Rivastigmine for Dementia Associated with Parkinson's Disease

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Dementia affects up to 80% of patients with Parkinson's disease (PD), it leads to a significant reduction in quality of life, and it is characterized by deficits in multiple cognitive domains, including attentional, executive, visuospatial, and working memory domains. At the time of this study, the mechanisms underlying PD dementia were unclear, though prior data supported dysfunction within the cholinergic system as a potential mechanism. In support, preliminary studies had also shown a clinical benefit of acetylcholinesterase inhibitors, such as rivastigmine, for the treatment of dementia in patients with PD. As such, the goal of this study was to assess the efficacy and safety of rivastigmine for the treatment of dementia in a larger population of PD patients.

Experimental design and statistics: This study was a randomized, multi-center, double-blind, placebo-controlled trial, which enrolled men and women (age $\geq$50yrs) with a clinical diagnosis of PD and a diagnosis of PD dementia based on DSM IV criteria; specifically, patients had to have an MMSE score of 10-24 and the onset of dementia occurring >2yrs after their initial PD diagnosis. Exclusion criteria is otherwise noted below.[1] Using these criteria, enrolled patients were randomly assigned to obtain 24 weeks of treatment with either rivastigmine (3 - 12mg starting at 1.5mg twice daily, with gradual up-titration to the max tolerable dose) or placebo.[2] The primary efficacy outcomes that were analyzed included scores on the ADAS-cog (Alzheimer's Disease Assessment Scale, higher scores = more cognitive impairment) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change, higher scores = more severe impairment). Efficacy assessments were conducted at baseline, 16wks, and 24wks, with the 24wk data used in the primary efficacy analysis. Secondary efficacy outcome variables (at 24wks) included several other behavioral tasks, assessing different domains of cognitive function.[3] Changes in the motor features of PD were also assessed at baseline, 16wks, and 24wks, via the UPDRS. Notably, patients who discontinued treatment early were encouraged to attend assessments when able, so their data could be included in the efficacy analyses. Finally, safety outcomes included any adverse event, lab work, EKG data, and patient vitals. Statistically, the primary + secondary efficacy variables were first quantified as changes from baseline (to 24wks) and then compared between treatment groups using analysis of covariance models or Cochran-Mantel-Haenszel tests (for binary outcomes). Frequencies of adverse events were compared using Fisher's exact tests.

Results: A total of 541 patients were enrolled, with 362 randomized to rivastigmine and 179 to placebo (2:1 ratio was planned to ensure adequate safety data for rivastigmine); 263 patients in the rivastigmine and 147 in the placebo group completed full treatment. In the rivastigmine group, the mean tolerable dose was 8.6mg/day. Otherwise, of those that completed treatment, baseline patient characteristics were similar between treatment groups (Table 1). Regarding the primary efficacy outcomes, mean ADAS-cog scores improved significantly at 24wks in the rivastigmine group (-2.1 pts) but worsened in the placebo group (0.7pts). Further, ADCS-CGIC score analyses revealed that significantly more patients in the rivastigmine group had a favorable outcome (i.e., marked or moderate clinical improvement) as

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[1] Exclusion criteria: any neurodegenerative disease other than PD, any other cause for dementia, history of MDD, presence of an active seizure disorder, any current, unstable disease, contraindications to anti-cholinergic medication use

[2] During the 24-week period, no dopaminergic medication dosage adjustments were permitted, nor were patients permitted to start new psychotropic medications.

[3] Behavioral tasks used for secondary efficacy outcomes: ADL scale, Neuropsychiatric Inventory scale, MMSE, Power of Attention testing, Verbal Fluency Test, Ten Point Clock-Drawing task

compared to placebo, and more patients in the placebo group worsened over time (Table 2, Figure 2)[4]. Patients in the rivastigmine group also showed significant improvement on all other behavioral tests assessed at 24wks as part of the secondary efficacy analysis as compared to the placebo group (Table 2). Finally, regarding safety outcomes, the most common ASEs of rivastigmine were mild nausea and vomiting (Table 3). Patients in the rivastigmine group were also more likely to experience Parkinsonian symptoms (i.e., tremor), but UPDRS scores were no different between the two groups at the end of the study.

Conclusions: Overall, this study was among the first to show the true clinical efficacy of at least short term rivastigmine use for dementia and cognitive dysfunction specifically associated with PD. Clinical improvement with rivastigmine was most apparent via the analysis of ADAS-cog scores, as the magnitude of change within the rivastigmine group was comparable to that of larger scale studies using cholinesterase inhibitors for AD. Though the ADCS-GCIC analysis also suggested a clinical benefit of rivastigmine, it should be noted that despite a higher frequency of marked and moderate improvement in the rivastigmine vs. placebo group, a large majority of patients treated with rivastigmine were with little to no clinical improvement. Regardless, with the relatively clean safety profile, this study was among the first to truly support rivastigmine use in patients with PD-associated dementia.

Additional Reading, if interested:

1) **Efficacy of Rivastigmine on Executive Function in Patients with Parkinson's Disease Dementia**. CNS Neuroscience and Therapeutics (2010), 16: 330-336

2) **Parkinson disease-associated cognitive impairment**. Nature Reviews Disease Primers (2021), 7 (47): 1-21. See Table 2 for a summary of other RCTs investigating pharmacological + non-pharmacological treatments for MCI in PD.

Summary created by Elaine Sinclair, DO/PhD

[4] Additional sensitivity analyses were performed on the primary efficacy outcome, which included patients who were enrolled but for whom no efficacy data were available owing to exclusion from the study. Such analyses revealed similar results as seen with the primary patient population.