Long-Term Safety and Tolerability of Rivastigmine in Patients With Alzheimer's Disease Switched From Donepezil: An Open-Label Extension Study

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Objectives: The objective of this article is to present safety and tolerability data from the long-term extension phase of a core study conducted in patients with Alzheimer's disease (AD) who were immediately switched to rivastigmine.

Method: This was a 26-week open-label extension (OLE) of a prospective, 26-week, open-label, single-arm, multicenter study conducted in the United States from October 2003 to January 2005. Patients had a diagnosis of Alzheimer's disease according to DSM-IV-TR and National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria. Safety and tolerability of rivastigmine were monitored through monthly telephone contacts. At week 52, patients or caregivers were contacted by telephone to evaluate the patient's well-being.

Results: 146 patients (approximately 79% of patients who completed the core phase) entered this OLE. Most patients (N = 115, 78.8%) completed the full 26 weeks of the extension phase, during which time they received a mean rivastigmine dosage of 10.5 mg/day. The number of patients reporting newly occurring or worsening adverse events decreased considerably during the OLE (N = 84, 57.5%) compared with the core phase (the first 26 weeks; N = 116, 79.5%). Most patients reported adverse events that were mild or moderate in severity. At the end of the OLE, the majority of patients (128/146; 87.7%) were still receiving treatment with rivastigmine. At week 52, most caregivers expressed satisfaction with rivastigmine treatment (77.4%) and with the changes observed in the patient's behavior during the study (71.9%).

Conclusions: For patients not tolerating or not responding to donepezil, treatment with rivastigmine was safe and well tolerated for at least 52 weeks.

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Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disorder characterized by a gradual progression of cognitive, functional, and behavioral deficits.[1] The disease is currently estimated to affect 4 million people in the United States; however, the prevalence increases with age.[2] In those aged 65 years, the prevalence is about 5%; beyond 65, the rate doubles approximately every 5 years.[3,4] The typical duration of the disease from onset to death is about 8 to 10 years,[5,6] hence affected patients generally require long-term symptomatic treatment. Consequently, long-term data on the safety and efficacy of therapeutic agents are essential in this patient population.

Although the exact pathophysiology of AD has not been fully established, the cognitive deficits associated with the disease are primarily related to cholinergic deficits.[7] Development of potential therapies has therefore focused on enhancing cholinergic neurotransmission. Cholinesterase inhibitors (ChEIs), which enhance cholinergic function, are the standard pharmacologic treatment for mild-to-moderate AD.

The currently available ChEIs, donepezil, rivastigmine, and galantamine, enhance cholinergic function by inhibiting cholinesterases that degrade acetylcholine, thereby increasing the availability of the neurotransmitter to stimulate nicotinic and muscarinic receptors in the brain. They have been shown to improve the cognitive, functional, and behavioral symptoms of AD and are approved for the symptomatic treatment of mild-to-moderate disease[8,9]; however, donepezil has recently received U.S. Food and Drug Administration approval for the treatment of severe AD.

The ChEIs differ in their affinity for acetylcholinesterase and butyrylcholinesterase; donepezil and galantamine are essentially selective for acetylcholinesterase, while rivastigmine inhibits both with similar affinity.[10] Rivastigmine differs from the rapidly reversible cholinesterase inhibitors, donepezil and galantamine, in that it is a slowly reversible (pseudo-reversible) ChEI of the carbamate class with brain-regional specificity for the cerebral cortex and hippocampus.[10]

Although donepezil, rivastigmine, and galantamine belong to different chemical classes, they have shown similar

levels of improvement in cognitive function in studies to date[8]; however, their differing pharmacologic, pharmacokinetic, tolerability, and drug interaction profiles may influence individual treatment response.[8,10] It may, therefore, be beneficial to switch between ChEIs if patients fail to respond to treatment, deteriorate, or are unable to tolerate their current treatment.[11,12]

A recent 26-week open-label study[13] showed that switching patients immediately (i.e., without a washout period) to rivastigmine 3 to 12 mg/day after poor response to donepezil improved or stabilized global functioning in almost 70% of patients. The immediate switch was also safe and well tolerated. Patients who completed the 26-week treatment period had the option to continue open-label treatment with rivastigmine for an additional 26 weeks. This report presents the final 52-week safety and tolerability data from this study, as well as outcomes data.

METHOD

The study protocol was reviewed and approved by an institutional review board/independent ethics committee and was conducted in accordance with the Declaration of Helsinki. Prior to their participation in the study, patients provided written informed consent if the patient was determined by the investigator to be mentally competent. In addition, an appropriately responsible party on the patient's behalf, as well as the patient's caregiver, provided written informed consent prior to the patient's participation in the study. If the patient was not able to provide written informed consent, written informed consent was obtained from the caregiver and the authorized representative on the patient's behalf, and verbal assent was also obtained from the patient if possible and permitted by state, local, and institutional review board regulations.

Study Design

This study, conducted from October 2003 to January 2005, was a 26-week open-label extension of a prospective, 26-week, open-label, single-arm, multicenter study conducted in the United States, the design and results of which have been reported in detail elsewhere.[13] In brief, eligible patients commenced treatment during the core phase with rivastigmine 1.5 mg b.i.d., and the time between the last dose of donepezil and the first dose of rivastigmine was not to have exceeded 7 days. If the patient tolerated the starting dose, the dose could be increased to 3 mg b.i.d. after a minimum of 4 weeks. All subsequent dose escalations were made in 3-mg/day increments after a minimum of 4 weeks at the current dose, to a maximum dose of 6 mg b.i.d. (12 mg/day). Continuation of medications for concomitant diseases was allowed; however, current treatment with nootropics, lithium, or anticholinergic agents and previous exposure to rivastigmine were not permitted.

Patients

Inclusion criteria. Patients were aged 50 to 90 years and had a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[14] diagnosis of dementia of the Alzheimer's type and probable/possible Alzheimer's disease according to criteria established by the Work Group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[15] Eligible patients had mild-to-moderate AD confirmed by a Mini-Mental State Examination (MMSE)[16] score of 10 to 26. Patients had to have received treatment with donepezil 10 mg/day for at least 3 months prior to baseline. Furthermore, patients had to be responding poorly to or declining on treatment as evidenced by either cognitive decline, assessed by a loss of ≥ 2 points on the MMSE within the previous 6 months, or clinical decline, as determined by the investigator, in at least 1 of the following domains: activities of daily living, behavior, global functioning, or caregiver dissatisfaction with patient response.

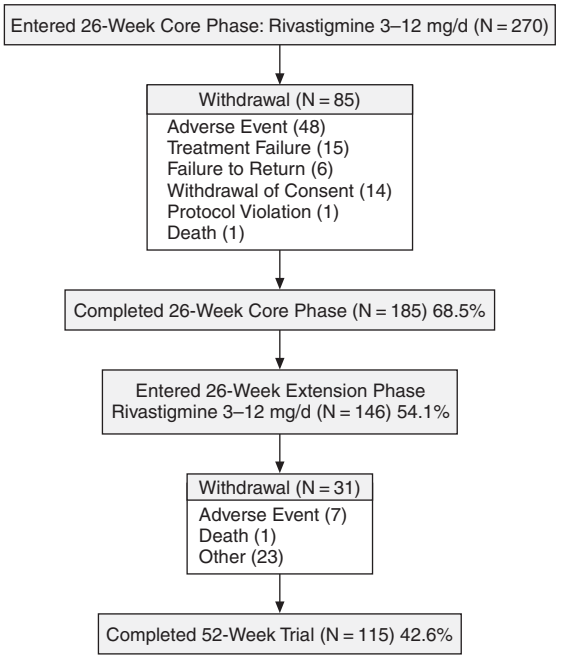
Patients who deviated slightly from these criteria were considered for inclusion on a case-by-case basis. The final decision concerning eligibility was made by the medical monitor from the clinical research organization conducting the study.

Exclusion criteria. Patients with an advanced, severe, or unstable medical condition of any type that might interfere with evaluations were excluded from the study. Also excluded were patients with a current diagnosis of active, uncontrolled peptic ulceration within the past 3 months; acute, severe, or unstable asthma or obstructive pulmonary disease; unstable cardiovascular disease; any primary neurodegenerative disorder other than AD; any psychiatric disorder that might interfere with response to study medication; or cerebrovascular accident within 6 months prior to baseline. However, patients with major depressive disorder who had been stabilized with an antidepressant for ≥ 1 month were permitted. Patients who were unable to maintain a minimum dose of 3 mg/day (1.5 mg b.i.d.) of rivastigmine were discontinued from the trial.

Safety and Tolerability Assessments

During the 26-week extension phase, safety and tolerability were monitored through monthly telephone contacts at weeks 30, 34, 38, 42, 46, and 50. During these contacts, information regarding adverse events and changes in concomitant medications/significant nondrug therapies was collected. The caregiver was instructed to return any unused medication to the study site at weeks 38 and 52. At week 52, patients/caregivers were contacted by telephone to evaluate the patient's well-being and to collect outcomes information. The outcomes form, which was to have been completed for all patients at week 52,

Figure 1. Patient Disposition



including those who discontinued the study prior to this timepoint, collected the following information: patient currently on rivastigmine treatment, patient/caregiver satisfied with rivastigmine, caregiver satisfied with the changes in the patient's behavior while on rivastigmine treatment, and patient placed in a nursing home or long-term institution.

Statistical Methods

The safety population comprised all patients who took at least 1 dose of study medication during the extension phase of the study. Assessment of safety was based on the frequency of adverse events (AEs) and discontinuations due to AEs. Demographic data are reported as mean ± SD.

RESULTS

Demographics and Baseline Characteristics

Of the 270 patients who entered the core phase of the study, 185 (68.5%) completed the study (Figure 1). One hundred forty-six patients (78.9% of the eligible patients) who completed the core phase entered the extension phase of the study, and 115 patients (78.8% of patients enrolled in the extension phase) completed all 52 weeks. The majority of the patients (62.3%) were female, with a mean age of 78.0 ± 7.2 years, and had been previously treated with donepezil for about 2 years (Table 1). Most of the patients met all of the inclusion criteria (Table 2).

Table 1. Patient Characteristics at Baseline of the Core Phase (first 26 weeks) of the Study (N = 146)

Characteristic	Value
Sex, N (%)	
Male	55 (37.7)
Female	91 (62.3)
Age, mean ± SD (range), y	78.0 ± 7.2 (55.0-91.0)
Dementia duration, mean ± SD (range), y	3.3 ± 1.8 (1.0-10.0)
MMSE total score, mean ± SD (range)	18.7 ± 4.35 (10–26)
Disease severity, N (%)	
Mild (MMSE score ≥ 16)	110 (75.3)
Moderate (MMSE score < 16)	36 (24.7)
Duration of donepezil treatment, mean ± SD (range), mo	23.5 ± 16.3 (2.0–70.0)

Abbreviation: MMSE = Mini-Mental State Examination.

Table 2. Patients Meeting Various Inclusion Criteria at Baseline of the Core Phase (first 26 weeks) of the Study (N = 146)

Inclusion Criterion	N (%)
Patients with decrease in total score of most recent 2 MMSEs while receiving donepezil	88 (60.3)
Patient experienced clinical decline while receiving donepezil	
At least 1 domain	140 (95.9)
At least 2 domains	90 (61.6)
At least 3 domains	43 (29.5)
Activities of daily living	91 (62.3)
Behavior	61 (41.8)
Global functioning	121 (82.9)
Caregiver dissatisfied with the patient's response to donepezil	133 (91.1)

Abbreviation: MMSE = Mini-Mental State Examination.

The mean total duration of prescribed treatment (core plus extension phases) was 347.5 ± 55.4 days (median: 365; range: 169–434 days). The mean last prescribed dose of rivastigmine at the end of the extension study was 10.5 ± 2.5 mg/day (median: 12.0; range: 3–12 mg/day). At the end of the extension phase, almost all of the patients (97.3%) were receiving therapeutic doses of rivastigmine (6–12 mg/day), with the following breakdown by dosage: 3 mg/day, 4 patients (2.7%); 6 mg/day, 18 patients (12.3%); 9 mg/day, 27 patients (18.5%); and 12 mg/day, 97 patients (66.4%).

Safety and Tolerability

Of the 146 patients who entered the extension phase of the study, 31 patients discontinued before the end of the 52 weeks. A total of 7 patients (4.8%) discontinued treatment due to AEs (gastrointestinal disorders, weight decrease, psychiatric disorders, nephrolithiasis, and night sweats), and 1 patient death was reported (myocardial infarction on study day 207, not suspected by the investigator to be related to study medication).

Eighty-four patients (57.5%) reported at least 1 newly occurring or worsening AE during the extension phase. The most common newly occurring or worsening AEs are

Table 3. Newly Occurring or Worsening Adverse Events in > 4% of Patients During the Extension Phase of the Study (N = 146)

Adverse Event	N (%)
Diarrhea	10 (6.8)
Fall	9 (6.2)
Urinary tract infection	9 (6.2)
Anxiety	8 (5.5)
Confusional state	7 (4.8)
Arthralgia	6 (4.1)
Vomiting	6 (4.1)

Table 4. Adverse Events Occurring in > 7% of Patients During the Core Phase (first 26 weeks) of the Study Compared With Adverse Events in the Extension Phase (last 26 weeks) of the Study (N = 146)

Adverse Event	Core Study, N (%)	Extension Study, N (%)
Nausea	41 (28.1)	3 (2.1)
Vomiting	26 (17.8)	6 (4.1)
Dizziness	14 (9.6)	5 (3.4)
Weight decrease	13 (8.9)	3 (2.1)
Fall	12 (8.2)	9 (6.2)
Hypertension	12 (8.2)	1 (0.7)
Diarrhea	11 (7.5)	10 (6.8)
Headache	11 (7.5)	3 (2.1)

Table 5. Long-Term Outcomes Assessed at Week 52

Category	N (%)
Patient currently on rivastigmine treatment	
Yes	128 (87.7)
No	13 (8.9)
Unknown	5 (3.4)
Patient/caregiver satisfied with rivastigmine treatment	
Yes	113 (77.4)
No	21 (14.4)
Unknown	12 (8.2)
Caregiver satisfied with the changes in the patient's behavior while on rivastigmine	
Yes	105 (71.9)
No	29 (19.9)
Unknown	12 (8.2)
Patient placed in a nursing home or long-term institution	
Yes	12 (8.2)
No	128 (87.7)
Unknown	6 (4.1)

listed in Table 3; these were diarrhea (N = 10, 6.8%), fall (N = 9, 6.2%), and urinary tract infection (N = 9, 6.2%). Nine patients had their dosage of rivastigmine changed due to AEs experienced in the extension phase. Most AEs were mild to moderate in severity, with 15 patients (10.3%) reporting severe AEs; however, only 1 patient reported a severe AE that was suspected of being related to treatment with rivastigmine (diarrhea).

In addition to a decrease in the number of patients experiencing AEs during the extension phase, there was a significant decrease in the frequency of gastrointestinal AEs, which is consistent with data from earlier trials of rivastigmine. The frequency of nausea and vomiting decreased from 28.1% and 17.8% to 2.1% and 4.1%, respectively (Table 4).

Seventeen patients (11.6%) reported 31 serious AEs during the extension phase of the study. The most common serious AEs were congestive cardiac failure (N = 4, 2.7%), anxiety (N = 2, 1.4%), and visual hallucination (N = 2, 1.4%); however, none of these serious AEs were suspected of being related to treatment with rivastigmine.

Patient Outcomes

The outcome of all the patients enrolled in the extension study was assessed at week 52 (Table 5). Most of the patients (87.7%) were still receiving rivastigmine and were being cared for at home (87.7%). At week 52, most caregivers expressed satisfaction with rivastigmine treatment (77.4%) and with the changes observed in the patient's behavior during the study (71.9%).

DISCUSSION

Approximately 79% of the eligible patients elected to participate in this extension study of rivastigmine treatment in patients who had previously not responded adequately with donepezil. Most patients (78.8%) completed the 26-week extension phase of the study, during which they received a mean rivastigmine dosage of 10.5 mg/day. The frequency of AEs decreased considerably during the extension phase of the study, compared with the core phase (the first 26 weeks). Seventeen patients reported serious AEs, none of which were suspected of being related to treatment with rivastigmine. At the end of the extension phase of the study, most patients were still receiving rivastigmine and were being cared for at home. At week 52, most caregivers expressed satisfaction with rivastigmine treatment (77.4%) and with the changes observed in the patient's behavior during the study (71.9%).

The long-term results are in agreement with an interim analysis of 61 patients from this trial that demonstrated that the immediate transition from donepezil to rivastigmine was safe and well tolerated during the first 28 days following the switch.[17] Our result on discontinuations due to AEs (N = 7, 4.8%) also agrees with the published results of a 26-week, open-label extension of a 26-week, double-blind, placebo-controlled study (62/532, 11.7%).[18]

The relatively low completion rate of 42.6% reported here for 52 weeks of treatment is similar to previous rates observed in clinical practice as contrasted with rates reported for randomized, clinical trials. A 42% completion rate was reported after a 52-week open-label study[19] of rivastigmine in nursing home residents. A retrospective study[20] of drug persistency that used information from a prescription database for outpatients with AD observed a 1-year continuation rate of 47% for both rivastigmine and donepezil. Finally, a retrospective study[21] of rivastigmine in patients in an outpatient geriatric setting observed

the following continuation rates: 1 year, 62%; 18 months, 40%; 2 years, 21%. Thus, large discontinuation rates are frequently observed in real-world conditions.

Patients with AD are generally elderly; therefore, safety and tolerability are more of a concern in this population.[22] The major clinical implication of our results is that AEs observed with 1 ChEI do not predict AEs with a different ChEI, which is consistent with the results seen in a previous trial.[11] The AEs observed during the initiation of rivastigmine treatment can be managed with correct dosing and titration schedules,[23] and AEs become much less of a problem with time.

The major limitation of this study is the open-label design. Also, no efficacy measurements were made during the extension period, so no information can be provided about the long-term efficacy of treatment with rivastigmine.

In summary, this 26-week extension study conducted in patients who were not adequately responding to donepezil showed that the immediate switch to rivastigmine was safe and well tolerated for at least 52 weeks. Further studies will need to be conducted to confirm the long-term efficacy of treatment with rivastigmine.

Drug names: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon and others).

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