Ropinirole for the Treatment of Early Parkinson Disease

A 12-Month Experience

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Objective: To evaluate ropinirole hydrochloride as dopaminergic monotherapy in patients with early Parkinson disease.

Design: A 6-month extension of a double-blind, placebo-controlled study.

Setting: Ambulatory care at 22 different sites in the United States.

Patients: Patients who successfully completed the initial 6-month study could enter the 6-month extension study (ropinirole, n = 70; placebo, n = 77).

Intervention: Use of ropinirole or placebo therapy.

Main Outcome Measures: The efficacy variables were the number of patients who successfully completed the 12-month study and did not require supplemental levodopa, the number of patients requiring supplemental levodopa, and the proportion of patients having an insufficient therapeutic response.

Results: Significantly fewer ropinirole-treated patients met criteria for insufficient therapeutic response (23 [19.8%] of 116) or required the initiation of levodopa therapy (22 [19%] of 116) compared with placebo-treated patients (60 [48%] of 125 patients for insufficient therapeutic response; 57 [45.6%] of 125 patients for additional levodopa). Significantly more ropinirole-treated patients (51 [44.0%] of 116) successfully completed the 12-month study and did not require supplemental levodopa compared with placebo-treated patients (28 [22.4%] of 125). The incidence of adverse experiences and patient withdrawals was low.

Conclusion: Ropinirole was effective and well tolerated as monotherapy for 12 months in patients with early Parkinson disease.

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LEVODOPA is the cornerstone of symptomatic therapy for Parkinson disease (PD). Long-term use of levodopa, however, is complicated by the potential development of dyskinesia and fluctuations in efficacy. The use of alternate therapies, such as dopamine agonists, in the initial treatment of patients with early PD has been investigated. There is an interest in the use of early dopaminergic agonist monotherapy to delay the initiation of levodopa therapy because this may be associated with fewer motor complications and improved long-term outcome.

Ropinirole hydrochloride, a nonergoline dopamine (D2) receptor agonist, has been shown to be effective in controlling motor symptoms in patients with early PD and is generally well tolerated. The results of a double-blind, placebo-controlled study of 6 months’ duration in patients with early PD were previously reported. Patients treated with ropinirole therapy demonstrated significant improvement in motor function as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) motor examination. Patients who completed the initial 6-month clinical study could elect to enter a 6-month, double-blind, placebo-controlled extension study. This extension study was undertaken to further assess the efficacy and safety of ropinirole use in patients with early PD during a 12-month period.

A total of 184 of 241 patients successfully completed the initial 6-month study: 79 of 116 patients in the ropinirole-treated group and 105 of 125 patients in the placebo-treated group. Thirty-seven ropinirole-treated patients (31.9%) withdrew from the initial study compared with placebo-treated patients (20 [16.0%] of 125). The leading cause of withdrawal in
METHODS

This was a multicenter (22 sites), double-blind, placebo-controlled 6-month extension of a 6-month study to evaluate the long-term efficacy and safety of ropinirole use in patients with early PD (Hoehn and Yahr stages I-III). All patients had motor symptoms of sufficient severity to warrant the introduction of dopaminergic therapy, but had not received levodopa or any dopaminergic agonist for more than 6 weeks prior to entry into the initial 6-month study. Patients who satisfactorily completed the initial 6-month study were eligible for enrollment in the 6-month extension study; included patients may have received symptomatic therapy with levodopa during the initial 6-month study. Use of anticholinergic therapy and amantadine hydrochloride were not permitted. Patients entering the initial 6-month study on a regimen of selegiline hydrochloride were required to remain on a stable dose of selegiline for 4 weeks prior to study entry and for the duration of either study.

Exclusion criteria included the following: history of severe systemic disease; history of severe dizziness or fainting; diastolic blood pressure higher than 110 mm Hg; history of major psychosis or dementia; crippling degenerative arthritis or limb amputations; recent history of alcohol or drug dependence; neurologic disorders other than PD; and treatment with vasodilators, antiarrhythmics, digoxin, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, or other antihypertensive agents (excluding diuretics).

After written informed consent was obtained, patients who elected to enter the 6-month extension study were reassessed. Assessments included vital signs, clinical laboratory tests (hematology, blood chemistry, and urinalysis), and adverse experiences. Study visits were scheduled on a monthly basis for a total study duration of 6 months. Patients were evaluated at each study visit using the Clinical Global Impression Scale. Recording of vital signs and adverse experiences was also performed at each study visit. Clinical laboratory testing and a complete UPDRS were performed at month 3 and month 6. Electrocardiography and physical examination were performed at the last study visit (week 48).

All eligible patients who elected to participate in the 6-month extension study continued to receive double-blind study medication regimen with no interruption. Medication use could be titrated upward or downward at weekly intervals (minimum dose, 1 mg 3 times daily; maximum dose, 8 mg 3 times daily) to maintain therapeutic benefit throughout the 6-month extension study. Study medication was administered with or immediately after meals.

If adequate symptomatic control was not achieved with the highest tolerated dose level of study medication, patients were administered a combination product of carbidopa and levodopa (Sinemet or Sinemet CR, Merck & Co Inc, DuPont Pharma, Wilmington, Del) while continuing to receive blinded study medication for the duration of the 6-month extension study. The dose level of levodopa could be adjusted as necessary. A UPDRS motor examination was performed immediately before initiating levodopa therapy.

Study medication was tapered over 7 days for all patients at the end of the 6-month extension study. Alternative therapy (levodopa, other dopamine agonists, or anticholinergic agents) could be introduced during the tapering period. All patients returned for a follow-up visit 7 to 10 days following the start of the tapering period. Compliance with study medication and adverse experiences were assessed at this visit.

EFFICACY VARIABLES

The primary efficacy variable was the number and percentage of patients who were receiving monotherapy for the entire 12-month study (initial 6-month study and 6-month extension study) and did not require levodopa therapy. Other efficacy variables included the proportion of patients designated as having an insufficient therapeutic response (ITR), defined as the initiation of levodopa therapy or withdrawal from the initial 6-month study or the 6-month extension study because of lack of efficacy; and the proportion of patients requiring additional symptomatic therapy with levodopa.

SAFETY AND TOLERABILITY

All patients who elected to enter the 6-month extension study were included in the safety evaluation. Safety and tolerability were assessed by monitoring and reporting adverse experiences, vital signs, and clinical laboratory evaluations. All adverse experiences were coded from the verbatim term according to the World Health Organization Adverse Reaction Terminology dictionary by body system and preferred term.

STATISTICAL ANALYSIS

Statistical analyses were performed on the intention-to-treat population, defined as all randomized patients who had at least 1 efficacy assessment in the initial 6-month study. Patients who successfully completed the initial 6-month study could elect to enter the extension study. Hypothesis testing was carried out at the 5% level of significance (P < .05). A 2-tailed χ² test with no adjustment for center, selegiline strata, or other baseline covariates was used to compare the 2 treatment groups for the number of patients with ITR and for the subset of patients who required additional symptomatic therapy with levodopa. In addition, a 2-tailed χ² test was used to compare the 2 treatment groups for the number of patients who successfully completed the 12-month study and did not require additional symptomatic therapy with levodopa. Treatment differences for these variables were presented with an estimate of the treatment odds ratio and the corresponding 95% confidence intervals (CIs). The odds ratio was based on the odds of being a responder in the ropinirole-treated group relative to the odds of being a responder in the placebo group. Therefore, an odds ratio of 1.0 indicates no difference in response rates. The difference in the proportion of responders in the 2 treatment groups was statistically significant (P < .05) at the 5% level if the corresponding 95% CI did not include 1.0. Heterogeneity between treatment groups was formally tested using the Breslow-Day statistic.
both treatment groups was attributable to adverse experiences (27 [23.3%] of 116 ropinirole-treated patients and 13 [10.4%] of 125 in the placebo-treated group). Of 184 patients who completed the initial 6-month study, 147 elected to enter the 6-month extension study (70 in the ropinirole-treated group and 77 in the placebo-treated group). Although a greater percentage of patients in the placebo-treated group (84%) completed the initial 6-month study compared with the ropinirole-treated group (68%), a greater percentage of ropinirole-treated patients (70 [88.6%] of 79) elected to enter the 6-month extension study compared with the placebo-treated group (69 [55%] of 125) (Table 1). A similar percentage of patients completing 12 months of therapy was observed in both treatment groups (65 [56%] of 116 in the ropinirole-treated group and 69 [55%] of 125 in the placebo-treated group).

Adverse experiences led to the withdrawal of 7 patients (3 patients [4.3%] in the ropinirole-treated group and 4 patients [3.2%] in the placebo-treated group) from the 6-month extension study. None of these patients had received levodopa therapy. No other reason (ie, lack of medication efficacy) compared with the placebo-treated group.

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The proportion of patients who received monotherapy for 12 months, without requiring additional symptom-atic therapy with levodopa, was twice as great in the ropinirole-treated group (51 [44%] of 116) than in the placebo-treated group (28 [22.4%] of 125) (Table 3). This difference was statistically significant (odds ratio, 2.7; 95% CI, 1.5-4.7; P<.001).

In both the initial 6-month study and the 6-month extension study, significantly fewer patients in the ropinirole-treated group met the criteria for ITR (receiving supplemental levodopa or withdrawn due to lack of medication efficacy) compared with the placebo-treated group. During the initial 6-month study, 14
(12%) of 116 ropinirole-treated patients met the criteria for ITR compared with 37 (30%) of 125 placebo-treated patients. At the end of the 12-month treatment period, significantly fewer patients in the ropinirole-treated group (23 [19.8%] of 116) met the criteria for ITR compared with those in the placebo-treated group (57 [45.6%] of 125) (P < .001).

Most patients who met the criteria for ITR in the extension study received additional symptomatic therapy with levodopa. Only 4 patients (1 treated with ropinirole and 3 treated with placebo) who met the criteria for ITR were withdrawn due to lack of medication efficacy. The proportion of patients who required levodopa for additional symptomatic relief was measured after the initial 6-month study (week 24), and after the 6-month extension study (week 48).

During the 6-month extension study, 9 (13%) of 70 ropinirole-treated patients required levodopa therapy compared with 21 (27.3%) of 77 placebo-treated patients. At the end of 12 months, fewer patients in the ropinirole-treated group (22 [19.0%] of 116) required additional symptomatic therapy with levodopa compared with patients in the placebo-treated group (57 [45.6%] of 125) (Table 3). This difference observed between ropinirole- and placebo-treated patients was statistically significant (odds ratio, 0.28; 95% CI, 0.1-0.5; P < .001). There was no significant interaction between selegiline strata and treatment for any of the efficacy variables.

Improvement in motor function was sustained for patients receiving a regimen of ropinirole alone during the entire 12-month treatment period. Although mean UPDRS motor score at baseline was slightly higher (worse) in the ropinirole-treated group (16.26) compared with the placebo group (13.56), ropinirole-treated patients had lower mean motor scores at week 24 (9.44) and week 48 (10.87) compared with placebo-treated patients (12.86 at week 24 and 14.96 at week 48) (Figure 1). A higher percentage of patients receiving a regimen of ropinirole alone during the 12-month treatment period were rated as very much improved or much improved (scores of 1 or 2 on the Clinical Global Impression global improvement item) at week 24 (66%) compared with placebo-treated patients (32.1% at week 24 and 17.9% at week 48) (Figure 2).

SAFETY AND TOLERABILITY

A total of 137 (93.2%) of 147 patients who elected to enter the 6-month extension study reported adverse experiences that occurred in or were ongoing at the start of the 6-month extension study. Within this group, a total of 127 patients (64 receiving ropinirole and 63, placebo) reported 1 or more emergent adverse experiences (first occurring or becoming more severe) during the 6-
Duration of levodopa therapy and severity of disease are often associated with adverse effects such as dyskinesia and motor response fluctuations, both of which are disabling and cause major management problems throughout the course of the disease. The use of dopamine agonists in patients with early PD may provide symptomatic improvement and delay the introduction of levodopa therapy. 

Our study is a 6-month extension of a 6-month study that investigated the use of ropinirole in the treatment of patients with early PD. In the initial 6-month study, ropinirole monotherapy was both effective and generally well tolerated. Ropinirole-treated patients showed significant improvement in motor function, and significantly fewer ropinirole-treated patients required supplemental levodopa compared with the placebo-treated patients. In the 6-month extension study, treatment with ropinirole continued to provide therapeutic benefit in patients with early PD. A significantly lower percentage of ropinirole-treated patients met the criteria for ITR or required additional symptomatic therapy with levodopa compared with the placebo-treated patients.

When the entire 12-month study (initial 6-month study and 6-month extension study) was assessed, ropinirole-treated patients continued to demonstrate sustained improvement in UPDRS total motor and Clinical Global Impression scores. Because only a small percentage of ropinirole-treated patients required additional symptomatic therapy with levodopa during the entire 12 months, it seems reasonable to consider the use of ropinirole to delay the introduction of levodopa as part of a long-term levodopa-sparing strategy for managing patients with PD.

### Table 4. Emergent Adverse Experiences (Overall Incidence >5%)

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Ropinirole Hydrochloride-Treated Patients (n = 70)</th>
<th>Placebo-Treated Patients (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>9 (12.9)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (11.4)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (11.4)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (10.0)</td>
<td>8 (10.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (10.0)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (8.6)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (7.1)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>5 (7.1)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Tremor</td>
<td>4 (5.7)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (5.7)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Injury</td>
<td>4 (5.7)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (5.7)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (5.7)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (5.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>4 (5.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (5.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*Values are number (percentage).

### Table 5. Withdrawals in the 6-Month Initial Study and the 6-Month Extension Study*  

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Ropinirole Hydrochloride-Treated Patients</th>
<th>Placebo-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo initial study</td>
<td>n = 116</td>
<td>n = 125</td>
</tr>
<tr>
<td>Adverse experiences</td>
<td>27 (23.3)</td>
<td>13 (10.4)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>1 (0.9)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Protocol violation, including noncompliance</td>
<td>5 (4.3)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>4 (3.4)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>6-mo extension study</td>
<td>n = 70</td>
<td>n = 77</td>
</tr>
<tr>
<td>Adverse experiences</td>
<td>3 (4.3)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0 (0.0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>2 (2.9)</td>
<td>2 (2.6)</td>
</tr>
</tbody>
</table>

*Values are number (percentage).

[Table 4](#)

[Table 5](#)

**COMMENT**

In the initial 6-month study, the most frequently reported adverse experiences in both the ropinirole- and placebo-treated patients were nausea, dizziness, and somnolence. In the 6-month extension study, the most frequently reported adverse experiences were nausea, dizziness, and somnolence (Table 4). The frequency of these adverse experiences during the 6-month extension study remained low. The most frequent adverse experiences in the ropinirole-treated group were somnolence, dizziness, and arthralgia (Table 4). The incidence of nausea was low in both treatment groups (8.6% in the ropinirole-treated group and 2.6% in the placebo-treated group).

Central nervous system adverse experiences were infrequent in the initial 6-month study. In the 6-month extension study, a total of 9 patients (7 ropinirole-treated patients and 2 placebo-treated patients) reported adverse experiences that were classified as central nervous system events. The frequency of hallucinations remained low during the 6-month extension study (5 ropinirole-treated patients and 2 placebo-treated patients). Only 2 ropinirole-treated patients reported amnesia and confusion.

A total of 5 ropinirole-treated patients (7.1%) withdrew from the study compared with 8 placebo-treated patients (10.4%). The leading cause of withdrawal was attributable to adverse experiences. Lack of medication efficacy and other reasons in some cases resulted in premature withdrawal. A total of 7 patients (3 ropinirole-treated patients and 4 placebo-treated patients) were withdrawn from the study because of adverse experiences (Table 5). No single adverse experience led to the withdrawal of more than 1 patient. In the ropinirole-treated patients, withdrawals were due to nausea and vomiting (1 patient), myalgia (1 patient), and hallucinations (1 patient). In the placebo-treated group, patients withdrew because of cardiac failure and myocardial infarction (1 patient), dizziness (1 patient), angina pectoris (1 patient), and nonspecific neoplasm (1 patient). Three of 7 patients were withdrawn because of serious adverse experiences unrelated to study medication: 1 ropinirole-treated patient (hospitalized and diagnosed as having mastitis) and 2 placebo-treated patients (both hospitalized, 1 because of worsening congestive heart failure and 1 diagnosed as having colon carcinoma). No deaths occurred during the 6-month extension study. No differences were observed in vital signs or laboratory parameters of potential clinical concern.
Ropinirole continued to be well tolerated in patients with early PD during the 6-month extension study. There was a low incidence of emergent adverse experiences, and few patients withdrew because of adverse experiences. Somnolence and dizziness, the most common adverse experiences, are expected peripheral dopaminergic effects of dopamine agonists.1,4,18 The incidence of neuropsychiatric adverse experiences was also reasonable; hallucinations were reported in both treatment groups (7.1% of ropinirole-treated patients; 2.6% of placebo-treated patients).

In conclusion, 12-month treatment with ropinirole continued to provide effective symptomatic control in patients with early PD and was generally well tolerated. Ropinirole-treated patients continued to do well over the 6-month extension study without initiation of levodopa therapy. Overall, the number of patients who successfully completed the 12-month study and did not receive additional symptomatic therapy with levodopa was much greater for the ropinirole-treated group compared with the placebo-treated group. These results extend the findings of the initial 6-month study,19 and support the use of ropinirole as an effective initial option for the treatment of patients with early PD.

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REFERENCES


