Adding Memantine to Rivastigmine Therapy in Patients With Mild-to-Moderate Alzheimer's Disease: Results of a 12-Week, Open-Label Pilot Study

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Objective: At present, inhibition of cholinesterase is the treatment of choice for subjects with mild-to-moderate Alzheimer's disease (AD). Memantine, a noncompetitive antagonist at *N*-methyl-D-aspartate receptors, is currently used to treat subjects with moderate-to-severe AD. The goal of this multicenter, open-label pilot study was to investigate whether combination therapy with memantine added to rivastigmine is safe and beneficial in subjects with mild-to-moderate AD.

Method: Patients with a DSM-IV diagnosis of dementia of the Alzheimer's type (N = 95), who were treated with rivastigmine (6–12 mg/day) for a maximum duration of 24 weeks prior to baseline, received memantine (5–20 mg/day) in combination with rivastigmine for 12 weeks. The primary efficacy variable was the change in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score at the end of 12 weeks compared with baseline. The study was conducted between September 15, 2003, and May 27, 2004.

Results: There was a statistically significant difference between baseline and week 12 for the ADAS-cog total score, showing a positive effect of combination therapy. Combination therapy did not evidence any unexpected safety concerns and was well-tolerated by most patients.

Conclusion: Memantine in combination with rivastigmine appears to be safe and beneficial in patients with mild-to-moderate AD. Our results need to be confirmed in a large, long-term, randomized, double-blind, placebo-controlled clinical trial.

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Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common cause of dementia. The prevalence of AD increases steadily after the age of 65, with an estimated prevalence of approximately 50% in patients aged 85 years or older.[1,2] As the population ages, the proportion of the population affected by AD will increase.[3]

At present, inhibition of cholinesterase (ChE) is the treatment of choice for subjects with mild-to-moderate AD.[4] In the absence of a cure for the disease, the aim is to delay cognitive decline and symptom progression to the greatest extent possible. For the ChE inhibitors (ChEIs) currently in use (rivastigmine, donepezil, and galantamine), improvements in cognition, general clinical impression, activities of daily living (ADL), and behavioral symptoms have all been demonstrated.[5] Unlike the selective acetylcholinesterase (AChE) inhibitors donepezil and galantamine, rivastigmine induces sustained inhibition of both AChE and butyrylcholinesterase, which may be advantageous across the spectrum of AD severity.[6,7]

Memantine is a noncompetitive antagonist at *N*-methyl-D-aspartate receptors and is currently used to treat subjects

with moderate-to-severe AD.[8] Memantine is used in patients with moderate-to-severe AD to improve cognitive symptoms.[8–11] Memantine is well-tolerated, without major side effects or drug-drug interactions with other commonly used pharmacologic substances.[12]

Recently, the combination of memantine and a ChEI (specifically donepezil) has been assessed in patients with moderate-to-severe AD.[13] Compared with AChE inhibition alone, combination therapy resulted in greater symptomatic improvements in both cognitive and behavioral efficacy measures, suggesting that the complementary mechanisms of action of ChEIs and memantine have additive or synergistic potential in delaying symptomatic decline in AD. The goal of the current study was to investigate whether combination therapy with rivastigmine and memantine presents unexpected safety or tolerability concerns and is beneficial in patients with mild-to-moderate AD.

METHOD

Study Design

This multicenter, open-label, historically controlled pilot study was conducted in 20 centers in Germany between September 15, 2003, and May 27, 2004. The study was carried out in accordance with the principles of the Declaration of Helsinki[14] and Guidelines for Good Clinical Practice.[15] Written informed consent was obtained from the patients and/or their caregivers.

Patients (N = 95), who had been treated with rivastigmine (6–12 mg/day) for a maximum duration of 24 weeks prior to baseline, received memantine (5–20 mg/day) in combination with rivastigmine for the 12-week duration of the study. All patients had been taking a stable rivastigmine dose (6–12 mg/day) for at least 2 weeks prior to the study. This rivastigmine dose was to be kept constant throughout the study. Patients were started on memantine treatment 5 mg/day. On a weekly basis, the dosage was increased in 5-mg/day increments to a maximum of 20 mg/day. Patients were treated with the highest dose of memantine that was well-tolerated. Both memantine and rivastigmine were administered twice a day.

Patients

Inclusion criteria. Male and female patients between 50 and 90 years of age with a diagnosis of dementia of the Alzheimer's type based on clinical criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[16] were eligible for the study if they fulfilled the following criteria: Mini-Mental State Examination (MMSE)[17] score ≥ 10 and ≤ 20 at baseline; treatment with rivastigmine (6–12 mg/day) for a maximum duration of 24 weeks prior to assignment to treatment; stable rivastigmine dosage (6–12 mg/day) for at least 2 weeks prior to the study; ability to read, write, and speak the German language; and having a single caregiver willing to accept responsibility for supervising the treatment and condition of the patient throughout the study.

Exclusion criteria. Patients were excluded from the study if they had any of the following: an advanced, severe, progressive, or unstable disease of any type that might interfere with efficacy and safety evaluations or put the patient at special risk; current diagnosis of any further severe neurologic and psychiatric disorder other than AD (e.g., active, uncontrolled epilepsy); treatment with donepezil, galantamine, or tacrine during the 4 weeks prior to baseline; history within the past year or current diagnosis of cerebrovascular disease (e.g., stroke, transient ischemic attacks, aneurysms); current DSM-IV diagnosis of major depressive disorder (patients were included if they had been successfully treated with an antidepressant and had been taking a stable dose for at least 4 weeks); and any other DSM-IV Axis I diagnosis that might interfere with the evaluation of the patient's response to study medication, e.g., schizophrenia or bipolar disorder.

Concomitant therapy. Patients taking vitamin E, ginkgo biloba, estrogens, nootropics (e.g., acetaminophen, acetyl carnitine, ergoloid), or psychotropic medication (neuroleptics, antidepressants, anxiolytics including benzodiazepines, or anticonvulsants) and for whom discontinuation was not feasible could continue with these agents, but the dose was to remain unchanged throughout the study. Treatment with zolpidem or zopiclone was permitted for insomnia.

Assessments

Efficacy. The primary efficacy variable was the change in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)[18] total score at the end of the treatment compared with baseline. The ADAS-cog consists of an 11-item scale and the ADAS-cog total score ranges from 0 to 70, where 0 indicates no impairment.

One secondary efficacy variable was the MMSE,[17] a brief, practical screening test for cognitive dysfunction. The MMSE has 5 sections (orientation, registration, attention-calculation, recall, and language) and consists of 11 items. The total score ranges from 0 to 30, where 30 indicates no impairment.

Another secondary efficacy variable was the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL),[19] a caregiver-based ADL scale composed of 23 items. It has been designed to assess the patient's performance of both basic and instrumental activities of daily living. The total score ranges from 0 to 78, where a low value indicates low performance.

An additional secondary efficacy variable was the Global Deterioration Scale (GDS),[20] a staging instrument to document progression of dementia. The scale is made

Table 1. Demographic and Baseline Characteristics of Patients in the Current Study (N = 95) and the Historical Placebo Control[a] (N = 235)

Characteristic	Current Study	Placebo Control Group[a]
Gender, N (%)		
Male	44 (46.3)	98 (41.7)
Female	51 (53.7)	137 (58.3)
Race, N (%)		
White	92 (96.8)	222 (94.5)
Other	3 (3.2)	13 (6.0)
Age, y		
Mean ± SD	74.2 ± 8.88	74.8[b]
Median (range)	74 (46–91)	(45–89)
Body mass index, kg/m^2		
Mean ± SD	25.5 ± 4.21	NA
Median (range)	24.8 (17–37.5)	NA
Duration of dementia, mo		
Mean ± SD	26.9 ± 25.1	40.4[b]
MMSE total score		
Mean ± SD	16.9 ± 3.3	20[b]
Median (range)	18 (10–29)	NA
ADAS-cog score		
Mean ± SD	27.6 ± 10.13	21.7[b]
Median (range)	27 (10–55)	NA

[a]The historical control group was taken from Corey-Bloom et al.[21] It was used only to provide an estimate of the deterioration in the ADAS-cog score at 12 weeks (mean ± SD = 2.1 ± 5.1).
[b]SD not available.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, MMSE = Mini-Mental State Examination, NA = not available.

up of detailed clinical descriptions of 7 major clinically distinguishable stages, ranging from normal cognition (0) to very severe dementia (7).

Various neuropsychological tests were also administered to assess the effects of treatment on different aspects of cognition. These included the block span test (assesses visual short-term memory), digit-span test (assesses attention and memory), and the verbal fluency test (measures the speed and flexibility of verbal thought processes). The results of these neuropsychological tests will be described in a separate article.

Comparison study. In a study of rivastigmine in patients with mild-to-moderately severe AD by Corey-Bloom et al.,[21] ADAS-cog scores deteriorated by a mean ± SD of 2.1 ± 5.1 points in the placebo group at 12 weeks. The placebo group from this study was used as the historical control for the current study. No other comparisons were made with the earlier study.

Safety and tolerability. Safety assessments consisted of monitoring and recording all adverse events, including serious adverse events, using laboratory tests, body weight, and electrocardiograms. Information about concomitant medications was obtained, and physical examinations were performed at baseline and at weeks 3, 5, and 12.

Statistical Methods

The safety population was defined as all patients who received at least 1 dose of combination therapy (memantine plus rivastigmine). Efficacy analyses were conducted on the intent-to-treat (ITT) population (all patients who took at least 1 dose of combination therapy and from whom measurements were obtained for a complete baseline ADAS-cog assessment and a corresponding postbaseline assessment with no more than 1 item missing). Missing values for the efficacy ITT population were imputed using the last-observation-carried-forward (LOCF) technique. An observed-cases analysis was also performed on all the patients who completed the study.

The primary efficacy variable was the change in the ADAS-cog score at the end of the treatment compared with baseline. A 1-sided t test was used to reject the null hypothesis that the deterioration in ADAS-cog score was equal to or greater than the deterioration observed in the historical control, i.e., 2.1 points. The significance level was set to 2.5%, 1-sided.

Changes in primary and secondary efficacy measures were calculated such that positive change values indicate improvement. Changes in secondary parameters from baseline to week 12 were also tested using t tests. A 2-sided p value lower than .05 was considered significant. Since this was a pilot study and the various measurements do not address the same neuropsychological construct, p values were not adjusted to control for type I error due to multiple comparisons.

Sample size for this clinical trial was based on the results of the historical control, in which a deterioration of 2.1 ADAS-cog points was observed, with a standard deviation of 5.1 points. Under the assumption of no change in this study with rivastigmine plus memantine, 80 patients were required to reach a power > 90% to reject the null hypothesis of a deterioration > 2 points.

RESULTS

Demographics

Eighty-six (90.5%) of 95 patients completed the study according to the protocol. A total of 9 patients discontinued the study. Reasons for early withdrawal included adverse events (4 patients), protocol violation (1 patient), withdrawn consent (3 patients), and lost to follow-up (1 patient).

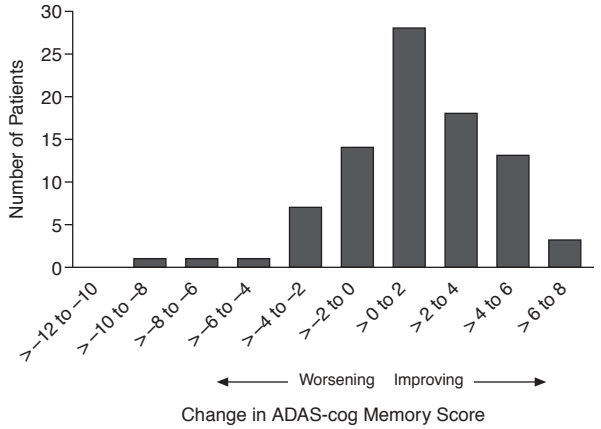
The demographic and baseline characteristics of the patients included in the current study and in the historical placebo control group (Corey-Bloom et al.[21]) are shown in Table 1. The historical control group was used only to provide an estimate of the mean ± SD deterioration in the ADAS-cog score at 12 weeks (2.1 ± 5.1 points). The mean ± SD days of exposure to combination therapy was 79.2 ± 16.71 days (median, 84 days). The mean daily dose of rivastigmine was 6.79 mg, with 79 patients (83.2%) receiving 6 mg, and the mean daily dose of memantine during the maintenance phase was 18.95 mg, with 85 patients (89.5%) receiving 20 mg.

Table 2. Summary Scores at Week 12 on Efficacy Variables for Patients Treated With Combination Therapy[a]

Assessment	N	Score at Baseline Mean (SD)	Score at Baseline Median	Change From Baseline[b] Mean (SD)	Change From Baseline[b] Median	p Value (2-sided)
Cognition						
ADAS-cog[c]	90	27.8 (9.91)	27	1.7 (5.64)	2	.0045
MMSE	88	17.0 (3.13)	18	1.2 (3.87)	1	.0052
GDS	90	4.6 (0.74)	5	0.1 (0.64)	0	.2520
Activities of daily living						
ADCS-ADL	89	47.2 (19.03)	49	–0.8 (6.30)	0	.2559

[a]Intent-to-treat population; last-observation-carried-forward analysis.
[b]Calculated so that positive changes from baseline indicate improvement.
[c]Primary efficacy variable.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living, GDS = Global Deterioration Scale, MMSE = Mini-Mental State Examination.

Figure 1. Change at Week 12 From Baseline[a] in the ADAS-cog Memory Score[b]



[a]Patients had been taking a stable dose of rivastigmine for at least 2 weeks.
[b]Positive changes indicate improvement.
Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale.

Efficacy

Primary efficacy measure. Because the efficacy analysis was performed for patients who had no more than 1 missing item on a particular test, the numbers of patients ranged from 88 to 90 for the LOCF analysis and from 81 to 83 for the observed-cases analysis. There was a statistically significant improvement between baseline and week 12 for the ADAS-cog total score, showing a positive effect of combination therapy (rivastigmine plus memantine) in the treatment of AD (Table 2). The p value for the null hypothesis of the mean change of ≤ -2 was $< .0001$; therefore, combination treatment produced a superior result compared with the historical placebo group. The mean change in the ADAS-cog memory subscore at week 12 for the ITT population was 0.84 ($p = .0072$; Figure 1). Similar results were observed for the observed-cases analysis (Table 3).

Secondary efficacy measures. There were statistically significant differences between baseline and week 12 scores on the MMSE, showing positive effects of combination therapy (Table 2). The ADCS-ADL and GDS scores showed no significant changes (Table 2); however, the study was not powered to detect changes in these secondary efficacy parameters. Again, similar results were observed for the observed-cases analysis (Table 3).

Safety and tolerability. Seven serious adverse events were observed in a total of 6 patients, but an association with the use of rivastigmine alone or the combination therapy was only presumed to be present in 2 cases. In 1 case, the patient accidentally received a double dose of rivastigmine (12 mg/day instead of 6 mg/day) and memantine (10 mg/day instead of 5 mg/day) and suffered from syncope the same day but made a complete recovery in 2 days. The other case involved a patient who was admitted to the hospital after suffering from syncope. Rivastigmine was permanently discontinued, and the patient made a complete recovery within a month. The length of hospitalization (1 month) was due to multiple comorbidities (arrhythmia, diabetes mellitus, and renal failure).

In this study, adverse events were reported for 30 patients ([31.6%]; suspected of being rivastigmine related, for 3 patients [3.2%]; suspected of being memantine related, for 9 [9.5%]; and suspected of being combination-therapy related, for 5 patients [5.3%]). The frequency and type of adverse events are summarized in Table 4. Vital signs (e.g., heart rate, systolic and diastolic blood pressure, weight) were not altered after initiation of add-on therapy with memantine.

DISCUSSION

The present study involved a wide range of patients in terms of age and disease severity. In our sample of patients with mild-to-moderate AD, combination therapy (rivastigmine plus memantine) improved ADAS-cog total scores, as well as MMSE scores. Combination therapy was also safe and well-tolerated by most of the patients.

Table 3. Summary Scores at Week 12 on Efficacy Variables for Patients Treated With Combination Therapy[a]

Assessment	N	Score at Baseline		Change From Baseline[b]		p Value (2-sided)
		Mean (SD)	Median	Mean (SD)	Median	
Cognition						
ADAS-cog[c]	83	27.9 (9.89)	27	1.7 (5.64)	2	.0067
MMSE	81	18.0 (4.98)	18	1.2 (3.89)	1	.0081
GDS	83	4.6 (0.74)	5	0.1 (0.61)	0	.3724
Activities of daily living						
ADCS-ADL	83	47.1 (19.23)	49	–0.7 (6.10)	0	.2842

[a]Observed-cases analysis.
[b]Calculated so that positive changes from baseline indicate improvement.
[c]Primary efficacy variable.
Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living, GDS = Global Deterioration Scale, MMSE = Mini-Mental State Examination.

Table 4. Patients With Adverse Events[a] by Primary Organ Class (safety population, N = 95)[b]

Adverse Event	Overall, N (%)	Adverse Events Suspected as Related to Memantine, N (%)	Adverse Events Suspected as Related to Rivastigmine, N (%)	Adverse Events Suspected as Related to Combined Treatment, N (%)
Any adverse event	30 (31.6)	9 (9.5)	3 (3.2)	5 (5.3)
System/organ class affected				
Nervous system disorder	10 (10.5)	1 (1.1)	1 (1.1)	2 (2.1)
Gastrointestinal disorder	8 (8.4)	4 (4.2)	0	4 (4.2)
Psychiatric disorder	6 (6.3)	3 (3.2)	0	1 (1.1)
Infections and infestations	4 (4.2)	0	0	0
Vascular disorders	4 (4.2)	0	0	0
Ear and labyrinth disorders	2 (2.1)	0	0	1 (1.1)
Injury, poisoning, and procedural complications	2 (2.1)	0	0	0
Respiratory, thoracic, and mediastinal disorders	2 (2.1)	0	0	0

[a]Frequency > 2%.
[b]Patients are counted only once in each organ class regardless of the number of adverse events experienced in that organ class.

The frequency of adverse events reported by patients may have been influenced by the open-label nature of this study.

Previous reports have not shown any significant interactions between ChEIs and memantine.[22] Similarly, our study did not reveal any health hazards of combination therapy with rivastigmine and memantine. The improvement of 1.7 in the total ADAS-cog score that we observed from baseline to week 12 is comparable with values reported for various AChEIs (1.8–4.9).[23] A previous randomized, double-blind, placebo-controlled study revealed an improvement in ADAS-cog scores of 1 point in patients with AD who were treated with rivastigmine monotherapy (6–12 mg) for 12 weeks.[21]

Treatment with rivastigmine as monotherapy has been studied for up to 5 years, and the results suggest that early therapy may confer some benefit in delaying long-term progression of symptoms.[24] Treatment with rivastigmine as monotherapy has also been shown to be associated with a delay in nursing home placement[25,26] and with a decreased use of psychotropic drugs.[27]

The beneficial effects of ChEIs and memantine on ADCS-ADL compared with placebo are small but may still be of clinical importance. The small effect observed has been equated to the prevention of a 2-month-per-year decline in a typical patient with AD.[28] In a recent study conducted in patients with mild-to-moderate AD, small changes in ADAS-cog were associated with substantial measurable effects on the daily lives of both patients and caregivers.[29] In another study, ChEI use had a clinically meaningful effect on the natural history of AD, with patients taking ChEIs being 2.5 times more likely to progress slowly and having a lower risk of nursing home admission after 2 years.[30] Thus, the modest changes in ADAS-cog and MMSE that we observe in this study with combination therapy may have a significant impact on the patient and the patient's family.

The change in ADAS-cog score observed with therapy in this study was statistically significant compared with the historical control; however, the change was less than the 4-point change recommended by the U.S. Food and Drug Administration for clinical relevance.[31] Nonetheless, the data do provide information concerning the impact of drugs on cognition. Limitations of this study are that it was a short-term, open-label pilot study conducted in a small number of patients. (Double-blind add-on stud-

ies are under consideration.) Another limitation is that a historical placebo group was used as a control arm of the study.

CONCLUSION

In summary, our results show that, in patients with mild-to-moderate AD, therapy with rivastigmine and memantine produces statistically significant improvement on the ADAS-cog total score and the MMSE score. The results also demonstrate that combination therapy with rivastigmine and memantine is safe and well-tolerated. Our results need to be confirmed in a large, long-term, randomized, double-blind, placebo-controlled clinical trial.

Drug names: donepezil (Aricept), ergoloid (Hydergine, Gerimal, and others), galantamine (Razadyne), memantine (Namenda), rivastigmine (Exelon), tacrine (Cognex), zolpidem (Ambien), zopiclone (Lunesta).

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