

Rasagiline Delays Symptoms in Early Parkinson's

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — Rasagiline may have a disease-modifying effect for patients with Parkinson's, delaying the progression of symptoms early in the disease at least in the short term, a new placebo-controlled trial has found.

The study was designed to assess the drug's neuroprotective potential with a delayed-start design. Patients initially randomized to rasagiline showed an immediate symptomatic benefit, while those on placebo declined. After 9 months, the placebo patients also began taking rasagiline. By the end of the second 9 months, they too had improved, although their symptoms remained significantly worse than those of the early-start group.

"We can say with certainty that early treatment provided benefits that couldn't be achieved with later introduction of the exact same drug," Dr. C. Warren Olanow said at the annual meeting of the European Federation of Neurological Societies. "The question now is, why did this occur? Even though we have to speculate, and we don't have long-term data, we believe it must be related somehow to neuroprotection. It can't be completely explained by symptomatic improvement."

Dr. Olanow, chairman of neurology at Mount Sinai School of Medicine, New York, was the principal investigator for the trial's North American arm. He and his colleague, Dr. Olivier Rascol of Toulouse (France) University Hospital, who supervised the European arm, jointly presented the newly released results.

The 18-month study included 1,176 patients with newly diagnosed Parkinson's

disease (mean time since diagnosis, 4.5 months). Their mean age was 62 years; they all had very mild symptoms at the time of enrollment, with a mean total score of just 20 on the Unified Parkinson's Disease Rating Scale (UPDRS). Their mean modified Hoehn and Yahr score was 1.5.

Patients were randomized to placebo or to 1 or 2 mg rasagiline daily for the first 36 weeks. At 36 weeks, patients taking the drug continued receiving it, while patients taking placebo were randomized to either 1 or 2 mg of rasagiline. Everyone was followed for another 36 weeks. The investigators only presented the results of the 1-mg dose, saying that by the end of the trial, the 2-mg dose did not provide significant benefit over placebo.

Within 12 weeks of starting rasagiline, patients showed a mean 2-point decrease (improvement) on the UPDRS. Placebo patients showed a slight improvement as well, but it was not statistically significant. At 12 weeks both groups began to experience increases (worsening) of the UPDRS; however, the placebo group's score increased significantly more quickly and to a higher level. By 36 weeks, the mean score in placebo patients had increased by 3 points from baseline, while the active patients had lost their initial improvement and returned to their baseline score.

At this time point, all placebo patients were randomized to 1 or 2 mg rasagiline, while the early-start patients continued with their original regimen. By 45 weeks (9 weeks after initiating rasagiline) the delayed-start group showed a significant 1-point improvement in the UPDRS.

There was a very small improvement in the early-start group as well, which Dr.

Rascol attributed to a placebo effect.

At week 45, both groups started to worsen. Although the UPDRS scores remained separated by about 2 points, the trajectory of worsening was virtually identical. By week 72—the end of the trial—the mean UPDRS in the early-start group was 2, while the mean score in the delayed-start group was 3.5—a significant difference.

If both groups had eventually reached the same level of clinical improvement, the trial would have shown that rasagiline works by improving symptoms, Dr. Rascol said. The fact that the delayed-start group improved, but never as much as the early-start group, indicates that something about early dosing slowed disease progression. "It showed that starting the treatment early improves the outcome of the patients in a way that cannot be simply explained by symptomatic benefit," he said.

He acknowledged that the 2-point separation in scores, on a scale that reaches almost 200, was quite small. "However, some of these patients were only exposed to the drug for 9 months, and it can't be expected that the separation between the scores will be very large, especially since these patients have very early disease which progresses slowly."

The follow-up period is enough to show that rasagiline provides very early benefit, Dr. Olanow said. Whether that benefit will remain constant, improve, or decline

over time is still an unknown. "If I want to know what happens to these patients after 15 years on this drug, I'd have to follow them for 15 years, and these people don't have 15 years to sit around and wait. If we can conclude the benefit of this drug is real and can't be attributed to symptomatic effect then we can impute that it has a real disease-modifying effect. If you had Parkinson's, would you rather take a drug that shows initial disease slowing—without knowing what it does in 10 years—or not? That is the choice we face."

Adverse events were mild and similar to those already documented. The most frequent were nausea and vomiting and orthostatic hypotension (4% each).

Rasagiline, which is already approved at the 1-mg dose for symptomatic treatment of Parkinson's, is a potent monoamine oxidase-B inhibitor. Its putative neuroprotective effects are not fully understood, Dr. Rascol said. "It may enhance the survival of the dopamine cell, or it may enhance the endogenous compensatory mechanisms the brain uses to cope with the loss of dopamine. Alternatively, rasagiline could reduce or avoid some undesirable adaptation of the brain involved in loss of dopamine."

The trial was cosponsored by the drug's developer and manufacturer Teva Pharmaceutical Industries, headquartered in Israel, and Lundbeck A/S of Copenhagen. Both Dr. Olanow and Dr. Rascol are paid consultants for the companies. ■

The putative neuroprotective effects of rasagiline—already approved at the 1-mg dose for symptomatic Parkinson's—are not fully understood.

Selegiline Reduces Some Adverse Events in Parkinson's

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — In a group of patients with motor fluctuations and dopamine agonist-related side effects, adding orally disintegrating selegiline and decreasing the dopamine agonist dose reduced these adverse events without worsening Parkinson's disease symptoms.

According to self-reports from the first 50 patients in a 12-week, multicenter, open-label study, daytime sleepiness (defined as a score greater than 10 on the Epworth Sleepiness Scale) was present in 41 patients at baseline and, of those, was reduced in 28 (68%) and resolved in an additional 9 (22%) at study completion.

Symptoms were also reduced or resolved for 14 patients with hallucinations (36% reduced, 57% resolved), 22 patients with pedal edema (46% reduced, 23% resolved), and 23 patients with impulsive behavior including

gambling, sexual urges, eating, and buying (48% reduced, 35% resolved), Dr. Rajesh Pahwa reported on behalf of the investigators of the A to Z Study in a poster at the 12th International Congress of Parkinson's Disease and Movement Disorders.

Motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) were not significantly different at baseline and week 12, reported Dr. Pahwa, who serves as director of the Parkinson's disease and movement disorder center at the University of Kansas Medical Center, Kansas City.

However, Dr. Pahwah and colleagues found that significant reductions from baseline were observed in the UPDRS activities of daily living scores (11.9 at baseline vs. 10.2 at week 12) and mentation scores (2.4 at baseline vs. 1.9 at week 12).

Orally disintegrating selegiline (Zelapar) is indicated as adjunct

therapy in Parkinson's disease patients who exhibit deterioration in their response to levodopa. There is no evidence from controlled trials that the monoamine oxidase type B inhibitor has any beneficial effect in the absence of concurrent levodopa therapy.

Patients in the study had idiopathic Parkinson's disease with

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levodopa-induced motor fluctuations that required reductions in the dopamine agonist (DA) dosage because of adverse events. In Dr. Pahwa's clinical experience, the addition of orally disintegrating selegiline in such patients has reduced the side effects of DA because it allows for a reduction in DA dose.

"I proposed the study based on my clinical experience with

dopamine agonists and Zelapar, and the results of the study confirmed my clinical experience," Dr. Pahwa said in an interview.

About 25%-30% of patients treated with DAs experience somnolence; 40% have pedal edema, 15%-20% have hallucinations, and 5% have impulse disorders, he said.

At baseline, 29 (58%) of the first 50 patients in the study were taking pramipexole (mean dosage, 2.3 mg/day) and 21 (42%) were taking ropinirole (mean dosage, 10.6

mg/day). The final mean pramipexole dosage was 0.5 mg/day and the mean ropinirole dosage was 3.0 mg/day.

The DA dosage was cut in half within 1 week of baseline, and orally disintegrating selegiline (1.25 mg once daily) was added. At week 3, if DA-related adverse events persisted and efficacy was unchanged, the DA dosage was

tapered to discontinuation, and orally disintegrating selegiline was continued. At week 6, orally disintegrating selegiline was increased to 2.5 mg/day.

If the DA dosage was not discontinued and DA-related adverse events were still present with efficacy unchanged, the DA dosage was further reduced. At the final visit, 44 patients were taking 2.5 mg/day orally disintegrating selegiline, and 6 patients were taking 1.25 mg/day, according to Dr. Pahwa.

Adverse events were assessed at baseline and at weeks 3, 6, and 12 by self-report, as well as by the Epworth Sleepiness Scale, the Neuropsychiatric Inventory, the Barratt Impulsiveness Scale, and ankle circumference.

The study was supported by Valeant Pharmaceuticals International, which markets Zelapar. Dr. Pahwa is a consultant and speaker for and has received research grants from Valeant, Boehringer Ingelheim GmbH, and GlaxoSmithKline. ■