Transdermal Rotigotine

Double-blind, Placebo-Controlled Trial in Parkinson Disease

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Objective: To assess the response to the rotigotine transdermal system (Neupro; Schwarz Pharma Ltd, Monheim, Germany), a nonergolinic dopamine agonist, in patients with early Parkinson disease.

Design: Randomized, double-blind, multicenter, placebo-controlled study.

Setting: Fifty sites in the United States and Canada.

Patients: Two hundred seventy-seven patients with early Parkinson disease. Eligibility was assessed by means of routine clinical and neurological examinations. Patients were randomized 2:1 to receive either rotigotine therapy or placebo.

Intervention: Treatment with the rotigotine transdermal system, 2, 4, or 6 mg during 24 hours, for 24 weeks.

Main Outcome Measure: Percentage of subjects achieving a 20% response or greater (reduction) as assessed with the Unified Parkinson Disease Rating Scale subtotal (parts II [activities of daily living] and III [motor function]) from baseline to the end of the maintenance phase.

Results: Significant differences were observed between the rotigotine-treated and placebo groups for the 20% responder rate (48% for the rotigotine group and 19% for the placebo group; \( P < .001 \)), least squares mean change in Unified Parkinson Disease Rating Scale subtotal (parts II and III) score (−941 for rotigotine vs −157 for placebo; \( P < .001 \)), and percentage changes in Unified Parkinson Disease Rating Scale subtotal (parts II and III) score (−15.1% for rotigotine vs 7.3% for placebo; \( P < .001 \)). Rotigotine treatment significantly increased the patients’ Clinical Global Impression Scale scores (57% for rotigotine vs 30% for placebo; \( P < .001 \)) and had a positive effect on their quality of life. The most common adverse events were application site reactions, nausea, and somnolence. Twenty-five (14%) of 181 patients in the rotigotine group withdrew from the study because of adverse effects.

Conclusion: The rotigotine transdermal system consistently demonstrated statistically significant and clinically relevant efficacy over placebo in patients with early Parkinson disease and was well tolerated.

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This has motivated investigators to seek treatment approaches that provide more constant physiological stimulation at the level of the dopamine receptor.7

This study was conducted to assess the safety and efficacy of rotigotine therapy and placebo in a phase III trial in patients with early PD for the first time. In addition to the primary end points and adverse effects, other important end points—including effects on subsets of the UPDRS, Clinical Global Impression Scale rating, Epworth Sleepiness Scale (ESS) scores, quality-of-life (QOL) measures, and serum prolactin and rotigotine plasma concentration data—were assessed in that trial and are described in this article.

**METHODS**

**PATIENTS**

This randomized, double-blind, multicenter, placebo-controlled trial was conducted in accord with the local laws of the countries involved and the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice, May 1996.8 All patients gave informed consent before enrolling in the study. Included in the study were male or female patients 30 years or older with an established diagnosis of idiopathic PD of 5 years’ duration or less and with at least 2 of the following cardinal signs, without any other known or suspected causes of parkinsonism: bradykinesia, resting tremor, rigidity, and postural instability. All patients had a UPDRS motor score (part III) of at least 10, a Hoehn and Yahr stage of III (disease that impairs balance or walking) or less, and a Mini-Mental State Examination score of 25 or higher (median score, 29 for persons with 9 years of schooling). We excluded patients who had previous or concurrent therapy with a dopamine agonist or with carbidopa or levodopa within 28 days of the baseline visit (visit 2); carbidopa or levodopa therapy for more than 6 months since diagnosis; atypical parkinsonism; surgical intervention for PD; clinically relevant hepatic, renal, or cardiac dysfunction; a diagnosis of epilepsy, a history of seizures as an adult, or stroke or a transient ischemic attack within the last year; pronounced skin hypersensitivity to adhesive or other transdermal patches or recent unresolved contact dermatitis; or known intolerance or hypersensitivity to the antiemetic ondansetron; were pregnancy or nursing; or used inadequate birth control methods. We also excluded patients receiving central nervous system active therapy unless their pharmacotherapy doses had been stable for at least 28 days before baseline and were likely to remain stable for the duration of the trial. Patients previously receiving an anticholinergic agent, monoamine oxidase-B inhibitor, or N-methyl-D-aspartate antagonist must have had a stable dose for at least 28 days before study baseline and were required to maintain that dose for the duration of the trial. Complete study methods and design and patient inclusion and exclusion criteria have been previously described.9

Patients who participated in the study were recruited at 50 clinical study sites located in the United States and Canada (see “Acknowledgment” section). The active drug was formulated to release 2, 4, or 6 mg of rotigotine during 24 hours (10-, 20-, and 30-cm² transdermal system size corresponding to the total drug content of 4.5, 9.0, and 13.5 mg, respectively). Placebo transdermal systems were identical in appearance and blinding was always fully maintained between active and placebo arms.

Patients were assessed for enrollment eligibility at the beginning of the pretreatment phase (Figure 1). Screening assessments included routine clinical laboratory evaluations (standard 12-lead electrocardiography, hematologic analysis, serum chemistry, and urinalysis) and neurological examinations (Hoehn and Yahr staging, Clinical Global Impression Scale, ESS, UPDRS, and physical examinations). After successful completion of all pretreatment requirements, patients were randomized 2:1 to receive either rotigotine or placebo at visit 2, at which time they were given rotigotine (2 mg/24 h) or placebo transdermal systems. During each of the successive 3 weeks, patient doses were titrated to an optimal daily dose per day by using transdermal systems of increasing size: 2, 4, or 6 mg/24 h (10, 20, or 30 cm², respectively). The maximum dose was 6 mg/d. If necessary, patients were allowed to “backtitrate” to the previous week’s dose. After the titration phase, patients began a 24-week maintenance phase. A withdrawal procedure and
Patients were randomized into the placebo group, and 255 patients received placebo. Ninety-nine patients in the study.

EQ-5D composite Health State Score. These 5 dimensions are further captured using the self-care, usual activities, pain/discomfort, and anxiety/depression dimensions according to the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These 5 dimensions are further captured using the EQ-5D composite Health State Score.

**SAFETY MEASUREMENTS**

Safety measurements included changes in vital signs, body weight, electrocardiogram readings, clinical laboratory values, findings at physical and neurological examinations, and adverse events, as reported spontaneously by the subject or observed by the investigator during the double-blind part of the trial. The severity (intensity), outcome, and cause of each reported adverse event were assessed and recorded. Severe application site reactions, somnolence, and severe cardiac arrhythmias, as well as any serious adverse events, were immediately reported to the study sponsor.

**DATA ANALYSIS**

The primary variable was the responder status at the end of the maintenance phase. A responder was a subject with a 20% decrease or greater in the sum of scores from the activities of daily living and motor examination components of the UPDRS (parts II and III) from the baseline visit to the end of the double-blind maintenance phase. The alternative hypothesis that the percentages in the 2 treatment groups differ (ie, rotigotine superior to placebo) was tested using asymptotic normal approximation methods against the null hypothesis that the proportion of responders is the same for both groups. Missing data were imputed by last observation carried forward.

The sample size calculation was based on the response end point. It was assumed that an absolute difference of 4 points in motor UPDRS score between active and placebo groups was clinically meaningful, as suggested by findings of previous studies, although a 3-point difference was considered a minimally clinically important change. The study was powered based on a higher anticipated effect of the new treatment. If we assume response rates of a maximum of 30% for placebo and a minimum of 50% for rotigotine continuous dopaminergic stimulation, a sample size of 160 subjects in the active group and 80 subjects in the placebo group (2:1 randomization) is sufficient to detect a statistically significant difference in response rates between the 2 groups, with a power of at least 80% using a 2-sided 5% Fisher exact test. The testing for secondary end points was performed in an exploratory manner by presenting P values, 95% confidence intervals, or both.

**RESULTS**

**DEMOGRAPHIC CHARACTERISTICS**

A total of 277 patients were randomly assigned to receive rotigotine treatment or placebo. Ninety-seven percent of patients in the rotigotine group and 96% in the placebo group were white, and 60% and 68% of patients in the placebo and rotigotine treatment groups, respectively, were men. On average, patients had received a diagnosis of PD less than 18 months (range, 0-6 years) before enrollment. Between treatment groups, similar percentages of subjects prematurely discontinued the study. Patient disposition is shown in Figure 2 and demographic data are given in Table 1.

Patients were exposed to rotigotine for a mean (SD) of 172 (52.8) days (range, 2-243 days) and to placebo for a mean (SD) of 176 (50.7) days (range, 2-224 days). The mean (SD) rotigotine dose was 5.7 (0.84) mg/24 h (range, 2-6 mg/24 h; n = 180).

**Figure 2.** Flowchart shows the disposition (enrollment and treatment) of patients in the study. *Completed the trial is defined as receiving the full 24 weeks of maintenance-phase medication.
EFFICACY END POINTS

Significant differences were observed between the rotigotine and placebo groups for the 20% responder rate (48% for rotigotine and 19% for placebo; P < .001). Statistically significant differences were observed between rotigotine and placebo treatment for changes from baseline to the end of the maintenance phase as improvement in UPDRS subtotal (parts II and III) score (P < .001), percentage changes in UPDRS subtotal (parts II and III) score (P < .001), and UPDRS part II (P < .002) and part III (P < .001) scores compared with the placebo group (Table 2 and Figure 3). Although the study was not powered to demonstrate this end point, the percentage reduction in UPDRS II plus III scores remained relatively constant during the first 8 weeks of the mainte-

nance phase and gradually diminished with time to the end of the observational safety period (Figure 3). Compared with baseline, at the end of the maintenance phase, patients receiving rotigotine experienced a mean reduction of 15% in UPDRS parts II and III subscores compared with an increase of 7.3% in patients receiving placebo (P < .002; Table 2).

At the end of the maintenance phase, a significantly higher overall percentage of patients completing the trial who were treated with rotigotine (n = 180) than those treated with placebo (n = 96) showed clinical improvement on the Clinical Global Impression Scale (57% vs 30%; P < .001; Figure 4). The percentage of patients considered moderately to markedly ill decreased from 23% to 20% for patients treated with rotigotine (P > .05) and increased from 24% to 32% for patients assigned to the placebo arm (P < .05).

Mean (SD) prolactin serum concentrations decreased from 6.8 (3.54) ng/mL at baseline to 5.0 (5.22) ng/mL by the end of the maintenance phase after treat-
ment with the 6 mg/24 h rotigotine transdermal system. During the maintenance phase, mean (SD) prolactin serum levels were 4.8 (4.08) to 5.4 (5.49) ng/mL in the rotigotine group. In the placebo group, mean (SD) prolactin levels were 6.6 (2.83) ng/mL and did not significantly change during the maintenance phase (6.4 [2.59] ng/mL vs 7.7 [3.69] ng/mL).

Mean (SD) rotigotine plasma concentrations increased proportionally to the dose during the titration phase up to 0.76 (0.43) ng/mL at a dose of 6 mg/24 h. Mean plasma concentrations remained stable throughout the maintenance phase. There was no relevant difference in rotigotine plasma concentrations determined before transdermal system removal and 1 to 4 hours after application of a new transdermal system.

At the end of the maintenance phase, the rotigotine group showed slight, statistically nonsignificant improvements from baseline in the EQ-5D QOL Index and the EQ-5D Health State Score. The mean level of QOL (EQ-5D Index) in the rotigotine group at the end of the treatment phase was 0.83 (range, 0.31-1.00; P>.05), which indicates a high level of QOL. The placebo group showed deterioration in both QOL measures, with a mean QOL index of 0.77 (range, 0.38-1.00), and a decrease in Health State Score, which was statistically significant compared with baseline (P=.04).

SAFETY EVALUATIONS

The 3 most common adverse effects of rotigotine compared with placebo were application site reaction (44% vs 12%), nausea (41% vs 17%), and somnolence (33% vs 20% (Table 3). Typical dopaminergic adverse events (eg, hallucinations, confusion, and leg edema) occurred at similar rates in both groups. Orthostatic hypotension was reported in 2% (n=4) of rotigotine-treated patients and 4% (n=4) of placebo-treated patients. Application site reactions were usually mild to moderate and none were serious or persistent. They led to discontinuation in only 5% (n=9) of patients receiving rotigotine. Most (73%) of the patients who reported an application site reaction elected to participate in the open-label extension phase of the trial.

Mean baseline ESS scores in both groups (full-analysis set) were within the normal range (<10), although there was wide interindividual variation (rotigotine, 0-19; placebo, 0-17). At the end of the maintenance phase, mean (SD) ESS scores increased by 0.83 (0.24) points in the rotigotine group (n=141) and decreased by 0.26 (0.31) points in the placebo group (n=81; P=.005). Mean (SD) ESS scores at the end of maintenance were 6.6 (4.0; range, 0-17) for rotigotine and 5.8 (3.2; range, 0-15) for placebo (P=.005).

In the rotigotine group, no clinically relevant changes or apparent trends were observed in mean changes from baseline for body weight, heart rate, blood pressure, clinical laboratory values, or findings at physical examination. A marginal increase (±3 beats/min) in median heart rate was observed with rotigotine treatment, which diminished with time. The incidence of orthostatic hypotension was slightly lower with rotigotine (37%) than placebo (44%), as was the incidence of treatment-emergent clinically relevant abnormal electrocardiographic findings (rotigotine, 2%; placebo, 3%).

**Table 3. Summary of the Most Common Treatment-Emergent Adverse Events With an Incidence of 5% or Greater***

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rotigotine Group (n = 181)</th>
<th>Placebo Group (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site disorders</td>
<td>79 (44)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Accident, not otherwise specified</td>
<td>14 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (8)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (2)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>2 (1)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>34 (19)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Headache</td>
<td>29 (16)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Tremor</td>
<td>11 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Parkinsonism aggravated</td>
<td>2 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>75 (41)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Skeletal pain</td>
<td>7 (4)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>60 (33)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (9)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Coughing</td>
<td>9 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (4)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (4)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (2)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.

Rotigotine consistently demonstrated statistically significant and clinically relevant efficacy over placebo in patients with early PD, as assessed by significantly greater improvement with time in the UPDRS subtotal scores (parts II and III) and UPDRS parts II and III individual scores. The initial maximum improvements after the end of the titration phase as measured by UPDRS scores diminished with time until the end of the 24-week maintenance phase in both groups. This can be explained by disease progression and loss of placebo effect. The absolute difference in UPDRS scores between placebo- and rotigotine-treated patients increased with time, and rotigotine-treated patients maintained improvements during 24 weeks of treatment compared with baseline. These beneficial effects are also reflected by the physician’s rating of clinical global impression in most patients treated with the rotigotine transdermal system.

Transdermal drug delivery may offer a therapeutic approach capable of providing a more convenient method of constant dopaminergic stimulation, possibly preventing or delaying the development of motor complications, as demonstrated in preclinical studies. The duration of our 6-month trial was not sufficient to test this hypothesis. However, the long-term data of the ongoing open-label extension phase of this trial may provide use-
ful observations. A total of 95% of the patients who completed the maintenance phase of the trial elected to continue into the open-label phase.

Mean rotigotine plasma concentrations increased with dose during the titration phase and remained stable during the maintenance phase. Thus, the rotigotine transdermal system, as a once-daily medication for PD, provides the basis for continuous dopaminergic stimulation for 6 months.

There are several advantages of the rotigotine transdermal system over conventional orally delivered dopaminergic therapy. The transdermal system can be applied by the patient at any time of the day or night independent of mealtimes. Because it is dosed once daily, it has the potential for increasing compliance over oral treatments that are taken multiple times per day with water.

The QOL in patients with PD decreases as the disease progresses, as shown in the study's placebo group by the measured decrease in mean EQ-5D score through the maintenance phase compared with baseline. Well-controlled studies of QOL in patients with PD receiving pharmacotherapy are rare. However, rotigotine treatment enabled patients to maintain a stable, high level of QOL as shown by the EQ-5D Index and the EQ-5D Health State Score. The secondary findings in this trial indicate that rotigotine treatment favorably affected QOL in patients with early PD.

The rotigotine transdermal system was well tolerated at doses up to 6 mg/24 h even though 25 patients in the rotigotine group and 6 patients in the placebo group withdrew because of adverse events. The adverse events observed in our study were similar to those found in other studies of dopamine agonists and presumably reflect effects of dopamine agonist therapy in patients with early PD with the exception of application site reactions, which were usually mild to moderate and transient. Leg edema, a common complication of oral dopamine, however, did not occur any more frequently in the rotigotine group compared with the placebo group in this trial. The observed association of rotigotine with an increase, albeit slight, in subjective sleepiness (ESS score) was not unexpected because dopamine agonists are known contributors to daytime somnolence in patients with PD. In conclusion, this double-blind, placebo-controlled trial provides evidence that the rotigotine transdermal system is effective and well tolerated in patients with early PD when titrated to a dose of 6 mg/24 h.

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