Parkinson Disease and Monoamine Oxidase Inhibition

Transtelephonic Home Blood Pressure to Assess the Monoamine Oxidase-B Inhibitor Rasagiline in Parkinson Disease

William B. White, Phyllis Salzman, Steven R. Schwid; for the Parkinson’s Rasagiline: Efficacy and Safety in the Treatment of “Off” Parkinson Study Group

Abstract—Monoamine oxidase inhibitors are associated with dietary tyramine interactions that can induce hypertensive crises. Rasagiline mesylate is a novel irreversible selective monoamine oxidase type B inhibitor for Parkinson disease that may have a low risk of interaction with dietary tyramine because of its selectivity. To study interactions of rasagiline with diets unrestricted in tyramine-containing foods, we incorporated transtelephonic, self-monitoring of the blood pressure (BP) into a randomized, placebo-controlled trial of rasagiline 0.5 and 1.0 mg daily in 414 levodopa-treated Parkinson patients with motor fluctuations. The proportion of patients with a systolic BP increase of >30 mm Hg was the primary BP end point. In 13,968 self-measured readings at baseline, the proportion of systolic BP values that increased by >30 mm Hg after a meal ranged from 9.5% to 12.9% in the 3 treatment groups. In 25,733 BPs obtained postprandially, the proportion of values with a >30-mm Hg systolic postprandial increase was 15% in the placebo group, 15% in the rasagiline 0.5-mg group, and 11% in the rasagiline 1-mg group after 3 weeks of double-blind therapy and 13%, 14%, and 12%, respectively, after 26 weeks of treatment. (P value was not significant for all of the comparisons among treatment groups). A postprandial increase in systolic BP to >180 mm Hg at any time after randomization was seen in 3.3%, 2.6%, and 2.9% of the placebo, 0.5-mg, and 1.0-mg rasagiline groups, respectively. These data demonstrate that rasagiline did not induce postprandial hypertension in patients with Parkinson disease who were on an unrestricted diet. (Hypertension. 2008;52:587-593.)

Key Words: rasagiline ■ self-monitored blood pressure ■ Parkinson disease ■ tyramine ■ monoamine oxidase inhibitor

The treatment of Parkinson disease with dopaminergic therapy (eg, levodopa) is commonly complicated by motor fluctuations and dyskinesias, which cause substantial morbidity for patients with this disorder.1 Inhibitors of monoamine oxidase (MAO) type B (MAO-B), the main enzyme that metabolizes dopamine in the brain, may potentiate the beneficial motor effects of the dopaminergic agents and reduce the severity of motor complications.2-3 Rasagiline (N-propargyl-1-(R)-aminodan) mesylate is a new irreversible MAO-B inhibitor with high selectivity for the B isoform of the enzyme shown to improve function in patients with Parkinson disease.4,5

Tyramine is an amino acid present in high concentrations in certain food types (aged cheeses, fermented meats, and sauerkraut) that can generate pressor responses unless it is metabolized by MAO in the gastrointestinal tract.6 The usefulness of nonselective MAO inhibitors for depression has been limited by the need to restrict dietary tyramine intake to avoid potentially severe hypertensive reactions. Selective MAO-B inhibitors, such as rasagiline, are relatively free of this limitation, because 90% of MAO activity in the intestine involves the MAO type A isoform.7 However, it is not clear whether the selectivity is adequate at higher doses or in tyramine-sensitive individuals.

To evaluate the safety of rasagiline in patients with an unrestricted diet, we performed a large novel study of self-monitored transtelephonic blood pressure (BP) before and after meals in the Parkinson’s Rasagiline: Efficacy and Safety in the Treatment of “Off” (PRESTO) Study, a randomized, placebo-controlled trial in patients with Parkinson disease and motor fluctuations.8 Although the value of self-monitored BP in clinical trials had been recognized for some time,9,10 there had been no safety trials involving the use of transtelephonic BP monitoring before the PRESTO Study.8

Methods

Patients

Levodopa-treated patients with Parkinson disease (n=472) were enrolled at 57 centers in the United States and Canada. Patients with...
idiopathic Parkinson disease and motor fluctuations, ≥30 years of age, on a stable dose of levodopa were included. Concomitant treatment with dopamine agonists, amantadine, anticholinergics, and entacapone were allowed, but these agents could not be introduced or changed in dose during the conduct of the study. Patients with pronounced cognitive impairment (mini-mental status examination score <24) and medically unstable cardiac, renal, or neurologic conditions were excluded. Patients with severe hypertension (systolic BP ≥180 mm Hg) were excluded from participation in the trial. Exclusionary medications were also MAO-B inhibitors (eg, selegiline), antiemetics, or neuroleptics with central dopamine agonist activity and St John’s wort.

Study Design
This was a multicenter, randomized, placebo-controlled, parallel group double-blind trial in patients with Parkinson disease receiving optimized levodopa therapy ≥3 times daily. The efficacy analyses and general safety of the PRESTO Trial have been reported elsewhere.8 After a baseline visit that included assessment of the ability to complete accurate home diaries and use home BP monitors (by the patient or a caregiver), patients were randomly assigned to receive once-daily rasagiline 0.5 mg, rasagiline 1.0 mg, or matching placebo. Computer-generated randomization provided for stratification by center and blocking to assure balance among the treatment groups at each center. For the evaluation of BP, patients had visits at baseline, 3 weeks, and 26 weeks. There were several other visits in between these visits to assess neurologic function, laboratory data, electrocardiography, and dermatologic exams, as described previously.8

BP Measurements
At clinic visits, patients underwent duplicate measurements of the BP using mercury column sphygmomanometry and pulse rate after 5 minutes in the supine position and after 2 minutes of standing. For home BP recordings, patients and their caregivers were instructed in the use of a transtelephonic, oscillometric self-BP monitor (Welch-Allyn, Inc). Before its use in the PRESTO Study, this oscillometric device was validated for accuracy and reliability in patients with Parkinson disease.11 This transtelephonic device has a simple telephone cord receptacle that allows patients to insert their telephone jack from their analog telephone (all of the patients in the study had analog telephones) to the self-BP device. Each self-BP monitor was programmed for a specific patient identification number and center number. Thus, whenever a measurement was recorded by the BP device, the data were transferred within several seconds over their telephone line to a central server, which captured the date, time, patient identification number, and BP values. Timing of measurements was recorded by patients or their caregivers on diary cards. Patients (or their caregivers) monitored duplicate BPs in the seated position 30 minutes before and 45 and 90 minutes after their main meal of the day for the 7 days preceding the baseline visit, week 3, or week 26 of double-blind therapy, and 26 weeks of double-blind therapy. All of the study coordinators were trained at investigator meetings in the use of the transtelephonic BP device, and they, in turn, trained the patients and their caregivers to use the device, paying attention to proper cuff/bladder size (American Heart Association guidelines)12 arm position, and arm support during the actual recordings. Unless impossible, patients were asked to avoid recording the BP if they had uncontrollable tremors, dyskinesias, or exceptional rigidity. If a measurement was associated with an error code on the device liquid crystal display, patients were instructed to repeat the measurement within 3 minutes.

All of the self-BP measurements were electronically captured and transferred to a data coordinating center (University of Connecticut Health Center, Farmington) for same- or next-day blinded review by a trained technician and the principal investigator (W.B.W.). Any data that were considered to be of clinical concern from a safety perspective were discussed with the site coordinator or investigator immediately. In addition, data for each patient were examined for quality control after the study week and stored until the final analysis was performed.

Statistical Analysis
Self-BP measurements taken at visits other than those during the 7 days before randomization (baseline), week 3, or week 26 (termination visit) were excluded from the analysis. It was prespecified in the analysis plan that BP measurements taken during the meal, >60 minutes before the meal, and those taken <15 minutes or >180 minutes after the meal were excluded from analyses. Self-BP data were also excluded if the readings were nonphysiologic or highly improbable, as follows: pulse pressure <15 mm Hg, systolic BP <60 mm Hg or >260 mm Hg, or diastolic BP <40 mm Hg or >140 mm Hg. (These criteria resulted in removal of 288 readings in the 0.5-mg group, 220 readings in the 1.0-mg group, and 261 readings from the placebo group. There were no systolic BPs in excess of 240 mm Hg in any of the treatment groups.) Duplicate BP measurements taken within 10 minutes of each other were included in the data analysis, and the means of the duplicates for all of the nonexcluded postprandial recordings were used in the statistical assessment of the primary safety end point.

The primary end point was the proportion of patients with postrandomization systolic BP responses defined as an increase from premeal to postmeal of >30 mm Hg that also resulted in a postmeal systolic BP of >140 mm Hg. A key secondary end point was a severe response defined as an increase from premeal to postmeal >30 mm Hg with a resultant systolic BP >180 mm Hg. The numbers of patients with hypertensive and severely hypertensive responses were calculated at baseline (for assessment of group comparability) and at weeks 3 and 26 postrandomization.

The principal analysis compared the number and proportion of subjects in each of the 2 rasagiline treatment groups with a systolic BP response compared with the number and proportion of patients receiving placebo who reached the end point (2 contrasts). The analysis used a baseline adjusted logistic regression (SAS GENMOD procedure, SAS Institute) incorporating the covariates of the proportion of patients with a systolic BP response at baseline, history of hypertension/antihypertensive therapy, age, and gender. Assessment of potential bias arising from removal of BP data according to BP artifact was evaluated and assessed by treatment group. Assessment of baseline comparability was evaluated using the Kruskal-Wallis test for continuous variables and the χ2 test for all of the categorical variables with the exception of the proportion of severe BP elevations at baseline, which was examined by Fisher’s exact test.

Results
Patient Disposition and Characteristics
Disposition of patients in the PRESTO Trial is shown in Figure 1. Overall, 414 patients (88% of enrolled) completed 26 weeks of treatment. Compliance was high, as measured by pill counts (95% took ≥90% of prescribed doses). As shown in Table 1, there were no significant differences at baseline with regard to demographic and clinical characteristics. The mean age of the population was 63 to 64 years, with a majority of white males and approximately one third taking antihypertensive drug therapy. BPs at baseline were in the normotensive range and showed an average reduction in systolic BP on standing of ~5 mm Hg (Table 1).

Changes in Clinic Supine and Standing BP
Mean changes from baseline in the systolic supine and standing BPs are shown in Figure 2. There were no significant differences between rasagiline and placebo groups.

Changes in Self-Measured BPs
More than 5000 home BP readings were obtained at each time point in the 3 treatment groups that met the inclusion criteria for the per-protocol analysis, with a similar number of
measurements in the 3 treatment groups. At baseline, there were significant reductions in the systolic BPs after meals, ranging between 3.5 and 5.2 mm Hg (P<0.001; Table 2). This postprandial BP effect persisted at weeks 3 and 26. There were no differences in the changes from baseline in the postmeal versus premeal BPs for rasagiline groups compared with placebo at weeks 3 and 26 (Table 2). Furthermore, premeal and postmeal mean BP values were not changed significantly on either dose of rasagiline or placebo during the course of the study (Table 2).

The number and proportion of patients whose systolic BP rose by >30 mm Hg are shown in Table 3. At baseline, 10% to 13% of patients demonstrated postprandial increases in systolic BP of >30 mm Hg (Table 3); <2% resulted in a systolic BP >180 mm Hg. After randomization, there were no statistically significant differences between either dose of rasagiline and placebo in the proportion of patients with a postprandial increase in systolic BP of >30 mm Hg at any time during the study (P=0.21 for the 0.5-mg/d treatment group and P=0.99 for the 1.0-mg/d treatment group for week 3 and week 26 combined). Similarly, there were no statistically significant differences between either dose of rasagiline and placebo in the proportion of patients with a postprandial increase in systolic BP >30 mm Hg that resulted in a value in excess of 180 mm Hg at any time (P=0.93 for the 0.5-mg/d treatment group and 0.85 for the 1.0-mg/d treatment group) for week 3 and for week 26 combined.

Of 58 patients who had postprandial increases in systolic BP at week 3, 19 (33%) had increases at baseline, and 39 patients (67%) did not. For these 39 patients with “newly” occurring systolic BP increases, the distribution was similar for the 3 treatment groups: 15 (11%) in the placebo group, 15 (11%) in the 0.5-mg rasagiline group, and 9 (7%) in the 1.0-mg rasagiline group. Similarly, at 26 weeks, 50 patients had postprandial increases in systolic BP; of those, 15 (30%)...
had elevations at baseline, and 35 (70%) did not. Of the 35 patients with newly occurring increases in systolic BP, the distribution was also similar for the 3 treatment groups (12 [10%] in the placebo group, 14 [11%] in the 0.5-mg rasagiline treatment group, and 9 [8%] in the 1.0-mg rasagiline group).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>0.5 mg/d</th>
<th>1.0 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>147</td>
<td>157</td>
<td>140</td>
</tr>
<tr>
<td>No. of self-BP readings</td>
<td>4581</td>
<td>5019</td>
<td>4368</td>
</tr>
<tr>
<td>BP before and after meal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premeal systolic BP, mm Hg</td>
<td>127±19</td>
<td>126±19</td>
<td>126±18</td>
</tr>
<tr>
<td>Postmeal systolic BP, mm Hg</td>
<td>122±18</td>
<td>121±19</td>
<td>123±16</td>
</tr>
<tr>
<td>Changes between postmeal and premeal</td>
<td>-5.2±15.9*</td>
<td>-4.9±14.8*</td>
<td>-3.5±15.8*</td>
</tr>
</tbody>
</table>

*P<0.001 vs premeal values (within groups).

Changes in BP According to Antihypertensive Drug Use and Time of Meal

The number and proportion of subjects taking antihypertensive therapy at baseline, week 3, and week 26 of the trial are shown in Table 4. There were no differences in antihypertensive drug use among the treatment groups, and there were no significant changes in the proportion of patients administered antihypertensive therapy during the course of the study in any of the 3 treatment groups. In addition, the proportion of patients achieving a postmeal systolic BP end point of >30 mm Hg with a resultant value of >140 mm Hg was not different among the 3 treatment groups at baseline or during the postrandomization period (Table 4).

The impact of meal times (midday meal [before 3 pm] versus evening meal) on postmeal systolic BP responses was evaluated for the 3 treatment groups. Approximately 80% to 83% of self-monitored BPs were recorded around an evening meal time. There were consistently more systolic BP increases associated with the evening meal than the midday meal for the placebo and 0.5-mg groups (Table 5); in the 1.0-mg group, there were similar proportions of patients with a postmeal systolic BP response >30 mm Hg for midday and evening meals.

There was no consistency in or persistence of the postmeal hypertensive response according to treatment group. For example, only 7 of 48 patients who had a systolic BP response at week 3 had a systolic BP response at week 26,
and these were divided equally among the 3 treatment groups (2 of 147 patients on placebo [1.4%], 3 of 157 patients on 0.5 mg [1.9%], and 2 of 140 patients on 1.0 mg [1.4%]).

Discussion

Principal Findings

Intensive self-monitoring of BP before and after the main meal of the day demonstrated no evidence of postprandial hypertension during treatment with 0.5 or 1.0 mg of rasagiline daily versus placebo in patients with Parkinson disease on an unrestricted diet. This finding is the case both after short-term administration (3 weeks) and long-term administration (26 weeks) of this selective MAO-B inhibitor. To our knowledge, this is the first study that has used transtelephonic home monitoring of BP to evaluate the safety of a noncardiac drug in a multicenter trial. We found that the technology was feasible and useful for clinical research even in a population with significant variations in motor function such as those in the PRESTO Trial. The ability to evaluate BP in the home environment around meal times was of great importance in understanding whether pressor effects from dietary intake of tyramine-containing foods might be occurring. Self-monitoring of home BP enhances the more typical tyramine pressor tests performed in clinical trial units, because it occurs in the patients’ natural environment and reflects responses to what they are actually eating rather than a laboratory surrogate.

Effect of Tyramine Administration in Patients Taking Selective MAO-B Inhibitors

Formal studies of the effects of tyramine in patients taking rasagiline in double-blind clinical trials have compared the

Table 5. Patients Achieving a Home BP End Point Postmeal According to Time of Meal

<table>
<thead>
<tr>
<th>Measurement (%)</th>
<th>Placebo, N (Total)</th>
<th>Dose of Rasagiline, n/N of Measurements (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>0.5 mg/d</td>
<td>1.0 mg/d</td>
</tr>
<tr>
<td>Baseline</td>
<td>n=1574</td>
<td>n=1727</td>
</tr>
<tr>
<td>Postmeal systolic BP &gt;30 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midday meal</td>
<td>2/259 (0.8)</td>
<td>2/234 (0.6)</td>
</tr>
<tr>
<td>Evening meal</td>
<td>21/1315 (1.6)</td>
<td>18/1393 (2.2)</td>
</tr>
<tr>
<td>At 3 wk</td>
<td>n=1560</td>
<td>n=1605</td>
</tr>
<tr>
<td>Postmeal systolic BP &gt;30 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midday meal</td>
<td>2/248 (0.8)</td>
<td>5/288 (1.7)</td>
</tr>
<tr>
<td>Evening meal</td>
<td>30/1312 (2.3)</td>
<td>29/1317 (2.2)</td>
</tr>
<tr>
<td>At 26 wk</td>
<td>n=1329</td>
<td>n=1459</td>
</tr>
<tr>
<td>Postmeal systolic BP &gt;30 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midday meal</td>
<td>2/181 (1.1)</td>
<td>1/268 (0.4)</td>
</tr>
<tr>
<td>Evening meal</td>
<td>25/1148 (2.2)</td>
<td>25/1191 (2.1)</td>
</tr>
</tbody>
</table>
drug to placebo. In one study, the doses of rasagiline were 1.0 and 2.0 mg versus placebo; in the second study, the doses of rasagiline were 0.5 and 1.0 mg versus placebo. Patients in these studies were given single doses of oral tyramine hydrochloride, 75 mg and 50 mg, respectively, after 26 weeks of treatment with rasagiline or placebo. Because pressor responses to tyramine in these interaction studies typically occur within ≤1 hour, the BP monitoring period was 2 to 4 hours postdosing of tyramine depending on BP stability. In one of these studies, 0 of 55 subjects met a primary end point of a sustained (≥15 minutes) rise in systolic BP of ≥30 mm Hg. In the other study (PRESTO), 4 of 55 patients met the systolic BP response end point (3 on 0.5 mg of rasagiline, 1 on placebo, and 0 on 1.0 mg of rasagiline). Examination of the transtelephonic home BP data in these 4 patients showed that 3 had no postprandial increases in systolic BP, and in 1 patient (0.5-mg dose), all of the postprandial systolic BPWs were increased >30 mm Hg, including the baseline measurement.

Tyramine pressor studies with 30 mg/d of selegiline, an older MAO-B inhibitor, have demonstrated that, after chronic administration of the oral form of the drug, there may be a 2-fold increase in sensitivity to large doses of tyramine (>200 mg). With a newer transdermal preparation of selegiline, 6 mg/24 h, larger doses of tyramine (>250 to 275 mg) may be necessary to induce a hypertensive response than with the oral form of the drug.

To put these findings from tyramine sensitivity studies in perspective, the average dose of free tyramine in large quantities of aged cheese is typically 5 to 20 mg. Nonselective MAO inhibitors typically only require 5 to 10 mg of tyramine ingestion to induce substantial elevations in systolic BP, but it is likely that much larger doses of tyramine would be required to have the same sort of pressor response when patients take selective MAO-B inhibitors. Thus, whereas the classical tyramine sensitivity tests assess the potential for an MAO inhibitor to increase BP in response to very large oral doses of tyramine, they may not be comparable to the amounts that are ingested in foodstuffs in everyday meals. Therefore, data from clinical pharmacology studies using much larger doses of tyramine to induce a BP response in patients taking selective MAO-B inhibitors are not inconsistent with the results of our study that monitored BP on an unrestricted diet.

Transtelephonic BP Measurement to Evaluate a Potential Food Effect in Patients

Taking Rasagiline

The primary objective of obtaining self-BP measurements within the PRESTO Trial was to determine whether patients were developing pressor responses to unrestricted diets while taking rasagiline (0.5 and 1.0 mg daily) as an adjunct therapy to levodopa. Transtelephonic monitoring allowed us to assess this potential in a real-world environment during the course of the trial with thousands of BP measurements collected during the study. It was clear from this study that BP variability around meal time is substantial (Tables 2 and 3). The finding that postprandial BP generally decreased in this older population with Parkinson disease is not unexpected and has been reported previously in older patients with autonomic dysfunction.

It was noted that, postrandomization, systolic BP variability was similar in all of the treatment groups, and the variability was nearly constant after 3 and 26 weeks of rasagiline treatment (Table 3). In our study, the stability of the BP response in 3500 to 5000 BP measurements in each treatment group during 1 week of double-blind therapy confirms this notion (Table 3).

Conclusions

Our study has demonstrated that postmeal BP values were similar for patients with Parkinson disease on an unrestricted diet during long-term, once-daily treatment with the selective MAO-B inhibitor rasagiline. These data, together with tyramine pressor tests conducted at the end of randomized, placebo-controlled trials of rasagiline, suggest that dietary restriction of tyramine-rich foodstuffs is not necessary in patients taking rasagiline for Parkinson disease. In addition, transtelephonic BP monitoring greatly facilitated the collection of BP safety data in this large, multicenter trial by having precise, automated transfer of several thousand BP values with date, time, and patient identification recorded by a central analysis unit.

Perspectives

Monoamine oxidase type A inhibitors are known to interfere with the metabolism of tyramine and may precipitate pressor responses, which can induce hypertensive emergencies. The use of nonselective MAO inhibitors, used in the treatment of depression, has been limited because of this interaction. The selective MAO-B inhibitors have been reported to have a much lesser interaction with tyramine compared with the older nonselective MAO inhibitors. These findings are particularly relevant because wider use of the MAO-B inhibitors is seen in patients with Parkinson disease, a group that is typically older and has a high incidence of hypertension. Use of rasagiline, a unique MAO-B inhibitor, may be effective as a monotherapy or in combination with levodopa in patients with Parkinson disease without inducing a BP increase after meals unrestricted in tyramine-rich foods. In our 26-week study, treatment with 0.5 mg and 1.0 mg of rasagiline was not associated with a clinically or statistically significant increase in systolic BP or in the proportion of patients with hypertensive responses after meals in a large number of patients with Parkinson disease who were also taking levodopa.

Of note, the amounts of tyramine bound in foods such as hard cheeses, fermented meats, organic beers, and chocolates are relatively low (<10 mg) and are unlikely to be ingested in large quantities by most patients. For patients taking rasagiline, our present real-world trial and earlier tyramine sensitivity studies that administered 50 to 75 mg of tyramine hydrochloride have not demonstrated clinically significant BP responses. This suggests that this drug could be used without the need for a dietary restriction of tyramine-rich foods.

Appendix

The following members of the Parkinson’s Rasagiline: Efficacy and Safety in the Treatment of “Off” Parkinson Study Group participated in this study, collected data, and critically reviewed this report.
Steering Committee
Ira Shoulson, MD (principal investigator): University of Rochester, Rochester, NY; Matthew Stern, MD (coprincipal investigator): University of Pennsylvania, Philadelphia, Pa; David Oakes, PhD (chief biostatistician), and Karl Kieburtz, MD: University of Rochester, Rochester, NY; Stanley Fahn, MD: Columbia-Presbyterian Medical Center, New York, NY; Karen Blindinger, MD: Medical College of Wisconsin, Milwaukee, WI; Antoinelle deMarcaida, MD: University of Connecticut, Farmington, Conn.

Participating Investigators and Coordinators
Kathy Davis: Medical College of Ohio, Toledo, Ohio; Enrico Fazzini, MD, and Linda Chin, RN: New York University Medical Center, New York, NY; Burton Scott, MD, and Carroll Wilcox, RN, Duke University Medical Center, Durham, NC; Amy Colcher, MD: University of Pennsylvania, Philadelphia, Pa; Robert Hauser, MD, and Lisa Gauger, BA: University of South Florida, Tampa, Fla; Maureen Leehey, MD: University of Colorado Health Sciences Center, Denver, Colo; William Ondo, MD: Baylor College of Medicine, Houston, Tex; Patricia Kaminski, RN, Clinical Neuroscience Center, Southfield, Mich; Madaline Harrison, MD, and Elke Rost-Ruffner, RN, BSN: University of Virginia, Charlottesville, Va; Rajesh Pahwa, MD: University of Kansas Medical Center, Kansas City, KS; Mark F. Lew, MD, and Connie Kawai, RN, BSN, CCRC: University of Southern California, Los Angeles, Calif; Jana Patterson, RN, University of Arkansas for Medical Sciences, Little Rock, Ark; Eric Molho, MD: Albany Medical College, Albany, NY; Lisa Shulman, MD: University of Miami, Miami, Fla; Christopher Goetz, MD: Rush-Presbyterian-St Luke’s Medical Center, Chicago, Ill; Richard Camicioli, MD: University of Alberta, Edmonton, Alberta, Canada; David Margolin, MD, PhD: Margolin Brain Institute, Fresno, Calif; Frederick Marshall, MD, and Debbra Berry, MSN, NP: University of Rochester, Rochester, New York; Mark Forrest Gordon, MD: Long Island Jewish Medical Center, New York, NY; Mohamed Hassan, MD, and Patricia Kelton, RN: University of Connecticut, Hartford, Conn; Neal Hermanowicz, MD, and Shari Shulman, MD: University of Miami, Miami, FL; Andrew Feigin, MD: North Shore University Hospital, Great Neck, NY; Vincent Calabrese, MD: Hunter College of the City University of New York, New York, NY; Burton Scott, MD, and Carroll Wilcox, RN: University of Rochester, Rochester, NY; Matthew Stern, MD (coprincipal investigator): University of Pennsylvania, Philadelphia, Pa; David Oakes, PhD (chief biostatistician), and Karl Kieburtz, MD: University of Rochester, Rochester, NY; Stanley Fahn, MD: Columbia-Presbyterian Medical Center, New York, NY; Karen Blindinger, MD: Medical College of Wisconsin, Milwaukee, WI; Antoinelle deMarcaida, MD: University of Connecticut, Farmington, Conn.

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Disclosures
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P.S. is a full-time employee of Teva Neuroscience, Inc. S.R.S. and the Parkinson Study Group PRESTO investigators listed in the Appendix received grant support from the sponsor through their academic institutions but did not have equity interests in or receive personal remuneration from the sponsor from the initiation of the study to publication of the primary study report.

References
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