American Journal of Alzheimer's Disease & Other Dementias®
Volume 24 Number 3
June/July 2009 267-275

10.1177/1533317509333037
http://ajadd.sagepub.com

Switching from Donepezil Tablets to Rivastigmine Transdermal Patch in Alzheimer's Disease

Carl H. Sadowsky, MD, Alan Dengiz, MD, Jason T. Olin, PhD, Barbara Koumaras, BA, Xiangyi Meng, PhD, and Stephen Brannan, MD, on behalf of the US38 study group

Objective: Evaluate safety and tolerability of switching from donepezil to rivastigmine transdermal patch in patients with mild to moderate Alzheimer's disease. *Methods:* Prospective, parallel-group, open-label study to evaluate immediate or delayed switch from 5-10 mg/day donepezil to 4.6 mg/24 h rivastigmine following a 4-week treatment period. *Results:* Rates of discontinuation due to any reason or adverse events were similar between groups. Incidences of gastrointestinal adverse events were 3.8% in the immediate and 0.8% in the delayed switch group. No patients discontinued secondary to nausea and vomiting. Discontinuations due to application site reactions were low (2.3%). Asymptomatic bradycardia was more common following the immediate switch (2.3% vs 0%); however, these patients had coexisting cardiac comorbidities. *Conclusion:* Both switch strategies were safe and well tolerated. The majority of patients may be able to switch directly to rivastigmine patches without a withdrawal period. Appropriate clinical judgment should be used for patients with existing bradycardia or receiving β blockers.

Keywords: Alzheimer's disease; clinical trial; donepezil; rivastigmine; switching; transdermal patch

Introduction

Oral forms of cholinesterase inhibitors (ChEIs), such as rivastigmine (Exelon®, Novartis Pharma AG, Basel, Switzerland), donepezil (Aricept®, Eisai Ltd, Tokyo, Japan) and galantamine (Razadyne®, Ortho-McNeil-Janssen Pharmaceuticals Inc, NJ), have been available as therapeutic agents for dementia for a number of years.[1] These agents have demonstrated efficacy in treating patients with Alzheimer's disease (AD)[2]; however, many of these patients only adhere to their prescribed treatment for a relatively short duration.[3] In general, nonadherence to prescribed treatment regimens in elderly patients appears to occur for a variety of reasons, such as forgetfulness, interference with daily life, lack of understanding of instructions, or complex dosing regimens.[4] In particular, the 2 main reasons for patients with AD discontinuing treatment are a perceived lack of clinical benefit and the occurrence of adverse events (AEs).[3]

In clinical practice, a proportion of patients with AD may fail to experience sustained clinical benefit from ChEI treatment due to a lack of initial efficacy, loss of efficacy during long-term treatment, or tolerability issues.[5] For these patients, switching to another ChEI may be warranted. In patients who progress to a more severe disease stage, an additional agent, such as the glutamate-modifying agent memantine, has been used concomitantly with the

From Nova SE University, Fort Lauderdale, Florida (CHS); Premiere Research Institute, Palm Beach Neurology, West Palm Beach, Florida (CHS); St Joseph Mercy Health System, Ann Arbor, Michigan (AD); Novartis Pharmaceuticals Corporation, East Hanover, New Jersey (JTO, BK, XM); and Takeda Pharmaceuticals North America, Deerfield, Illinois (SB).

CHS has served as a consultant to Novartis Pharmaceuticals Corporation, has served as a speaker for Novartis Pharmaceuticals Corporation and Forest Pharmaceuticals, and has received honoraria from both companies. AD has served as a consultant to Novartis Pharmaceuticals Corporation, has received research support from Novartis Pharmaceuticals Corporation, and has served on the Speakers Bureau for Novartis Pharmaceuticals Corporation and Forest Pharmaceuticals. JTO, XM, and BK are full-time employees and stockholders of Novartis Pharmaceuticals Corporation. SB is a full-time employee of Takeda Pharmaceuticals North America and was a full-time employee and stockholder of Novartis Pharmaceuticals Corporation.

Address correspondence to: Carl H. Sadowsky, Premiere Research Institute, 4631 North Congress Ave Suite 200, West Palm Beach, FL 33407; e-mail: CHsadow@aol.com.

patient's ChEI treatment.[6] A number of studies have demonstrated that patients with AD who do not respond to treatment with either donepezil or galantamine tablets may show improvements in symptoms upon switching to rivastigmine capsules.[5,7-9] Rivastigmine capsules are currently approved in the European Union and United States (US) for the treatment of mild to moderate AD, based on its superiority over placebo on measures of cognition, activities of daily living (ADL), and global functioning.[10,11] As with all ChEIs, the most common AEs occurring with this agent are gastrointestinal (GI) in nature (eg, nausea, vomiting, and diarrhea).[10,11] The US prescribing information (PI) also reports class effects associated with ChEIs, including seizure, urinary obstruction, worsening of asthma and chronic obstructive pulmonary disease, vagotonic effects, and GI bleeding. None of these AEs has been associated with the rivastigmine capsule or transdermal patch, based on clinical trials data.[10-12]

In 2007, a transdermal patch formulation of rivastigmine became available in the US for the treatment of mild to moderate AD. The transdermal patch formulation provides continuous drug delivery over 24 hours and reduces fluctuations in plasma concentrations compared with the capsule formulation of rivastigmine. A 24-week, double-blind, double-dummy, randomized, placebo- and active-controlled study involving over 1100 patients with AD directly compared the capsule and transdermal patch formulations of rivastigmine.[12] The 9.5 mg/24 h rivastigmine transdermal patch had similar efficacy to the rivastigmine capsule (12 mg/day), with one-third of the incidence of GI side effects.[12] This tolerability profile could potentially result in greater treatment adherence with the rivastigmine transdermal patch.[3,12] It is worth noting that more than 70% of caregivers who participated in this study preferred the rivastigmine transdermal patch over the rivastigmine capsules, based on a questionnaire completed during the study.[13]

The switch from donepezil tablets to rivastigmine capsules has been investigated in a number of studies. Those employing either a gradual switch or a cross-tapering strategy had both demonstrated high rates of study completion and low incidences of AEs.[7,14,15] Good tolerability and retention were also seen with an immediate switch from donepezil to both 1.5 mg and 3 mg rivastigmine (twice daily [bid]).[9,16] However, a withdrawal period from ChEI treatment may leave patients at risk of decline in cognitive function.[17]

The objective of this study was to provide guidance to physicians when considering switching patients from donepezil tablets to the rivastigmine transdermal patch. This study assessed the safety and tolerability of 2 switching strategies: an "immediate" switch and a "delayed" switch following a 7-day withdrawal period.

Methods

Patients

Male or female patients, aged 50 years or older, with a diagnosis of mild to moderate dementia of the Alzheimer type (according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision)[18] and a clinical diagnosis of probable AD according to the National Institute of Neurological Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association criteria[19] were included in the study. Mild to moderate dementia was defined as a Mini-Mental State Examination (MMSE) score of 10 to 24, inclusive.[20] Patients were required to have a primary caregiver willing to accept responsibility for supervising treatment (eg, the daily application and removal of the transdermal patch at approximately the same time each day), assessing the condition of the patient throughout the study, and for providing input into the efficacy assessments in accordance with all protocol requirements. Patients were required to have been receiving donepezil tablets for at least 6 months and taking a stable dose of 510 mg/day for at least 3 months prior to study entry.

The main exclusion criteria included any primary neurodegenerative disorder other than AD or any other causes of dementia, any disability or unstable disease that may prevent the patient from completing all study requirements, a current diagnosis of bradycardia (heart rate <50 bpm), sick sinus syndrome, conduction defects, severe or unstable cardiovascular disease, significant urinary obstruction, peptic ulceration or GI bleeding, an unstable respiratory condition, any active skin lesion or disorder that would prevent accurate assessment of the adhesion and any potential skin irritation of the rivastigmine transdermal patch.

Patients who were receiving donepezil tablets and concomitant memantine at the beginning of the study were allowed to continue on the same dose of memantine throughout the study; however, not more than 50% of the total study population was to have been receiving combination therapy.

Patients were recruited into the study from clinical and research centers in the US. The study

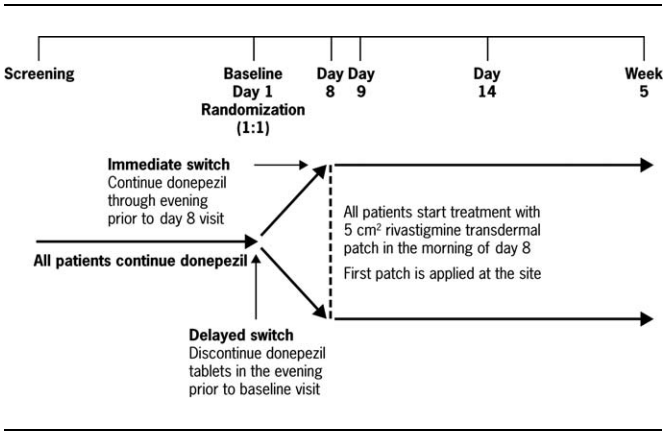

Figure 1. Study design.

was conducted in accordance with the Declaration of Helsinki and Good Clinical Reporting Practice. The study protocol was approved by an Institutional Review Board, an Independent Ethics Committee, and a Research Ethics Board. Prior to participation in the study, patients were to provide, if mentally competent, written informed consent along with consent from an appropriately responsible party on the patient's behalf and the patient's caregiver. If the patient was not able to provide written informed consent, then this was obtained from the caregiver and the appropriately authorized representative on the patient's behalf; and verbal assent was obtained from the patient if possible and permitted by state, local, and Institutional Review Board regulations.

Study Design

This was a prospective, randomized, multicenter, parallel-group, open-label safety and tolerability study. Patients were assessed between February 6, 2007 and September 19, 2007. Patients who completed the 5-week core phase of the study had the option to enter a 20-week open-label extension phase for further treatment and evaluation, data from which will be reported elsewhere.

Following a screening period of approximately 28 days, eligible patients were randomly assigned in a 1:1 ratio to either an immediate switch from 5-10 mg/day donepezil tablets to the 5 cm^2 rivastigmine transdermal patch (4.6 mg/24 h), or a delayed switch from 5-10 mg/day donepezil tablets to the 4.6 mg/24 h rivastigmine transdermal patch, following a 7-day withdrawal period (Figure 1). Patients in the delayed switch group discontinued donepezil tablets on the evening prior to day 1 and received no ChEI treatment for the first 7 days of the study (ie, during the withdrawal period). Patients in the immediate switch group continued on donepezil tablets up to and including day 7 of the study, so that all patients switching to the rivastigmine transdermal patch received the new treatment for the same period of time (ie, during the last 4-week period of the 5-week core phase). Patients in each treatment group were stratified by concomitant memantine use.

The rivastigmine transdermal patches were applied by the caregiver to clean, dry, and intact skin on the patient's upper or lower back, upper arm, or chest. Patches were changed every 24 hours in the morning to different sites within these areas, in rotation.

Assessments and Outcomes

The primary outcome of the study was safety and tolerability of the 2 different switching strategies, based on the incidence of discontinuation due to any reason from baseline to week 5. Other safety/tolerability measures included discontinuations due to AEs and the incidence of AEs during the core phase, and changes in 12-lead electrocardiogram (ECG) parameters from baseline to day 9. Vital signs were also assessed at baseline and at weeks 2 and 5.

A Clinical Global Impression of Change (CGIC) was conducted during an interview by a rater at baseline and at the end of week 5. Other assessments, which are reported elsewhere, were obtained via interviews with the caregiver at baseline and at week 25 (or early discontinuation) and included scores for Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI), NPI caregiver distress scale, and MMSE.

Statistical Analysis

The safety population consisted of patients who had received at least 1 dose of study medication and who had at least 1 post-baseline safety assessment. The intent-to-treat (ITT) population consisted of all randomized patients who had received at least 1 dose of study medication and who had at least 1 post-baseline safety/tolerability assessment. The sample size was based on the assumption of a 5% study discontinuation rate for any reason, which resulted in 120 patients for each treatment group to permit an accurate estimation of the discontinuation rate with a standard error of 0.03.

Discontinuation rates, the corresponding standard errors, and the 95% confidence intervals (CI) for the difference between the 2 treatment groups were calculated. Differences within treatment groups,

Table 1. Baseline Patient Demographics and Disease Characteristics[a]

	Immediate Switch Group (n = 131)	Delayed Switch Group (n = 130)	Total (n = 261)
Mean ± SD age, years	77.8 ± 7.66	76.7 ± 8.41	77.3 ± 8.04
Sex, n (%)			
Female	79 (60.3)	72 (55.4)	151 (57.9)
Male	52 (39.7)	58 (44.6)	110 (42.1)
Race, n (%)			
Caucasian	118 (90.1)	111 (85.4)	229 (87.7)
Black	4 (3.1)	10 (7.7)	14 (5.4)
Other	9 (6.9)	9 (7.0)	18 (6.9)
Mean ± SD weight, kg	72.0 ± 13.23	72.8 ± 16.40	72.4 ± 14.87
Duration of dementia, years			
Mean ± SD	4.0 ± 2.53	3.8 ± 2.70	3.9 ± 2.61
Median (range)	3.0 (0[b]-13)	3.0 (1-20)	3.0 (0-20)
Mean ± SD total MMSE score	18.6 ± 3.99	18.1 ± 3.99	18.3 ± 3.99
Duration of oral donepezil treatment, months			
Mean ± SD	30.2 ± 25.25	27.9 ± 20.20	29.1 ± 22.86
Median (range)	24.0 (6-144)	24.0 (5-130)	24.0 (5-144)
Current treatment with memantine, n (%)			
Yes	68 (51.9)	67 (51.5)	135 (51.7)
No	63 (48.1)	63 (48.5)	126 (48.3)

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.
[a] Values obtained from the safety population.
[b] Indicates less than 6 months.

based on concomitant memantine usage, for all-cause discontinuations and discontinuations due to AEs were estimated in a similar manner. All safety data were summarized according to both treatment group and the total population. Adverse events were summarized by presenting the number and percentage of patients having any AE, having an AE in each body system, and having each individual AE. Summary statistics (n, mean, standard deviation [SD], median, minimum and maximum) for each vital sign assessment and its change from baseline were produced for each treatment group at each visit. Summary statistics for all ECG parameters were calculated.

Descriptive statistics for the CGIC at week 5 were presented, together with number and percent of patients with no decline on the CGIC (CGIC score $\leq$4).

Results

Study Population and Disposition

A total of 345 patients were screened; of these, 262 patients were randomized (n = 131 in the immediate switch group; n = 131 in the delayed switch group). The safety and ITT populations consisted of 261 patients, as 1 patient in the delayed switch group discontinued during the baseline visit immediately following randomization. Overall, the mean age (±SD) was 77.3 ± 8.0 years, 57.9% of patients were female and the majority (87.7%) were Caucasian. The mean ± SD duration of AD and donepezil treatment was 3.9 ± 2.6 years and 29.1 ± 22.9 months, respectively, and the mean ± SD total MMSE score was 18.3 ± 4.0. Baseline demographics and clinical characteristics were similar for both treatment groups (Table 1). Approximately 15% of patients were reported to have experienced AEs or intolerability of donepezil. While receiving donepezil treatment, 46.4%, 29.9%, 62.8%, and 79.3% of patients were considered by the investigator to have experienced a decline in ADLs, behavior, global functioning, and cognition, respectively. In the immediate switch group, 51.9% of patients were receiving concomitant memantine compared with 51.5% of patients in the delayed switch group.

Treatment Discontinuation

Of the 261 treated patients, 240 (92.0%) completed the core phase. The primary reason for discontinuations in both treatment groups was AEs (Table 2).

Both immediate and delayed switching strategies were well tolerated, as measured by the discontinuation rate due to any reason or due to AEs. Eleven (8.4%) and 10 (7.7%) patients discontinued due to

Table 2. Reasons for Study Discontinuation[a]

Reason for Discontinuation	Immediate Switch Group (n = 131) n (%)	Delayed Switch Group (n = 130) n (%)
Total	11 (8.4)	10 (7.7)
Adverse events	6 (4.6)	4 (3.1)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	1 (0.8)
Unsatisfactory therapeutic effect	2 (1.5)	0 (0.0)
Withdrawal of consent	3 (2.3)	4 (3.1)
Lost to follow-up	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	1 (0.8)

[a] Values obtained from the safety population.

Table 3. Adverse Events Rates Reported (≥2% of Patients in any Treatment Group) During the Core Phase[a]

	Immediate Switch Group (n = 131) n (%)	Delayed Switch Group (n = 130) n (%)
Agitation	3 (2.3)	3 (2.3)
Application site reaction	1 (0.8)	5 (3.8)
Bradycardia	3 (2.3)	0 (0.0)
Constipation	0 (0.0)	6 (4.6)
Decreased appetite	4 (3.1)	0 (0.0)
Hallucination	3 (2.3)	0 (0.0)
Nausea	5 (3.8)	1 (0.8)
Vomiting	1 (0.8)	0 (0.0)
Somnolence	2 (1.5)	4 (3.1)

[a] Values obtained from the safety population.

any reason in the immediate and delayed switch groups, respectively (95% CI for between-regimen difference: [–8.1, 6.7]). Six (4.6%) and 4 (3.1%) patients discontinued due to AEs in the immediate and delayed switch groups, respectively (95% CI for between-regimen difference: [–6.9, 3.9]). Only 1 patient, in the delayed switch group, discontinued due to a GI AE (diarrhea). In the immediate switch group, AEs resulting in discontinuation were asymptomatic bradycardia, bundle branch block, decreased appetite, disease progression, hallucination, and stupor with deafness (1 case of each). In the delayed switch group, AEs resulting in discontinuation were bundle branch block, agitation, restlessness, benign vaginal neoplasm, and diarrhea (1 case of each). Three patients in the delayed switch group discontinued during the first week (ie, prior to the application of the first rivastigmine transdermal patch). There were no statistically significant differences between treatment groups in terms of the number of patients who discontinued due to any reason, including AEs. In the immediate and delayed switch groups, respectively, 5 (7.4%) and 3 (4.5%) patients receiving concomitant memantine discontinued due to AEs (95% CI for between-regimen difference: [–12.3, 6.5]). One patient in each of the switching groups (<2%) who were not receiving concomitant memantine discontinued due to AEs (95% CI for between-regimen difference: [–6.0, 6.0]).

Safety and Tolerability

The rivastigmine transdermal patch was well tolerated by patients in both treatment groups. A total of 36 (27.5%) patients in the immediate switch group and 45 (34.6%) patients in the delayed switch group experienced at least 1 AE during the core phase. The most frequently reported AEs in the immediate switch group were nausea (5 patients, 3.8%) and decreased appetite (4 patients, 3.1%), while in the delayed switch group the most frequently reported AEs were constipation (6 patients, 4.6%) and application site reaction (5 patients, 3.8%; Table 3).

One patient in the immediate switch group and 5 patients in the delayed switch group experienced at least one application site reaction, all of which were suspected to be related to the study medication. In 5 of the 6 patients in whom application site reaction was reported, the events were mild in severity; an application site reaction of moderate severity was reported in 1 patient in the delayed switch group. None of the reports of application site reactions were classed as serious and no patients discontinued the study due to this event.

Of all the AEs reported, the majority were considered to be mild or moderate in severity. Of those who experienced AEs, 34 experienced at least 1 AE that the investigator suspected to be related to the study medication.

Serious AEs were reported for 4 (3.1%) and 2 (1.5%) patients in the immediate and delayed switch groups, respectively. Two of these serious AEs were considered by the investigator to be related to the study medication (both in the immediate switch group): 1 patient with lethargy and 1 patient with asymptomatic bradycardia. No patient deaths were reported during the study.

Mean changes in quantitative ECG parameters were not clinically relevant and newly occurring

Table 4. Mean Change From Baseline in Vital Signs and Electrocardiogram Parameters[a]

	Immediate Switch Group	Delayed Switch Group
Change from baseline to week 5[b]		
Supine pulse rate, bpm		
n	117	117
Mean ± SD change from baseline	0.5 ± 9.91	1.7 ± 9.80
Supine systolic blood pressure, mm Hg		
n	117	117
Mean ± SD change from baseline	1.1 ± 12.59	−2.0 ± 14.21
Supine diastolic blood pressure, mm Hg		
n	117	117
Mean ± SD change from baseline	0.9 ± 7.92	0.8 ± 9.09
Change from baseline to day 9		
Heart rate, bpm		
n	130	125
Mean ± SD change from baseline	2.3 ± 8.62	2.7 ± 9.11
PR interval, msec		
n	121	116
Mean ± SD change from baseline	2.4 ± 34.94	−2.2 ± 25.03
QT interval (corrected), msec		
n	130	125
Mean ± SD change from baseline	2.1 ± 23.03	−2.6 ± 23.51
QRS interval, msec		
n	130	125
Mean ± SD change from baseline	−1.9 ± 15.03	0.7 ± 16.10

Abbreviations: bpm, beats per minute; msec, milliseconds; SD, standard deviation.
[a] Values obtained from the safety population.
[b] Values for vital signs obtained from only 117 patients in each group, as 3 patients in each group who completed the core phase did not enter the extension phase.

ECG abnormalities were infrequent in both treatment groups (Tables 4 and 5). In the immediate switch group, 6 patients who were normal at screening displayed a QT interval of >440 milliseconds at day 9; of these, 1 exhibited first-degree atrioventricular block at day 9 and another experienced right bundle branch block (RBBB) at day 36. In the delayed switch group, 3 patients who were normal at screening displayed a QT interval of >440 milliseconds at day 9 and, of these, 1 experienced incomplete RBBB, with right ventricular hypertrophy, and inferior and anterior T-wave changes at day 8, which resolved by day 18.

Mean change from baseline to week 5 in heart rate, supine pulse rate, systolic blood pressure, and diastolic blood pressure were small and not clinically meaningful (Table 4). The incidence of asymptomatic bradycardia was low (3 patients, 2.3%) in the immediate switch group (leading to discontinuation in 1 patient). Patient 1 had RBBB, patient 2 had received metoprolol at baseline for hypertension, and patient 3 had a history of bradycardia and was receiving metoprolol. In 2 of the 3 cases, the investigator did not find the bradycardia to be related to the study drug. No occurrences of asymptomatic bradycardia were reported in the delayed switch group.

Mean patient body weight remained stable at the end of the core phase and no patient in either treatment group experienced a clinically significant (≥7% change) increase or decrease in body weight. Mean ± SD change in body weight from baseline in the immediate switch group was 0.2 ± 1.3 kg, compared with 0.0 ± 1.5 kg in the delayed switch group.

Efficacy

At week 5, the mean rating of change in CGIC scores was 3.9 and 4.0 for the immediate and delayed switch groups, respectively. No significant decline from baseline (ie, improvement or no change in their condition [CGIC rating score ≤4]) was seen in 94 (82.5%) patients in the immediate switch group and 85 (75.2%) patients in the delayed switch group.

Discussion

The results from this study suggest that there are no clinically meaningful differences between immediate and delayed switching strategies from donepezil tablets to the rivastigmine transdermal patch, based upon discontinuation rates. Overall, good tolerability

Table 5. Newly Occurring Clinically Significant Abnormal Electrocardiogram Parameters Observed During the Core Phase[a]

	Immediate Switch Group n (%)	Delayed Switch Group n (%)
Heart rate		
n	131	127
>105 bpm	0 (0.0)	0 (0.0)
<48 bpm	2 (1.5)	2 (1.6)
PR interval		
n	122	118
>200 msec	2 (1.6)	3 (2.5)
<120 msec	3 (2.5)	2 (1.7)
QT interval (uncorrected)		
n	131	127
>440 msec	6 (4.6)	3 (2.4)
<330 msec	0 (0.0)	3 (2.4)
QRS interval		
n	131	127
>110 msec	2 (1.5)	5 (3.9)
<80 msec	0 (0.0)	0 (0.0)

Abbreviations: bpm, beats per minute; msec, milliseconds.
[a] Values obtained from the safety population.

was observed. Both switching strategies were associated with similar discontinuation rates due to any reason or due to AEs. The rates of both severe and serious AEs were similar between treatment groups. This safety profile may be due to the majority of patients who entered this study already receiving stable ChEI therapy and, thus, generally displaying a good tolerability to this class of therapeutic agents.

The overall incidence of GI AEs was low in both treatment groups, and only 1 patient, in the delayed switch group, discontinued treatment due to diarrhea. No patients discontinued due to nausea or vomiting. Newly occurring ECG abnormalities were infrequent with both switching strategies, and vital signs and body weight remained stable during the 5-week core phase. Few patients experienced application site reactions and none discontinued treatment due to this event. Asymptomatic bradycardia was recorded for 2.3% of patients in the immediate switch group, compared with none in the delayed switch group; however, 2 of the 3 cases of bradycardia were not thought to be related to the study drug by the investigator. As all of these patients had comorbidities that could have contributed to this AE, this finding may reflect random variation in a background of low incidence. However, it cannot be ruled out that an immediate switch to the rivastigmine transdermal patch may have exacerbated these cholinergic-mediated AEs. Thus, an individual, tailored approach may be beneficial for patients with existing bradycardia.

Regarding efficacy, as assessed by the CGIC, the majority of patients in this study did not experience a decline in function after the switch from donepezil tablets, and the mean ratings of change in CGIC scores were similar in both the immediate and the delayed switch groups.

These data suggest that the majority of patients receiving stable donepezil tablets or donepezil and memantine may be safely switched to the rivastigmine transdermal patch without a withdrawal period. The findings of this study are largely in agreement with those from the studies evaluating an immediate switch from donepezil tablets to rivastigmine capsules.[7,9] The incidence of nausea and vomiting in the present study appears lower than associated with the rivastigmine capsule, although no direct comparison was made. This finding is consistent with an earlier study that directly compared the capsule (12 mg/day) and transdermal patch (9.5 mg/24 h) formulations of rivastigmine.[12]

Potential limitations of this study include the lack of direct comparisons to rivastigmine capsules or placebo, and the open-label study design. Also the very low rates of AEs make it difficult to detect reliable safety "signals" of concern. Because only patients on stable donepezil tablets and stable memantine treatment (for patients on combination therapy) were randomized, it may not be possible to generalize these findings to other groups of patients with AD. Finally, the sample size of this study was relatively modest. Thus, caution should be used when drawing any conclusions regarding these findings. In particular, we cannot rule out the possibility that a small subgroup of patients might show better tolerability having a brief withdrawal period prior to switching to the patch.

Conclusion

The results of this study suggest that most patients receiving donepezil tablets or donepezil and memantine combination therapy can be safely switched to rivastigmine transdermal patches without a withdrawal period. The frequency of asymptomatic bradycardia in the immediate switch group, although low and possibly unrelated to the study drug, may suggest that physicians should use appropriate clinical judgment for patients with existing bradycardia or those who are receiving β blockers. Thus, the rivastigmine transdermal patch may provide a treatment option for those patients who require a change in

their current oral ChEI therapy due to either safety or tolerability concerns, or a lack of therapeutic efficacy.

List of US38 Investigators

Dr Carl Sadowsky, Nova SE University, Fort Lauderdale, Florida; Dr Alan Dengiz, Premiere Research Institute, West Palm Beach, Florida; Dr Gus Alva, ATP Clinical Research, Costa Mesa, California; Dr Troy Anderson, Dedicated Clinical Research, Litchfield Park, Arizona; Dr Padmini Atri, International Clinical Research Associates, Richmond, Virginia; Dr Vinod Bhatnagar, Center for Clinical Trials and Research, Venice, Florida; Dr Ronald Brenner, Neurobehavioral Research, Inc, Cedarhurst, New York; Dr Ruben Bravo, Caribbean Education and Research Center, Bayamon, Porto Rico; Dr Mahan Chehrenama, The Innovative Clinical Research Center, Alexandria, Virginia; Dr Scott Cooper, Medical Association of North Georgia, Canton, Georgia; Dr Terry Copeland, Infinity Research Group, Oklahoma City, Oklahoma; Dr Keith Edwards, Neurological Research Center, Inc, Bennington, Vermont; Dr Jay Ellis, Neuroscience Research of the Berkshires, Pittsfield, Massachusetts; Dr Miguel Flores, Berma Research Group, Hialeah, Florida; Dr Bill Fulk, Specpro Research, Inc, Ft Myers, Florida; Dr Jeffrey Geohas, Radiant Research, Chicago, Illinois; Dr Gary Gerard, Neurology & Neuroscience Center of Ohio, Toledo, Ohio; Dr Jerome Goldstein, San Francisco Clinical Research Center, San Francisco, California; Dr Phillip Green, Borgess Research Institute, Kalamazoo, Michigan; Dr John Grubbs, Four Rivers Clinical Research, Paducah, Kentucky; Dr Barbara Harris, PsyPharma Clinical Research, Phoenix, Arizona; Dr Sean Hurley, Rowan Research, Spokane, Washington; Dr Arvind Jariwala, Wake Research Associates, Raleigh, North Carolina; Dr Marvin Kalafer, The Clinical Trial Center, Jenkintown, Pennsylvania; Dr Bennett Machanic, Mountain View Clinical Research, Inc, Denver, Colorado; Dr Derek Loewy, PsyPharma Clinical Research, Tucson, Arizona; Dr William Maier, PRO Research, Eugene, Oregon; Dr David Margolin, The Margolin Brain Institute, Fresno, California; Dr Ashok Patel, Bio Behavioral Health, Deer Chase Professional Park, Toms River, New Jersey; Dr Meenakshi Patel, Centerville, Ohio; Dr Patricio Reyes, Barrow Neurology Clinic, Phoenix, Arizona; Dr Ralph Richter, Tulsa Clinical Research, Tulsa, Oklahoma; Dr Joel Ross, Memory Enhancement Center of America, Inc, Eatontown, New Jersey; Dr Beth Safirstein, Hallandale Beach, Florida; Dr Michael Sauter, Westmoreland Neurology, Inc, Greensburg, Pennsylvania; Dr Douglas Scharre, The Ohio State University, Columbus, Ohio; Dr Harvey Schwartz, Sunrise Clinical Research, Hollywood, Florida; Dr Ram Shrivastava, Eastside Comprehensive Medical Center, New York, New York; Dr Joshua Shua-Haim, Mid Atlantic Geriatric Associates–Ocean Alzheimer's Research Corporation, Manchester, New Jersey; Dr Alan Siegal, Geriatric and Adult Psychiatry, Hamden, Connecticut; Dr Richard Singer, Neurology Clinical Research, Inc, Sunrise, Florida; Dr Steve Sitar, Orange County Clinical Trials, Anaheim, California; Dr David Spangler, Witham Health Services, Lebanon, Indiana; Dr Mary Stedman, Stedman Clinical Trials, Tampa, Florida; Dr Susan Steen, Axiom Clinical Research of Florida, Tampa, Florida; Dr James Sutton, Pacific Neuroscience, Oxnard, California; Dr Todd Swick, Houston, Texas; Dr Thomas Vidic, Elkhart Clinic, Elkhart, Indiana; and Dr Jaron Winston, Senior Adults Specialty Research, Austin, Texas.

Acknowledgment

This study was funded and sponsored by Novartis Pharmaceuticals Corporation.

References

1. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1154-1166.
2. Geldmacher DS. Treatment guidelines for Alzheimer's disease: redefining perceptions in primary care. *Prim Care Companion J Clin Psychiatry*. 2007;9:113-121.
3. Small G, Dubois B. A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. *Curr Med Res Opin*. 2007;23:2705-2713.
4. Ryan AA. Medication compliance and older people: a review of the literature. *Int J Nurs Stud*. 1999;36:153-162.
5. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. *Curr Med Res Opin*. 2003;19:707-714.
6. Farlow MR, Miller ML, Pejovic V. Treatment options in Alzheimer's disease: maximizing benefit, managing expectations. *Dement Geriatr Cogn Disord*. 2008;25:408-422.

7. Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. *Curr Med Res Opin*. 2002;18:129-138.
8. Emre M. Switching cholinesterase inhibitors in patients with Alzheimer's disease. *Int J Clin Pract Suppl*. 2002;(127):64-72.
9. Sadowsky CH, Farlow MR, Atkinson L, et al. Switching from donepezil to rivastigmine is well tolerated: results of an open-label safety and tolerability study. *Prim Care Companion J Clin Psychiatry*. 2005;7:43-48.
10. Corey-Bloom J, Anand R, Veach J. 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 Pyschopharmacol*. 1998;1:55-65.
11. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ*. 1999;318:633-638.
12. Winblad B, Grossberg G, Frolich L, et al. IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology*. 2007;69(4 suppl 1):S14-S22.
13. Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. *Int J Geriatr Psychiatry*. 2007;22:485-491.
14. Shua-Haim J, Smith JM, Amin S. Crossover results of donepezil (Aricept) to rivastigmine (Exelon) in Alzheimer's disease patients: a two-month prospective study. Poster presented at: the Annual Scientific Meeting of the American Geriatric Society; May 9-13, 2001; Chicago, Ill (P329).
15. Shua-Haim J, Smith J, Amin S. Results of switching from donepezil (Aricept) to rivastigmine (Exelon) in Alzheimer's disease patients: a two-month prospective study. Poster presented at: the 7th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy; April 3-6, 2002. Geneva, Switzerland (A43A).
16. Figiel GS, Sadowsky CH, Strigas J, Koumaras B, Meng X, Gunay I. Safety and efficacy of rivastigmine in patients with Alzheimer's disease not responding adequately to donepezil: an open-label study. *Prim Care Companion J Clin Psychiatry*. 2008;10:291-298.
17. Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. *Am J Geriatr Psychiatry*. 2003;11:131-145.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (*DSM-IV-TR*®) 1994.
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.