RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Safety and tolerability of rivastigmine capsule with memantine in patients with probable Alzheimer's disease: a 26-week, open-label, prospective trial (Study ENA713B US32)†

Jason T. Olin[1], Vinod Bhatnagar[2], Patricio Reyes[3], Barbara Koumaras[1], Xiangyi Meng[1] and Stephen Brannan[4]

[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[2]Center for Clinical Trials and Research, Inc., Venice, FL, USA
[3]Barrow Neurological Institute, Phoenix, AZ, USA
[4]Takeda Pharmaceuticals North America, (formerly Novartis Pharmaceuticals Corporation) Deerfield, IL, USA
Correspondence to: J. T. Olin, PhD, E-mail: jason.olin@novartis.com

†Previous presentation: 161st Annual Meeting of the American Psychiatric Association: Washington, DC, May 3–8, 2008.

Objective: Rivastigmine, a dual cholinesterase inhibitor (ChEI), is widely approved for the symptomatic treatment of both mild-to-moderate Alzheimer's disease (AD) and Parkinson's disease dementia. Orally administered ChEIs may be associated with gastrointestinal (GI) side effects and add-on therapy with memantine, an *N*-methyl-D-aspartate receptor antagonist, approved for moderate-to-severe AD, may ameliorate such side effects. This was a 26-week, prospective, multicenter, single-arm, open-label pilot study to assess the safety and tolerability of rivastigmine capsules plus memantine in patients with moderate AD.

Methods: The primary objective was to assess the safety and tolerability of rivastigmine capsules 6–12 mg/day plus memantine (5–20 mg/day) as measured by the incidences of vomiting and nausea compared with those reported in the rivastigmine United States Prescribing Information (US PI). A total of 117 patients were enrolled with 116 receiving at least one dose of study medication.

Results: The incidences of nausea and vomiting (30% and 13%, respectively) observed in patients who received 6–12 mg/day rivastigmine plus memantine were lower than those stated in the US PI for rivastigmine monotherapy 6–12 mg/day (47% and 31%, respectively). The most common adverse events were nausea, vomiting, and dizziness.

Conclusion: Results from this study suggest the combination of rivastigmine capsule and memantine in patients with moderate AD is safe and tolerable. Improved GI tolerability of rivastigmine has been established with rivastigmine transdermal patch. Copyright © 2009 John Wiley & Sons, Ltd.

Key words: Alzheimer's disease; cholinesterase inhibitor; dementia; memantine; rivastigmine; tolerability
History: Received 12 December 2008; Accepted 3 June 2009; Published online 10 August 2009 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/gps.2355

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder characterized by cognitive deficits and functional decline. Cholinesterase inhibitors (ChEIs), such as rivastigmine and donepezil, and the *N*-methyl-D-aspartate (NMDA)-receptor antagonist memantine are currently available for the treatment of AD.

Rivastigmine is a slowly reversible, centrally selective ChEI that has been shown to inhibit both acetylcholinesterase and butyrylcholinesterase [BuChE, which is not described in the United States Prescribing Information (US PI)]. This dual inhibition is associated with sustained cholinesterase inhibition over the course of AD (Cutler *et al.*, 1998; Polinsky, 1998; Ballard, 2002). In patients with mild-to-moderate AD, improvements in cognitive and global functioning were observed in patients treated with rivastigmine (6–12 mg/day), for periods of 6 months and 1 year, compared with the progressive deterioration seen in

patients receiving placebo (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999; Birks *et al.*, 2009).

As with other ChEIs, the most frequently reported adverse events (AEs) associated with rivastigmine capsule therapy are gastrointestinal (GI), the incidence of which appears to be dose-related (Rösler *et al.*, 1999). In particular, the US PI notes that rivastigmine capsule (6–12 mg/day) therapy is associated with significant GI adverse reactions, including nausea (47%) and vomiting (31%), diarrhea (19%), and anorexia (17%). Although these AEs are generally transient and mild-to-moderate in severity, they may be dose limiting in some patients (Rösler *et al.*, 1999). The US PI also reports class effects associated with ChEIs, including seizure, urinary obstruction, worsening of asthma and COPD, vagotonic effects, and GI bleeding. None of these AEs has been associated with rivastigmine capsule or transdermal patch, based on clinical trials data.

Memantine is a non-competitive NMDA receptor antagonist, approved for the treatment of moderate-to-severe AD and its efficacy has been established in several 6-month trials (Reisberg *et al.*, 2003; Doody *et al.*, 2004; Areosa *et al.*, 2005; McShane *et al.*, 2006; Winblad *et al.*, 2007). A randomized, placebo-controlled study of memantine in patients with moderately severe to severe AD receiving stable donepezil treatment for at least 6 months prior to the study, demonstrated a superior therapeutic benefit as well as a lower incidence of GI AEs compared with placebo. In that study, patients had previously been taking donepezil for a mean of 129 and 126 weeks in the placebo and memantine groups, respectively, and the mean doses of donepezil were 9.49 and 9.25 mg/day, respectively. The incidence of nausea in this study was reduced from 3.5% with donepezil monotherapy to 0.5% for patients receiving memantine add-on therapy, representing a reduction of 86%, suggesting that memantine may reduce the incidence of GI AEs associated with ChEIs (Tariot *et al.*, 2004). In addition, the study by Tariot *et al.* indicated that the memantine group showed greater improvements in clinical outcomes compared with the placebo group, including Severe Impairment Battery (SIB) (0.9 *vs.* −2.5; $p < 0.001$), the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-19 ($ADCS\text{-}ADL_{19}$) (−2.0 *vs.* −3.4; $p = 0.03$), and a Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus) (4.41 *vs.* 4.66; $p = 0.03$) (Tariot *et al.*, 2004). The efficacy of memantine in samples of mild-to-moderate AD patients has not been established, based on three large placebo-controlled trials (McShane *et al.*, 2006).

The primary objective of this study was to assess the safety and tolerability of rivastigmine capsules 6–12 mg/day and concomitant memantine 10 mg twice daily (bid), as measured by the incidences of nausea and vomiting, compared with those stated in the US PI for rivastigmine (Exelon Capsule, 2001), in patients with moderate AD. Secondary objectives evaluated whether patients receiving rivastigmine and memantine were able to reach and maintain higher doses of rivastigmine, compared with historical data from patients receiving rivastigmine monotherapy. Additional exploratory objectives included evaluation of the effects of memantine add-on therapy to rivastigmine on measures of cognition, global functioning, and activities of daily living (ADLs).

Methods

Study population

In brief, male and female participants who were at least 50 years of age, met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for dementia of the Alzheimer type, and criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA), a Mini-Mental State Examination (MMSE) total score of $\geq$10 and $\leq$20, and who had brain imaging (CT or MRI scan) supporting the diagnosis of AD within 3 years prior to baseline were included. Female patients were required to be surgically sterile or postmenopausal for at least 1 year. Patients who were receiving treatment with a ChEI other than rivastigmine were permitted provided they were on therapy for at least 6 months, on a stable dose for at least 3 months prior to screening and were experiencing a decline in cognition, ADL or behavior, or whose caregiver was dissatisfied with current therapy. Exclusion criteria included any other conditions that could explain the patient's dementia, or any advanced, severe, unstable, or progressive disease that may interfere with the evaluation of the patient or put the patient at special risk. Patients taking dopaminergic or centrally acting anticholinergic agents, and those who had received an investigational drug within 4 weeks prior to screening were also excluded.

Caregivers were required to supervise the patients' treatment during the study, accompany them to all study visits, provide input into efficacy assessments, and be able to monitor treatment compliance. Written informed consent was provided by each patient, if mentally competent, prior to study participation. An appropriately responsible party on the patient's behalf

and the patient's caregiver also provided written informed consent prior to the patient's participation (whether or not the patient was able to provide written informed consent). If unable to give written consent, the patient's verbal assent was obtained from the patient if possible and permitted by state, local, and Institutional Review Board (IRB) regulations. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Reporting Practice. The study protocol was approved by an IRB, an Independent Ethics Committee, and Research Ethics board.

Study design

This was a 26-week, prospective, multicenter (20 sites), single-arm, open-label pilot study conducted within the US (Novartis Study ENA713B US32). All patients began treatment with rivastigmine capsules 3 mg/day (1.5 mg bid, dosed morning and evening with meals) for 2 weeks prior to starting memantine (Table 1). Memantine, was then initiated at 5 mg/day, with titration in 5 mg/day weekly increments, to reach a target dose of 20 mg/day (10 mg bid, dosed morning and evening with or without food). All patients were maintained on memantine 20 mg/day for the remainder of the study. During the dose titration of memantine, and for a subsequent 2-week stabilization period, the dose of rivastigmine was maintained at 3 mg/day. After this, rivastigmine dose increases were made in 3 mg/day increments, in two divided doses, at a minimum of 4 weeks between dose increases (according to the investigator's assessment of individual patient tolerability), to a maximum dose of 12 mg/day or the individual patient's best tolerated dose. To remain in the study, patients were required to be able to tolerate minimum doses of rivastigmine 3 mg/day and memantine 20 mg/day. Patients on less than 20 mg/day memantine were included as part of the safety analysis if they had taken at least one dose of rivastigmine. Patients were not permitted to take any ChEIs other than rivastigmine or NMDA antagonists other than memantine for the duration of the study.

Safety assessments

The primary objective of this study was to assess the safety and tolerability of rivastigmine capsules 6–12 mg/day (3–6 mg bid) taken with concomitant memantine 10 mg bid, as measured by the incidences of nausea and vomiting, compared with those stated in the US PI for rivastigmine capsule monotherapy (Exelon Capsule, 2001). Safety assessments included the report of AEs throughout the study, vital sign measurements at each study visit, as well as clinical laboratory evaluations and 12-lead electrocardiogram (ECG) measurements at baseline and weeks 12 and 26 (or at study withdrawal). A secondary objective of the study was to evaluate whether patients receiving rivastigmine and memantine were able to reach and maintain higher doses of rivastigmine, compared with historical data from patients receiving rivastigmine monotherapy.

Efficacy assessments

Other secondary objectives evaluated the effects of rivastigmine capsule and memantine add-on therapy on the measures of cognition, global functioning, and ADLs. These objectives were evaluated using the MMSE, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), and ADCS-ADL scales. Evaluations were performed at baseline and Weeks 12 and 26 (or at study withdrawal). In addition to the standard global score, the ADCS-CGIC was modified to generate a severity score for each area of the worksheet at each visit based on both the caregiver and patient interviews. A change in score was generated for each of the three domains, in addition to the standard global score.

Statistical analysis

The safety population comprised all patients who had taken at least one dose of study medication. The efficacy analysis was based on the intention-to-treat

Table 1 Dosing schedule for rivastigmine and memantine

	Screening	Baseline (mg bid)	Dose titration (mg bid)					Maintenance
Weeks	−2	0	1–2	3–8	9–12	13–16	17–20	21–26
Rivastigmine	0	0	1.5	1.5	3[a]	4.5[a]	6[a]	6[a]
Memantine	0	0	0	4-week titration in 5 mg/day increments plus 2-week stabilization at 10 mg bid	10	10	10	10

[a]Or best tolerated dose; bid = twice daily.

(ITT) population and comprised those patients who received at least one dose of study medication and completed at least one postbaseline efficacy assessment. Exposure to study medication was summarized using descriptive statistics.

To evaluate the primary objective, a two-sided 95% confidence interval for nausea and vomiting using patients who received rivastigmine 6 mg/day for at least 1 day following the memantine stabilization phase was calculated and compared with the incidence of nausea and vomiting stated in the rivastigmine US PI. The frequency of AEs was also summarized.

All efficacy analyses were performed on the ITT population using both the observed case (OC; primary analysis) and last observation carried forward imputations. Only the ITT-OC results are described here. The percentage of patients with no decline from baseline in MMSE total score, ADCS-CGIC, as well as the change from baseline in ADCS-ADL, MMSE, and caregiver- and patient-assessed ADCS-CGIC total scores were all summarized at Weeks 12 and 26. No formal statistical testing was performed for the efficacy parameters.

Results

Patients participated in this study from March 2, 2006 through to August 29, 2007. A total of 117 patients were enrolled in the study, 116 of whom received at least one dose of study medication (safety population) and 74 (64%) of whom completed the study. Reasons for early withdrawal were AEs ($n = 19$; 16.4%), withdrawal of consent ($n = 12$; 10.3%), lost to follow-up ($n = 2$; 1.7%), and other reasons ($n = 9$; 7.8%). Patients had a mean ± standard deviation (SD) age of 78.4 years (SD = 7.99), duration of dementia of 3.5 years (SD = 2.73), and an MMSE total score of 16.6 (SD = 3.05). The majority of patients were Caucasian, female and ChEI-naïve (Table 2).

Table 2 Baseline patient characteristics (safety population)

	$n = 116$
Mean ± SD age (years)	78.4 ± 7.99
Sex, *n* (%)	
Male	31 (26.7)
Female	85 (73.3)
Race, *n* (%)	
Caucasian	98 (84.5)
Black	7 (6.0)
Other	11 (9.5)
Mean ± SD weight (kg)	69.9 ± 15.77
Mean ± SD duration of dementia (years)	3.5 ± 2.73
Taking ChEI therapy prior to study, *n* (%)	35 (30.2)
Donepezil	31 (26.7)
Galantamine	4 (3.4)
Mean ± SD total duration of ChEI therapy (months)	22.8 ± 19.67[a]
Mean ± SD MMSE total score	16.6 ± 3.05

ChEI, cholinesterase inhibitors; MMSE, Mini-Mental State Examination; SD, standard deviation.
[a]$n = 35$.

Study drug exposure

The median duration of study drug exposure was 180.0 days (range: 1–211), with a mean (SD) duration of 142.8 days (SD = 61.23). For the safety population, the mean last prescribed dose (SD) of rivastigmine was 7.8 mg/day (SD = 3.78) and the mean last prescribed dose of memantine was 19.4 mg/day (SD = 2.69). A total of 42 (36.2%) patients achieved and maintained a rivastigmine dose of 12 mg/day, while a total of 81 patients (69.8%) had a last prescribed dose of 6–12 mg/day, indicating that many patients were not maintaining the highest possible dose; however, the majority were in the recommended dose range. For 35 (30.2%), 20 (17.2%), 19 (16.4%), and 42 (36.2%) patients, the last prescribed dose was 3, 6, 9, and 12 mg/day, respectively. During the study, 60 (51.7%) patients required a rivastigmine dose reduction or suspension. A total of 104 patients (89.7%) achieved and maintained a memantine dose of 20 mg/day. Six patients (5.2%) did not receive a dose of memantine during the study and, for six patients (5.2%) the last administered dose of memantine was less than 20 mg/day.

Safety and tolerability

Incidence of nausea and vomiting. Overall, the incidences of nausea and vomiting were 26.7% and 10.3%, respectively (Table 3). The incidences of nausea and vomiting observed in the subgroup of patients who received 6 mg/day rivastigmine for at least 1 day (30% and 13%, respectively) were lower than those stated in the US PI for rivastigmine monotherapy 6–12 mg/day (47% and 31%, respectively) (Figure 1; Exelon Capsule, 2001). Most of the cases of nausea and vomiting with rivastigmine and memantine were mild, with few severe cases reported (2.6% and 2.6%, respectively).

Adverse events. At least one treatment-emergent AE was experienced by 95 (81.9%) patients, with the most common being nausea, dizziness, vomiting, and diarrhea, which were experienced by 31 (26.7%), 13 (11.2%), 12 (10.3%), and 12 (10.3%) patients, respectively (Table 4). A total of 25 (21.6%) patients experienced at least one serious AE (SAE): fall, $n = 4$; pneumonia, $n = 3$; chronic obstructive pulmonary disease,

Table 3 Incidence of treatment-emergent nausea and vomiting

	Number of patients taking study medication	Number of patients with event	Incidence rate and 95% CI
All patients (safety population)			
Nausea	116	31	26.7 (18.9, 35.7)
Vomiting	116	12	10.3 (5.5, 17.4)
Nausea and vomiting	116	8	6.9 (3.0, 13.1)
Patients receiving rivastigmine ≥6 mg/day for ≥1 day			
Nausea	91	27	29.7 (20.6, 40.2)
Vomiting	91	12	13.2 (7.0, 21.9)
Nausea and vomiting	91	8	8.8 (3.9, 16.6)

CI, confidence interval.

$n = 3$; bronchitis, $n = 2$; confusional state, $n = 2$; and mental status changes, $n = 2$. One patient experienced nausea, and one patient experienced vomiting as an SAE. Four patients experienced severe nausea or vomiting. A total of 19 (16.4%) patients discontinued due to AEs (nausea, $n = 4$; diarrhea, $n = 3$). One patient experienced cardiogenic shock secondary to acute myocardial infarction on day 90 of the study. This patient died following a second myocardial infarction, 5 days after the last dose of study drug. This death was considered by the study investigator as suspected to be related to study drug.

Electrocardiograms and vital signs. At baseline and Week 26, no patients exhibited clinically significant ECG abnormalities. Mean (SD) changes from baseline to study end in sitting/standing systolic or diastolic blood pressure after 1 min were −1.3 mm Hg (SD = 16.47) and −0.8 mm Hg (SD = 9.86), respectively; change in mean pulse rate was also minimal. Few patients presented with clinically notable vital sign values (Table 5).

Mean (SD) change from baseline in body weight was −0.8 kg (SD = 3.43). Three patients (2.6%) experienced a clinically notable (≥7%) increase in body weight, and 14 patients experienced a clinically notable (≥7%) decrease in body weight. The mean (SD) decrease in weight in these 14 patients was −7.34 kg (SD = 2.12).

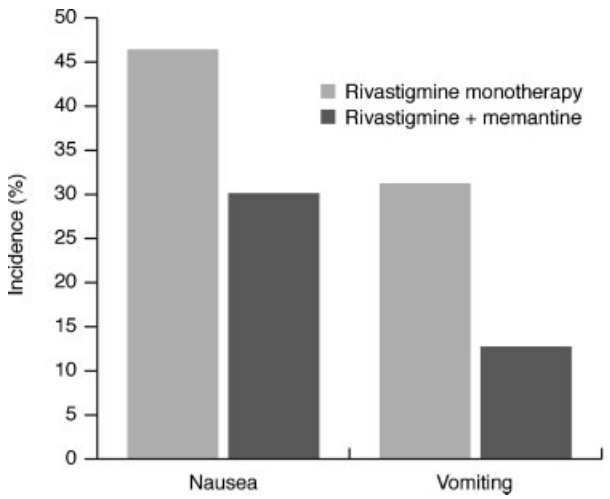

Figure 1 Comparison of the incidences of nausea and vomiting in trial participants (rivastigmine + memantine) with the incidence rates from the United States Prescribing Information for rivastigmine capsules (rivastigmine monotherapy). Results presented here compare rivastigmine + memantine combination therapy with historical rivastigmine monotherapy data, and are not from a direct within-study comparison.

Efficacy

At Week 26, 59.0% of patients experienced no decline from baseline in MMSE total score (ITT-OC) and the mean (SD) change from baseline in MMSE total score was 0.7 (SD = 3.53; $n = 78$; Table 6).

There was no change from baseline in global ADCS-CGIC scores at Week 26, and caregiver- and patient-

Table 4 Most frequently reported treatment-emergent adverse events (safety population; ≥5% of patients)

	Patients ($n = 116$) n (%)
Nausea	31 (26.7)
Dizziness	13 (11.2)
Vomiting	12 (10.3)
Diarrhea	12 (10.3)
Fall	11 (9.5)
Weight decreased	9 (7.8)
Agitation	9 (7.8)
Anxiety	9 (7.8)
Depression	9 (7.8)
Urinary tract infection	8 (6.9)
Decreased appetite	8 (6.9)
Insomnia	8 (6.9)
Confusional state	7 (6.0)
Asthenia	6 (5.2)
Contusion	6 (5.2)
Lethargy	6 (5.2)
Somnolence	6 (5.2)

Table 5 Summary of clinically notable vital sign abnormalities (safety population)

Vital sign abnormality	Rivastigmine/memantine ($n = 116$), *n* (%)
Sitting/standing systolic blood pressure >180 mm Hg and increase from baseline ≥20 mm Hg	
After 1 min	3 (2.6)
After 3 min	2 (1.7)
Sitting/standing systolic blood pressure <90 mm Hg and decrease from baseline ≥20 mm Hg	
After 1 min	1 (0.9)
After 3 min	1 (0.9)
Sitting/standing diastolic blood pressure >105 mm Hg and increase from baseline ≥15 mm Hg	
After 3 min	1 (0.9)
Sitting/standing diastolic blood pressure <50 mm Hg and decreased from baseline ≥15 mm Hg	
After 1 min	5 (4.3)
After 3 min	5 (4.3)
Supine pulse after 5 min <50 bpm and decrease from baseline ≥15 bpm	2 (1.7)
Supine systolic blood pressure after 5 min >180 mm Hg and increase from baseline ≥20 mm Hg	4 (3.4)
Supine systolic blood pressure after 5 min <90 mm Hg and decrease from baseline ≥20 mm Hg	2 (1.7)
Supine diastolic blood pressure after 5 min <50 mm Hg and decrease from baseline ≥15 mm Hg	4 (3.4)

Safety population included all patients who took at least one dose of study drug (rivastigmine). Percentage was calculated as 100 × (*n*/total); total refers to the number of patients with at least one postbaseline assessment for all categories of clinically notable vital sign abnormalities.
bpm, beats per minute; mm Hg, millimeters of mercury.

assessed mental/cognitive state, and behavior and functioning severity scores were maintained to a similar extent throughout the study period (Table 6). The mean overall rating on the ADCS-CGIC was 4.0 (SD = 1.30) and at Week 26, 49 (64.5%) patients were considered to be unchanged or improved (ITT-OC). Mean ADCS-ADL scores significantly declined by −2.9 (SD = 10.59) during the study period from 52.0 (SD = 16.66) at baseline (Table 6). Cognition, behavior and global functioning were unchanged or improved in 63.2%, 71.1%, and 77.6% of patients at Week 26, respectively.

Discussion

Findings from this study suggest the potential for improved tolerability of rivastigmine capsule with memantine combination therapy in patients with moderate AD. Potential tolerability benefits of rivastigmine capsule with memantine combination therapy were indicated by the decreased incidence of nausea (31% *vs*. 47% of patients) and vomiting (13% *vs*. 31%) with rivastigmine plus memantine in comparison with those documented in the US PI for rivastigmine. These reductions do not approach the added improvement in GI tolerability seen with the transdermal patch formulation of rivastigmine, where the 9.5 mg/24 hours patch showed similar efficacy to 6 mg bid capsule (Winblad *et al*., 2007).

Although the incidences of nausea and vomiting were higher in patients who had received at least one dose of the higher doses of rivastigmine (≥6 mg/day) compared with all patients (i.e., patients receiving rivastigmine 3–12 mg/day), this difference was small and, notably, over two-thirds of patients achieved rivastigmine doses ≥6 mg/day. In the study evaluating add-on memantine therapy to donepezil, the incidence of nausea was greatly lower in patients receiving memantine add-on therapy compared with those receiving donepezil monotherapy (Tariot *et al*., 2004), suggesting that this beneficial effect of memantine on GI tolerability may be applicable across ChEIs. It is also

Table 6 Summary of efficacy parameters (intent-to-treat population and observed case analysis)

	MMSE total score ($n = 108$)	ADCS-CGIC caregiver-assessed total score ($n = 107$)	ADCS-CGIC patient-assessed total score ($n = 108$)	ADCS-ADL total score ($n = 107$)
Baseline	16.6 ± 3.01	38.0 ± 11.48	33.3 ± 9.92	52.0 ± 16.66
Change from baseline to Week 12	0.6 ± 3.24	−0.5 ± 6.98	0.5 ± 6.14	−1.5 ± 8.30
Change from baseline to Week 26	0.7 ± 3.53	−0.5 ± 7.36	0.7 ± 6.36	−2.9 ± 10.59

Values are mean ± SD; change from baseline in ADCS-CGIC caregiver-based assessment severity scores.
ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; MMSE, Mini-Mental State Examination.

possible that the reduced incidence of GI AEs could be ascribed to the tendency to use lower doses of rivastigmine in this study, compared with other studies. Indeed, the mean dose of rivastigmine at endpoint was 7.8 mg/day (SD = 3.78), whereas the mean doses used in the study by Corey-Bloom *et al*. (1998) and Rösler *et al*. (1999) studies were 9.7 mg and 10.4 mg/day, respectively, in the 6–12 mg/day groups. Nevertheless, 36.2% of the patients in our study were on the highest dose (12 mg/day) of rivastigmine at endpoint and 69.8% were on 6–12 mg/day.

Of note, the prevalence of GI AEs in our study was lower than that observed in the global and US-based studies by Rösler *et al*. and Corey-Bloom *et al*. on which the information in the US PI is in part based. The studies compared low (1–4 mg/day) and high (6–12 mg/day) doses of rivastigmine with placebo (Corey-Bloom *et al*., 1998; Rösler *et al*., 1999) and utilized a forced-dose titration schedule, in which patients up-titrated their dose of rivastigmine every week (over a 7-week period) rather than every month as used in the present study. In the absence of memantine, the prevalence of GI AEs was lower in our study than in the studies by Rösler *et al*. and Corey-Bloom *et al*., despite comparable target doses (both: 6–12 mg/day). The addition of memantine to rivastigmine reduced the rate of GI AEs in our study to be comparable with that in the low-dose group (1–4 mg/day) in the study by Rösler *et al*., even though our patients were titrated to 6–12 mg/day. The use of a more rapid titration schedule can be associated with an increased occurrence of AEs. As such, the schedule utilized in the US PI studies compared with our study may account for some of the differences in the report of AEs observed between the studies discussed here. The use of the slower dose-titration scheduled in the present study was necessary because the dose of memantine was also being up-titrated and the tolerability of the combination treatment was uncertain.

Finally, it is also possible that the improved GI tolerability observed in the present study could be partly due to the fact that patients were instructed to take rivastigmine with food. Consuming food at the time of rivastigmine ingestion has been shown to delay the absorption of rivastigmine and has been reported to reduce the incidence of AEs, most likely due to the lower blood levels of the drug (Nordberg and Svensson, 1998). Nevertheless, comparable improvements in GI AE profiles have been observed when adding memantine medication to patients treated with stable doses of donepezil (Tariot *et al*., 2004). These findings suggest that although there was a tendency for lower doses of rivastigmine to be used in the present study, there appears to be synergistic benefits of administering rivastigmine with food and in combination with memantine in terms of GI AEs.

Use of memantine is associated with increased frequencies of dizziness, confusion, headache, and constipation (Namenda, 2007). In this study, the overall rates of dizziness (11%) and confusion (6%) were higher than the Exelon® US PI, suggesting that the increased frequency of these AEs may have been a result of the concomitant memantine.

Combination therapy with rivastigmine and memantine over the 6-month study period was not associated with decline in cognitive function as assessed by the MMSE and ADSC-CGIC, and a decline in ADLs that may be considered clinically meaningful in this patient population.

A primary limitation of this study is the lack of a control group and the use of US PI data to compare safety rates. A placebo-controlled study with the rivastigmine patch would offer further support of these findings.

Conclusion

The results support the combination of rivastigmine and memantine in patients with moderate AD. These findings suggest that combined use was both tolerable and safe, with reduced incidence of GI AEs, in particular. Improved GI tolerability has been established with the rivastigmine transdermal patch.

Conflicts of interest

Jason Olin, Xiangyi Meng, and Barbara Koumaras are full-time employees and stockholders of Novartis Pharmaceuticals Corporation. Dr Brannan is a full-time employee of Takeda Pharmaceuticals North America and was a full-time employee and stockholder of Novartis Pharmaceuticals Corporation. Dr Reyes has served as a speaker for Novartis Pharmaceuticals Corporation and has received a research grant as investigator from Novartis Pharmaceuticals Corporation. Dr Bhatnagar has served as a speaker and speaker trainer for Novartis Pharmaceuticals Corporation.

List of US32 investigators

Dr Bernardo Arias, Gulf Coast Education and Research Center, Port Charlotte, FL; Dr Mohammed A. Bari, Synergy Clinical Research Center, National City;

Key points

- Rivastigmine, a dual ChEI, is approved in the US for the symptomatic treatment of both mild-to-moderate AD and Parkinson's disease dementia.
- Orally administered ChEIs are associated with GI side effects, particularly during titration.
- Add-on therapy with memantine, an NMDA-receptor antagonist, approved for moderate-to-severe AD, may ameliorate GI side effects typically associated with ChEIs.
- Results from this study suggest a rationale for the combined use of rivastigmine and memantine in patients with moderate AD.

Dr Vinod K. Bhatnagar, Center for Clinical Trials and Research, Venice, FL; Dr Ruben Bravo, Caribbean Education and Research Center, Inc., Bayamon, PR; Dr Jay Ellis, NeuroScience Research of the Berkshires, Pittsfield, MA; Dr Donald Freidenberg, Neurobehavior and Neurology, Columbus, OH; Dr Jerome Goldstein, San Francisco Clinical Research Center, San Francisco, CA; Dr George Joseph, CNS Healthcare, Jacksonville, FL; Dr Marvin Kalafer, The Clinical Trial Center, Jenkintown, PA; Dr Douglas Katz, Braintree Clinic Research Center, Braintree, MA; Dr Leslie Moldauer, Radiant Research, Denver, CO; Dr Luis Pagani, River Hills Healthcare Corporation, Cincinnati, OH; Dr Ashok Patel, Bio Behavioral Health, Toms River, NJ; Dr Patricio Reyes, Barrows Neurology Clinics at St. Joseph's Hospital and Medical Center, Phoenix, AZ; Dr Ralph Richter, Tulsa Clinical Research, Tulsa, OK; Dr Beth Safirstein, MD Clinical; Hallandale Beach, FL; Dr Michael Sauter, Westmoreland Neurology Associates, Inc., Greensburg, PA; Dr Joshua ShuaHaim, Alzheimer's Research Corporation (ARC), Manchester, NJ; Dr John Stoukides, Rhode Island Mood and Memory Research Institute, E. Providence, RI; Dr Jack Tomlinson, Grayline Clinical Drug Trials, Wichita Falls, TX; Dr Daniel B. Vine, Pivotal Research Centers, Midvale, UT; Dr Earl K. Wilson, Mountain Empire Neurological Associates, Bristol, TN; Dr Jaron Winston, Senior Adults Specialty Research, Austin, TX; Dr Joel Young, Rochester Center for Behavioral Medicine, Rochester Hills, MI; Dr Ronald Ziman, Northridge Neurological Research, Northridge, CA.

Acknowledgements

The authors would like to thank Diya Lahiri, PhD, Medicus International, for her editorial and medical writing contributions to this manuscript. This study was funded by Novartis Pharmaceuticals Corporation (study no. ENA713D US32).

References

Areosa SA, Sherriff F, McShane R. 2005. Memantine for dementia. *Cochrane Database Syst Rev* (3): CD003154.

Ballard CG. 2002. Advances in the treatment of Alzheimer's disease: benefits of dual cholinesterase inhibition. *Eur Neurol* **47**: 64–70.

Birks J, Grimley Evans J, Iakovidou V, *et al.* 2009. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev* (2): CD001191.

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.

Doody R, Wirth Y, Schmitt F, Mobius HJ. 2004. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* **18**: 227–232.

Exelon Capsule. 2001. Prescribing information. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf.

McShane R, Areosa Sastre A, Minakaran N. 2006. Memantine for dementia. *Cochrane Database Syst Rev* (3): CD003154.

Namenda. 2007. Prescribing information. Available at: http://www.frx.com/pi/namenda_pi.pdf.

Nordberg A, Svensson AL. 1998. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. *Drug Saf* **19**: 465–480.

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

Reisberg B, Doody R, Stoffler A, *et al.* 2003. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* **348**: 1333–1341.

Rösler M, Anand R, Cicin-Sain A, *et al.* 1999. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* **318**: 633–638.

Tariot PN, Farlow MR, Grossberg GT, *et al.* 2004. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* **291**: 317–324.

Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. 2007. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. *Dement Geriatr Cogn Disord* **24**: 20–27.

