

Rasagiline May Slow Progression of Parkinson's

BY MARY ANN MOON

Rasagiline appears to slow the progression of Parkinson's disease, not just ameliorate its symptoms in the short term, according to a report in the *New England Journal of Medicine*.

A complex study design that incorporates several complicated statistical methods—the delayed-start study design—was used to differentiate the drug's short-term symptom effects from true disease-modifying effects, and the results were mixed. A 1-mg dose of rasagiline seemed to slow PD progression over the course of 18 months, but a 2-mg dose did not (*N. Engl. J. Med.* 2009;361:1268-78).

"From a practical point of view, the study findings suggest a possible benefit of the early use of rasagiline at a dose of 1 mg per day; however, given the negative findings for the 2-mg dose, we cannot definitively conclude that rasagiline at a dose of 1 mg per day has disease-

modifying effects," said Dr. C. Warren Olanow of the department of neurology, Mount Sinai School of Medicine, New York, and his associates.

"It will be important to determine whether these results can be confirmed and whether benefits seen at 18 months will endure and translate into reduced cumulative disability in clinically meaningful areas such as impairment of gait and balance and cognitive dysfunction," they noted.

The investigators conducted the study in 1,176 PD patients aged 30-80 who had not received any treatment for the disease and were recruited from 129 medical centers in 14 countries. The mean duration of PD at baseline was 4.5 months.

In the first 36-week phase of the trial, subjects were randomly assigned to receive the 1-mg dose of rasagiline, the 2-mg dose, or matching placebos. In the second 36-week phase, subjects in the placebo groups switched to one of

the active treatments, while those taking rasagiline continued their assigned treatment.

Theoretically, improvements seen in the first phase of a delayed-start study reflect the drug's symptom effects, and the difference between improvements in the early-start and delayed-start groups reflects the drug's disease-modifying effects.

In this study, subjects' mental function, activities of daily living, and motor function were assessed frequently using the Unified Parkinson's Disease Rating Scale. The mean total UPDRS score was 20.4 at baseline.

Teva Pharmaceutical Industries, manufacturer of rasagiline, funded the study and was responsible for data collection, monitoring, and statistical analysis.

The 1-mg dose of rasagiline met the three primary end points for results to be considered positive: There was less worsening in UPDRS scores during phase 1 with the drug than with placebo (0.09

points per week vs. 0.04 ppw), less worsening during phase 2 among subjects in the early-start group (2.82 ppw vs. 4.50 ppw) than in the delayed-start group, and noninferiority in the rate of worsening among the delayed-start patients during phase 2 (0.085 ppw in both).

The 2-mg dose did not meet these end points, though it did improve symptoms. "It is difficult to explain why the two doses did not provide similar results [and] to imagine that protective effects could be lost with a mere doubling of the dose," Dr. Olanow and his colleagues said.

Dr. Olanow reported receiving consulting and lecture fees from Teva and Lundbeck; receiving consulting fees from Boehringer Ingelheim, Novartis/Orion, Solvay, Ceregene, and Merck Serona; and owning equity in Ceregene.

His colleagues also reported receiving consulting and lecture fees from Teva and other pharmaceutical companies. ■

Onset of Memory Loss in Alzheimer's Tied to APOE Status

BY JEFF EVANS

Divergence in the age-related memory performance of individuals according to their apolipoprotein e4 allele status begins around the age of 55-60 years in neuropsychologic testing, according to a longitudinal analysis of 815 individuals.

The divergence in memory performance may "date the onset of cognitive decline due to Alzheimer's disease for the first time," said Dr. Richard J. Caselli, who reported the findings with his colleagues in the July 16 issue of the *New England Journal of Medicine*.

"We're following people before they're changing and have captured the change point," said Dr. Caselli of the Mayo Clinic, Scottsdale, Ariz., noting that one might be able to detect Alzheimer's disease-related changes even earlier with imaging or at a pathologic, microscopic level.

Dr. Caselli and his associates followed 498 noncarriers of the apolipoprotein e4 (APOE e4) allele and 79 homozygous APOE e4 and 238 heterozygous APOE e4 carriers during a period of about 5 years in either the Arizona APOE cohort or the Arizona Alzheimer's Disease Center cohort. The patients' ages ranged from 21 to 97 years. All of the e4 heterozygotes carried an APOE e3 allele, rather than an e2 allele, which is known to be protective against Alzheimer's disease (*N. Engl. J. Med.* 2009;361:255-63).

In analyses that isolated the longitudinal aspect of age on cognitive measures in cross-sectional and longitudinal data, the researchers found that APOE e4 carriers had significantly greater predicted decline on the Auditory-Ver-

bal Learning Test—the primary end point of the study—beginning in their 50s, compared with the predicted annual decline of noncarriers beginning in their 70s. This decline in memory performance was significantly correlated with a trend in APOE e4 allele dose on the Auditory-Verbal Learning Test, although the test results were only directly significant for the comparison between APOE e4 homozygotes and noncarriers.

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DR. CASELLI

that accelerated memory decline among persons with the APOE e4 allele may be caused by subclinical Alzheimer's disease," Dr. Caselli said in an interview. "Also consistent with this possibility was the observation that visuospatial function subsequently decreased in homozygous carriers of the APOE e4 allele."

A previous study by this group of investigators that was led by Dr. Eric Reiman of the Banner Alzheimer's Institute and the Translational Genomics Research Institute, Phoenix, showed that amyloid levels in the brain correlated with an individual's dose of the APOE e4 allele. The frontotemporal region of the brain was the most heavily affected by amyloid deposition, and it was the site of the greatest correlation with APOE e4 dose. But medial temporal regions—the sites of memory loss—were much less affected.

Dr. Caselli reported receiving consulting fees from Myriad Pharmaceuticals and Medication, as well as having an equity interest in Pfizer Inc. ■



Anxiety and Depression Prevail After 'Coiling'

BY AMY ROTHMAN SCHONFELD

BOCA RATON, FLA. — A group of researchers is looking at how patients who undergo endovascular coiling for aneurysmal subarachnoid hemorrhage fare psychologically in the years after the procedure.

The findings indicate that although the aneurysms were successfully repaired, some patients manifest clinical levels of anxiety and depression, as well as some deficits on a quality of life assessment scale, according to Dr. Antonio DeSimone, who presented his results at the annual meeting of the Society of Neurointerventional Surgery meeting.

"Our findings underline the need for focused interventions because of possible psychological morbidity even in good-outcome subjects," says Dr. DeSimone, a neuroradiologist at the San Giovanni Bosco Hospital in Naples, Italy.

In one study, a group of 30 subjects was selected from a database of 248 subjects who had undergone coiling for intracranial aneurysms from June 2002 to February 2009. Patients had good outcomes with resumption of normal activities, had no evidence of aneurysm recurrence, and at least 1 year had elapsed since treatment.

On the Hospital Anxiety and Depression scale, seven patients (23%) showed anxiety in the clinical range while three other pa-

tients (10%) had borderline scores. Four patients (13%) had scores within the clinical range for depression, and an additional five patients (17%) had borderline symptoms.

The same group of subjects was asked to complete the validated Italian version of the Medical Outcome Study 36-item short form questionnaire (SF-36), a widely used tool for assessing quality of life. No difference was noted between the overall scores of the patients versus those of a reference population.

Patients who had undergone coiling did show significant deficits in some domains, such as social functioning (*P* less than .05), role limitations because of emotional problems (*P* less than .05), and mental health (*P* less than .01).

"After an aneurysm is secured either by coiling or clipping, a sympathetic physician must give patients a chance to share their subjective feelings. In most cases, this is enough.

But a competent physician/neurologist can also screen out the patients—according to our data, up to one-third even in those rated as 'good outcome'—who definitely need structured psychological support," Dr. DeSimone said.

He points out that these patients and their families live in a disconcerting state of limbo and suggests that psychological support be made available to aneurysm patients. ■