Rivastigmine for Dementia Associated with Parkinson’s Disease


Rating: •Of importance.

Introduction: James Parkinson delineated the major features of the disease that bears his name with remarkable accuracy in 1817 [10]. He was incorrect when he stated that in "shaking palsy the senses and intellects are uninjured" [10]. Since Parkinson’s time, it has become gradually recognized that the majority of PD patients develop dementia as their disease progresses into the later stages. Estimates of the incidence and prevalence of dementia in PD have varied widely across multiple studies depending on the criteria used to define dementia, the methodology used, and the population or sample studied.

Brown and Marsden [11] conservatively estimated that the lifetime prevalence of dementia in PD was about 20%. Cross-sectional studies subsequently demonstrated that perhaps 40% of patients with PD met criteria for overt dementia and essentially all PD patients developed some mental status changes over time [12]. Recently, some authors have demonstrated a cumulative prevalence of dementia of 78% in a cohort of PD patients followed prospectively for 8 years [13].

Despite improved recognition of PD dementia and its known association with increased mortality in PD [14], controlled clinical trials are lacking. In fact, there is some controversy about its very existence. Prior to this study, there had been no large-scale, well-controlled clinical trials of cholinesterase inhibitors in patients with PD dementia.

Aims: The purpose of this study was to evaluate the efficacy and safety of the dual cholinesterase inhibitor rivastigmine in PD dementia.

Methods: This was a 24-week, multicenter, prospective, randomized, placebo-controlled study of rivastigmine in PD-associated dementia. Men and women aged 50 years or older who met the United Kingdom PD Brain Bank criteria for the diagnosis of PD and who developed PD dementia (by Diagnostic and Statistical Manual IV criteria) 2 or more years after the diagnosis of PD were eligible. Patients were recruited throughout Europe and had to have mild-to-moderately severe dementia as defined by a Mini-Mental State Examination (MMSE) score between 10 and 24. Patients with other causes of dementia, a history of a major depressive episode, an active seizure disorder, any disability or unstable disease unrelated to PD, known sensitivity to rivastigmine or similar drugs, or the use of cholinesterase inhibitors or anticholinergics drugs during the 4 weeks before randomization were excluded from the study. No changes in dopaminergic medications and no new psychotropic medications were allowed during the study (except atypical neuroleptics for acute psychosis).

Patients were randomly assigned to treatment with 3 to 12 mg/d of rivastigmine or placebo in a 2:1 ratio. Treatment started with 1.5 mg of rivastigmine or placebo twice daily. Patients were gradually titrated over 16 weeks to the highest well-tolerated dose for each patient, and they were maintained at this dose for the remainder of the study. Dose adjustments were permitted for adverse events.

Assessments were conducted at baseline, week 16, and week 24, with primary efficacy variables being the subscale score for the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and the Alzheimer’s Disease Cooperative Study—Clinician’s Global Impression of Change (ADCS-CGIC) at week 24. Higher scores on the ADAS-cog indicate more impairment, with a range of scores between 0 and 70. The ADCS-CGIC scale is a 7-point scale with scores ranging from 1 (indicating marked improvement) to 7 (indicating marked worsening). Secondary efficacy variables were the 24-week scores for six instruments: 1) the Alzheimer’s Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) scale; 2) the Neuropsychiatric Inventory (NPI-10); 3) the MMSE; 4) the Cognitive Drug Research (CDR) Computerized Assessment System power of attention tests; 5) the Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test; and 6) the Ten Point Clock-Drawing test. Vital signs, body weight, adverse events, laboratory tests, and electrocardiograms were obtained as safety measurements. PD symptoms were assessed using the UHDRS motor section (part III) at baseline, 16 weeks, and 24 weeks. Concomitant medications and dose changes were recorded as well.

Patients that received at least one dose of study medication and had at least one safety evaluation after the baseline visit were included in the safety analysis. All randomized patients that received at least one dose of study medication who were assessed for one of the primary efficacy variables at baseline and at least once after baseline were included in the analysis. The last-observation-carried-forward method was used to impute values for patients without follow-up information. Analysis of covariance was used to assess changes of ADAS-cog scores from baseline, and ADCS-CGIC scores were analyzed using the Cochran-Mantel-Hantzel test. Frequencies of adverse events were compared between groups using Fisher’s exact test.

Results: Five hundred forty-one patients were randomized, with 361 patients receiving rivastigmine and 180 patients receiving placebo. The average age for patients was 72.7 years at baseline and 35.1% of patients were women. Only two of the 541 patients entered into the study were not white. Approximately 95% of patients were
taking levodopa and 46% of patients were taking dopamine agonists. Patients carried a diagnosis of PD for an average of 9 years before entry into the study. Eighty percent of patients were Hoehn & Yahr stages I–III, and the average UPDRS III motor score was about 33 for each group. Patients had been diagnosed with dementia for approximately 1 year prior to entry, and the average MMSE score was 19 of 30 at entry. There were no differences at baseline between the rivastigmine and placebo groups.

There were 218 patients (40.3%) who had psychiatric disorders at baseline (depression, anxiety, insomnia, and psychosis).

There were 518 patients included in the primary efficacy analysis, with 131 patients exiting the study prematurely. Adverse events were the primary reason, causing 17.1% of patients in the rivastigmine group to exit and 7.8% in the placebo group to exit. The mean dose of rivastigmine was 8.6 mg/d at the end of dose escalation. Seventy-seven percent of patients were receiving 6 mg/d or greater of the drug. Almost all patients were receiving 3 mg/d or more.

At week 24 there was significant improvement in the rivastigmine group, with a mean improvement of 2.1 points on the ADAS-cog and a mean deterioration of 0.7 points in the placebo group (P < 0.0001). More patients also had a favorable outcome on the ADCS-CGIC at week 24 relative to placebo (P = 0.007). A clinically meaningful (moderate or marked) improvement was observed in 19.8% of patients in the rivastigmine group and 14.5% in the placebo group.

All secondary efficacy variables were also significantly better in the rivastigmine group relative to the placebo group.

Adverse events were cholinergic in nature, with nausea (29.0% reported in the rivastigmine group and 11.2% in the placebo group; P < 0.001) and vomiting (16.6% vs 1.7%; P < 0.001) being the most frequent. Nausea was a contributor to early withdrawal in 3.6% of patients in the rivastigmine group versus 0.6% in the placebo group (P = 0.04). Rivastigmine-treated patients also had more reported worsening of parkinsonian symptoms as adverse events relative to placebo-treated patients (27.3% vs 15.6%; P = 0.002) and complained of more tremor relative to placebo (10.2% vs 3.9%; P = 0.01). Only 1.7% of patients in the rivastigmine group, however, withdrew from the study due to tremor. Placebo patients were more likely to have hallucinations and orthostatic hypotension.

Despite more reported adverse events due to worsening of parkinsonian symptoms and tremor in rivastigmine-treated patients, UPDRS motor scores did not differ significantly between treatment groups (including the tremor-related items).

Electrocardiograms, laboratory tests, and vital signs were similar between groups, and both groups of patients had some weight loss (1 to 1.5 kg) over the 24 weeks.

Discussion: Rivastigmine demonstrated moderate but significant efficacy in global ratings of dementia, cognition, and behavioral problems related to PD dementia in this study. Rivastigmine also demonstrated a good safety profile in demented PD patients.

Editor’s comments

A large number of PD patients will develop dementia as PD progresses and patients age. PD dementia, however, has considerable clinical and neuropathologic overlap with dementia with Lewy bodies (DLB), and many demented PD patients have Alzheimer’s disease (AD) pathology (plaques and tangles) at autopsy [15,16]. Dementia in PD seems to correlate best with limbic and cortical Lewy bodies [16]. Neurochemically, demented PD patients have cortical deficits of acetylcholine that are even greater than those observed in AD [16,17]. Given the beneficial effects of cholinesterase inhibitors in AD and DLB [18] and the significant cholinergic cortical deficit in PD patients, the results of this study are very plausible. Further efforts to define the neuropathology and mechanism(s) of PD dementia in longitudinally characterized samples of PD patients will be essential for future studies.

One weakness of the methods used in this study is the lack of longitudinal data on how the ADAS-cog and ADSC-CGIC change over time in PD dementia. Given that AD is a cortical dementia and PD dementia is a subcortical dementia with secondary memory impairment, these scales may not be optimal for following patients over time or for determining the response of these patients to various pharmacotherapies. The secondary measures used in this study were selected to assess common areas of dysfunction in PD dementia (attention and concentration, visuospatial functioning, and verbal fluency), and it is encouraging that rivastigmine-treated patients did better than placebo-treated patients on these measures. For future studies, perhaps the Repeatable Battery for the Assessment of Neuropsychological Status may be useful to follow in patients with PD dementia, given that this test can differentiate between cortical and subcortical dementia [19].

It is interesting to note that as a part of the predefined analysis in the study, the authors found that 80.2% of rivastigmine-treated patients had no clinically meaningful improvement as reflected by the ADCS-CGIC. Perhaps a longer-duration study (or different primary measures) could demonstrate a difference in these patients as the dementia progresses. Another explanation may be the dose of rivastigmine employed. A recent PET scan study showed suboptimal inhibition of acetylcholine (Ach) in patients with AD treated with an AchE inhibitor [20]. Perhaps a larger dose of AchE inhibitor may be more effective. However, one will have to be concerned about worsening of parkinsonism at higher doses of an AchE inhibitor.