

Adding Safinamide to Dopamine Agonists Eases Parkinson's

BY AMY ROTHMAN SCHONFELD
Contributing Writer

BOSTON — The addition of safinamide to ongoing dopamine agonist monotherapy lessened motor and cognitive symptoms in a group of patients with Parkinson's disease, according to the results of a randomized, placebo-controlled, multinational Phase III trial.

The higher dose tested offered no advantage over the lower dose, according to the presentation made by Dr. Fabrizio Stocchi at the 59th annual meeting of the American Academy of Neurology.

"Dopamine agonists tend to lose their effects [with extended use]," says Dr. Stocchi, a professor of neurology at the Institute of Neurology IRCCS San Raffaele Pisana in Rome. "We asked whether another compound can expand dopamine agonist monotherapy."

Safinamide is a selective and reversible inhibitor of MAO-B. It inhibits dopamine reuptake and glutamate release, and does not potentiate the effects of tyramine.

A total of 270 patients with early Parkinson's disease (PD) maintained for at least 4 weeks on dopamine agonist monotherapy were randomized into three groups receiving either supplemental safinamide in low dose (50-100 mg/day), high dose (150-200 mg/day), or placebo.

The results showed that after 24 weeks of treatment with low-dose safinamide plus dopamine agonist, the Unified Parkinson's

Disease Rating Scale (UPDRS) Part III motor score was significantly improved over the effect of dopamine monotherapy (mean change from baseline: low dose vs. control: -6.0 plus or minus 7.2 vs. -3.6 plus or minus 7.1; $P=.0125$).

Scores for the high-dose safinamide group (-3.9 plus or minus 6.0) were not significantly better than those of the controls. The number of responders (patients showing a 30% improvement or more) on the UPDRS III also increased with the low-dose combination therapy.

Safinamide/dopamine agonist combination therapy had other benefits.

Significant improvements with low-dose safinamide were also noted on the UPDRS Part II Activities of Daily Living Score, the EuroQoL, and the Clinical Global Impression-C. No clinically significant side effects were reported with either dose of safinamide.

Low-dose safinamide-treated patients also performed better on the Cogtest battery, designed to evaluate cognitive domains known to be impaired in Parkinson's patients.

Improved scores were noted in several cognitive domains, including spatial working memory, strategic target detection, and auditory number sequencing.

Dr. Stocchi is involved in a 1-year extension phase of the study. A Phase III pivotal study of safinamide as an add-on to levodopa in patients with mid- to late-stage Parkinson's is underway. ■

Iron Accumulation in Gray Matter Of MS Patients Is Quantified

BY AMY ROTHMAN SCHONFELD
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CHICAGO — With the use of a new method that provides objective and specific measurement of iron deposition in brain tissue in vivo, investigators have been able to quantify the increased iron accumulation in the deep gray matter of patients with multiple sclerosis.

The iron accumulation was positively correlated with both lesion load and neuropsychological test performance, according to Dr. Yulin Ge, who presented his findings at the annual meeting of the American Society of Neuroradiology.

The reason why iron has accumulated in these regions "is probably because the axons are transected by the MS lesions, interrupting iron outflow from iron-rich deep gray matter nuclei to projected cortical sites," he said.

Dr. Ge's work was awarded the 2007 ASNR Cornelius G. Dyke Memorial Award for excel-

lence in original, unpublished research in neuro-radiology.

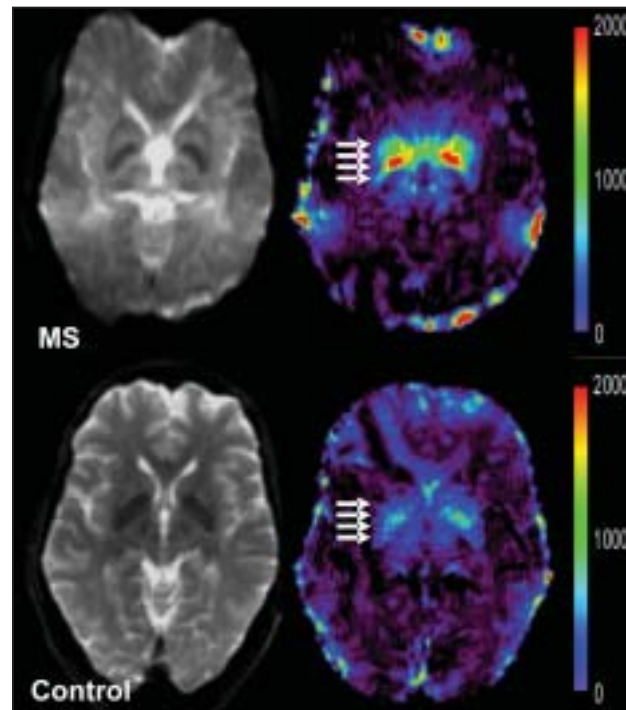
Using magnetic field correlation (MFC) imaging, Dr. Ge and his colleagues studied 17 patients with relapsing-remitting multiple sclerosis (MS) and 14 age-matched normal controls with a 3-T MR system. MFC imaging is a recently developed MR method that applies a unique iron contrast mechanism for measuring the iron deposition in vivo.

There was significantly more iron deposition in the deep gray matter of patients with MS than that in normal controls (P less than .03), with an average increase of 24% in the globus pallidus, 39.5% in the putamen, and 30.6% in the thalamus. Low iron concentrations in patients relative to controls were noted in the frontal white matter and the genu and splenium of the corpus callosum.

Increased iron deposition measured with MFC in the deep gray matter of MS patients was positively correlated with total number of brain lesions (thalamus: $P = .01$; globus pallidus: $P = .02$).

Increased iron in deep gray matter was correlated inversely and significantly with performance on several neuropsychological tests, including the Rey Complex Figure Test, the California Verbal Learning Test, and the Digit Span Backward test, Dr. Ge reported. "This is very exciting," says Dr. Ge, a radiologist at New York University, New York. "Researchers used to feel MS is a white matter disease. Now we know there are deep gray matter neurodegenerative abnormalities, which we think are mainly due to excessive iron accumulation in these regions."

Abnormal iron deposition is a causal factor of neurodegenerative pathology in MS, said Dr. Ge, who noted that his MFC findings support observations made using diffusion tensor imaging and MR spectroscopy demonstrating gray matter involvement in MS. In addition to providing mechanistic clues of MS pathophysiology, MFC will be a sensitive tool to evaluate MS patients and to monitor the effects of iron chelating agents and other neuroprotective MS treatments, he said. ■



T2-weighted images (left) and MFC color maps (right) in a 29-year-old MS patient (top) and a 32-year-old control (bottom). High iron levels are seen in deep gray matter regions (arrows) in MS. COURTESY DR. YULIN GE

Parkinson's Risk Increases With Greater Pesticide Exposure

BY JONATHAN GARDNER
London Bureau

Exposure to pesticides is associated with a significantly increased risk of developing Parkinson's disease and other degenerative parkinsonian syndromes, a large European multicenter study shows.

Moreover, the risk of Parkinson's increased, depending on the level of pesticide exposure. That suggests a cause-and-effect relationship. "Many previous studies have found such an association, but few have established an exposure-response relationship," investigators wrote in their report, which was published online in May in *Occupational and Environmental Medicine*.

Having ever been knocked unconscious and first-degree family history of Parkinson's disease also were each significantly

associated with increased Parkinson's risk, wrote Dr. Finlay Dick of the department of environmental and occupational medicine at Aberdeen (Scotland) University and associates.

The researchers enrolled 959 patients with parkinsonism, including 767 with Parkinson's disease, from centers in Italy, Malta, Romania, Scotland, and Sweden, along with 1,989 age- and gender-matched controls from clinics or the community at each site. Subjects completed a questionnaire about lifetime occupational and hobby exposure to solvents, pesticides, iron, copper, and manganese.

Adjusted logistic regression analysis showed that the strongest association was among patients with a first-degree family history of Parkinson's disease (odds ratio 4.85).

Significant dose-response associations

were seen between the development of Parkinson's disease/parkinsonism and exposure to pesticides (odds ratio 1.13 for low exposure vs. no exposure; OR 1.41 for high vs. no exposure) and ever having been knocked unconscious (OR 1.35 for once vs. never; OR 2.53 for more than once vs. never). The researchers stressed that the study did not make clear whether head injuries occurred before disease onset, adding that the association might be due to recall bias or an increased risk of falls in Parkinson disease. "Head injury has previously been linked to an increased risk of Parkinson's disease, but the results have been incon-

sistent," they noted (*Occup. Environ. Med.* 2007 May 30 [Epub doi:10.1136/oem.2006.027003]).

Patients taking, for more than 1 year, medication for depression (OR 1.92) or anxiety (OR 1.95), or sleeping pills (OR 1.33) also were at significantly elevated risk for developing Parkinson's disease and parkinsonism. "One explanation for this finding is that depression has been associated with an increased risk of Parkinson's disease later in life. The use of psychotropic medication may simply reflect the well recognized psychiatric effects of Parkinson's disease," the researchers wrote. ■

Patients taking medication for depression and anxiety for more than 1 year were also at significantly elevated risk for developing Parkinson's.