Safety and Efficacy of Rivastigmine in Patients With Alzheimer's Disease Not Responding Adequately to Donepezil: An Open-Label Study

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Objective: Switching patients with Alzheimer's disease from one cholinesterase inhibitor to another represents a viable option for patients not responding to current therapy. The objective of this large U.S.-based study was to evaluate the safety and efficacy of a treatment switch to rivastigmine in patients not responding adequately to or declining on treatment with donepezil.

Method: In this 26-week, prospective, open-label, single-arm, multicenter study conducted from April 24, 2003, to June 25, 2004, patients with mild-to-moderate Alzheimer's disease (DSM-IV-TR criteria) who were not responding to donepezil were treated with rivastigmine 3–12 mg/day. Safety and tolerability were measured by the occurrence of adverse events and patient disposition. Treatment effects on global functioning were assessed using the Clinical Global Impression of Change (CGIC) scale.

Results: Two hundred seventy patients with a mean age of 78.5 (SD = 7.56) years and a mean duration of dementia of 3.5 (SD = 2.06) years were included in the study. Sixty-nine percent of patients completed the study with 17.8% discontinuing due to adverse events. Eighty-three percent of patients reported at least 1 adverse event, with the most frequently occurring adverse events affecting the gastrointestinal system (54%). The majority of patients were reported to have either improvement or no decline on the CGIC. A limitation of the study is that the interpretation of the results is based on an overall completion rate of 69%.

Conclusion: Immediately switching patients from donepezil to rivastigmine without a washout period was safe and well tolerated in the current study. Additionally, these results suggest that patients not responding adequately to or declining while taking donepezil may improve or stabilize after switching to rivastigmine.

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Cholinesterase inhibitors (ChEIs), which enhance cholinergic function, are currently the standard pharmacologic treatment option for patients with mild-to-moderate Alzheimer's disease (AD).[1] The 3 commonly used ChEIs are donepezil, rivastigmine, and galantamine. Donepezil and galantamine inhibit acetylcholinesterase (AChE), while only rivastigmine inhibits both AChE and butyrylcholinesterase. Although rivastigmine inhibits both enzymes, the clinical relevance of this has not been well established. The different pharmacologic characteristics of the 3 commonly used ChEIs may influence individual treatment response.[2,3] Consistent with these observations, previous studies have shown that patients who have an inadequate response to or cannot tolerate donepezil may experience symptom improvement after switching to rivastigmine.[4–6]

Factors that may influence the decision to switch between ChEIs include progressive cognitive decline after a treatment trial of at least 6 months, intolerable side effects, and family preferences.[7] When changing to another ChEI, the treatment objective is to avoid the possibility of both symptomatic deterioration related to the cessation of the first medication and the emergence (or re-emergence) of treatment-related adverse events following the initiation of the second ChEI and ultimately to either stabilize or improve the clinical course of the patient.

Washout periods between the treatments were included in these earlier trials primarily due to theoretical concerns

of cholinergic toxicity. However, prolonged washout periods when switching from 1 ChEI to another may not be desirable because of the potential loss of treatment effect and decline in cognitive functioning that may be associated with discontinuation of treatment.[8–11] In fact, a recent open-label trial in 61 patients with mild-to-moderate AD who were poor responders to donepezil suggested that an immediate switch from donepezil to rivastigmine was safe and well tolerated, similar to earlier findings in patients receiving rivastigmine who were not previously treated with a ChEI.[6]

The primary objective of this study was to evaluate the effects of rivastigmine on global functioning in a large population of patients with mild-to-moderate AD who were switching from treatment with donepezil because, in the investigator's clinical judgment, the patient was responding poorly to or declining with treatment or the caregiver was dissatisfied with the patient's response to donepezil. Secondary objectives included safety and tolerability assessments, more specifically, assessing the impact of a rapid switch to rivastigmine and evaluating the effects of rivastigmine on caregiver burden, activities of daily living (ADL), behavior, and cognition.

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 participation in the study, patients provided written informed consent if determined by the investigator to be mentally competent. In addition, an appropriately responsible party on the patient's behalf and 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, it 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 was a prospective, 26-week, open-label, single-arm, multicenter study conducted in the United States from April 24, 2003, to June 25, 2004. Screening was performed approximately 14 days prior to the baseline (visit 2), and visits 3, 4, and 5 occurred during weeks 4, 12, and 26, respectively. Patients who completed the 26-week treatment period may have had the option to continue in a 26-week open-label extension phase. Results in this article include data from the first 26 weeks.

All patients were started on rivastigmine 1.5 mg twice daily, and the first dose was to have been taken between 24 and 36 hours after the last dose of donepezil. If the patient had already discontinued donepezil prior to the baseline visit, the time between the last dose of donepezil and the first dose of rivastigmine could not exceed 7 days. If the patient demonstrated good tolerability to initial treatment, the dose was increased to 3 mg twice daily after a minimum of 4 weeks. If the investigator believed the patient might benefit from a more rapid increase in dose, the investigator had the option to increase the patient's dose to 3.0 mg twice daily after only 2 weeks. All subsequent dose escalations were made in 3-mg/day increments after a minimum of 4 weeks at the current dose. The maximum dose permitted was 6 mg twice daily. Finally, patients who were unable to maintain a minimum dose of 3 mg/day (1.5 mg twice daily) of rivastigmine were discontinued from the trial.

If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) caused intolerance during treatment, the patient may have been instructed to discontinue treatment for several doses or to skip a dose per day for a couple of days and then restart at the same or next lower dose level. Another strategy that could have been employed for treating nausea and vomiting was the use of trimethobenzamide. A single oral dose of 250 mg could be given to alleviate nausea and vomiting on an as-required basis, to a maximum daily dose of 750 mg. Dose decreases were permitted at any time throughout the study and were used to improve tolerability.

Patients

Inclusion criteria. Patients were men and women aged 50 to 90 years who satisfied the DSM-IV-TR criteria for a diagnosis of dementia of the Alzheimer's type and met the criteria for probable/possible AD 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.[12] Eligible patients had mild-to-moderate disease confirmed by a Mini-Mental Status Examination[13] (MMSE) score of 10 to 26.

Additionally, patients had to have received treatment with donepezil 10 mg/day for a minimum of 3 months prior to baseline and must, in the investigator's clinical judgment, have been responding poorly to or declining on their current treatment. Patients who had discontinued donepezil prior to the baseline visit may have been eligible for participation provided that the time between their last dose of donepezil and the baseline visit was not greater than 1 week. "Poor response" or decline was defined as a loss of at least 2 points on the MMSE within the previous 6 months or a decline in ADL, behavior, or global functioning as determined by the investigator or caregiver dissatisfaction with patient response. All patients were required to have a caregiver in contact with the patient a minimum of 3 days per week and available to accompany the patient to all study visits.

Patients who deviated slightly from these criteria were considered for study 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 were excluded from the study if they had an advanced, severe, or unstable medical condition of any type that might interfere with the evaluations or if they had taken rivastigmine previously. Patients were also excluded if they had a cerebrovascular accident within 6 months prior to baseline; a current diagnosis of active, uncontrolled seizure disorder; or any psychiatric diagnosis that might interfere with the response of the patient to study medication. However, patients with major depression who had been stabilized with an antidepressant for greater than or equal to 1 month were included. Patients were also excluded if they had a current diagnosis of active, uncontrolled peptic ulceration within the past 3 months or a current diagnosis of acute, severe, or unstable asthma or obstructive pulmonary disease.

Patients were permitted to continue medications for concomitant diseases; however, nootropics, medications for Parkinson's disease, lithium, anticholinergic drugs, and previous exposure to rivastigmine were not permitted. Doses of psychotropic medications must have been stable for at least 1 month prior to entry in the study.

Assessments

An interview for the Clinical Global Impression of Change (CGIC) scale,[14] the primary efficacy variable, was performed at baseline, and an assessment of change from baseline was performed at week 12 and week 26 (or early termination). The CGIC was rated on a 7-point scale ranging from 1 ("very much improved") to 7 ("very much worse") with 4 indicating "no change." The CGIC was used to determine the primary variable, the percentage of patients who either stabilized or improved following 26 weeks of treatment with rivastigmine (i.e., received scores ≤ 4).

Responders to treatment were defined as patients with CGIC scores of 4 or less, and nonresponders had CGIC scores of 5, 6, or 7. According to the protocol, a patient was to have been assessed by the same clinician who interviewed the patient at the baseline visit. If this was not possible, the new rater was to have access to notes from the other rater's baseline interview. For all ratings of change from baseline on the CGIC, the clinician relied solely on information obtained from the patient at the baseline visit, as well as clinical information obtained throughout the study period. The clinician did not have access to any efficacy data collected during the current study visit. For this reason, the CGIC was rated prior to all other efficacy evaluations.

The secondary outcome measures outlined here were used to assess the effects of treatment with rivastigmine on behavior, caregiver burden, cognitive functioning, and ADL. These assessments were performed at baseline, week 12, and week 26.

The Neuropsychiatric Inventory[15] (NPI) assesses 10 different behavioral domains. For each domain reported as present, frequency is rated on a 4-point scale (occasionally, often, frequently, and very frequently), and severity is rated on a 3-point scale (mild, moderate, and severe). The score for each domain is calculated by multiplying frequency and severity for a maximum possible score of 12. The total NPI score represents the sum of all assessed domain scores and can range from 0 to 120, with higher scores representing an increase in severity.

The Screen for Caregiver Burden[16] (SCB) is a self-administered questionnaire for caregivers. It contains 25 items that cover various issues involved in caregiving for a person with AD. Items are rated on a 5-point scale, from 0 = did not occur to 4 = severe distress. The SCB is scored in 2 ways, resulting in either an objective burden total score (total number of items answered as present) or a subjective burden total score (sum of the ratings for each of the 25 items). Higher scores represent an increase in caregiver burden.

The MMSE is a brief screening test for cognitive dysfunction. It consists of a total of 20 questions divided into 5 sections (orientation, registration, attention calculation, recall, and language). The total MMSE score ranges from 0 to 30, with lower scores indicating greater dysfunction.

The Dementia Severity Scale[17] (DSS) is a 47-item scale completed by the patient's caregiver and assesses the following: the patient's ability to perform ADL, the patient's behavior and behavioral disturbances, and the caregiver's perception of the patient's current cognitive abilities. Scores are summed within each subscale, and the subscale scores are summed to derive the total DSS score. Higher scores indicate greater severity of dementia. Two sets of 5-point Likert-type scale response options are used in the DSS. One series of items focuses on caregiver ratings of patient ability to perform tasks, and the response options for this set of questions range from "no assistance needed" to "unable to perform." The second series of items asks the caregiver to assess how often the patient experiences symptoms of dementia, with the response options ranging from "not at all" to "all of the time." This instrument was validated in a separate study while this trial was ongoing; only the results from the validated scale are presented.

Safety and tolerability were assessed at each visit during the treatment period through the collection of adverse events, including serious adverse events. In addition, patients or caregivers were contacted by telephone at 4-week intervals between scheduled visits to assess patient well-being and tolerability of the current dose of rivastigmine. Safety assessments also consisted of periodic measurements of vital signs.

Figure 1. Study Flowchart for Patients With Alzheimer's Disease

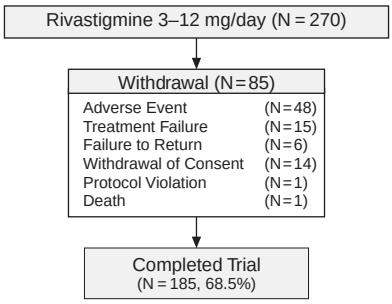


Table 1. Characteristics of Patients With Alzheimer's Disease at Baseline (N = 270)

Characteristic	Value
Sex, N (%)	
Male	104 (38.5)
Female	166 (61.5)
Age, mean ± SD (range), y	78.5 ± 7.56 (56–92)
Dementia duration, mean ± SD (range), y	3.5 ± 2.06 (1–13)
Disease severity, N (%)	
Mild (MMSE score ≥ 16)	190 (70.4)
Moderate (MMSE score < 16)	80 (29.6)
Duration of donepezil treatment, mean ± SD (range), mo	24.2 ± 16.89 (2–84)

Abbreviation: MMSE = Mini-Mental Status Examination.

Statistical Methods

All patients who took at least 1 dose of study medication were included in the safety analysis. All patients who took at least 1 dose of study medication and provided a valid baseline and at least 1 postbaseline measurement were included in the intent-to-treat (ITT) population.

Two analyses were performed on the ITT population. In the last-observation-carried-forward (LOCF) analysis, missing values were imputed using the LOCF method, while in the observed cases (OC) analysis, missing values were not imputed and were excluded from the analysis. The primary analysis time point was week 26, and changes from baseline on efficacy measures were tested using paired t tests, employing a significance level of 0.05. The 95% confidence interval was presented for the percentage of patients who demonstrated improvement or no change from baseline on the CGIC. In the sample size calculation, at least 200 patients were needed in order to have a greater than 90% probability of observing that the percentage of stabilized (i.e., CGIC score ≤ 4) LOCF patients was at least 50%, if the true percentage was 55% or higher.

RESULTS

Baseline Characteristics

A total of 270 patients were treated in this study, and 185 patients (68.5%) completed all 26 weeks (Figure 1). On average, patients had dementia for 3.5 years at baseline, and the average duration of prior treatment with donepezil was 2 years. Approximately two thirds of the study population were women (Table 1). Mean and median MMSE scores were 18.2 and 18.0, respectively. Almost all of the patients (269/270, 99.6%) had at least 1 past or concurrent medical condition. The most common concurrent medical conditions were psychiatric disorders (65.6%), vascular disorders (60.7%), metabolism and nutrition disorders (58.5%), gastrointestinal disorders (47.8%), cardiac disorders (43.7%), or nervous system disorders (42.6%). Concomitant medications were taken by 210 patients (77.8%).

Prior to initiating treatment with rivastigmine, 95.6% of the patients had experienced clinical decline as assessed by the clinician during prior treatment with donepezil. Clinical decline included deterioration in at least 1 of the following domains: 61.9% of the patients had experienced deterioration in ADL, 42.6% had experienced worsening in behavioral disturbances, and 83.3% had experienced deterioration in global functioning. Approximately 91.5% reported caregiver dissatisfaction with the patient's response to current treatment. For the 155 patients in whom a decline in MMSE score during the previous 6 to 12 months was reported, the mean ± SD decline was 4.0 ± 2.8 points. The majority of patients switched immediately to rivastigmine, with an average duration of 1.6 days between the last dose of donepezil and the first dose of rivastigmine.

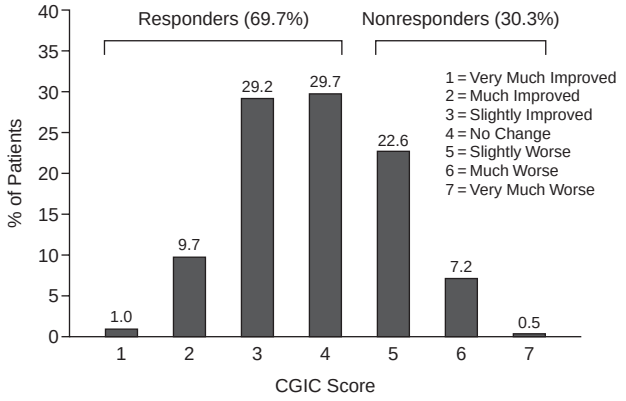
Data collected at baseline regarding the patients' caregivers indicated that 131 (48.5%) were retired and 80 (29.6%) were employed full-time. The highest level of education completed by the caregivers was elementary school for 14 (5.2%), high school for 106 (39.3%), vocational training for 29 (10.7%), university for 85 (31.5%), and university postgraduate school for 36 (13.3%).

Disposition and Dosing

The most common reason for study withdrawal was adverse event (N = 48, 17.8%), followed by treatment failure (N = 15, 5.6%) or withdrawal of consent (N = 14, 5.2%). Most of the patients who withdrew because of treatment failure had baseline MMSE scores between 10 and 15 (N = 9), and the remaining 6 patients had baseline MMSE scores between 16 and 26.

The mean ± SD duration of treatment for the patients who discontinued prematurely was 91 ± 56.1 days, and most patients were being treated with rivastigmine 6 to 12 mg/day (N = 14). The mean last prescribed dose of rivastigmine was 9.4 mg/day, and the final dose of rivastigmine was 12 mg/day for 139 patients (51.5%) and 9 mg/day for 52 patients (19.3%).

Figure 2. Clinical Global Impression of Change (CGIC) Score at Week 26 (observed cases analysis, N = 195)



Efficacy

Primary efficacy measure: CGIC. At week 26, approximately 69.7% of patients (136/195, OC analysis) demonstrated improvement or no further deterioration in global functioning as assessed by the CGIC rating of change from baseline (CGIC scores ≤ 4, Figure 2). Furthermore, 40.0% of patients (78/195) showed symptom improvement with rivastigmine as indicated by CGIC scores less than 4 at week 26. The mean ± SD CGIC score at week 26 was 3.9 ± 1.15 for the OC population. Similar results were observed for the LOCF analysis, with 65.1% of patients (166/255) demonstrating improvement or no further deterioration and 33.3% of patients (85/255) showing symptom improvement with rivastigmine. The mean ± SD CGIC score at week 26 was 4.0 ± 1.16 for the LOCF population.

Secondary efficacy measures. Of the 226 patients with at least 1 NPI symptom present at baseline, 52.7% showed greater than 10% improvement of NPI scores from baseline, 46.9% showed greater than 20% improvement, and 42.0% showed greater than 30% improvement (30% is thought to be clinically meaningful improvement). The mean ± SD changes from baseline for the NPI total scores were –1.5 ± 11.2 and –1.3 ± 10.6 for the OC and LOCF analyses, respectively. For each of the NPI symptom domains, the mean changes from baseline at week 26 among patients who had that symptom at baseline are shown in Figure 3 (OC analysis). All NPI symptom domains, except hallucinations, showed statistically significant improvement from baseline.

The baseline values for the different secondary efficacy variables are shown in Table 2, and the changes from baseline are shown in Table 3 for both OC and LOCF analyses. Other efficacy variables, such as MMSE and SCB objective burden, showed changes that were not statistically different from baseline. The remaining efficacy measure, DSS, showed small deterioration relative to baseline that was statistically significant.

One hundred ninety-five patients had SCB scores available at week 26. The total change score from baseline to week 26 (OC analysis) showed improvement of less than 4 points for 26 patients (13.3%) and 52 patients (26.7%) for the subjective and objective scores, respectively. The corresponding numbers for the patients with total change scores showing improvement between 4 to 20 points were 58 (29.7%) and 29 (14.9%) for subjective and objective scores, respectively.

The changes between baseline and week 26 (OC analysis) on the SCB and NPI were also examined for the group of patients who were classified as responders on the CGIC (CGIC score ≤ 4) versus nonresponders (CGIC score > 4). Responders showed statistically significantly greater improvement on the tests compared with nonresponders. The difference between the change scores at week 26 for nonresponders minus responders was 5.37 ($p = .0001$), 2.65 ($p < .0001$), and 8.38 ($p < .0001$) for SCB subjective, SCB objective, and total NPI scores, respectively.

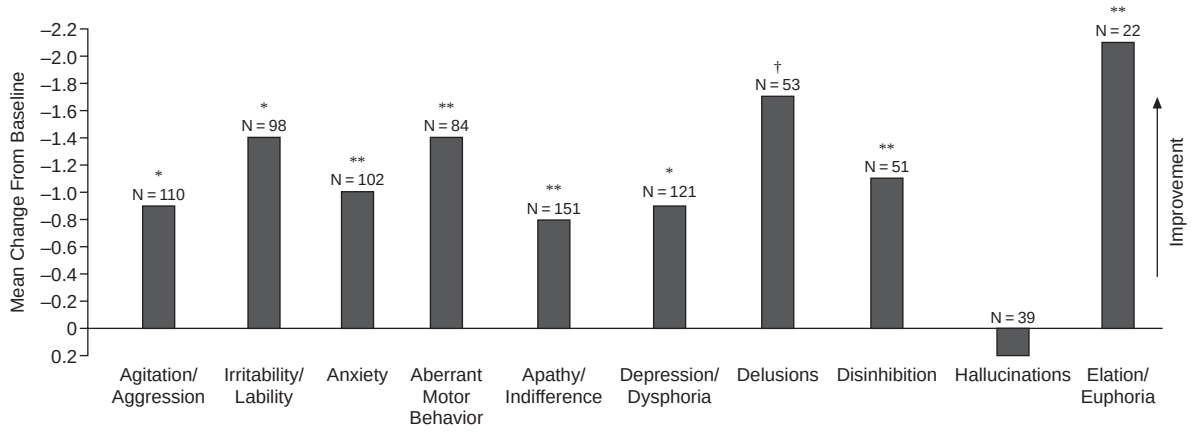
An analysis was performed on the subgroup of patients who had shown the largest deterioration—a decline of 4 points or more on the MMSE—during prior treatment with donepezil. In the LOCF analysis, 70 patients met the criterion, and 42 of those patients (60.0%) showed improvement or stabilization on the CGIC at week 26. Similar results were observed with the OC analysis in which 33 of 51 patients (64.7%) showed improvement or stabilization on the CGIC. However, no statistically significant improvement was observed in this subgroup for any of the secondary efficacy measures.

Safety and Tolerability

Forty-eight patients (17.8%) discontinued the study due to adverse events. The most common adverse events that resulted in discontinuation were nausea (N = 16, 5.9%), vomiting (N = 14, 5.2%), anorexia (N = 8, 3.0%), and confusional state (N = 7, 2.6%). Three deaths occurred during the clinical study (N = 1: sepsis secondary to *Clostridium difficile* colitis and N = 2: cerebrovascular accident); a relationship with study medication was not suspected for any of these events.

Overall, 223 patients (82.6%) reported at least 1 adverse event, and most were of mild-to-moderate severity. The most frequently reported adverse events (> 5%) are summarized in Table 4. Most of the adverse events were experienced during the titration phase of treatment, which consisted of day 1 through day 90 (183 patients, 67.8%). Of those adverse events that occurred most frequently during the titration phase, nausea, vomiting, and dizziness were the most common (> 10%), were mostly treatment related, and were reduced dramatically during the maintenance phase. Although confusional state and agitation

Figure 3. Mean Change From Baseline at Week 26 (last-observation-carried-forward analysis) by Neuropsychiatric Inventory Symptom Domain for Patients With That Symptom Present at Baseline



*p < .0001.
**p < .01.
†p < .001.

Table 2. Baseline Values for Secondary Efficacy Measures Among Patients With Alzheimer's Disease (N = 270)

Efficacy Measure	Mean (SD)	Median	Range
NPI total score	11.3 (12.41)	8	0–86
SCB subjective burden score	17.0 (11.59)	15.0	0–58
SCB objective burden score	8.6 (4.37)	9.0	0–22
MMSE score	18.2 (4.38)	18	10–26
DSS total score	35.8 (20.03)	35.0	1–97

Abbreviations: DSS = Dementia Severity Scale, MMSE = Mini-Mental Status Examination, NPI = Neuropsychiatric Inventory, SCB = Screen for Caregiver Burden.

were reported by greater than or equal to 5% of patients, the majority were not reported to be treatment related.

During the 26-week treatment period, 48 patients (17.8%) were reported to have experienced at least 1 serious adverse event. The most common serious adverse events were pneumonia (N = 6, 2.2%), dehydration (N = 4, 1.5%), and syncope (N = 4, 1.5%). Only 5 patients reported serious adverse events that were suspected by the investigator to be treatment related (gastrointestinal: N = 1, 0.4%; metabolism and nutrition disorders: N = 2, 0.7%; nervous system disorders: N = 1, 0.4%; and psychiatric disorders: N = 2, 0.7%).

DISCUSSION

The results of this study provide further support that switching patients immediately from donepezil to rivastigmine is safe and was tolerated by most of the patients. Almost 70% of this population of patients who were not responding adequately to donepezil showed either improvement or no further deterioration in global functioning as assessed by the CGIC. Furthermore, statistically significant changes from baseline were observed in most NPI symptom domains for patients who had NPI symptoms present at baseline. Although not statistically significant, minimal worsening in MMSE scores occurred in the overall population. These patients would have been expected to show further decline in MMSE scores if treated with a placebo or if they had continued treatment with donepezil.

The statistical significance of the NPI results depends upon the specific population of patients being considered. Thus, the mean change from baseline for the NPI total score was not statistically significant for the entire population of patients (e.g., Table 3). However, when the population was restricted to those patients who had a specific behavioral symptom present at baseline, then statistically significant changes were observed from baseline for most of the behavioral subscales (e.g., Figure 3).

Results from the current study agree with previous studies conducted in patients who were switched from donepezil to rivastigmine.[4–6,18] All of these previous studies were similar to the current study in that they were open-label in design without a comparison group. In a report of 382 patients who were treated in an open-label study,[4] patients were switched from donepezil to rivastigmine following a demonstrated lack of efficacy (80%) while receiving donepezil treatment, intolerability (11%) to donepezil treatment, or both (9%). Efficacy was assessed using measures of global functioning (CGIC), cognitive performance (MMSE), and ADL (Instrumental ADL scale). In this study, over 50% of the patients demonstrated stabilization or improvement as assessed by the 3 different scales.[4]

Table 3. Changes From Baseline at 26 Weeks for Secondary Efficacy Measures Among Patients With Alzheimer's Disease

	Change From Baseline at Week 26					
Outcome Measure	Observed Cases (mean ± SD)	N	p	Last Observation Carried Forward (mean ± SD)	N	p
NPI total score[a]	–1.5 ± 11.15	189	.0610	–1.3 ± 10.56	254	.0570
MMSE score	–0.4 ± 3.84	195	.1517	–0.6 ± 3.98	253	.0111
SCB subjective burden score[a]	–0.9 ± 9.14	195	.1795	–1.2 ± 9.74	253	.0595
SCB objective burden score[a]	0.1 ± 3.75	195	.6667	0.0 ± 3.83	253	.9005
DSS score[a]	0.1 ± 0.45	195	.00062	0.1 ± 0.44	253	< .0001

[a]Negative changes indicate improvement.
Abbreviations: DSS = Dementia Severity Scale, MMSE = Mini-Mental Status Examination, NPI = Neuropsychiatric Inventory, SCB = Screen for Caregiver Burden.

Table 4. Adverse Events Reported in at Least 5% of Patients With Alzheimer's Disease

Adverse Event, N (%)	Overall Summary (N = 270)
Patients reporting at least 1 adverse event	223 (82.6)
Nausea[a]	86 (31.9)
Vomiting[a]	60 (22.2)
Dizziness[a]	30 (11.1)
Weight decreased	28 (10.4)
Anorexia[a]	23 (8.5)
Confusional state	20 (7.4)
Diarrhea	20 (7.4)
Fall	20 (7.4)
Constipation	18 (6.7)
Agitation	17 (6.3)
Urinary tract infection	16 (5.9)
Asthenia	15 (5.6)
Hypertension	15 (5.6)
Decreased appetite	14 (5.2)
Somnolence	14 (5.2)

[a]One of the most common adverse events resulting in discontinuation.

In another open-label study,[5] 40 patients were switched from donepezil to rivastigmine due to lack of efficacy (55%) or adverse events (45%). Nearly half of the patients who were switched due to lack of efficacy and two thirds of the patients who were switched due to the experience of adverse events demonstrated improvement in cognition while receiving rivastigmine treatment. In a prospective, open-label multicenter study, 201 patients who failed previous treatment with donepezil (N = 116, 57.7%) or galantamine (N = 84, 41.8%) were switched to rivastigmine (3–12 mg/day) for 16 weeks.[18] Ninety-three patients (46.3%) responded to rivastigmine as assessed by improved (28.4%) or stabilized (17.9%) MMSE scores.

This study is limited by its open-label design and by the lack of prospective, objective, quantitative information about the rate of deterioration before switching to rivastigmine. A placebo group was not included in the study due to ethical concerns about not providing treatment to patients who were already poor responders to donepezil. The lack of a control group and the absence of randomization limit the conclusions that can be drawn from the study. However, patients who showed worsening from baseline on some efficacy measures may still have deteriorated at a slower rate than if they had continued treatment with donepezil. Another limitation of the study is the lack of a comparison group; however, there were ethical concerns about patients taking donepezil after they had shown poor response to the drug. Finally, the interpretation of the data in this study is based on an overall completion rate of 69%.

There are several important clinical implications of the results reported here. The first is that it is possible to switch patients from donepezil to rivastigmine without a washout period. These results are consistent with a previous report of safety and tolerability data from the first 28 days of treatment in an open-label study involving 61 patients, which concluded that switching patients from donepezil to rivastigmine without a washout period was safe and well tolerated.[6] Immediate switching to rivastigmine may be beneficial to patients in avoiding the potential loss of treatment effect and decline in cognitive functioning associated with discontinuation of treatment.[8]

Because of the lack of randomization and a comparison group, it is difficult to make any conclusions regarding efficacy. However, our results suggest that most patients (50%–70%) who no longer respond to donepezil may still show stabilization or improvement in overall global functioning or behavior with rivastigmine. This improvement or stabilization, as assessed with the CGIC, was even observed in most (60%) of the patients who had experienced a prior deterioration of 4 points or more on the MMSE during treatment with donepezil. Thus, when contemplating switching a patient from donepezil to rivastigmine, not only the patient's overall performance in cognition and global function should be considered, but also the patient's behavioral performance.

In summary, the results of this study suggest that poor responders to donepezil may experience symptom improvement or stabilization when switched to rivastigmine. Patients with behavioral symptoms present at baseline may show improvement after switching to rivastigmine, even though those effects may not be statistically signifi-

cant, and caregivers may experience a decreased subjective sense of burden. Furthermore, an immediate switch from donepezil to rivastigmine was safe and generally well tolerated by most of the patients with AD. Given the importance of the clinical implications of this study, further randomized, controlled studies should be undertaken to determine the potential clinical benefits of switching to rivastigmine for patients who are not responding to donepezil.

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

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