Long-term Effects of Cabergoline and Levodopa in Japanese Patients with Early Parkinson’s Disease: A 5-Year Prospective Study

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Several international studies have suggested that treatment of early Parkinson’s disease (PD) with a dopamine agonist instead of levodopa delays the occurrence of motor complications. This 5-year prospective, open, multicenter randomized study aimed to compare the effects of cabergoline on the onset of motor complications with those of levodopa in Japanese patients with early PD. Patients who had never been treated with dopamine agonists or levodopa were enrolled in this study. Four of 45 patients in the cabergoline group and 11 of 46 patients in the levodopa group developed motor complications. The estimated cumulative incidence of motor complications in the cabergoline and levodopa groups was 17% and 34% (hazard ratio, 0.57; 95% confidence interval, 0.18–1.81; p = 0.347). Thirty-five adverse events (AEs) were reported in 24 patients in the cabergoline group, while 16 AEs were reported in 13 patients in the levodopa group. Patients in the cabergoline group showed fewer motor complications than did those in the levodopa group, although the difference was not statistically significant. However, the hazard ratio found in this study was similar to those in previous reports.

Key words: cabergoline, levodopa, Parkinson’s disease, motor complications

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disorder characterized by the classic motor symptoms of tremor, rigidity, bradykinesia, and postural instability. The annual incidence of PD in the Japanese population was 16.9/100,000 in 1997 [1]. In addition, the annual incidence was 1.8-fold higher in 2004 when compared with that in 1980 because of the aging of the population [2]. Although symptomatic therapy for PD is usually effective for several years, the disorder slowly progresses and finally results in impaired quality of life (QOL) with significant disability.

Since the 1960s, dopamine replacement therapy using levodopa has been the most effective choice of treatment for PD despite the development of motor complications like dyskinesia, wearing off, and on-off motor fluctuations after a few years of therapy [3]. Recently, initial therapy with a dopamine agonist has been proposed in patients with early PD [4] on the basis of reports demonstrating that initial therapy with a dopamine agonist, and not levodopa, delayed the onset of dyskinesia [5–7], wearing off, and on-off motor fluctuations [5–10] during long-term treatment.

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The PD treatment guidelines updated in 2002 suggested that either levodopa or a dopamine agonist can be used for patients requiring initiation of symptomatic therapy [11]. However, to the best of our knowledge, a long-term study comparing the effectiveness of a dopamine agonist with that of levodopa has not yet been conducted in Japanese patients with early PD.

The aim of the present postmarketing study in Japanese patients with early PD was to evaluate whether initial treatment with a long-acting dopamine receptor agonist, cabergoline, caused fewer motor complications during the long-term treatment period than those caused by treatment with levodopa.

**Subjects and Methods**

**Subjects.** One hundred fifty-six patients were initially considered for participation in the study. Male and female patients aged between 40 and 70 years with a clinical diagnosis of PD and a Hoehn and Yahr stage [12] of I, II, or III were enrolled at 13 institutions. These patients had never been treated with any dopamine agonists or levodopa. Patients were excluded if they had severe hepatic, renal, or orthopedic dysfunction or symptomatic dementia, or if they were pregnant. The study patients were then randomly assigned to either the initial cabergoline treatment arm or initial levodopa treatment arm by N Yamaguchi, MD, PhD. The protocol was approved by an ethics committee at each institution. Written informed consent was obtained from each patient.

The first patient visits were scheduled for the 2nd week, followed by every 4 weeks for the first 4–24 weeks, and every 3 months thereafter.

**Treatment.** Open-label cabergoline and levodopa treatments were initiated with doses of 0.25–2mg once daily and 100–300mg/day 2–3 times daily. The dosage was then titrated to a maintenance dose of up to 6mg/day for cabergoline and 600mg/day for levodopa. In cases in which the lowest Unified Parkinson’s Disease Rating Scale (UPDRS) score [13] worsened by more than 30% during the first 12–24 weeks of study treatment, the dosage was titrated up to 6mg/day cabergoline or 600mg/day levodopa. If the investigator judged it necessary to start additional therapy for PD because of medical reasons, levodopa (after the cabergoline dose was titrated to more than 4mg once daily) and cabergoline were added to the initial cabergoline and levodopa groups. Administration of selegiline and dopamine agonists other than cabergoline was prohibited. Administration of anticholinergics and amantadine was permitted prior to study enrollment only. After onset of the primary endpoint, administration of any anti-PD drug was permitted.

**Outcomes.** The primary endpoint was the development of motor complications (dyskinesia, wearing off, or on-off motor fluctuations). The presence or absence of motor complications was assessed by each investigator at every patient visit. The secondary endpoints were the patient’s physical and mental status as evaluated by UPDRS and doses of study drugs at the end of the study. These outcomes were subjective; therefore, double or single blinding was the preferred design for this type of study [14]. However, our limited resources did not permit treatment with a placebo. In addition, since the assessment of outcomes by nonattending physicians at every patient visit could harm the patients’ relationships with the researchers, we were compelled to use an open design.

**Cardiac valve regurgitation substudy.** During the patients’ follow-up periods, the risk of cardiac valvulopathy was reported in PD patients treated with ergot-derived dopamine agonists [15–19]. In June 2007, we decided to conduct a substudy to evaluate the level of cardiac valvular regurgitation in our study patients. Informed consent was again obtained from the patients enrolled in the initial cabergoline group, and echocardiography was performed for these patients. Abnormalities in the cardiac valves were quantified by each study investigator in the following manner: absent (grade 0), trace (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4). The regurgitation data obtained from this substudy was not included in the adverse event (AE) data, because this type of examination is not routinely performed for asymptomatic patients.

**Statistical analysis.** The cumulative incidence, between-group statistical differences, and hazard ratio of the primary outcome were calculated by the Kaplan-Meier method, logrank test, and unadjusted Cox proportional hazards regression model, respectively. Changes in UPDRS scores between baseline and the end of follow-up were analyzed using repeated mea-
asures analysis of variance with adjustments for the corresponding baseline absolute score. Missing values were replaced by the last-observation-carried-forward method. The difference between the 2 groups was assessed by the Wilcoxon signed-rank test or Fisher’s exact test. All statistical tests were two-sided, and a 5% level of significance (p < 0.05) was applied.

Results

Patient characteristics. A total of 98 patients were enrolled between April 2002 and November 2003 (Fig. 1). These patients were randomly allocated to either the initial cabergoline group (n = 49) or the initial levodopa group (n = 49). Patients excluded from the analysis included 4 from the cabergoline group (2 for not following up, 1 for not taking any study drug, and 1 for withdrawal of consent) and 3 from the levodopa group (1 for not taking any study drug and 2 for diagnosis of non-PD after randomization).

The ratio of males was slightly higher in the cabergoline group than in the levodopa group (p = 0.0598, Table 1). The baseline UPDRS mental subscore was lower in the cabergoline group than in the levodopa group (p = 0.0327).

Patient follow-up and treatment. In the initial cabergoline group, treatment was initiated with 0.25 mg/day cabergoline in 29 patients, 0.5 mg/day in 13 patients, and a higher dosage (1–2 mg/day) in 3 patients. In the initial levodopa group, treatment was initiated with 50 mg/day levodopa in 4 patients, 100 mg/day in 35 patients, and a higher dosage (200–300 mg/day) in 7 patients. Twelve patients in the ini-

![Fig. 1 Random assignment to treatment, completion of the trial, and the reasons for not completing the trial. ( ) = number of patients.](image-url)

| Table 1 Demographic and disease severity at baseline of the study subjects with early Parkinson’s disease with cabergoline or levodopa as initial therapy |
|---------------------------------|-----------------|-----------------|
| Patient Characteristics        | Cabergoline (n = 45) | Levodopa (n = 46) |
| Age (years old)                 | 62.0 ± 6.7        | 62.6 ± 6.8        |
| Male, n (%)                     | 26 (57.8)         | 17 (37.0)         |
| Time since diagnosis (years)    | 2.0 ± 1.7         | 1.7 ± 1.2         |
| Body weight (kg)                | 57.2 ± 10.3       | 58.9 ± 13.2       |
| Severity of disease             |                  |                  |
| Hoehn and Yahr stage, n (%)     | 9 (20.0)/20 (44.4)/16 (35.6) | 15 (32.6)/17 (37.0)/14 (30.4) |
| Unified Parkinson’s Disease Rating Scale score |                  |                  |
| Total                           | 30.6 ± 14.7       | 26.9 ± 13.8       |
| Mental component                | 0.6 ± 1.2         | 1.3 ± 1.6         |
| Activity of daily living component | 8.6 ± 4.6        | 7.7 ± 4.8         |
| Motor component                 | 21.6 ± 11.1       | 18.1 ± 10.1       |
| Pretreatment, n (%)             |                  |                  |
| Trihexyphenidyl                 | 6 (13.3)          | 3 (6.5)           |
| Amantadine                      | 8 (17.8)          | 7 (15.2)          |
| Mean ± SD                       |                  |                  |
tial cabergoline group (5 were maintained on monotherapy) and 27 patients in the initial levodopa group (19 were maintained on monotherapy) completed the planned 5-year study period. The median follow-up duration was 30.0 months (interquartile range [IQR], 9.0–54.0 months) in the initial cabergoline group and 48.0 months (IQR, 25.5–60.0 months) in the initial levodopa group. The daily dosage of cabergoline at the final visit was 0.25–6 mg/day (mean ± standard deviation, 2.9 ± 1.5 mg/day) in the initial cabergoline group and 0.25–5 mg/day (1.6 ± 1.3 mg/day, 13 patients) in the initial levodopa group. The daily dosage of levodopa was 100–700 mg/day (325 ± 162 mg/day, 20 patients) in the initial cabergoline group and 100–900 mg/day (336 ± 135 mg/day) in the initial levodopa group.

Motor complications. Four motor complications were reported in the initial cabergoline group (2 occurred after levodopa was added) and 11 in the initial levodopa group (none occurred after cabergoline was added). The estimated cumulative incidence of motor complications was 17% (95% confidence interval [CI], 0–33) in the initial cabergoline group and 34% (95% CI, 15–49) in the initial levodopa group (Fig. 2). The hazard ratio was 0.57 (95% CI, 0.18–1.81; p = 0.347). Dyskinesia, wearing off, and on-off motor fluctuations were reported in 0, 4, and 2 patients, respectively, in the initial cabergoline group and 3, 11, and 0 patients, respectively, in the initial levodopa group.

Unified Parkinson’s disease rating scale. In both treatment groups, the activities of daily living (ADL) score, motor UPDRS score, and total of the scores slowly decayed with time after the initial drastic improvements (Fig. 3). The changes in the ADL, motor UPDRS and total scores from baseline to 60 months were not significantly different between the initial cabergoline and levodopa groups (p = 0.280, p = 0.398, and p = 0.140, respectively).

Hoehn and Yahr stage. The changes in the Hoehn and Yahr stage from the baseline did not differ between the initial cabergoline group and the initial levodopa group (1-point decrease, 4 and 7 patients; no change, 29 and 27 patients; 1-point increase, 8 and 8 patients; and 2-point increase, 4 and 4 patients, respectively; p = 0.848).

Adverse events. Thirty-five AEs were reported in 24 patients in the initial cabergoline group, whereas 16 AEs were reported in 13 patients in the initial levodopa group (Table 2). The incidence of AEs was

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**Fig. 2** Kaplan-Meier plots for the estimated cumulative probability of developing the first confirmed motor complication in the initial cabergoline treatment arm and initial levodopa treatment arm.
higher in the initial cabergoline group than in the initial levodopa group \( p = 0.019 \). The most frequent AE was edema. There were 8 cases of serious AEs: 3 malignant neoplasms (2 in the initial cabergoline and 1 in the initial levodopa group), 1 suicide attempt in the initial levodopa group, and 1 instance of melena, 1 of fracture and pneumonia together, 1 of cerebral hemorrhage, and 1 of gallstone in the initial cabergoline group.

**Cardiac valvular regurgitation substudy.**

The cardiac valve function of 16 patients (7 males and 9 females, aged 47–70 years at enrollment) in the initial cabergoline group was evaluated by echocardiography. Moderate (4 aortic and 1 aortic and mitral) and severe (1 aortic) valvular regurgitations were detected in 6 of 16 patients (37.5%) (Table 3). One patient in which moderate aortic and mild mitral regurgitation was detected had mitral regurgitation and hypertension at enrollment, and another patient with moderate aortic and mitral regurgitation had a history of myocardial infarction. There were no marked differences in sex, age at examination, cabergoline treatment term, and cumulative doses of cabergoline.
Table 3  Summary of patient characteristics at baseline and results of echocardiographic evaluation in the patients with initial cabergoline treatment arm of cardiac valvulopathy substudy

<table>
<thead>
<tr>
<th>Grade* (n = 16)</th>
<th>Male (n)</th>
<th>Age (y.o.)</th>
<th>Term (months)</th>
<th>Cabergoline (g)</th>
<th>Calcification (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent (n = 2)</td>
<td>0</td>
<td>59.4 ± 0.7</td>
<td>52.3 ± 11.2</td>
<td>5.3 ± 1.3</td>
<td>0</td>
</tr>
<tr>
<td>Trace (n = 2)</td>
<td>1</td>
<td>66.6 ± 1.7</td>
<td>54.3 ± 6.9</td>
<td>3.6 ± 0.1</td>
<td>0</td>
</tr>
<tr>
<td>Mild (n = 6)</td>
<td>3</td>
<td>65.2 ± 8.7</td>
<td>49.3 ± 5.1</td>
<td>5.6 ± 2.7</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (n = 5)</td>
<td>3</td>
<td>67.6 ± 6.4</td>
<td>53.4 ± 3.4</td>
<td>3.4 ± 1.8</td>
<td>1</td>
</tr>
<tr>
<td>Severe (n = 1)</td>
<td>0</td>
<td>71.3</td>
<td>42.1</td>
<td>7.4</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: *Worst abnormality in aortic, mitral, tricuspid and pulmonary valve; Term, months at evaluation after treatment started; Cabergoline, cumulative cabergoline exposure. Values are expressed as patient number or mean ± SD.

among the subgroups when divided by valvular regurgitation grading, except for the 1 patient who had severe valvular regurgitation.

Discussion

In the present study, we have demonstrated that the occurrence of motor complications tended to be lower in the initial cabergoline group than in the initial levodopa group, although the difference was not statistically significant. The hazard ratio obtained in this study (0.57) was similar to that reported in previous foreign studies (0.25–0.68) [5–10]. These results suggest that cabergoline delays the onset of motor complications, even though the present results were not conclusive because they were not statistically significant.

The early use of a dopamine agonist is more effective for reducing the onset of dyskinesia than reducing the onset of the wearing off and on-off motor fluctuations [6–9]. In our study, only 3 patients (6.5%) in the initial levodopa group demonstrated an onset of dyskinesia. This incidence was lower than that reported in previous studies (21.2% [10], 30% [8], 45% [6], 43.8% [7]), and may be attributed to the lower daily levodopa dosage (mean of 336mg/day at the final visit) compared with those in previous western reports (500–800mg/day).

As shown in Fig. 3, the changes in total, ADL, and motor UPDRS scores were not significantly different between the 2 groups, although the initial levodopa group had slightly less impairment than the initial cabergoline group. This result was congruent with those of previous studies [6–9].

The AE rate in the initial levodopa group was lower than that in the initial cabergoline group (p = 0.019). Similarly, a lower AE rate in the levodopa group has also been reported in studies comparing dopamine agonists with levodopa [7–9]. The slightly lesser improvement in UPDRS status (Fig. 3) and higher AE rate in the initial cabergoline group may have contributed to the higher dropout rate in this group (73%) compared with that in the initial levodopa group (42%).

Although we had no baseline or control data for comparison, our cardiac valve regurgitation substudy revealed 6 patients with moderate or severe valvular regurgitation after undergoing about 4 years of cabergoline treatment. Only 2 of the 6 patients had risk factors [20] such as mitral regurgitation, hypertension, or myocardial infarction at enrollment. The other 4 patients with aortic regurgitation had no risk factors for cardiac valvular regurgitation at baseline. A recently published report suggested that higher daily and cumulative doses have a strong association with valvular regurgitation [21]. In our study, only 1 patient was categorized as having severe valvular regurgitation. This patient was treated with the highest cumulative cabergoline dose in this substudy (Table 3). However, 3 patients who were treated with more than 6g of cabergoline also demonstrated mild (cumulative cabergoline dose, 6.71g and 6.41g) or absent (6.22g) valvular regurgitation. Therefore, we did not find a clear association between cabergoline dose and valvular regurgitation. Further investigations may be needed to determine this association.

The present results demonstrated a tendency of fewer motor complications in the initial cabergoline-treated Japanese patients with early PD than in levodopa-treated patients, but the difference was not
statistically significant. The calculated hazard ratio was 0.57, suggesting a 43% reduction in the risk of motor complications, a value similar to those obtained in previous studies conducted in Western countries.

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References

20. Bowon RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon