1 ± 1.0
Cumulative Illness Rating Scale	6.6 ± 0.9	6.7 ± 1.4	5.1 ± 0.9	5.2 ± 0.9

Abbreviations: MID, multi-infarct dementia; sVAD, subcortical vascular dementia; BEHAVE-AD, Behavioral Pathology in AD Rating Scale; MMSE, Mini-Mental Status Examination.
[a]All values in mean ± standard deviation.

Table 4. Differences at Baseline in the 2 Groups Considered According to a Wilcoxon Signed Rank Test

Score	MID	sVAD	*P*
BEHAVE-AD total	44. 58 ± 7.72	40.58 ± 7.51	−4.08, $P < .001$
BEHAVE-AD, subscores			
Delusions	10.04 ± 0.60	8.50 ± 1.58	−2.32, $P < .05$
Hallucinations	8.92 ± 2.25	6.86 ± 2.26	−1.56, $P < .05$
Aberrant activity	3.38 ± 1.14	4.20 ± 1.18	−1.45, $P < .05$
Aggressiveness	6.04 ± 1.38	4.04 ± 0.92	−2.193, $P < .05$
Sleep disorders	2.02 ± 0.25	2.04 ± 0.28	NS
Affective disorders	2.68 ± 1.32	3.56 ± 1.28	−1.56, $P < .05$
Anxiety	8.86 ± 1.78	10.28 ± 1.96	−2.34, $P < .05$
Geriatric Depression Scale	8.16 ± 3.73	13.58 ± 2.81	−5.52, $P < .001$
CDR	1.84 ± 0.24	1.56 ± 0.16	−5.29, $P < .001$
Tinetti Gait Scale	5.86 ± 1.55	11.24 ± 0.80	−6.06, $P < .001$
CIRS	6.62 ± 0.95	5.12 ± 0.90	NS
Ryden Aggression Scale	20.52 ± 7.16	8.38 ± 4.54	−11.36, $P < .001$
MMSE	18.64 ± 2.13	20.72 ± 1.97	NS
Phonological fluency	16.48 ± 1.98	18.14 ± 1.78	NS
Semantic fluency	12.22 ± 1.36	13.42 ± 2.69	NS
TPCT	4.32 ± 1.43	5.12 ± 0.82	NS

Abbreviation: MID, multi-infarct dementia; sVAD, subcortical vascular dementia; BEHAVE-AD, Behavioral Pathology in AD Rating Scale; CDR, Clinical Dementia Rating Scale; CIRS, Cumulative Illness Rating Scale; MMSE, Mini-Mental Status Examination; TPCT, 10-point clock drawing test; NS, not significant.

MID group ($P = .0003$) and in the sVAD group ($P = .02$), whereas a more pronounced deterioration of the semantic fluency score with nimodipine was found only in the sVaD group ($P < .0001$). Also, the Tinetti gait score deteriorated with both drugs; the deterioration was more pronounced with nimodipine in the sVaD group ($P = .0005$; Table 5).

At the end of the study, the proportion of MID patients taking neuroleptics diminished by 35% in the rivastigmine subgroup (from n = 20 down to 13) and

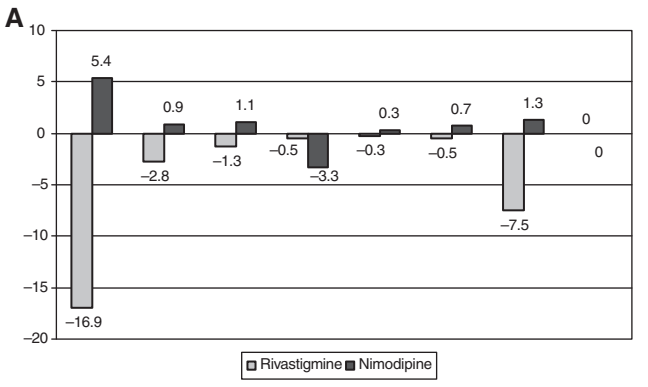

Figure 1. Changes in BEHAVE-AD scores in MID at month 14. All differences $P < .0001$ except aggressiveness ($P = .01$), affective disturbances ($P = .003$), and delusions ($P = .43$).

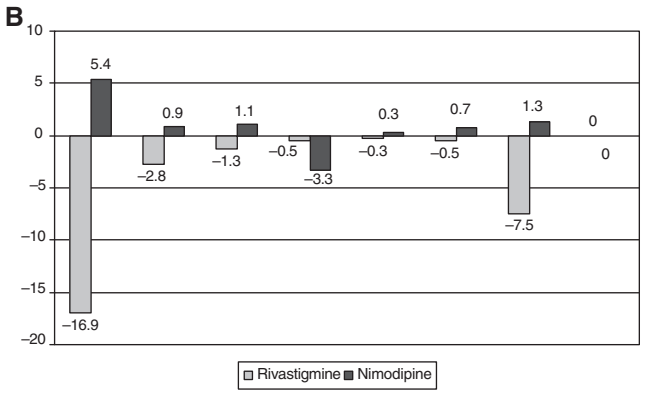

Figure 2. Changes in BEHAVE-AD scores in sVAD at month 14. All differences $P < .0001$ except delusions ($P = .20$).

Table 5. Mean Changes (Standard Deviation) in Secondary Endpoint Scores From Baseline at Month 14

	MID			sVaD		
Parameter Scores	Rivastigmine	Nimodipine	*P*	Rivastigmine	Nimodipine	*P*
BEHAVE-AD, total score	−19.7 (7.1)	+3.6 (8.9)	<.0001	−16.9 (0.4)	+5.4 (2.0)	<.0001
BEHAVE-AD, subscores						
Hallucinations	−2.5 (3.9)	+1.7 (5.0)	<.0001	−2.8 (2.5)	+0.9 (2.4)	<.0001
Activity disturbances	−0.5 (1.2)	+0.8 (2.0)	<.0001	−1.3 (0.9)	+1.1 (0.9)	<.0001
Aggressiveness	−2.3 (1.9)	−0.6 (3.6)	.01	−0.5 (1.0)	−3.3 (0.9)	<.0001
Sleep disturbances	−0.3 (0.8)	+0.3 (0.6)	<.0001	−0.3 (0.8)	+0.3 (0.6)	<.0001
Affective disturbances	0.0 (1.4)	+0.6 (1.4)	.003	−0.5 (1.0)	+0.7 (1.0)	<.0001
Anxieties	−4.0 (2.8)	+2.7 (2.6)	<.0001	−7.5 (2.1)	+1.3 (1.9)	<.0001
Delusions	−0.5 (3.5)	−0.3 (4.7)	.43	0.0 (2.7)	0.0 (0.2)	.20
Ryden Aggression Scale	−11.7 (5.8)	+7.1 (14.9)	<.0001	−0.6 (2.8)	+10.4 (6.4)	<.0001
Geriatric Depression Scale	−3.1 (3.9)	+4.1 (4.9)	<.0001	−3.5 (3.6)	+0.7 (2.6)	<.0001
Clinical Dementia Rating Scale	+0.4 (0.4)	+0.4 (0.4)	.23	+0.4 (0.3)	+0.7 (0.3)	<.0001
Ten-point clock drawing	−0.9 (1.5)	−1.3 (1.3)	.57	−0.5 (1.1)	−1.3 (1.0)	<.0001
MMSE	−3.2 (2.6)	−3.1 (2.9)	.30	−3.8 (2.1)	−3.2 (2.7)	.53
Phonological fluency	−5.1 (2.2)	−6.6 (2.3)	.0003	−3.3 (2.5)	−4.3 (3.4)	.02
Semantic fluency	−4.4 (1.9)	−5.0 (2.4)	.56	−2.6 (2.2)	−3.8 (2.8)	<.0001
Tinetti Gait Scale	−0.2 (1.6)	−0.2 (1.8)	.44	−2.1 (1.3)	−2.9 (1.8)	.0005
Cumulative Illness Rating Scale	+1.5 (1.4)	+1.4 (1.6)	.23	−0.1 (0.8)	−0.3 (1.1)	.59

Abbreviations: MID, multi-infarct dementia; sVAD, subcortical vascular dementia; BEHAVE-AD, Behavioral Pathology in AD Rating Scale; MMSE, Mini-Mental Status Examination.

increased by 37.5% in the nimodipine subgroup (from n = 25 to 40); the corresponding values for benzodiazepine usage were −55% (from n = 20 to 9) and +11% (from n = 9 to 10) ($P < .001$). The number of sVaD patients taking neuroleptics increased slightly in the rivastigmine subgroup (from n = 12 to 14; +17%) and more than trebled in the nimodipine subgroup (from n = 11 to 34; +200%) ($P < .001$); benzodiazepine usage diminished drastically in the rivastigmine group (6 vs 1; $P < .001$) and remained the same in the nimodipine subgroup (7 vs 7; not significant). The course of the cumulative illness score did not differ significantly between the 2 drugs.

Both drugs were well tolerated. No patient withdrew because of adverse events before the end of the study, and no serious adverse events or adverse reactions were reported. No clinically significant changes in laboratory tests occurred. The reports on nausea, muscle contractions, and postural instability are reported in Table 6. The 3 undesirable effects occurred

Table 6. Elicited Data on Tolerability (Number of Patients)

	MID		sVAD	
Parameter	Rivastigmine	Nimodipine	Rivastigmine	Nimodipine
Nausea				
Titration phase	17	19	21	15
Treatment phase	8	10	7	6
Muscle contractions				
Titration phase	13	10	9	5
Treatment phase	0	0	0	0
Postural instability				
Titration phase	9	0	16	23
Treatment phase	0	9	0	0

Abbreviations: MID, multi-infarct dementia; sVAD, subcortical vascular dementia.

in all treatment groups during the titration phase. Nausea was always mild, was usually transient, and never caused any weight loss. Muscle contraction and postural instability always resolved spontaneously during the titration phase.

Discussion

The recent ideal proposal is that VaD is not a univocal and unique pathology: the etio-pathogeneses of MID and sVAD are quite different. Future studies need to consider these entities separately to obtain good results for a group of patients for whom, until now, there have been few therapeutic options.

Clinical trials performed in patients defined as affected by VaD have so far achieved unsatisfactory results. Recently, preliminary results have been published demonstrating a general stable performance in cognitive tasks, with slightly better performances in executive functions and a better behavioral response in a group of sVaD patients treated with rivastigmine.

This study shows that long-term treatment with rivastigmine, at dosages approved for therapeutic use in Alzheimer's disease, produces significant improvement in some behavioral symptoms, specifically tested in 2 forms of VaD, MID and sVaD, except delusions. The study also suggests that rivastigmine may enable a reduction in concomitant neuroleptics and benzodiazepines in VaD, especially in MID.

This study gives 3 results:

1. It confirms that multi-infarct dementia is different from sVaD, in clinical presentation, from a neuropsychological perspective and from a pharmacological definition.[13]
2. It confirms the effectiveness of rivastigmine in sVaD, as previously stated; a recent meta-analysis of three 6-month placebo-controlled trials with rivastigmine in 1840 patients with mild to moderate Alzheimer's disease indicated that the drug is able to improve behavioral and psychological symptoms of dementia in Alzheimer's disease,[33] and an open-label 22-month study had already suggested that the drug improves behavioral symptoms in sVaD, albeit using a different scale (Neuropsychiatric Inventory).[34] Moreover, a decrease in the use of psychotropic medications had already been reported together with improvements in behavioral and psychological symptoms in two 12-month open-label studies with rivastigmine.[35] The only inconsistency is that AD-BEHAVE scores in the meta-analysis showed improvement also of delusions, which were not significantly reduced in the present study. However, there was a trend in favor of rivastigmine in MID but not in SVaD (as also seen in this study); thus, the lack of any significant difference in MID may be because of the lower sample size. The new aspect is that rivastigmine seems to work also in MID, as evidenced by a significant reduction of neuroleptic intake.
3. It confirms that rivastigmine is well tolerated in VaD. Independent of its type, 100 patients (50 with MID and 50 with sVaD) were exposed to rivastigmine for 14 months and no patient withdrew because of intolerance and no patient reported a serious or severe adverse event.

To our knowledge, this is the first time that MID and sVaD were studied separately. This disclosed additional benefits afforded by rivastigmine in sVaD: significant reduction in the deterioration of executive function measured by the 10-point clock drawing

test, of semantic fluency, of cognitive function measured by the Clinical Dementia Rating Scale, and of gait disorder measured by the Tinetti Gait Scale. The amelioration of executive dysfunction, which is the core feature of sVaD, is consistent with the improvement in blood flow produced by rivastigmine in the frontal lobe, which is known to be the key cerebral area associated with executive function.[35-37] Improvements in executive function measured by the 10-point clock drawing test and in cognitive function measured by the Clinical Dementia Rating scale were documented also in the open-label 22-month trial mentioned above.[35,36]

MMSE did not show any significant improvement, notwithstanding the improvement in the Clinical Dementia Rating score. This was probably because of the fact that the scale is relatively insensitive to changes in executive function.

In conclusion, this study suggests that long-term treatment with rivastigmine, given at dosages approved for therapeutic use in Alzheimer's disease, is well tolerated and effective in ameliorating behavioral symptoms in MID and sVAD; however, the study focuses on the following:

1. The possibility to define a specificity of drugs employment in different types of VaD.
2. The real definition of a set of interventions, focusing on specific target symptoms, such as apathia, cognitive abulia, and dysexecutive syndrome, as primary endpoint.

References

1. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
2. Chui HC, Victoroff JI, Margolin D, Jaqust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology*. 1992;42:473-480.
3. American Psychiatric Association. *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
4. Erkinjuntti T. Vascular dementia: challenge of clinical diagnosis. *Int Psychogeriatr*. 1997;9:77-83.
5. Cummings JL. Fronto-subcortical circuits and human behaviour. *Arch Neurol*. 1993;50:873-880.
6. Moretti R, Torre P, Antonello RM, Vilotti C, Pizzolato G. New treatment options for vascular dementia. *Aging Health*. 2007;3:209-222.
7. McPherson SE, Cummings JL. Neurospychological aspects of vascular dementia. *Brain Cogn*. 1996;31:261-282.
8. Looi JCL, Sachdev PS. Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology*. 1999;53:670-678.
9. Erkinjuntti T, Gauthier S. *Vascular Cognitive Impairment*. London, UK: Martin Dunitz; 2002.
10. Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996;53:175-182.
11. Meyer JS, Rogers RL, McClintic K, Mortel KF, Lotfi J. Randomized clinical trail of daily aspirin therapy in multi-infarct dementia. A pilot study. *J Am Geriatr Soc*. 1989;37:549-555.
12. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56: 1154-1166.
13. Pantoni L, Rossi R, Inzitari D, et al. Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial. *J Neurol Sci*. 2000;175:124-134.
14. López-Arrieta JB. Nimodepine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst Rev*. 2002;(3):CD00147.
15. Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. *Dement Geriatr Cogn Disord*. 2005;20:338-344.
16. Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2004;(1): CD004395.
17. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in vascular dementia. *Expert Opin Pharmacother*. 2004;5:1399-1410.
18. Farlow MR. Update on rivastigmine. *Neurologist*. 2003;9: 230-234.
19. Craig D, Birks J. Rivastigmine for vascular cognitive impairment. *Cochrane Database Syst Rev*. 2005;(2): CD004744.
20. Moretti R, ed. *Subcortical Vascular Dementia*. New York, NY: Novascience; 2006.
21. Hughes CP, Berg L, Ganziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;15:211-214.
22. Folstein M, Folstein S, McHugh P. Mini-Mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12: 189-198.

23. Wechsler D. *Wechsler Adult Intelligence Scale–R Manual*. New York, NY: Psychological Corp; 1981.
24. Manos PJ. The utility of the ten-point clock test as a screen for cognitive impairment in general hospital patients. *Gen Hosp Psychiatry*. 1997;8:469-476.
25. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc*. 1986;34: 119-126.
26. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioural symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry*. 1987;48(suppl):9-15.
27. Ryden MB. Aggressive behaviour in persons with dementia who live in the community. *Alzheimer Dis Assoc Disord*. 1988;2:342-355.
28. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1983;17:37-49.
29. Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. *J Am Geriatr Soc*. 1993;41:38-41.
30. Parmalee PA, Thuras PD, Katz IR, Lawton MP. Validation of the cumulative illness rating scale in a geriatric residential population. *J Am Geriatr Soc*. 1995;43:130-137.
31. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other [mis]uses of baseline data in clinical trials. *Lancet*. 2000;355:1064-1069.
32. Kock GG, Tangen CM, Jung JW, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and nonparametric strategies for addressing them. *Stat Med*. 1998;17:1863-1892.
33. Teri L, Logsdon RG, Uomoto J, McCurry SM. Behavioral treatment of depression in dementia patients: a controlled clinical trial. *J Gerontol B Psychol Sci Soc Sci*. 1997;52:P159-P166.
34. Moretti R, Torre P, Antonello RM, Cazzato G. Behavioral alterations and vascular dementia. *Neurologist*. 2006; 12:43-47.
35. Finkel SI. Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. *Clin Ther*. 2004;26:980-990.
36. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: an open 22-month study. *J Neurol Sci*. 2002;203-204: 141-146.
37. Venneri A, Shanks MF, Staff RT, et al. Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *Neuroreport*. 2002;13:83-87.