European Journal of Neurology 2000, **7:** 159–169

An efficacy and safety analysis of Exelon® in Alzheimer's disease patients with concurrent vascular risk factors

V. Kumar[a], R. Anand[b], J. Messina[b], R. Hartman[b] and J. Veach[b]

[a]*Florida Institute of Neurosciences and Clinical Research, 530 S. Nokomis Avenue, Suite 14, Venice, FL 34284; and* [b]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*

Keywords:
Alzheimer's disease, cholinesterase inhibitors, rivastigmine, vascular risk factors

Received 28 May 1999
Accepted 7 December 1999

We evaluated the efficacy and safety of the centrally acting cholinesterase inhibitor, rivastigmine tartrate, for patients with mild to moderately severe Alzheimer's disease (AD) with or without concurrent vascular risk factors (VRF). Patients (45–90 years of age) were randomized to placebo (n = 235), low-dose rivastigmine (1–4 mg/day, n = 233), or high-dose rivastigmine (6–12 mg/day, n = 231) for 26 weeks. Efficacy measures included the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), the Clinician's Interview Based Impression of Change (CIBIC-Plus), the Progressive Deterioration Scale (PDS), the Global Deterioration Scale (GDS), and the Mini-Mental State Examination (MMSE). For efficacy and safety analysis, patients were categorized by baseline Modified Hachinski Ischemic Score (MHIS) for the determination of VRF (MHIS $>$ 0: presence of VRF; MHIS = 0: absence of VRF). As early as 12 weeks, the mean change from the baseline ADAS-Cog score was significantly different for those patients treated with high-dose rivastigmine compared with placebo controls in both MHIS categories. However, the treatment difference between high-dose rivastigmine and placebo at each time-point was larger for patients with MHIS $>$ 0. The proportion of responders was significantly greater in the high-dose rivastigmine group for each level of improvement. No differences were noted between treatment groups regarding safety evaluations. Rivastigmine is effective in both categories of patients, and those with VRF experience greater clinical benefit (cognition, activities of daily living, and disease severity).

Introduction

The most prevalent forms of dementia include Alzheimer's disease (AD) (50–60% of cases) and vascular dementia (VaD) (10–20%) (Tomlinson *et al*., 1970; O'Brien, 1977; Nyenhuis and Gorelick, 1998). Although studies have suggested that pure vascular dementia is uncommon at brain necropsy (Tomlinson *et al*., 1970; Hulette *et al*., 1997), findings from a recent study suggest that cerebrovascular changes may play an important role in the clinical expression of AD (Snowdon *et al*., 1997) and vascular changes may often coexist with AD (Gearing *et al*., 1995). These two major forms of dementia often coexist in mixed dementia (10–20% of cases). Mixed dementia includes AD patients with cerebrovascular lesions on neuroimaging or patients who have clinical features of both AD and VaD (Rockwood *et al*., 1997). This includes up to one-third of AD patients. However, approximately 25% of AD patients have vascular lesions that are undetectable upon neuroimaging but are evident at autopsy (Rasmusson *et al*., 1996), indicating that patients with AD often have vascular pathology that contributes to the symptoms of their dementia.

The difficulty in determining an accurate diagnosis impacts on the treatment options available to the clinician. The use of ischaemia scoring scales was one of the first attempts to differentiate degenerative dementia from vascular dementia based on clinical signs and cardiovascular risk factors, as originally proposed by Hachinski and colleagues (Hachinski *et al*., 1975). The most important value of the ischemic scales lies in their ability to isolate cases of AD from other forms of dementia, and particularly patients who may have complicating cerebrovascular disease (Tatemichi *et al*., 1994). One such ischemic score, the Modified Hachinski Ischemic Score (MHIS), was developed as an exclusionary criterion for vascular dementia, and autopsy studies indicate that it is an accurate predictor of vascular disease of the brain (Rosen *et al*., 1980; Wade *et al*., 1987). Using the MHIS, scores of ≤ 4 are consistent with probable AD. Vascular risk factors

Correspondence: Dr V. Kumar at Florida Institute of Neurosciences and Clinical Research, 530 S. Nokomis Avenue, Suite 14, Venice, FL 34285, USA (fax: +1 941 412 0477; e-mail: kumarV1@aol.com).

defined in the MHIS include abrupt onset (of dementia), stepwise deterioration, somatic complaints, emotional incontinence, history of strokes, focal neurological signs and symptoms, and history or presence of hypertension.

It appears that the neuropathogenesis of dementia involves several mechanisms including cholinergic deficits and multifocal ischemic lesions (Carlsson, 1987; Markstein, 1989). Cholinergic indices, including hippocampal choline acetyl transferase (ChAT) activity and the number of muscarinic cholinergic receptor sites were reduced in VaD patients compared with controls but were generally similar to AD patients (Sakurada *et al.*, 1990). Other findings showed that the acetylcholine (ACh) concentration found in the cerebrospinal fluid (CSF) was significantly lower in VaD patients compared with controls, but was significantly higher than in AD patients (Tohgi *et al.*, 1996). Also, the choline (Ch) concentration found in CSF of VaD patients was significantly higher than in controls or AD patients (Tohgi *et al.*, 1996). In addition, serum G4 isoenzyme AChE activity was significantly increased in patients with VaD compared with controls, and was significantly decreased in AD patients. The difference between VaD and AD was also significant (Yamamoto *et al.*, 1990). These studies appear to suggest that patients with vascular changes have cholinergic deficits that may benefit from cholinergic replacement therapy in a similar fashion as patients with pure AD.

Rivastigmine is a centrally selective cholinesterase (ChE) inhibitor that demonstrates brain-region selectivity for the hippocampus and cortex (Polinsky, 1998). Rivastigmine also inhibits butyrylcholinesterase (BChE) in AD patients (Cutler *et al.*, 1998), an enzyme that in normal subjects constitutes a small percentage of esterase activity in the brain but in AD patients is significantly increased to approximately 30% (Mesulam and Geula, 1994), and is also found in neurofibrillary plaques (Mesulam and Geula, 1994; Guillozet *et al.*, 1997). The results of two double-blind, six-month, placebo-controlled studies with rivastigmine in patients with mild to moderately severe AD were previously reported (Corey-Bloom *et al.*, 1998; Rosler *et al.*, 1999). In both studies, patients treated with high-dose rivastigmine demonstrated a distinct clinical benefit on all outcome measures, including cognition, global assessment of change including behaviour, activities of daily living and disease severity.

Despite the neuro-anatomical differences between AD and VaD, they may share similar neurochemical characteristics that would permit a response to therapy in the form of cholinesterase inhibition. Results of prospective clinical trials with cholinesterase inhibitors for AD patients with vascular risk factors have not yet been published. The rivastigmine trials included a large number of AD patients with concurrent vascular risk factors providing an opportunity to assess the response of this subgroup of patients to rivastigmine. Therefore, an analysis was conducted to assess the efficacy and safety of rivastigmine during a six-month period in AD patients with vascular risk factors categorized by baseline MHIS.

Methodology

Both the patient population and the study design have been described previously in detail (Corey-Bloom *et al.*, 1998). Only selected features are described below.

Patient population

Eligible patients were between 45 and 89 years of age who fulfilled the criteria for having dementia of Alzheimer's type, as described in the fourth edition of the *Diagnostic and Statistical Manual of Psychiatric Disorders* (DSM-IV) of the American Psychiatric Association (American Psychiatric Association, 1994), and had probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) (McKhann *et al.*, 1984). Patients had a mild to moderately severe impairment based on a Mini-Mental State Examination (MMSE) score (Folstein *et al.*, 1975) of 10–26, inclusive. A computed tomography (CT) of the head or magnetic resonance imaging (MRI) scan was conducted at baseline or within 12 months, with results consistent with the diagnosis of AD also being required for patient inclusion.

Modified Hachinski Ischemic Score (MHIS)

The MHIS was determined at baseline for patient eligibility (Rosen *et al.*, 1980). Patients with a composite score of ≥ 5 were excluded from the study entry as their vascular risk was considered to be inconsistent with probable AD as defined by NINCDS-ADRDA.

Study design

This was a 26-week, randomized, double-blind, placebo-controlled study conducted within the USA at 22 investigational sites. Patients were randomized at baseline to one of three treatment groups: rivastigmine 6–12 mg/day, rivastigmine 1–4 mg/day or placebo. During weeks 1–7 (fixed-dose titration phase) patients received escalating doses of rivastigmine or placebo; at week 7, if patients had not tolerated the minimum

dosage within their assigned range they were discontinued from the study. During weeks 8–26 (flexible dose-titration phase), investigators either maintained, increased or decreased the dose within the dose range of 6–12 mg/day.

Efficacy measures included the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (Rosen *et al*., 1984), the Clinician's Interview Based Impression of Change, incorporating input from the caregiver (CIBIC-Plus) (Reisberg *et al*., 1992, 1997), and the Progressive Deterioration Scale (PDS) (DeJong *et al*., 1989), which is an activities of daily living (ADL) assessment that is completed by the caregiver. Efficacy evaluations were conducted at baseline and at weeks 12, 18 and 26 (or early termination visit). Two additional efficacy measures included staging instruments, the MMSE (Folstein *et al*., 1975) and the Global Deterioration Scale (GDS) (Reisberg *et al*., 1992, 1997), which were completed at baseline and at week 26.

Safety evaluations were performed regularly throughout the study and included vital signs, electrocardiograms, laboratory evaluations (haematology, blood chemistry, urinalysis) and adverse event monitoring.

Statistical methodology

In this analysis, patients were dichotomized as having MHIS = 0 or MHIS > 0 at baseline. All analyses and summaries were then based on the patients' MHIS dichotomization and randomized treatment group (6–12 mg/day, 1–4 mg/day and placebo). Efficacy analyses were performed on one data set, the observed cases (OC, randomized patients with at least one evaluation while on study medication at designated assessment times). The statistical methods have been described previously (Corey-Bloom *et al*., 1998). The safety analyses consisted of data for all patients who received at least one dose of study medication and who had a subsequent on-drug safety evaluation. Comparisons to placebo for safety were made using ANOVA for changes from baseline and Fisher's exact test for the occurrence of abnormalities.

For analysis of the ADAS-Cog mean change from baseline score, a two-way analysis of variance model was fit:

$$y_{ijk} = \mu + \alpha\beta_{ij} + \epsilon_{ijk},$$

where μ is the mean effect, y_{ijk} is the individual patient response (e.g. ADAS-Cog change from baseline), $\alpha\beta_{ij}$ is the effect of the interaction between randomized treatment group (three levels) and MHIS dichotomization (two levels) at level ij. ϵ_{ijk} is the experimental error. This model is analogous to a one-way analysis of variance where the above interaction is treated as a single parameter with six levels. Comparisons were made between the six levels using pairwise *t*-tests. Similarly, for comparison of responders, pairwise comparisons were made using Fisher's exact tests.

Results

Demographics

Of the 699 patients enrolled in the trial, 378 had an MHIS = 0 and 319 had an MHIS > 0 at baseline. Two patients did not have an MHIS determined at baseline and were not included in the analysis. Patient demographics are summarized in Table 1. For both categories of patients combined (MHIS = 0 and MHIS > 0), the mean age of the patients was approximately 74 years. There were more females in both categories of patients; however, there was a larger proportion of females in the MHIS > 0 category. There were no significant differences between the categories with regard to baseline disease or demographic characteristics. There was a similar distribution of patients by MHIS of 0, 1, 2, 3 and 4 in each treatment group (Table 2). The relative frequency of the items occurring in the MHIS > 0 category for each treatment group are presented in Table 3. Of the 319 patients in the MHIS > 0 category, 73% had a history of hypertension compared with 76% of patients with MHIS = 1, 60% with MHIS = 2, 70% with MHIS = 3, and 50% of patients with MHIS = 4.

Table 1 Baseline demographic and disease information by MHIS category

Variable	MHIS = 0 (n = 378)	MHIS > 0 (n = 319)
Age group (years)		
≤ 65	43 (11)	39 (12)
66–75	161 (43)	116 (36)
76–85	160 (42)	144 (45)
> 85	14 (4)	20 (6)
Mean age ± SEM	74.3 ± 0.37	74.8 ± 0.42
Sex (%)		
Male	163 (43)	110 (34)
Female	215 (57)	209 (66)
Dementia duration (months)		
Mean ± SEM	39.2 ± 1.28	39.7 ± 1.39
Range	6–180	3–138
MMSE total score		
Mean ± SEM	20.2 ± 0.22	19.2 ± 0.25
GDS SCORE		
Mean ± SEM	3.8 ± 0.043	4.1 ± 0.044
ADAS-Cog score		
Mean ± SEM	21.2 ± 0.56	23.3 ± 0.65

Table 2 Distribution of MHIS by treatment group

MHIS	Rivastigmine 6–12 mg/day $n = 230$ (%)	Rivastigmine 1–4 mg/day $n = 232$ (%)	Placebo $n = 235$ (%)	Total $n = 697$ (%)
Score = 0	123 (53)	123 (53)	132 (56)	378 (54)
Score = 1	84 (37)	83 (36)	79 (34)	246 (35)
Score = 2	14 (6)	21 (9)	12 (5)	47 (7)
Score = 3	7 (3)	3 (1)	10 (4)	20 (3)
Score = 4	2 (1)	2 (1)	2 (1)	6 (1)
Total MHIS > 0	107 (47)	109 (47)	103 (44)	319 (46)

Patients in both categories had a substantial level of comorbidity, with 99% of patients with MHIS > 0 and 89% of patients with MHIS = 0 reporting a baseline medical condition. The pattern of reported medical conditions between the MHIS categories was similar except for cardiovascular disorders, with 70% of patients in the MHIS > 0 category reporting general cardiovascular disorders at baseline compared with 5% of patients in the MHIS = 0 category. Patients in the MHIS > 0 category reported a higher use of concomitant medications than those in the MHIS = 0 category.

Disposition

Of the 699 patients enrolled in the study, 545 completed treatment [294 (78%) with MHIS = 0 and 251 (79%) with MHIS > 0]. The patient withdrawal rates were comparable between the two categories of patients (MHIS = 0 and MHIS > 0): 6–12 mg/day, 37 and 33%; 1–4 mg/day, 14 and 15%; and placebo, 16 and 17%. Adverse events were the most frequent reason for withdrawal in both MHIS categories and within each treatment group.

Efficacy

This paper will focus on the OC results as these represent actual data and results not influenced by scores being carried forward for patients who did not have time to deteriorate.

ADAS-Cog

The decline in cognitive performance for patients treated with rivastigmine 6–12 mg/day was less compared with patients treated with placebo ($P < 0.001$, Table 4, Figure 1). At week 26, improvement in cognition was observed for patients receiving a regimen of rivastigmine 6–12 mg/day in the MHIS > 0 category ($P < 0.001$, Table 5). However, the treatment difference was larger in the MHIS > 0 category (6.15 points vs. 4.03 points). Also, a difference was observed in the MHIS > 0 category between patients receiving placebo and those receiving 1–4 mg/day rivastigmine ($P = 0.002$).

For placebo-treated patients, there was no difference in the level of decline as measured by the ADAS-Cog mean change from baseline scores between the two MHIS categories ($P = 0.552$). However, for patients treated with 6–12 mg/day rivastigmine, the difference in mean change from baseline ADAS-Cog scores between the two MHIS categories was different with patients in the MHIS > 0 category exhibiting a greater therapeutic benefit from rivastigmine (treatment difference = 2.3 ADAS-Cog points, $P = 0.02$).

The percentage of patients who improved by 0, 4 and 7 points from baseline in their ADAS-Cog score for

Table 3 The relative frequency of MHIS items by treatment group

Hachinski symptom	Rivastigmine 6–12 mg/day ($n = 107$)	Rivastigmine 1–4 mg/day ($n = 109$)	Placebo ($n = 103$)	Total ($n = 319$)
MHIS > 0				
Abrupt onset	0 (0)	0 (0)	1 (1)	1 (< 1)
Stepwise deterioration	2 (2)	3 (3)	3 (3)	8 (3)
Somatic complaints	26 (24)	23 (21)	19 (18)	68 (21)
Emotional incontinence	11 (10)	14 (13)	17 (17)	42 (13)
History of hypertension	78 (73)	80 (73)	74 (72)	232 (73)
History of strokes	5 (5)	4 (4)	5 (5)	14 (4)
Focal neurological symptoms	2 (2)	2 (2)	4 (4)	8 (3)
Focal neurological signs	5 (5)	5 (5)	4 (4)	14 (4)

	Placebo	Rivastigmine 1–4 mg/day	Rivastigmine 6–12 mg/day
Primary efficacy variables			
ADAS-Cog (0–70 points)	$n = 107$	$n = 104$	$n = 76$
Endpoint, mean change from baseline ± SEM	− 3.7	− 2.6	− 0.4
Drug–placebo difference		1.1	3.3
P (treatment vs. placebo)		0.205	< 0.001
CIBIC-Plus (ratings 1–7; 4 = no change)	$n = 110$	$n = 103$	$n = 76$
Endpoint, mean rating ± SEM	4.54 ± 0.093	4.17 ± 0.12	4.21 ± 0.14
Drug–placebo difference		0.37	0.33
P (treatment vs. placebo)		0.023	0.06
Secondary efficacy variables			
PDS (1–100 points)	$n = 105$	$n = 102$	$n = 76$
Endpoint, mean change from baseline ± SEM	− 5.6 ± 1.01	− 6.6 ± 1.044	− 2.1 ± 1.32
Drug–placebo difference		1.0	3.5
P (treatment vs. placebo)		0.468	0.03
GDS (1–7 points)	$n = 114$	$n = 110$	$n = 87$
Baseline, mean ± SEM	3.69 ± 0.077	3.91 ± 0.083	3.87 ± 0.089
Baseline, range	2.0–5.0	2.0–6.0	2.0–6.0
Endpoint, mean change from baseline ± SEM	0.34 ± 0.068	0.15 ± 0.066	0.21 ± 0.071
Drug–placebo difference		0.19	0.13
P (treatment vs. placebo)		0.028	0.155
MMSE (0 – 30 points)	$n = 113$	$n = 110$	$n = 88$
Endpoint, mean change from baseline ± SEM	− 0.8 ± 0.32	− 0.4 ± 0.31	0.03 ± 0.32
Drug–placebo difference		0.42	0.7
P (treatment vs. placebo)		0.322	0.086

Table 4 Results of pairwise comparisons for primary and secondary efficacy variables at week 26 for patients in the MHIS = 0 category

ADAS-Cog is a measure of cognition: an increase in score is associated with worsening. CIBIC-Plus is used as a global assessment of change: rating of 4 indicates no change; 1, 2 and 3 indicate marked, moderate and minimal improvement and 5, 6 and 7 indicate minimal, moderate and marked worsening. PDS is a 29-item measure of ADLs: a lower score is associated with worsening. GDS is a rating of disease severity: a higher score is associated with worsening disease. MMSE is a screening test for cognition: a lower score is associated with worsening.

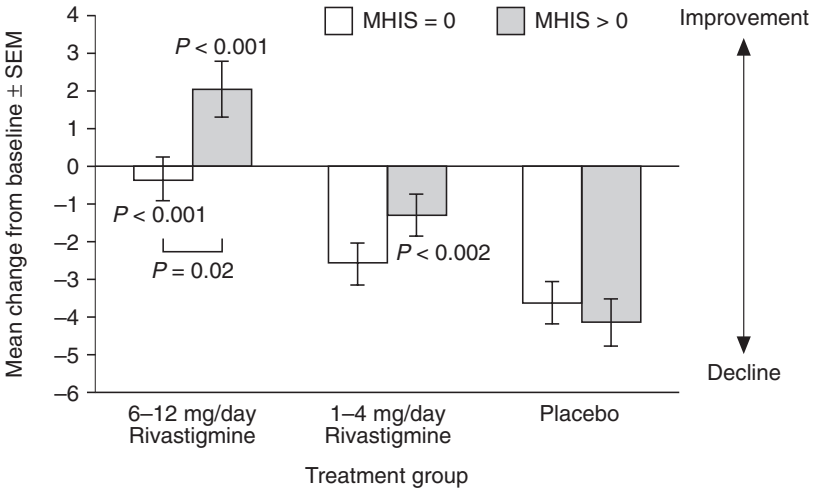

Figure 1 ADAS-Cog mean change from baseline scores at week 26 (OC analysis).

	Placebo	Rivastigmine 1–4 mg/day	Rivastigmine 6–12 mg/day
Primary efficacy variables			
ADAS-Cog (0–70 points)	$n = 85$	$n = 90$	$n = 69$
Endpoint, mean change from baseline ± SEM	− 4.2 ± 0.69	− 1.4 ± 0.54	− 1.9 ± 0.78
Drug–placebo difference		2.8	6.1
P (treatment vs. placebo)		< 0.002	< 0.001
CIBIC-Plus (ratings 1–7; 4 = no change)	$n = 87$	$n = 92$	$n = 69$
Endpoint, mean rating ± SEM	4.4 ± 0.13	4.23 ± 0.10	4.12 ± 0.14
Drug–placebo difference		0.170	0.28
P (treatment vs. placebo)		0.315	0.125
Secondary efficacy variables			
PDS (1–100 points)	$n = 87$	$n = 89$	$n = 69$
Endpoint, mean change from baseline ± SEM	− 6.3 ± 1.18	− 3.8 ± 0.88	− 0.4 ± 1.29
Drug–placebo difference		2.5	5.9
P (treatment vs. placebo)		0.118	< 0.001
GDS (1–7 points)	$n = 95$	$n = 96$	$n = 82$
Baseline, mean ± SEM	4.09 ± 0.087	4.06 ± 0.078	4.21 ± 0.084
Baseline, range	2.0–6.0	3.0–5.0	3.0–6.0
Endpoint, mean change from baseline ± SEM	0.33 ± 0.070	0.23 ± 0.06	0.11 ± 0.064
Drug–placebo difference		0.10	0.22
P (treatment vs. placebo)		0.315	0.032
MMSE (0–30 points)	$n = 95$	$n = 94$	$n = 80$
Endpoint, mean change from baseline ± SEM	− 0.6 ± 0.28	− 0.4 ± 0.28	0.6 ± 0.37
Drug–placebo difference		0.3	1.26
P (treatment vs. placebo)		0.53	0.005

ADAS-Cog is a measure of cognition, and an increase in score is associated with worsening. CIBIC-Plus is used as a global assessment of change: a rating of 4 indicates no change; 1, 2 and 3 indicate marked, moderate and minimal improvement and 5, 6 and 7 indicate minimal, moderate and marked worsening. PDS is a 29-item measure of ADLs: a lower score is associated with worsening. GDS is a rating of disease severity: a higher score is associated with worsening disease. MMSE is a screening test for cognition: a lower score is associated with worsening.

Table 5 Results of pairwise comparisons for primary and secondary efficacy variables at week 26 for patients in the MHIS > 0 category

both MHIS categories are provided in Table 6. In the MHIS > 0 category, more patients treated with 6–12 mg/day rivastigmine improved than patients treated with placebo for each level of improvement. Similar results were seen in the MHIS = 0 category; however, the magnitude of response was less than that observed in the MHIS > 0 category.

Pds

At week 26, the PDS mean change from baseline score demonstrated superiority for patients receiving high-dose rivastigmine vs. placebo in the MHIS = 0 category ($P = 0.03$) and MIHS > 0 category ($P < 0.001$, Tables 4 and 5, Figure 2). However, the treatment difference was larger in the MHIS > 0 category (5.9 points vs. 3.5 points). Furthermore, in both MHIS categories, more patients treated with 6–12 mg/day rivastigmine exhibited ≥ 10% improvement on PDS at study end-point compared with the placebo group ($P < 0.05$, Table 6).

CIBIC-Plus

In both MHIS categories, lower mean CIBIC-Plus ratings were observed in the rivastigmine-treated groups indicating less deterioration compared with the placebo group at week 26 (Tables 4 and 5, Figure 3). The mean CIBIC-Plus rating for the 1–4 mg/day group was lower compared with the placebo group in the MHIS = 0 category ($P = 0.023$). Both rivastigmine treatment groups had higher percentages of responders

Table 6 Percentage of patients with improvement in ADAS-Cog, CIBIC-Plus and PDS at week 26 vs. baseline in both MHIS categories (B352 OC analysis)

	MHIS = 0 category			MHIS > 0 category		
Efficacy variable/ definition of improvement	Placebo	Rivastigmine 1–4 mg/day	Rivastigmine 6–12 mg/day	Placebo	Rivastigmine 1–4 mg/day	Rivastigmine 6–12 mg/day
ADAS-Cog	$n = 107$	$n = 104$	$n = 76$	$n = 85$	$n = 90$	$n = 69$
≥ 0-point improvement	33 (31)	32 (31)	37 (49)*	18 (21)	35 (39)*	43 (62)†
≥ 4-point improvement	7 (7)	9 (9)	14 (18)*	6 (7)	14 (16)	22 (32) †
≥ 7-point improvement	1 (1)	1 (1)	6 (8)*	2 (2)	3 (3)	11 (16)*
CIBIC-Plus	$n = 110$	$n = 103$	$n = 76$	$n = 87$	$n = 92$	$n = 69$
Rating of 1, 2 or 3 (improved)	12 (11)	26 (25)*	19 (25)*	19 (22)	22 (24)	16 (23)
Rating of 4 (no change)	49 (45)	39 (38)	24 (32)	28 (32)	33 (36)	28 (41)
Rating of 5, 6 or 7 (worsening)	49 (45)	38 (37)	33 (43)	40 (46)	37 (40)	25 (36)
PDS	$n = 105$	$n = 102$	$n = 76$	$n = 87$	$n = 89$	$n = 69$
≥ 10% improvement	12 (11)	11 (11)	18 (24)*	13 (15)	13 (15)	20 (29)*

*$P < 0.05$ (treatment vs. placebo); †$P < 0.001$ (treatment vs. placebo).

on CIBIC-Plus compared with the placebo treatment group in the MHIS = 0 category ($P < 0.05$, Table 6).

MMSE and GDS

In both MHIS categories, the MMSE mean change from baseline scores were higher indicating less deterioration in the 6–12 mg/day group compared with the placebo group (MHIS = 0, $P = 0.086$; MHIS > 0, $P = 0.005$). However, the treatment difference was larger in the MHIS > 0 category (Table 5, Figure 4). At week 26, the mean change from baseline GDS score for patients receiving 6–12 mg/day indicated less disease worsening in the MHIS > 0 category ($P = 0.032$, Table 5). Furthermore, a similar finding was observed for the 1–4 mg/day rivastigmine group compared with the placebo group in the MHIS = 0 category ($P = 0.028$, Table 4).

Safety

Treatment with rivastigmine was not associated with any increase in mortality, serious adverse events (AEs), effects on laboratory parameters, ECGs or cardiovascular vital signs in either MHIS category.

The AEs reported by patients in both MHIS categories were primarily mild to moderate in severity, dose related during the titration phase, and of limited duration (Corey-Bloom *et al.*, 1998). For both categories (MHIS = 0 and MHIS > 0), the most common AEs were cholinergic, primarily gastrointestinal (67 and 54%), e.g. nausea (41 and 25%), vomiting (16% for both categories), diarrhea (23 and 17%) and anorexia

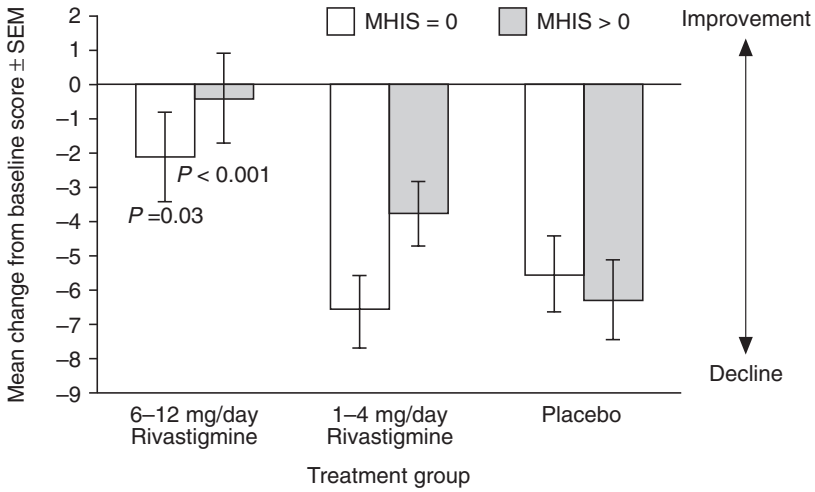

Figure 2 PDS mean change from baseline score at week 26 (OC analysis).

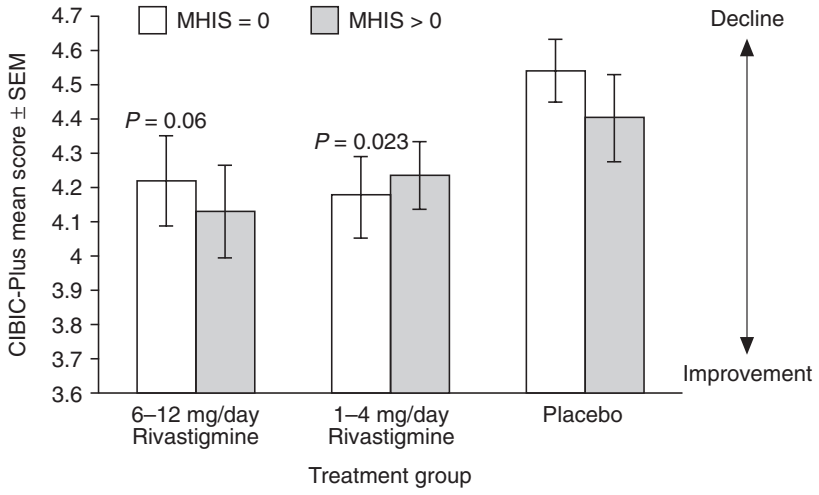

Figure 3 CIBIC-Plus mean score for population (OC analysis).

(15 and 12%). There were no major differences in the type or nature of AEs reported between the two MHIS categories. The incidence of the various AEs reported for each respective treatment group was also similar between the two categories.

Discussion

In this report, the data indicate that rivastigmine was associated with improvements over placebo for a wide variety of efficacy measures (cognitive performance, ADL and disease severity) for patients with and without vascular risk factors. The treatment effect was generally larger in MHIS > 0 patients with vascular risk factors (ADAS-Cog, PDS, MMSE and GDS mean change from baseline scores). The treatment difference at week 26 for patients in the MHIS > 0 category treated with 6–12 mg/day rivastigmine vs. placebo was 6.15 ADAS-Cog points, exceeding that reported in Study B352 (Corey-Bloom *et al.*, 1998) or in other studies with rivastigmine (Schneider *et al.*, 1998; Rosler *et al.*, 1999).

While the mean 6–12 mg/day and placebo difference on ADAS-Cog was greater in those patients with vascular risk factors compared with patients without vascular risk factors, this difference in effect size is attributed to the larger improvement from baseline in the MHIS > 0 category 6–12 mg group, as the placebo decline in both groups was not different. The observation that the rivastigmine effect was greater in patients with MHIS > 0 cannot be explained by the differences in the decline of the placebo population.

The clinical utility of the cognitive effects is further supported by the benefits seen in ADL in these patients. While significant improvement was seen in AD patients with and without vascular risk factors, the treatment

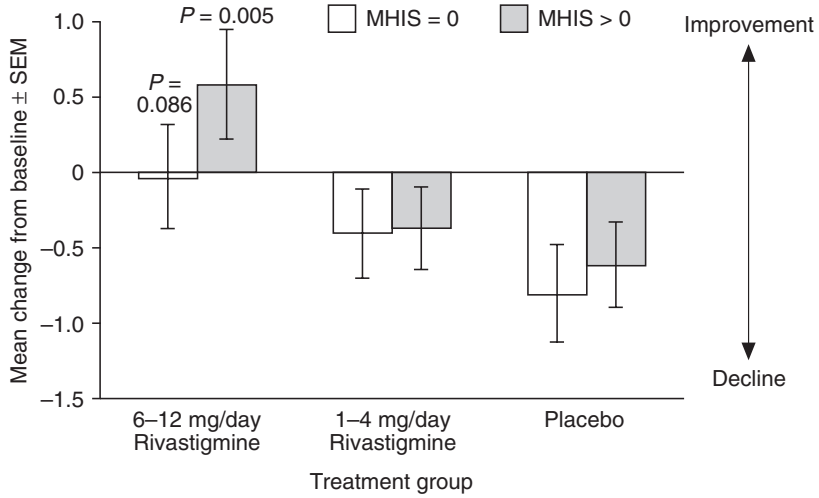

Figure 4 MMSE mean change from baseline score at week 26 (OC analysis).

differences were larger for the group with vascular risk factors. These effects were also corroborated by the GDS and MMSE results seen in these patients. The CIBIC-Plus results showed slightly more benefit in the MHIS > 0 category for 6–12 mg/day and for 1–4 mg/day. However, due to the decreasing sample size, statistical significance was not observed in the MHIS > 0, 6–12 mg/day group when compared with MHIS > 0 placebo group.

Whether the effects are unique to rivastigmine or are common to the class of ChE inhibitor is unknown. Rivastigmine, however, does have some unique properties previously observed that may help explain these results. Pre-clinical studies involving a gerbil model have suggested that rivastigmine may be protective in ischemic brain conditions since decreases in cholinergic indices following transient cerebral ischemia in rivastigmine-treated gerbils were prevented (Tsujimoto *et al*., 1993; Tanaka *et al*., 1993; Tanaka *et al*., 1994a; Tanaka *et al*., 1995). Furthermore, chronic administration of rivastigmine in the senescent rat brain completely prevented ACh and ChAT reductions (Tanaka *et al*., 1994b). These findings suggest a possible neuroprotective effect throughout the cholinergic synapse which maintains the concentration of acetylcholine and may also protect against the ageing-induced depletion of pre- and postsynaptic cholinergic indices.

Another possible explanation for the increase in effect on cognition in patients with vascular risk factors observed with rivastigmine may be its ability to increase cerebral blood flow (Sauter *et al*., 1989; Tsujimoto *et al*., 1993; Sadoshima *et al*., 1995). Cholinesterase appears to be involved in the regulation of cerebral blood flow, as both cholinesterase inhibition and direct cholinergic stimulation with agonists have been shown to increase cerebral blood flow. Cerebral blood flow has been reported to be reduced in patients with both the cerebrovascular type and the Alzheimer type of dementia (Hachinski *et al*., 1975). In some instances, the decrease in cerebral blood flow precedes the onset of vascular dementia (Mayer *et al*., 1986; Rogers *et al*., 1986). It also seems possible that a chronic decrease of cerebral blood flow may play a significant role in progressive neuronal degeneration. Therefore, the increase in cerebral blood flow with an agent such as rivastigmine may enhance collateral circulation via vessel dilatation, and protect against focal ischemia (Tsujimoto *et al*., 1993) and a worsening of vascular pathology.

Of importance is the finding that hypertension with its attendant need for medication did not pose as an issue with rivastigmine use as there were no drug interactions (Hay and Grossberg, 1998). Similarly, the mild and transient nature of the adverse events reported in these analyses is consistent with the safety profile of rivastigmine reported for pooled data from three clinical studies (Schneider *et al*., 1998). In fact, it supports earlier findings that rivastigmine is tolerated well by medically compromised, elderly, patients with dementia (Corey-Bloom *et al*., 1998; Rosler *et al*., 1999).

The potential clinical significance of the positive therapeutic effect observed in AD patients with vascular risk factors is immense. The difficulty in making an accurate differential clinical diagnosis of AD vs. VaD or other types of dementia is well known. Based on the results presented above, highlighting the therapeutic benefits of rivastigmine on cognitive performance, disease severity and ADL in AD patients with vascular risk factors, the concern of treating patients with rivastigmine who may have undetectable vascular changes in addition to AD with a cholinesterase inhibitor may be attenuated. It is important to note, however, that no drug therapy has been established to date to treat the cognitive impairment associated with vascular dementia, although compounds including pentoxifylline (Black *et al*., 1992), nimodipine (Fishhof *et al*., 1989), propentofyllin (Marcusson, 1995) and hydergine (Schneider and Olin, 1994) have been studied. Their effects appear to be modest, with the most clinically significant effects having been observed in subgroups of patients with VaD. The potential benefit of rivastigmine in treating this type of dementia needs to be further investigated in prospective placebo-controlled studies. Future studies need to assess other factors, such as APOE4 status, which may influence the amount of cholinergic deficit and therefore partially explain increased response in patients with vascular pathology.

References

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* 4th edn. Washington, DC: American Psychiatric Association.

Black RS, Barclay LL, Nolan KA, Thaler HT, Hardiman ST, Blass JP (1992). Pentoxifylline in cerebrovascular dementia. *J Am Geriatr Soc* **40**:237–244.

Carlsson A (1987). Brain neurotransmitters in aging and dementia: similar changes across diagnostic dementia groups. *Gerontology* **33**:159–167.

Corey-Bloom J, Anand R, Veach J (1998). A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* **1**:55–65.

Cutler NR, Polinsky RJ, Sramek JJ *et al*. (1998). Dose-dependent CSF acetylcholinesterase inhibition by SDZ ENA 713 in Alzheimer's disease. *Acta Neurol Scand* **97**:244–250.

DeJong R, Osterlund OW, Roy GW (1989). Measurement of

quality-of-life changes in patients with Alzheimer's disease. *Clin Ther* **11**:545–554.

Fishhof PK, Wagner G, Littschaier L *et al.* (1989). Therapeutic results with nimodipine in primary degenerative dementia and multi-infarct dementia. In: Bergener H, Reisberg B eds. *Diagnosis and Treatment of Senile Dementia*. Berlin: Springer Verlag, pp. 350–359.

Folstein MF, Folstein SE, McHugh PR (1975). 'Mini-Mental State.' A practical method for grading the cognitive status of patients for the clinician. *J Psychiatr Res* **12**:189–198.

Gearing M, Mirra SS, Hedreen JC, Sumi SM, Hansen LA, Hyman A (1995). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology* **45**:461–466.

Guillozet AL, Smiley JF, Mash DC, Mesulam MM (1997). Butyrylcholinesterase in the life cycle of amyloid plaques. *Ann Neurol* **42**:909–918.

Hachinski V, Iliff L, Zilhka E *et al.* (1975). Cerebral blood flow in dementia. *Arch Neurol* **32**:632–637.

Hay L, Grossberg GT (1998). Polypharmacy in the elderly: clinical implications. *Int J Geriatr Psychopharmacol* **1**:S15–S19.

Hulette C, Nochlin D, McKeel D *et al.* (1997). Clinical neuropathological findings in multi-infarct dementia: a report of six autopsied cases. *Neurology* **48**:668–672.

Marcusson J (1995). HWA 285 for the treatment of dementia – results of a 12 month clinical trial. *J Cereb Blood Flow Metabolism* **15**:S107.

Markstein R (1989). Pharmacological approaches in the treatment of senile dementia. *Eur Neurol* **29**:33–41.

Mayer JS, Judd BW, Tawaklna T, Rogers RL, Mortel KF (1986). Improved cognition after control of risk factors for multi-infarct dementia. *JAMA* **256**:2203–2209.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**:939–944.

Mesulam MM, Geula C (1994). Butyrylcholinesterase reactivity differentiates the amyloid plaques of aging from those of dementia. *Ann Neurol* **36**:722–727.

Nyenhuis DL, Gorelick PB (1998). Vascular dementia: a contemporary review of epidemiology, diagnosis, prevention, and treatment. *J Am Geriatr Soc* **46**:1437–1448.

O'brien MD (1977). Vascular disease and dementia in the elderly. In: Smith WL, Kinsbourne M eds. *Aging and Dementia*. New York: Spectrum, pp. 77–90.

Polinsky R (1998). Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Clin Ther* **20**: 634–647.

Rasmusson DX, Brandt J, Steele C, Hedreen JC, Troncoso JC, Folstein MF (1996). Accuracy of clinical diagnosis of Alzheimer disease and clinical features of patients with non-Alzheimer disease neuropathology. *Alzheimer Dis Assoc Disord* **10**:180–188.

Reisberg B, De Ferris SH, Leon MJ, Crook T (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* **139**:1136–1139.

Reisberg B, Schneider L, Doody R *et al.* (1997). Clinical global measure of dementia: position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord* **11**: 8–18.

Rockwood K, Ebly E, Hackinski V, Hogan D (1997). Presence and treatment of vascular risk factors in patients with vascular cognitive impairment. *Arch Neurol* **54**:33–39.

Rogers RL, Meyer JS, Mortel KF, Mahurin RK, Judd BW (1986). Decreased cerebral blood flow precedes multi-infarct dementia, but follows senile dementia of the Alzheimer type. *Neurology* **36**:1–6.

Rosen WG, Mohs RC, Davis KL (1984). A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**:1356–1364.

Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A (1980). Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol* **7**:486–488.

Rosler M, Anand R, Cicin-Sain A *et al.* (1999). Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomized controlled trial. *Br Med J* **318**:633–640.

Sadoshima S, Ibayashi S, Fujii K, Nagao T, Sugimori H, Fujishima M (1995). Inhibition of acetylcholinesterase modulates the autoregulation of cerebral blood flow and attenuates ischemic brain metabolism in hypertensive rats. *J Cereb Blood Flow Metab* **15**:845–851.

Sakurada T, Alufuzoff I, Winblad B, Nordberg A (1990). Substance P-like immunoreactivity, choline acetyltransferase activity and cholinergic muscarinic receptors in Alzheimer's disease and multi-infarct dementia. *Brain Res* **521**:329–332.

Sauter A, Rudin M, Enz A (1989). *Neurotransmission and Cerebrovascular Function 1*. Seylaz J, Mackenzie E, eds. New York, USA: Elsevier, 373—376.

Schneider LS, Anand R, Farlow MR (1998). A systematic review of the efficacy of rivastigmine for patients with Alzheimer's disease (1998). *Int J Geriatr Psychopharmacol* **1**:S26–S34.

Schneider LS, Olin JS (1994). Overview of clinical trials of hydergine in dementia. *Arch Neurol* **51**:787–798.

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR (1997). Brain infarction and the clinical expression of Alzheimer's disease: the Nun Study. *JAMA* **277**:813–817.

Tanaka K, Mizukawa K, Ogawa N, Mori A (1995). Post-ischemic administration of the acetylcholinesterase inhibitor ENA-713 prevents delayed neuronal death in the gerbil hippocampus. *Neurochem Res* **20**:663–667.

Tanaka K, Ogawa N, Asanuma M *et al.* (1993). Effects of the acetylcholinesterase inhibitor ENA-713 on ischemia-induced changes in acetylcholine and aromatic amine levels in the gerbil brain. *Arch Int Pharmacodyn Ther* **323**:85–96.

Tanaka K, Ogawa N, Asanuma M, Kondo Y, Mori A (1994b). Chronic administration of acetylcholinesterase inhibitor in the senescent rat brain. *Neurobiol Aging* **15**:721–725.

Tanaka K, Ogawa N, Mizukawa K *et al.* (1994a). Acetylcholinesterase inhibitor ENA-713 protects against ischemia-induced decrease in pre- and postsynaptic cholinergic indices in the gerbil brain following transient ischemia. *Neurochem Res* **19**:117–122.

Tatemichi TK, Sacktor N, Mayeux R (1994). Dementia associated with cerebrovascular disease, other degenerative diseases, and metabolic disorders. In: Terry RD, Katzman R, Bick KL eds. *Alzheimer's Disease*. New York: Raven Press, pp. 123–166.

Tohgi H, Abe T, Kimura M, Saheki M, Takahashi S (1996). Cerebrospinal fluid acetylcholine and choline in vascular

dementia of Binswager and multiple small infarct types as compared with Alzheimer-type dementia. *J Neural Transm* **103**:1211–1220.

Tomlinson BE, Blessed G, Roth M (1970). Observations of the brains of demented old people. *J Neurol Sci* **11**:205–242.

Tsujimoto S, Sakaki T, Morimoto T, Tominaga M (1993). The effect of acetylcholinesterase inhibitor (SDZ ENA 713) for r-CBF and focal cerebral ischaemia. *Acta Neurochir* **124**:127–131.

Wade JP, Mirsen TR, Hachinski VC, Fisman M, Lau C, Merskey H (1987). The clinical diagnosis of Alzheimer's disease. *Arch Neurol* **44**:24–29.

Yamamoto Y, Nakano S, Kawashima S *et al*. (1990). Plasma and serum G4 isoenzyme of acetylcholinesterase in patients with Alzheimer-type dementia and vascular dementia. *Ann Clin Biochem* **27**:321–326.