

Rivastigmine for Treatment of Alzheimer's Disease

Rösler 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;318:633-8.

Study Overview

Objective. To measure the effects of rivastigmine on major clinical markers of Alzheimer's disease (AD).

Design. Randomized, double-blind controlled trial. Analysis was by intention to treat.

Setting and participants. Patients aged 50 to 85 years who had mild to moderately severe AD were enrolled from 45 medical centers in Europe and North America. All study participants met criteria for Alzheimer's type dementia as described in the *DSM-IV* [1] and criteria for probable AD from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [2]. Patients were excluded who were taking psychotropic or anticholinergic drugs, memory enhancers, insulin, or health food supplements.

Intervention. Subjects were randomized into 1 of 3 groups: low-dose rivastigmine (1 to 4 mg), higher-dose rivastigmine (6 to 12 mg), or placebo. Treatment doses were increased weekly by 1.5 mg and had to be within the target dose range by week 7. In the event of side effects, a rivastigmine dose could be skipped, maintained without increase for 2 consecutive weeks, or the patient could receive antiemetic drugs; however, doses could not be decreased. Between weeks 12 and 36, the goal was to maintain patients on the highest possible dose that was assigned to each study group.

Main outcome measures. Efficacy of the intervention was assessed using the cognitive subscale of the Alzheimer's disease assessment scale [3]; the clinician interview-based impression of change [4], a measure of behavior and activities of daily living (ADLs) that incorporates information from interviews with patients and caregivers; and the progressive deterioration scale [5], which measures ADLs as reported by the caregiver. These evaluations were performed at baseline and at weeks 12, 18, and 26 or at early withdrawal from the study. Measures obtained from the Mini-Mental State Examination [6] and from the global deterioration scale [7]

were used for staging at baseline and week 26.

Main results. A total of 831 patients were recruited; 106 were excluded because of severe comorbidities, unstable cardiac disease, chronic obstructive pulmonary disease, malignancies, or other life-threatening illnesses. 239 patients were assigned to the placebo group, 243 to the low-dose rivastigmine group, and 243 to the high-dose rivastigmine group. Demographic variables were similar among groups. Overall, there were more female patients (59%), and most patients were white. Mean age was 72 years. The mean duration of dementia was 39 months; 41% of the study cohort had mild dementia, 57% had moderate dementia, and 2% suffered from severe disease. Patients had an average of 2.5 other medical conditions, and about 81% of patients were taking other drugs. Drop-out rates were 13% in the placebo group, 14% in the low-dose group, and 32% in the high-dose group.

Scores obtained from the cognitive subscale of the Alzheimer's disease assessment scale worsened progressively in patients taking placebo. More patients in the higher-dose group showed meaningful improvement in their score (a 4 or more-point increase) than in the placebo group (27% versus 14%). The clinician interview-based impression of change demonstrated a score improvement of 20% in the placebo group versus 30% ($P < 0.05$) in the low-dose group and 37% ($P < 0.001$) in the high-dose group. On the progressive deterioration scale, more patients from the high-dose group showed improvement (29% versus 19% for the placebo group; $P < 0.01$); the changes were not significant in the low-dose group. At 26 weeks, a significant improvement was seen in global deterioration scores and Mini-Mental scores in the high-dose group, with a 0.21-point increase over baseline. In contrast, there was 0.47-point deterioration in the placebo group scores. Most patients who withdrew from the study because of adverse events did so during dose escalation (69% in the high-dose group). Gastrointestinal side effects (eg, nausea, vomiting) were more common during the dose escalation phase, with 23% occurring in the high-dose group, 7% in the placebo group, and 7% in the low-dose group.

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Conclusion

Rivastigmine at doses of 6 to 12 mg per day improves cognition, participation in daily activities, and global evaluation ratings in patients with mild to moderate AD.

Commentary

Recently, Novartis launched a major campaign to promote rivastigmine (Exelon) as a new pharmacologic treatment for AD. Thus, although published last year, this study by Rosler and colleagues is worth a second look. A MEDLINE search using "rivastigmine" and "randomized control trial" as keywords yielded only 2 more recent studies. One by Forette et al [8] showed results similar to those reported by Rosler et al; however, the number of patients in the later trial was smaller ($n = 114$). A study conducted this year by Kumar and colleagues [9] investigated the efficacy and safety of rivastigmine in patients with mild to moderate AD and concomitant cardiovascular disease; again, results were similar to findings by Rosler et al.

Rivastigmine is the third anticholinesterase inhibitor approved for AD therapy. The previously approved agents, donepezil and tacrine, have provided only modest benefits, and no trials have been published that compare donepezil with rivastigmine. Rosler et al's study has several strengths, including the large number of patients enrolled, complete follow-ups, and an intention-to-treat analysis that allowed researchers to account for all patients (including drop-outs) at the end of the study. The authors' assessment methods have been validated extensively in previous trials of clinical scales to measure the progression of AD. One weakness in the study was that follow-ups were relatively short for the assessment of a chronic disease. Furthermore, the number of patients with severe AD was too small to show any potential benefit in that group. Future research should be conducted to establish rivastigmine's long-term effects and safety. A head-to-head study with donepezil, for example, should be undertaken to determine which agent is more effective. Other topics for further study include the impact rivastigmine may have on caretakers' quality of life and on preventing admissions to long-term care facilities.

Applications for Clinical Practice

This study demonstrates that rivastigmine has modest effects on patients with mild to moderate AD. When the agent is prescribed, doses should be titrated and patients and their caregivers should be warned of gastrointestinal side effects, especially during the titration phase. Also, patients and their families should be made aware that the effects of rivastigmine may not be lasting. At this time, the question of whether rivastigmine is more effective than donepezil remains unclear.

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