Long-Term Selegiline Monotherapy for the Treatment of Early Parkinson Disease

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Objectives: The aim of this open-label study was to investigate the long-term safety and efficacy of selegiline as monotherapy in Japanese patients with early Parkinson disease (PD).

Methods: We conducted a 56-week prospective study in patients with early PD (N = 134) who had previously completed the randomized, double-blind, placebo-controlled phase III trial of selegiline monotherapy for 12 weeks. In the present study, dosing was titrated from 2.5 to 10 mg/d in increments of 2.5 mg/d for 2 weeks. From the seventh week, the dosage was maintained at 10 mg/d until week 56. The primary outcome was any change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score (part I + II + III) from baseline. Secondary outcomes, including changes in the UPDRS subscores and safety profile, were also evaluated.

Results: Ninety-one (67.9%) patients completed the 56-week study. Treatment with selegiline significantly reduced total UPDRS score from week 4 (mean ± SD, −2.62 ± 3.83; P < 0.0001) to week 56 (−3.39 ± 9.27; P < 0.01). The peak effect was seen at week 20 (−5.79 ± 5.57; P < 0.0001). In addition, we found similar improvements in the UPDRS parts II and III scores. The incidence rate of adverse drug reactions was 44.3% (58 patients) and did not increase during the period of 10 mg selegiline administration.

Conclusions: Long-term monotherapy with selegiline (10 mg/d) was effective and well tolerated in patients with early PD in this 56-week study.

Key Words: Parkinson disease, selegiline, long-term study, monotherapy, side effects

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Currently, there is no cure for Parkinson disease (PD); however, medications and medical devices that control the symptoms are available. Medications, such as levodopa, dopamine agonists, and monoamine oxidase type B (MAO-B) inhibitors (selegiline or rasagiline), have been recommended for early treatment of de novo patients with PD. There is sufficient evidence of the safety and efficacy of long-term use of selegiline with or without levodopa. In Japan, selegiline was approved for combination use with levodopa at a recommended dose of 7.5 mg selegiline in 1998, and data on the safety and efficacy of the combination therapy have been accumulating to date. Selegiline has been approved as a monotherapy with a maximum dose of 10 mg in other countries, however not for patients with early PD in Japan, and its efficacy and safety have not been investigated. Therefore, we conducted a phase III trial and the present 56-week prospective study to evaluate the efficacy and safety of 10 mg selegiline as a monotherapy for Japanese patients in the early stages of PD. In this study, we report the results of the open-label, long-term (up to 56 weeks) study aimed at evaluating the efficacy and safety of selegiline monotherapy in patients with early PD.

MATERIALS AND METHODS

Patients

The eligibility criterion for the present open-label study was patients who had completed the previous double-blind phase III clinical trial, which included 292 patients with early PD who had been randomly assigned to receive placebo or selegiline treatment alone. In this long-term study, patients were enrolled if they could attend all scheduled visits, receive scheduled tests, and provide informed consent. Patients were excluded from the study if they had received any drugs contraindicated to selegiline, such as pethidine and tricyclic antidepressants, after the initiation of the phase III trial, or if they were women who were pregnant, lactating, or willing to become pregnant during the study. Some patients were also excluded due to negligence that was decided by the investigators. In addition, patients could not use other antiparkinsonian medications, including levodopa or contraindications to selegiline (such as pethidine), during the study.

Study Design

This was a 56-week, open-label, prospective study conducted from April 2012 to July 2014 at 42 clinical institutions in Japan in accordance with Good Clinical Practice. The study was approved by the institutional review boards according to the principles described in the Declaration of Helsinki.

Administration of selegiline was started at a dose of 2.5 mg/d and titrated up to 10 mg/d in increments of 2.5 mg/d for 2 weeks. From week 7, administration of selegiline was maintained at a dose of 10 mg/d until week 56. The daily regimen consisted of 2.5 mg after breakfast during weeks 1 to 2, 2.5 mg twice daily after breakfast and lunch during weeks 3 to 4, 5 mg after breakfast and 2.5 mg after lunch during weeks 5 to 6, and 5 mg twice daily after breakfast and lunch during weeks 7 to 56.

Outcome Measures

The primary outcome measure was any change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score (part I + II + III) from baseline. Secondary outcome measures included changes in (1) the UPDRS part II + III score, (2) any of the 4 UPDRS subscales from baseline, and (3) the proportion of responders who had achieved a greater than 20%, greater than
25%, or greater than 30% reduction in the total UPDRS scores at the final visit. In addition, we examined other secondary outcome measures, including modified Hoehn and Yahr (H/Y) stage at each visit, and Clinical Global Impression of Improvement (CGI-I) scores at week 28 and the final visit. Safety assessments were measured using the number of adverse events (AEs), vital signs, electrocardiogram results, and laboratory tests.

Post hoc analyses included changes in UPDRS-tremor (items 16, 20, and 21; range, 0–32), UPDRS-rigidity (item 22; range, 0–20), UPDRS-bradykinesia (items 23–26 and 31; range, 0–36), and UPDRS–postural instability and gait disturbances (PIGD) (items 13–15, 29, and 30; range, 0–20) scores. Further post hoc analyses were conducted on the integrative data from the phase III trial and this long-term study with respect to changes in the total UPDRS score.

Statistical Analysis
Statistical analyses were performed using SAS software 9.2 (TS2M3, SAS Institute Inc, Cary, North Carolina).15 All efficacy analyses were performed on the full analysis set, which included all subjects who had received at least 1 dose of selegiline and had recorded at least 1 posttreatment efficacy measurement. If there were any missing values, the last observation carried forward imputation method was applied. All the safety analyses were conducted on the safety population, which included patients who had received at least 1 dose of selegiline and recorded at least 1 safety measurement. The primary and secondary efficacy measurements from all study visits (except the modified H/Y scale, CGI-I, and a proportion of responders) were compared with measurements at baseline using the Dunnett test.16 Measurements at the final visit were compared using paired t tests. The modified H/Y stage and CGI-I scores were indicated with numbers and percentages of patients in the respective categories. In the post hoc integrative data analyses, total UPDRS score at baseline from the phase III trial was compared between groups using independent t tests. Differences in the changes from baseline in total UPDRS scores at week 12 in the phase III trial, or at week 0 in the present study, were evaluated between the phase III–placebo and phase III–selegiline groups by analysis of covariance. Results are expressed as mean ± SD, and a P value of <0.05 was considered to be statistically significant.

RESULTS

Population
One hundred thirty-six patients consented to take part in the study and were screened after completion of the phase III trial (Fig. 1). Two patients dropped out before their enrollment or initiation of the treatment. After initiation of the selegiline treatment, 43 patients were excluded because of the following reasons: disease progression (n = 16), participation refusal or consent withdrawal (n = 11), AEs (n = 5), contraindications (n = 4), and others (n = 7). As a whole, 67.9% (91/134) of patients completed the 56-week study (Fig. 2). The safety population and full analysis set analyses were performed on 131 patients, including those who had discontinued after initiation of the therapy. Three patients were excluded after the study due to Good Clinical Practice violation. The baseline characteristics of the patients are presented in

![Flowchart showing the screening, enrollment, and final numbers of patients in each group.](https://www.clinicalneuropharm.com)
Table 1. The mean total UPDRS score and modified H/Y stage of all patients included in this study were 23.2 ± 11.3 and 2.0 ± 0.6, respectively.

Efficacy

Selegiline monotherapy led to a significant reduction in total UPDRS score (the primary outcome measure) from week 4 (−2.62 ± 3.83; P < 0.0001) to week 56 (−3.39 ± 9.27; P < 0.01) or the final visit (−2.63 ± 8.32; 95% confidence interval, −4.071 to −1.183; P < 0.05) when compared with the baseline score (Fig. 3). A significant reduction in the primary outcome measure at week 4 was achieved with a selegiline dosage of 7.5 mg/d. After selegiline was titrated up to 10 mg/d, further reduction was observed at week 8 (−4.39 ± 4.76), with a peak effect seen at week 20 (−5.79 ± 5.57; P < 0.0001). A similar trend was observed for both UPDRS parts II and III scores; however, there was no significant decrease in UPDRS part I scores at all time points.

The proportion of responders who achieved a greater than 20%, greater than 25%, and greater than 30% reduction in total UPDRS scores were 45.4%, 40.8%, and 35.4%, respectively (Table 2). There was an increase in the proportion of patients with modified H/Y stage 0–2 from baseline (71.8%) to week 24 (79.5%), followed by a decrease from week 32 (79.2%) to the final evaluation (70.8%), which was similar to the primary outcome measure results (Fig. 4). There was an increase in the proportion of patients with modified H/Y stage 1 from baseline (14.5%) to week 56 (27.0%) or the final visit (22.3%). In contrast, there was no increase in the proportion of patients with modified H/Y stage 2.5, 3, 4, or 5 from baseline (28.2%) until week 56 (24.7%) or the final visit (29.2%). The changes in CGI-I score from baseline at week 28 or the final evaluation are reported in Figure 5. The combined proportion of patients rated as “very much improved” and “much improved” were 43.7% (52/119) and 31.7% (38/120) at week 28 and the final evaluation, respectively.

Post hoc analyses assessed the efficacy for each cardinal PD symptom with the UPDRS subscales (Fig. 6). There was a significant decrease in changes from baseline in the UPDRS-tremor score from week 4 (−0.481 ± 1.218; P < 0.0001) to the final visit (−0.447 ± 1.936; P < 0.05), except in week 56 (−0.421 ± 2.144). In addition, there were significant decreases in the changes from baseline in the UPDRS-rigidity score from week 4 (−0.58 ± 1.215;
P < 0.0001) to the final visit (−0.626 ± 1.903; P < 0.05), except in week 52 (−0.708 ± 2.191). We found significant decreases in the changes from baseline in the UPDRS-bradykinesia score from week 4 (−0.985 ± 1.784; P < 0.0001) to the final visit (−0.962 ± 3.004; P < 0.05). Finally, we found significant decreases in the changes in UPDRS-PIGD scores from baseline from week 4 (−0.229 ± 0.819; P < 0.01) to week 20 (−0.397 ± 1.054; P < 0.05). The maximum effect in these 4 items was observed at week 20 (Fig. 6), which was in line with the maximum effect found in the total UPDRS, UPDRS part II, and UPDRS part III scores (Fig. 3).

We implemented this study with patients who had completed the phase III trial and performed the integrative data analyses on these studies as post hoc analyses (Fig. 7). We analyzed 131 patients in the long-term study that were randomly allocated to the placebo (n = 63) or selegiline (phase III–selegiline, n = 68) groups from the phase III trial. The washout periods of the phase III–placebo and phase III–selegiline groups were 18.89 ± 9.30 (range, 6–63 days; median, 15 days) and 18.51 ± 10.65 (range, 8–85 days; median, 15 days), respectively.

The total UPDRS scores of the phase III–selegiline and phase III–placebo groups at baseline were 25.66 ± 10.15 and 24.86 ± 10.71, respectively (P = 0.6596). At week 12 in the phase III trial, there was a significantly greater change from baseline in the total UPDRS score of the phase III–selegiline group (−7.07 ± 7.73, n = 67) compared with the phase III–placebo group (−3.98 ± 6.24, n = 63), as shown in Figure 7 (P = 0.0151). At the end of the phase III washout period, there was a significant difference in the change from baseline in the total UPDRS score between the phase III–selegiline (−3.71 ± 5.82, n = 68) and phase III–placebo (−0.33 ± 4.91, n = 63; P = 0.0006) groups. Furthermore, this difference remained until week 28 of the selegiline treatment, but not up to week 56 (Fig. 7).

**Safety**

The incidence rate of adverse drug reactions (ADRs) was 44.3% (58/131 patients). Adverse drug reactions with an incidence rate of 2% or greater are shown in Table 3. The most common ADRs were insomnia (5.3%, 7/131), constipation (4.6%, 6/131), increased blood creatine kinase (3.8%, 5/131), back pain (3.1%, 4/131), hypertension (3.1%, 4/131), vomiting (2.3%, 3/131), falls (2.3%, 3/131), decreased white blood cell count (2.3%, 3/131), somnolence (2.3%, 3/131), and orthostatic hypotension (2.3%, 3/131). Adverse drug reaction incidence rates did not increase during the administration of 10 mg selegiline (weeks 9–56; Table 4). Five patients discontinued treatment because of the following AEs: anxiety disorder (n = 1), rash (n = 1), hallucinations (grade 2; n = 1), disturbances in attention (grade 3; n = 1), and sudden death (grade 5; n = 1). Death and other serious AEs were observed in 6 patients [including the sudden death noted above that led to treatment discontinuation; loss of consciousness

<table>
<thead>
<tr>
<th>Reduction in the Total UPDRS</th>
<th>Responder</th>
<th>Nonresponder</th>
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<tbody>
<tr>
<td>≥20%</td>
<td>59 (45.4)</td>
<td>71 (54.6)</td>
</tr>
<tr>
<td>≥25%</td>
<td>53 (40.8)</td>
<td>77 (59.2)</td>
</tr>
<tr>
<td>≥30%</td>
<td>46 (35.4)</td>
<td>84 (64.6)</td>
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</tbody>
</table>

Each value represents the number of patients (percentage). Patients evaluated: n = 130.
accompanying orthostatic hypotension (n = 1); thoracic compression fracture (n = 1); external inguinal hernia (n = 1); and stomach cancer (n = 1). All AEs, except sudden death and loss of consciousness accompanying orthostatic hypotension, were not attributed to selegiline. Any changes in medical measurements, such as laboratory tests, vital signs, and electrocardiogram, from baseline were not considered clinically meaningful.

**DISCUSSION**

Long-term treatment with 10 mg of selegiline increased efficacy up to week 56 in terms of the primary end point when compared with baseline scores, by relieving the typical symptoms of PD: tremor, rigidity, bradykinesia, and PIGD. Long-term treatment with 10 mg of selegiline was well tolerated, and there was no increase in ADRs in weeks 9 to 56. From 134 randomized patients, 91 (67.9%) completed the 56-week study. The efficacy and tolerability of 56 weeks of monotherapy with 10 mg selegiline in patients with early PD were comparable to the phase III double-blind, placebo-controlled trial of selegiline monotherapy in Japan14 or randomized placebo-controlled studies in other countries.8–10,12,13

In the present study, the maximum treatment effect, as measured by a 5.79-point reduction in total UPDRS score, was seen at week 20. Previous studies have reported that a greater than 3.5 point change in total UPDRS score has clinical importance17; the efficacy of selegiline in this long-term study is clinically important and statistically significant. A similar maximum change...
in total UPDRS score was reported in the selegiline-treated group in the prior phase III trial (6.26-point reduction at week 12), and with 600 mg levodopa in the ELLDOPA study (6-point reduction at week 24) in patients with early PD. Disease severity at baseline was evaluated according to the modified H/Y staging in these studies and was comparable to the mean modified H/Y stage at baseline in the present study. This result suggests that there are sufficient remaining dopaminergic neurons in selegiline-treated patients with early PD to induce vigorous dopaminergic activation compared with patients with advanced PD via MAO-B.

**FIGURE 6.** Mean changes in cardinal symptoms from baseline as measured by the UPDRS score. Cardinal symptoms: tremor, rigidity, bradykinesia, and postural instability/gait disturbance. A, Mean changes in UPDRS tremor–related score. B, Mean changes in UPDRS rigidity–related score. C, Mean changes in UPDRS bradykinesia–related score. D, Mean changes in UPDRS postural instability/gait disturbance–related score. Data are expressed as mean ± SD (N = 131). Statistically significant versus baseline *P < 0.05, †P < 0.01, ‡P < 0.001, §P < 0.0001 by Dunnett test, ¶P < 0.05 by paired t test.

**FIGURE 7.** Mean changes in the total UPDRS scores from baseline in the phase III and long-term study. Phase III–placebo, n = 63; phase III–selegiline, n = 68. There were significant differences in changes from baseline in total UPDRS score at week 12 of the phase III trial between the phase III–selegiline and phase III–placebo groups: *P < 0.05, at week 0 of the long-term study; †P < 0.01 (analysis of covariance). The mean washout periods were 18.51 ± 10.65 (phase III–selegiline) and 18.89 ± 9.30 (phase III–placebo). Data are expressed as mean ± SD.
TABLE 3. Common ADRs With an Incidence of ≥2%

<table>
<thead>
<tr>
<th>Patients Evaluated: n = 131</th>
<th>≥2% ADRs</th>
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<tbody>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
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<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
</tr>
<tr>
<td>Blood examination results</td>
<td>7</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>12</td>
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<tr>
<td>White blood cell count decreased</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>3</td>
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inhibition, leading to an improvement of motor functions. This interpretation is supported by the PD MED pragmatically randomized trial in patients with early PD, which suggests that MAO-B inhibitors are as effective as dopamine agonists, based on Parkinson’s disease Questionnaire-39 evaluation. Together, our results have shown that selegiline monotherapy is an effective treatment option for patients with early PD.

In the present study, we observed a significant improvement in total UPDRS score (Fig. 3A) and 4 major motor symptoms (Fig. 6) at week 4, and further improvements from week 4 to 8. Notably, a similar improvement pattern was observed in the phase III trial with the same parameters. These results clearly indicate that treatment with selegiline produces a dose-dependent improvement in a total UPDRS score. We applied a “forced titration” design in this study; therefore, it remains unclear whether the long-term administration of smaller doses of selegiline is less effective, as measured by total UPDRS score.

The incidence rates of ADRs associated with selegiline treatment did not increase during administration of 10 mg selegiline in this study (weeks 9–56; Table 3), indicating that the ADRs were not influenced by medication duration. In the present study, the most common ADRs were insomnia (5.3%, 7/131), constipation (4.6%, 6/131), increases in blood creatine kinase (3.8%, 5/131), back pain (3.1%, 4/131), hypertension (3.1%, 4/131), vomiting (2.3%, 3/131), falls (2.3%, 3/131), decreases in white blood cell counts (2.3%, 3/131), somnolence (2.3%, 3/131), orthostatic hypotension (2.3%, 3/131), dizziness (1.5%, 2/131), nausea (1.5%, 2/131), dry mouth (1.5%, 2/131), headache (none/131), fatigue (none/131), and anxiety (none/131). The deprenyl and toecopherol antioxidative therapy of parkinsonism study revealed selegiline-associated ADRs (22%; median administration period, 719 days) were elevated alanine aminotransferase (7.8%, 31/399), muscle-skeletal injury (7.3%, 29/399), elevated aspartate aminotransferase (7.0%, 28/399), nausea (2.0%, 8/399), and cardiac arrhythmia (2.0%, 8/399). Pålhagen et al. reported that the most common ADRs associated with selegiline treatment (median administration period, 12.7 months) were gastrointestinal adverse reactions (dry mouth, cholecystitis, flatulence, gastrointestinal discomfort, nausea, and diarrhea; 14.8%, 12/81). Data from long-term double-blind studies using selegiline monotherapy in patients with early PD from Europe and the United States reported the most common ADRs were insomnia (10.9%, 20/183), dizziness (9.3%, 17/183), nausea (6.0%, 11/183), headache (5.5%, 10/183), fatigue (1.6%, 3/183), dry mouth (1.6%, 3/183), and anxiety (0.5%, 1/183). The incidence rates of ADRs in the selegiline group were not significantly different from those of the placebo group; however, the reason underlying the differences in ADR profiles between studies has not been elucidated. Nonetheless, individual ADR incidence rates in our study were relatively low and similar to other studies, including 1 study that reported accumulated ADRs and suggested positive tolerability of selegiline. Consequently, the long-term monotherapy of selegiline for early PD is reported as safe in the US and European studies. In line with this, we consider that 10 mg selegiline is well tolerated for long-term use in Japanese patients with early PD.

Post hoc integrative analyses of the phase III trial data and the present study revealed that the phase III–selegiline group had a significantly lower total UPDRS score compared with the phase III–placebo group (P = 0.0006) at the end of the drug washout period (median, 15 days). This indicated that selegiline may have sustained efficacy in patients with early PD. We speculated that this might be due to neuronal plasticity and as its symptomatic effects associated with dopamine augmentation via MAO-B inhibition. The differences in score between groups at the end of the drug washout period gradually reduced and then disappeared; however, post hoc analysis showed sustained symptomatic effects of selegiline, but we could not determine any disease-modifying or neuroprotective effects. Therefore, additional long-term, double-blind studies are required to clarify the disease-modifying effect of selegiline.

The limitation of this study resides in its open-label study design, which does not include a parallel, randomized, control

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**TABLE 4. Incidence of AEs and ADRs During Different Periods**

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<tbody>
<tr>
<td>Type of events</td>
<td>AE</td>
<td>ADR</td>
<td>AE</td>
<td>ADR</td>
<td>AE</td>
<td>ADR</td>
<td>AE</td>
</tr>
<tr>
<td>No. AEs or ADRs</td>
<td>67</td>
<td>35</td>
<td>41</td>
<td>15</td>
<td>39</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>No. patients with AEs or ADRs</td>
<td>46</td>
<td>26</td>
<td>30</td>
<td>10</td>
<td>32</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Incidence rate, %</td>
<td>35.1</td>
<td>19.8</td>
<td>23.6</td>
<td>7.9</td>
<td>27.1</td>
<td>18.6</td>
<td>27.5</td>
</tr>
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arm. Nonetheless, we consider this study is important, as it showed the long-term safety of selegiline monotherapy in Japanese patients.

In conclusion, this study demonstrated that selegiline monotherapy was well tolerated and produced sustained symptomatic improvements in Japanese patients with early PD in this 52-week study.

ACKNOWLEDGMENTS

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REFERENCES


