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Research Article

A Pilot Phase IV Open-Label Study Investigating the Safety and Tolerability of Donepezil 23mg Once Daily in Patients with Moderate to Severe AD Switched from Exelon Patch 9.5mg Daily

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Abstract

Introduction: Since previous studies demonstrated the AD subjects treated with Donepezil23-mg showed a statistically significant improvement on cognition compared to AD subjects on 10mg daily, we evaluated the effects of treatment with donepezil23mg on moderate to severe AD when switched from rivastigmine patch 9.5mg daily using a titration schedule.

Methods: This was a 24-week, randomized, open label, study of the effect of switching from Exelon patch 9.5 mg to a regimen of Donepezil 23 mg daily in moderate to severe AD with a titration schedule. Subjects received the MMSE and Clinical Dementia Rating scale (CDR) at study entry and termination/completion. 26 individuals were recruited for this study (17 males (65.4%) and 9 females (34.6%). Mean age was 78.9 years (SD=9.35 years; Range 53-92 years).

Results: 31% (8/26= 30.8%) of participants completed the study. The mean baseline MMSE score for the entire group was 10.7 (SD=5.9; Median=11.5; Range=1-19) with no statistically significant difference (p=.778) between individuals who completed through Week 24 of the study (Mean=10.14 SD=5.4; Median=12.0; Range=1-16) and those who did not complete the study (Mean=10.89; SD= 6.15; Median=11.00; Range=1-19). The baseline CDR Sum of Boxes and CDR Global scores were also not found to be significantly different between completers and non-completers (p=.582 and p=.308 respectively). Adverse events included nausea (38.5%), vomiting (30.8%), diarrhoea (15.4%), hypersomnia (11.5%), dizziness and headache (7.7%).Introducing alternating doses of 10 mg and 23 mg donepizil improved tolerability.

Conclusions: Switching from rivastigmine patch 9.5mg to donepezil 23mg is a treatment option but this should be implemented with a titration schedule of alternating day 10mg/23mg to improve tolerability.

INTRODUCTION

Cholinesterase inhibitors are the most common therapeutic class of drugs used in treating AD. Four centrally acting acetyl cholinesterase inhibitors (AChEIs) have been approved for the treatment of mild to moderate AD: donepezil, glutamine, rivastigmine, and tacrine. Three drugs, donepezil, rivastigmine and memantine, a glutamate receptor antagonist, have been approved in patients with moderate to severe AD. Dosing of cholinesterase inhibitors was based on decisions regarding the balance of efficacy and tolerability in the course of drug development programs. In most cases, the highest doses of the agents were not explored, and possible added efficacy of higher doses was not determined.

In a previous study [1], Patients who received donepezil 23-mg showed a statistically significant improvement in cognition, as measured by the Severe Impairment Battery, compared to those taking donepizil10 mg. The difference in LS mean change from baseline to week 24 between the 23-mg and10-mg groups

was 2.2 points (P=.0001).In a post hoc analysis of patients with more severe cognitive impairment at baseline (baseline MMSE 0-16), a significant difference favoring donepezil 23 mg was demonstrated on both the SIB and CIBIC+. The difference in LS mean change on the SIB was 3.1 points (P<.0001). CIBIC+ scores at Week 24 were 4.31 and 4.42 in the donepezil 23 mg and donepezil 10 mg groups, respectively (P=.0279). Adverse events (AE) were generally mild to moderate, with the most common AEs being nausea (11.8% *vs* 3.4%), vomiting (9.2% *vs* 2.5%), diarrhea (8.3% *vs* 5.3%), and anorexia (5.3% vs 1.7%).These AEstypically occurred during the first month of treatment with the higher dose. This study demonstrated that treatment with donepezil 23 mg provided additional cognitive benefit in patients with moderate to severe AD compared with 10 mg donepezil. Consistent with the previous body of data showing greater benefit is achieved by increasing dosage from 5mg to 10 mg [2], these results indicate that providing still greater AChE inhibition by a further increase in AChEI dose is a worthwhile goal to optimize treatment of AD in patients with more advanced disease.

Two studies recently published have suggested that a significant portion of patients who fail to benefit from or to tolerate treatment with donepezil experienced improvement in their symptoms after being switched to treatment with rivastigmine [3,4].In an open-label study of 382 patients with probable AD who were switched from donepezil to rivastigmine found that 56% of subjects who switched to rivastigmine treatment demonstrated stabilization or improvement in global functioning.Approximately50% demonstrated stabilization or improvement in cognitive functioning, and 57% demonstrated stabilization or improvement in ability to perform activities of daily living.

Additional evidence from a study conducted by Bullock et al [4] found that individuals who switched from donepezil to rivastigmine due to lack of efficacy or adverse events demonstrated improvement while on rivastigmine treatment.

The primary objective of the current study was to evaluate the safety and tolerability of 23 mg of donepizil in patients with moderate to severe AD switched from rivastigmine patch 9.5mg daily with a titration schedule used for transition. The secondary objective was to evaluate changes in clinical measures from baseline to study completion.

METHODS

Subjects

26 individuals were recruited for this study (17 males (65.4%) and 9 females (34.6%)). Mean age for the sample was 78.9 years.

Study design

This was a 24-week randomized open-label study of the feasibility of switching from rivastigmine patch 9.5 mg to donepezil 23 mg daily in subjects with moderate to severe AD. A placebo comparison group was not used. The intended sample size was 40 patients to be treated with Donepezil 23 mg once daily switched from rivastigmine 9.5 mg cutaneous patch once daily. For those subjects experiencing adverse events after switching to donepezil 23 mg (nausea, vomiting, diarrhea, and anorexia), a rescue strategy of lowering the dose of donepezil to 10mg daily for 7 to 10 days was employed. The MMSE [5] and Clinical Dementia Rating scale (CDR) [6] were administered at study entry and termination/completion. The study also complied with the requirements of the study site's Institutional Review Board/ Human Resources Research Committee.

The inclusion criteria was age ≥ 50, diagnosis of probable AD for at least 1 year based on the NINCDS-ADRDA criteria [7]. Patient's severity of AD must be moderate to severe, documented with a MMSE score between 0-20 at screening and Hachinski score ≤ 4 [8]. At enrollment, subjects were taking Exelon patch 9.5mg or two 4.6 mg patches daily for at least 30 days. Subjects were allowed to take memantine daily but had to be on a stable dose for 30 days prior to treatment assignment. The exclusion criteria included: current evidence or history within the last 3 years of a neurological or psychiatric illness that could contribute to dementia including, but not limited to epilepsy, focal brain lesion, Parkinson's disease, seizure disorder, head injury with loss of consciousness, DSM-IV criteria for any major psychiatric disorder including psychosis, major depression and bipolar disorder, and alcohol or substance abuse within the last five years; the subject could not be living alone; have poorly controlled hypertension; have a history of myocardial infarction or signs or symptoms of unstable coronary artery disease within the last year (including revascularization procedure/angioplasty)nor should have had a history of life threatening arrhythmias. Severe pulmonary or thyroid disease was excluded. Active neoplastic disease (skin tumors other than melanoma were not excluded) was excluded. Other exclusions included: pregnancy or female of child bearing age; sensitivity to donepezil; and any other disease or condition that, in the opinion of the investigator, would have made the subject unsuitable to participate in this clinical trial.

Statistical Analysis

Statistical analysis was performed using Predictive Analytics Software Portfolio (PASW Statistics 18.0, 2009), SPSS Inc. Descriptive statistics were utilized to characterize the study sample. Differences between proportions were tested with the χ^2 test or Fisher's Exact Test as indicated. Differences between means were assessed with ANOVA, unpaired or paired Student's *t*-tests or non-parametrics as appropriate. A 2-tailed $P<0.05$ was considered statistically significant.

RESULTS

There were 26 individuals who participated in this study. The average MMSE score for the sample was 10.7 (SD=5.9; Range 1-19; Median=11.5) with roughly equivalent scores between completers and non-completers. There was a statistically significant difference between males and females (ANOVA p<.05) on the MMSE with a mean score of 12.5 (SD=5.7; range 1-19; Median=12.0) for males and a mean score of 7.33 (SD=4.7; Range=1-15; Median=5.0) for females. 31% (8/26=30.8%) of participants completed the study. Adverse effects were high with almost 80% (actual 79.2%) of study participants reporting adverse effects. Among the individuals who completed the study, 62.5% (5/8) did not report adverse effects related to study treatment. The baseline MMSE mean score for the entire group was 10.7 (SD=5.9; Median=11.5; Range=1-19) with no

statistically significant difference (p=.778) between individuals who completed through Week 24 (Mean=10.14 SD=5.4; Median=12.0; Range=1-16) and those who didn't complete the study (Mean=10.89; SD=6.15; Median=11.00; Range=1-19). The baseline CDR SOB and CDR Global scores were also not found to be significantly different between completers and non-completers (p=.582 and p=.308 respectively). In completers, the CDR SOB and CDR global scores did not change significantly (-0.93 (SD=2.49), 0.00 (SD=0.58) respectively, NS). Similarly, there were no significant changes in MMSE scores in completers compared to baseline.

Safety data

There were 8 individuals who completed the study. One of these individuals sprained an ankle; but, it was deemed not to be study-related. The majority of individuals who did not complete the study experienced side effects. One individual was admitted to an AD facility and was lost to follow-up and another individual withdrew from the study early. The reason for withdrawal is unknown. Accounting for the two losses, there were 24 individuals included in this analysis. The time to AE was 11.2 days (SD=19.5) with 20 subjects of the sample being on 23mg and 4 subjects being on 10mg. In completers, the time to AE was 18.7 days (SD=32.3) with 3 of 8 being on 23mg. Study completers were significantly (p=0.014) younger than non-completers (Figure 1).

AEs included nausea (38.5%), vomiting (30.8%), diarrhoea (15.4%), hypersomnia (11.5%), dizziness and headache (7.7%) Implementation of a titration schedule improved tolerability. Adverse events (AEs) accounted for most of the early terminations. The majority of AEs were classified as 'Mild' (70.4%; 19/27). Approximately one-third (29.6%; 8/27) were classified as 'Moderate' and there were no AEs classified as 'Severe.' Gastrointestinal disorders including nausea, vomiting or diarrhoea accounted for the majority of adverse events. These events were predominantly mild in nature with 86.6% (11/13) classified as 'Mild' and 15.4% classified as 'Moderate. The next most common adverse event was related to sensorium and included blurred vision, dizziness, and headache. Sixty percent (3/5) were classified as 'Mild' and 40% (2/5) as 'Moderate.' Sleep-related AEs included hypersomnia, insomnia and restless sleep. All were classified as 'Mild' (100%; 4/4). Behavioral AEs included confusion and hallucinations, 1/3 (33.3%) was classified as "Mild' and 2/3 (66.7%) as 'Moderate.' There was a single cutaneous AE (skin lesions) that was classified as 'Moderate,' and a single cardiac-related AE (bradycardia) that was also classified as 'Moderate.'

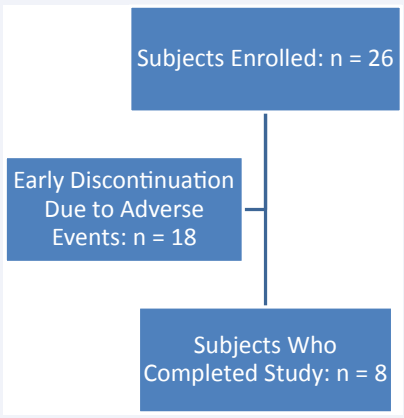

Figure 1 Flowchart of Study Enrollment.

DISCUSSION

This study sought to address three main objectives: 1) the feasibility (and how to) of switching from the patch to 23mg, 2) the safety/tolerability after switching, and 3) the changes in clinical measures from baseline to end of study after switching. Specifically, it sought to explore the feasibility of switching from rivastigmine patch 9.5mg daily to Donepezil 23mg daily. Prior to the protocol amendment, switching from rivastigmine patch 9.5mg daily to donepezil 23mg daily was associated with high proportion of side effects and lower tolerability. Following the protocol amendment, where a titration schedule was implemented using alternate day dosing of 10mg and 23 mg donepezil, tolerability improved. The effect of switching to donepezil 23 mg was not associated with changes in brief cognitive measure (MMSE) or global assessment measure (CDR).

Treatment options for AD continue to be limited to symptomatic therapy. Disease modifying drugs in phase III development have not been successful [9,10]. Thus we are limited to symptomatic treatments for the near future. Among the strategies being deployed is to escalate doses of medications. Farlow et al [11] found that the 13.3 mg rivastigmine patch was superior in terms of efficacy when compared to the 4.6 mg patch. This study also found no significant differences in adverse events between the two dosing groups (AEs; 74.6% and 73.3%, respectively), (SAEs; 14.9% and 13.6%, respectively).The side effects and AEs reported in this study were treatment related and previously reported. Most were GI in nature and are expected with the class of cholinesterase inhibitors. In our study, our AE rate was similar to that of Farlow et al [10] suggesting AEs are related to the class of cholinesterase inhibitors.

There are significant limitations to the current study. Only 28% of the cohort completed the study and there were no significant changes in cognition noted. Study completers were significantly younger (p=0.014) than non-completers suggesting an age-tolerability interaction. This has been observed in other studies [12].

In the current pharmacotherapeutic regimen in treating AD, switching from rivastigmine 9.5 mg patch to 23mg donepezil is a viable treatment option when there is a titration schedule added that includes alternate day dosing of 10mg donepezil and 23 mg donepezil on alternate days for one month. This can be a suitable alternate choice to escalating rivastigmine 9.5mg patch to 13.3mg patch. Switching from rivastigmine patch 9.5mg to donepezil 23mg should be implemented with a titration schedule of alternating day 10mg/23mg to improve tolerability.

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