Rivastigmine May Delay Dementia in Parkinson's

BY JEFF EVANS

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The cholinesterase inhibitor rivastigmine transiently halted cognitive deterioration associated with Parkinson's disease but fell short of actually modifying the course of either Parkinsonism or related dementia, according to the results of a randomized clinical trial reported by Murat Emre, M.D., of Istanbul (Turkey) University and his colleagues.

In the double-blind study of patients with mild to moderately severe dementia associated with Parkinson's disease, scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale were significantly improved in the 329 patients given 24 weeks of treatment with rivastigmine compared with 160 patients who received placebo (N. Engl. J. Med. 2004;351:2509-18).

Patients also showed significant, though moderate, improvement with rivastigmine, compared with placebo, according to scores on the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change. About 80% of the patients who received rivastigmine did not have clinically meaningful improvement on that scale.

Rivastigmine patients received an average 8.6 mg of the drug per day. During the study, 95% of patients took levodopa and 46% took dopamine agonists.

Significantly more rivastigmine patients reported Parkinsonian symptoms than did placebo patients (27% vs. 16%), but this was not reflected in overall motor function scores on the Unified Parkinson's Disease Rating Scale, the researchers said.

Dr. Emre and many of the other investigators in the study reported being paid for work performed for Novartis, which funded the study and markets rivastigmine as Exelon.

Daniel Z. Press, M.D., of Harvard Medical School, Boston, said in an editorial that clinicians' ability to treat the motor symptoms of Parkinson's disease far outstrips their ability to treat cognitive symptoms (N. Engl. J. Med. 2004;351:2547-9). Yet the optimal approach to the management of motor symptoms remains controversial.

Another randomized study showed that levodopa improved motor symptoms at sufficiently high doses but did not alter the course of Parkinson's disease for better or worse.

Stanley Fahn, M.D., of Columbia University, New York, and his colleagues conducted a double-blind trial of levodopa in patients who were considered not likely to require therapy for the symptoms of Parkinson's disease during the 9 months that followed enrollment.

Clinical deterioration of the symptoms of Parkinson's disease did not occur in 81 patients who received carbidopa and levodopa at 600 mg/day after 42 weeks, according to scores on the Unified Parkinson's Disease Rating Scale. Patients who took lower daily doses of carbidopa and levodopa (150 mg and 300 mg) experienced some deterioration, but significantly less than the 70 placebo patients (N. Engl. J. Med. 2004;351:2498-508).

In a separate substudy using single photon emission CT (SPECT), striatal dopamine transporter density in the 106 patients who received levodopa was similar to that of 29 patients on placebo after 40 weeks of treatment. But when they excluded 19 patients with normal dopaminergic activity, the patients who took levodopa had a significantly greater decrease in the density of striatal dopamine transporters than did patients on placebo.

Counter to the neuroprotective effects of levodopa seen in the clinical part of the study, the result of the SPECT study "suggests the possibility of a levodopa-induced toxic effect on dopamine neurons," according to the investigators.

All of the patients took levodopa during the SPECT study. Levodopa could have had a pharmacologic effect on the dopamine transporter by interfering with and reducing the binding of the radioligand used to detect the density of dopamine transporters.

But the small number of patients in the study and the relatively short period of treatment make it impossible to "exclude the possibility that levodopa may simply downregulate the dopamine transporter," said Dr. Fahn, who has served as an unpaid consultant to Teva Pharmaceuticals, which supplied the drugs used in the study.

Only levodopa at doses of 600 mg/day was associated with a significantly higher adverse event (dyskinesia, headache, hypertonia, infection) rate than placebo. ■