The Efficacy of Istradefylline for Treating Mild Wearing-Off in Parkinson Disease

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Objectives: The adenosine A2A antagonist istradefylline has been used to treat Parkinson disease (PD) with symptoms of wearing-off since 2013 in Japan. Previous randomized controlled trials of istradefylline compared with placebo included PD patients experiencing an average daily OFF time of more than 2 hours. The purpose of this study is to assess the efficacy of 20 mg/d istradefylline in PD subjects experiencing an average daily OFF time of 3 hours or less.

Methods: Fifteen patients were enrolled into this retrospective study. They received 20 mg/d istradefylline for 12 weeks. Changes in the Unified Parkinson's Disease Rating Scale part III scores in the ON state (ON-UPDRS-III) scores and daily OFF time were assessed at baseline and after 4, 8, and 12 weeks of administration of istradefylline.

Results: At baseline, all subjects had shorter daily OFF times, lower doses of L-DOPA and higher ON-UPDRS-III scores than those in previous randomized controlled trials. Twelve weeks of istradefylline significantly reduced ON-UPDRS-III scores ($P < 0.001$, Wilcoxon signed rank test). Eleven patients (73%) showed more than 50% reductions in ON-UPDRS-III scores. Improvement of ON-UPDRS-III was significantly correlated with baseline ON-UPDRS-III, and the mean ON-UPDRS-III score at end point was 12.1.

Conclusions: Our result suggests that 20 mg/d istradefylline significantly improved motor functions in PD patients with mild wearing-off.

Key Words: Parkinson disease, istradefylline, wearing-off

(*Clin Neuropharm* 2017;40: 261–263)

Adenosine A2A antagonists facilitate dopamine D2 receptors and improve motor function in animal models of Parkinson disease (PD).[1–3] However, the effects of A2A antagonists, unlike the effects of dopamine agonists, depend on the dose of L-DOPA. A2A antagonists potentiate the effects of *suboptimal* doses of L-DOPA without worsening dyskinesia,[1,2] but that A2A antagonists with *maximal* doses of L-DOPA are less effective.[1]

Previous randomized controlled trials (RCTs) of the A2A antagonist istradefylline compared with placebo as an adjunct to L-DOPA have reported that istradefylline significantly reduces both daily OFF time and ON-UPDRS-III, but the weighted mean difference in ON-UPDRS-III scores between 20 mg istradefylline and placebo is only −0.94.[4] Two RCTs have reported a significant improvement in ON-UPDRS-III scores with the administration of 40 mg/d of istradefylline, but the change from baseline was less than 5.[5–7] These RCTs included PD patients experiencing an average daily OFF time of 2 hours or more, and mean daily OFF time at baseline of more than 6 hours.

Here, we report the efficacy of istradefylline 20 mg/d as an adjunct to L-DOPA in PD subjects experiencing an average daily OFF time of 3 hours or less.

MATERIALS AND METHODS

This study was approved by the institutional review board of Hokkaido University. Fifteen patients found to satisfy the following criteria were enrolled into this retrospective study from November 2014 until November 2016. All 15 patients were diagnosed with idiopathic PD according to the United Kingdom PD Society Brain Bank Diagnostic Criteria with a modified Hoehn and Yahr stage between 1 and 3 (in the OFF state) and had an average daily OFF time of 3 hours or less. All subjects were receiving L-DOPA, and most of them (80%) were receiving other PD medications. Three patients (20%) had developed dyskinesias. After giving informed consent, all subjects received 20 mg/d istradefylline for 12 weeks. The patients maintained usual levodopa and other antiparkinsonian medications. Changes in the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores in the ON state (ON-UPDRS-III) scores and daily OFF time (MDS-UPDRS 4.3) were assessed at the baseline and at the end of weeks 4, 8, and 12.

RESULTS

At baseline, the subjects had shorter daily OFF times, lower doses of L-DOPA, and higher ON-UPDRS-III scores than those in previous RCTs (Table 1).[5–7] Mean tremor subscores at baseline, 4, 8, and 12 weeks were 1.8, 0.7, 0.6, and 0.4, respectively. Mean rigidity subscores at baseline, 4, 8, and 12 weeks were 6.0, 2.8, 2.6, and 2.3, respectively. Mean akinesia subscores at baseline, 4, 8, and 12 weeks were 13.7, 7.7, 7.5, and 6.4, respectively. After 12 weeks of istradefylline administration, 11 patients (73%) showed more than 50% reductions in ON-UPDRS-III scores, and there was a significant reduction in ON-UPDRS-III scores ($P < 0.001$, Wilcoxon signed rank test). Improvement of ON-UPDRS-III was significantly correlated with baseline ON-UPDRS-III (Fig. 1) (Spearman correlation coefficient $\rho = 0.7671$, $P < 0.001$), but not with age, the duration of the disease, levodopa dosage, or ON-UPRDRS-III after 12 weeks administration of istradefylline. The mean ON-UPDRS-III score at end point was 12.1. Istradefylline tended to reduce the daily OFF time ($P = 0.06$). Dyskinesias developed in 2 patients and worsened in 2 other patients. Mean dyskinesia subscores at baseline, 4, 8, and 12 weeks were 0.3, 0.3, 0.2, and 0.4, respectively.

DISCUSSION

Twenty mg/d of istradefylline dramatically improved ON-UPDRS-III scores in PD patients with mild wearing-off.

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Conflicts of Interest and Source of Funding: The authors have no conflicts of interest to declare.

Author contributions: I.Y. and M.K. had full access to all of the data in the study. Study concept and design: I.Y. and M.K. Acquisition of data: I.Y., I.T., and M.M. Statistical analysis: M.K. Analysis and interpretation of data: I.Y. and M.K. Drafting of the manuscript: I.Y. and M.K. Critical revision of the manuscript for important intellectual content: I.T., M.M., and H.S. Study supervision: H.S.

DOI: 10.1097/WNF.0000000000000249

TABLE 1. Comparison of the Present Study and Previous Studies

	Present Study	Hauser (2008)	Pourcher (2012)	Mizuno (2013)
Study design	Case study	RCT	RCT	RCT
No. patients	15	115	149	120
Inclusion criteria				
Hoehn and Yahr stage	1–3	2–4	2–4	2–4
Daily OFF time (h)	≤3	≥3	≥3	≥2
Baseline characteristics				
Age (y), mean (SD)	70.1 (6.0)	63.0 (9.5)	64.0 (9.3)	66.1 (8.6)
Disease duration (y), mean (SD)	9.1 (6.0)	10.0 (5.5)	8.9 (4.6)	7.3 (4.2)
Daily OFF time (h), mean (SD)	1.4 (0.6)	6.7 (2.8)	6.7 (2.2)	6.5 (2.7)
ON-UPDRS-III score, mean (SD)	29.7 (9.1)	23.9 (11.3)	22.3 (11.3)	21.3 (10.8)
Daily ON time with dyskinesia (h), mean (SD)	0.3 (0.6)	2.8 (3.6)	N/A	1.6 (2.8)
L-DOPA (mg/d), mean (SD)	395 (217)	652 (371)	602 (357)	431 (157)
Mean changes from baseline to end point				
ON-UPDRS-III score	−17.6*	−3.2	−0.8	−3.7
Daily OFF time (h)	−0.5	−1.6†	−1.1	−0.99‡

Baseline versus end point: *$P < 0.001$.
Istradefylline versus placebo: †$P < 0.05$, ‡$P < 0.01$.
N/A indicates not applicable.

The high responder rate in this study may help us to understand the factors influencing clinical effects of istradefylline on parkinsonian motor symptoms despite the small number of subjects.

L-DOPA dosage and age at disease onset have been reported to influence the occurrence of motor fluctuations.[8] One of the authors of this paper has previously reported that a chronic low-dose levodopa treatment proved satisfactory benefit with a low incidence of motor complications in Japanese PD patients.[9] Because the subjects in the present study had older age at disease onset and were treated with low dosages of L-DOPA despite higher ON-UPDRS-III scores than those in the previous RCTs, older age at onset and low (suboptimal) L-DOPA dosages may be associated with stable response to L-DOPA. It should be noted that more severely affected patients showed greater improvement in ON-UPDRS-III, which suggests that istradefylline can potentiate the effects of *subthreshold* dosage of L-DOPA above the threshold (Fig. 1). Although a few previous RCTs have not shown a statistically significant reduction in OFF time because of a placebo effect,[6] many other RCTs have revealed that istradefylline 20 mg/d, 40 mg/d, and 60 mg/d significantly reduce daily OFF time. The present results suggest that istradefylline 20 mg/d can reduce daily OFF time in PD patients with mild wearing-off. Further evaluations of early use of istradefylline combined with suboptimal L-DOPA in controlled clinical trials are needed.

The present study, as well as previous animal studies, suggests that adding istradefylline to low doses of L-DOPA and dopamine

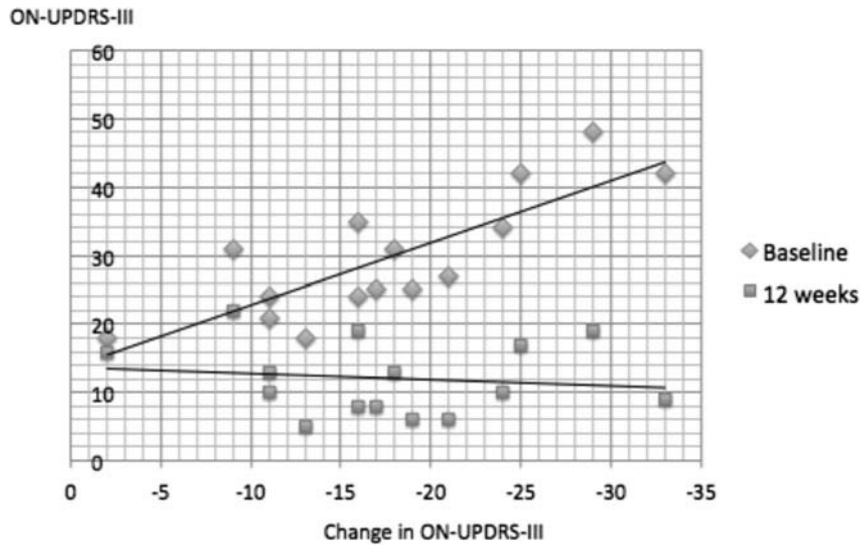

FIGURE 1. The correlation between the changes in ON-UPDRS-III and ON-UPDRS-III scores at baseline or after 12 weeks administration of istradefylline. Improvement of ON-UPDRS-III was significantly correlated with baseline ON-UPDRS-III (Spearman correlation coefficient $\rho = 0.7671$, $P < 0.001$), but not with ON-UPRDRS-III after 12 weeks administration of istradefylline.

agonists is superior to the later use in PD patients treated with high doses of L-DOPA. It may be effective to administer istradefylline before the OFF symptoms progress.

Limitations

This study is limited by the fact that it is retrospective. Further evaluations on the early use of istradefylline combined with low doses of L-DOPA in double-blinded randomized controlled clinical trials are naturally needed.

ACKNOWLEDGMENT

The authors thank the patients for their participation in this study.

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