A Pooled Analysis From Phase 2b and 3 Studies in Japan of Istradefylline in Parkinson’s Disease

Nobutaka Hattori, MD,1 Hiroki Kitabayashi, MSc,2 Tomoyuki Kanda, PhD,2 Takeanobu Nomura, PhD,2 Keizo Toyama, MSc,3 and Akihisa Morii, PhD2

1Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan 2Medical Affairs Department, Kyowa Kirin Co., Ltd., Tokyo, Japan 3R&D Division, Kyowa Kirin Co., Ltd., Tokyo, Japan

ABSTRACT: Background: Characterization of patient factors associated with istradefylline efficacy may facilitate personally optimized treatment. Objectives: We aimed to examine which patient factors are associated with favorable istradefylline treatment outcomes in PD patients with motor complications. Methods: We performed a pooled analysis of data from two identical phase 2b and 3 Japanese studies of istradefylline. Logistic regression models were used to assess the association of 12 patient characteristics with favorable outcomes. Results: Off time reduction and increased good on time with istradefylline provided a significantly favorable response in patients aged ≥65 years. Off time reduction was more favorable in patients with ≥8-hour daily off time at baseline. Improvement in UPDRS Part III was favorable in patients with UPDRS Part III baseline score ≥20.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

*Correspondence to: Prof. Nobutaka Hattori, Department of Neurology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan; E-mail: nhattori@juntendo.ac.jp

Relevant conflicts of interest/financial disclosures: Nobutaka Hattori has received honoraria for manuscript writing and advisory board fees from Kyowa Kirin Co., Ltd. and has a patent pending for an antiparkinsonian agent. Hiroki Kitabayashi is an employee of Kyowa Kirin Co., Ltd. and has a patent pending for an antiparkinsonian agent. Takeanobu Nomura is an employee of Kyowa Kirin Co., Ltd. and has a patent pending for an antiparkinsonian agent. Tomoyuki Kanda is an employee of Kyowa Kirin Co., Ltd. and has a patent pending for an antiparkinsonian agent. Keizo Toyama is an employee of Kyowa Kirin Co., Ltd. and has a patent pending for an antiparkinsonian agent.

Full financial disclosures and author roles may be found in the online version of this article.

Funding agencies: Kyowa Kirin Co., Ltd. funded data collection, data analysis, and medical writing by the contract research organization.

Received: 3 November 2019; Revised: 17 April 2020; Accepted: 19 April 2020

Published online 5 June 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28095
Conclusions: Several patient factors influenced the effect of istradefylline on motor fluctuations, motor function, activities of daily living, and clinical impression. © 2020 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: efficacy; istradefylline; Japan; Parkinson’s disease; treatment outcome

Parkinson’s disease (PD) is a progressive neurodegenerative disorder that affects 1% of people aged >65 years.1 PD treatment research has been dominated by dopaminergic therapies with levodopa, which currently is the most effective symptomatic treatment for PD.2 However, onset of motor complications limits pharmacological interventions.2 Therefore, the characterization and specific needs of patients with motor subtypes and motor complication subtypes are of interest to facilitate a personalized therapeutic approach.3

Istradefylline (KW-6002) is the first selective adenosine A2A receptor antagonist available in Japan and the United States for treatment of the off time in PD patients treated with l-dopa-containing preparations. Istradefylline is considered a nondopaminergic symptomatic anti-PD pharmacotherapy,4,5 with adenosine A2A receptor antagonism in the basal ganglia, but also a lack of influence on dopaminergic receptors/ enzymes, and has demonstrated antiparkinsonian effects in clinical studies.6,7 In phase 2b and 3 clinical studies in PD patients treated with l-dopa in Japan, istradefylline elicited a reduction in off time.8,9

We aimed to establish which patient factors are likely to influence patient outcomes after istradefylline therapy and hence its future use in personally optimized treatment.

Patients and Methods

Patient Population and Study Design

We performed a pooled analysis of two Japanese studies8,9 of istradefylline as an adjunct to l-dopa. Both studies were identically designed, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies and enrolled PD patients with motor fluctuations. Additional details are provided in the Supporting Information Methods.

Efficacy Outcomes

The primary efficacy outcome was change in daily off time from baseline to 12 weeks. Other efficacy outcomes included change in on time without troublesome dyskinesia (“Good” on time),10 UPDRS scores, and Clinical Global Impressions-Improvement of illness (CGI-I) score from baseline. Treatment effect was determined as the difference in mean change during follow-up between the placebo and istradefylline arms. Definitions of the cut-off values for efficacy outcomes are described in the Supporting Information Methods.

Statistical Analysis

Patient background characteristics for both the total patients and the groups stratified by treatment arms are summarized using descriptive statistics. We conducted the following analyses only for patients without any missing data. To explore demographic factors associated with favorable outcomes following treatment with istradefylline, a logistic regression model was applied to estimate the odds ratio (OR) and 95% confidence interval after controlling for 12 baseline factors in three steps (described in the Supporting Information Methods). Prediction models were constructed with five outcomes (details are described in the Results.) with reference to the results of the multivariable logistic regression model as an exploratory analysis. Model performance was evaluated by the area under the curve from receiver operating characteristics curves. Presence of statistical significance and effect modification were considered with a two-tailed P value <0.05 and an interaction term <0.10, respectively.11 All analyses were performed using SAS software (version 9.2 or 9.3; SAS Institute, Inc., Cary, NC).

Results

Patients

The patient disposition for the studies is presented in Supporting Information Figure S1. The total pooled full analysis set population was 723 (placebo, n = 241; istradefylline, 20 mg/d n = 235 and 40 mg/d n = 247). Most demographic and baseline characteristics were comparable between the treatment arms within the two studies (Supporting Information Table S1), except for concomitant anti-PD drugs used at baseline, because zonisamide was not available during the phase 2b study.

Efficacy

The overall efficacy of istradefylline is described in Figure 1, Supporting Information Figure S2, and Supporting Information Table S2. Data distributions for each treatment group were comparable among groups. Compared with placebo, both istradefylline doses were associated with significant reductions in daily off time as well as a significant increase in Good on time. Significant improvements in UPDRS Part III score (on) were also observed for both doses compared with placebo.
FIG. 1. Changes from baseline at week 12 in mean daily off time (A), daily on time without troublesome dyskinesia (Good on time) (B), UPDRS Part II (off; C), UPDRS Part III (D), and CGI-I (E) in each treatment group. Data are presented as means and standard deviations for each treatment group in panels (A), (B), (C), and (D), with P values for each comparison.
**TABLE 1.** Correlation between effectiveness and patient demographic factors by multivariate logistic regression analysis

| Characteristic                  | Off Time | P for Heterogeneity | On Time Without Troublesome Dyskinesia | P for Heterogeneity | UPDRS Part II Score (off) | P for Heterogeneity | UPDRS Part III Score | P for Heterogeneity | CGI-I | P for Heterogeneity |
|--------------------------------|----------|---------------------|----------------------------------------|---------------------|---------------------------|-----------------------|---------------------|---------------------|--------|---------------------|
|                                | 20 mg/d  | 40 mg/d             | 20 mg/d                                | 40 mg/d             | 20 mg/d                   | 40 mg/d               | 20 mg/d             | 40 mg/d             | 20 mg/d | 40 mg/d             |
| Age, y                         | n.s.     | <0.10               | n.s.                                   | n.s.                | n.s.                      | n.s.                  | n.s.                | n.s.                | n.s.    | n.s.                |
| <65                            | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| ≥65                            | 2.68 [1.65–4.28]| 1.47 [0.76–2.85] | 2.88 [1.41–5.89]                      | 0.90 [0.36–1.46]    | 0.65 [0.40–1.06]          | 1.17 [0.74–1.85]     | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Sex                            | n.s.     | n.s.                | n.s.                                   | n.s.                | n.s.                      | n.s.                  | n.s.                | n.s.                | n.s.    | n.s.                |
| Male                           | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Female                         | 0.86 [0.55–1.36]| 0.85 [0.54–1.35] | 1.71 [1.06–2.74]                      | 1.65 [1.01–2.69]    | 1.56 [1.00–2.44]          | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Combos of concomitant drug     | <0.10    | n.s.                | n.s.                                   | n.s.                | n.s.                      | n.s.                  | n.s.                | n.s.                | n.s.    | n.s.                |
| L-dopa, L-dopa + DA            | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| L-dopa + DA + SEL/ENT/ZNS      | 2.18 [0.97–4.80] | 0.63 [0.28–1.45] | 1.07 [0.62–1.84]                      | 1.34 [0.75–2.37]    | 1.20 [0.67–2.17]          | 0.94 [0.54–1.61]     | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| L-dopa + DA + SEL/ENT/ZNS + AMA| 1.11 [0.43–3.03] | 0.85 [0.43–1.70] | 2.28 [1.12–4.64]                      | 1.57 [0.75–3.28]    | 1.03 [0.52–2.04]          |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Duration of PD, y              | n.s.     | n.s.                | n.s.                                   | n.s.                | n.s.                      | n.s.                  | n.s.                | n.s.                | n.s.    | n.s.                |
| <5                             | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| 5 to <10                       | 1.32 [0.78–2.35]| 1.43 [0.84–2.43] | 1.41 [0.82–2.41]                      | 1.04 [0.60–1.81]    | 1.23 [0.73–2.06]          | 1.21 [0.63–2.33]     | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| ≥10                            | 1.41 [0.72–2.75]| 1.78 [0.92–3.48] | 1.07 [0.53–2.15]                      | 0.82 [0.41–1.63]    | 1.21 [0.63–2.33]          |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Duration of motor complications| n.s.     | n.s.                | n.s.                                   | n.s.                | n.s.                      | n.s.                  | n.s.                | n.s.                | n.s.    | n.s.                |
| <3                             | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| ≥3                             | 0.93 [0.57–1.53]| 1.01 [0.63–1.84] | 1.00 (ref)                             | 1.07 [0.65–1.78]    | 1.08 [0.67–1.73]          |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| L-dopa dose, mg/d              | n.s.     | <0.10               | n.s.                                   | n.s.                | <0.10                     |                      | n.s.                | n.s.                | n.s.    | n.s.                |
| <400                           | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| ≥400                           | 0.80 [0.48–1.35]| 0.80 [0.46–1.34] | 0.98 [0.57–1.67]                      | 1.31 [0.55–3.14]    | 0.71 [0.42–1.19]          |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| L-dopa equivalent dose, mg/d   | n.s.     | n.s.                | n.s.                                   | n.s.                | <0.10                     |                      | n.s.                | n.s.                | n.s.    | n.s.                |
| <700                           | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| ≥700                           | 0.95 [0.56–1.67]| 0.88 [0.51–1.50] | 0.81 [0.46–1.42]                      | 1.04 [0.43–2.50]    | 1.22 [0.71–2.09]          |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Dyskinesia on baseline presence| n.s.     | n.s.                | n.s.                                   | n.s.                | <0.10                     |                      | n.s.                | n.s.                | n.s.    | n.s.                |
| Presence                       | 1.00 (ref)| 1.00 (ref)          | 1.00 (ref)                             | 1.00 (ref)          | 1.00 (ref)                | 1.00 (ref)            | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Absence                        | 0.74 [0.46–1.20]| 0.61 [0.50–1.32] | 2.27 [1.17–4.85]                      | 0.87 [0.41–1.84]    | 0.79                      |                      | 1.00 (ref)          | 1.00 (ref)          | 1.00    | 1.00 (ref)          |
| Mean daily off time, h         | <0.10    | <0.10               | n.s.                                   | n.s.                | n.s.                      |                      | n.s.                | n.s.                | n.s.    | n.s.                |

(Continues)
TABLE 1. POOLED ANALYSIS OF ISTRADEFYLLINE IN PD PTS

Association Between Efficacy and Patient Demographic Factors by Multivariate Logistic Regression Analysis

We analyzed the association between the five outcomes (1, off time reduction; 2, increase in Good on time; 3, improvement in UPDRS Part II score [off state]; 4, improvement in UPDRS Part III score; and 5, CGI-I score) and 12 interaction factors (1, age; 2, sex; 3, presence or absence of dyskinesia at baseline; 4, mean daily off time; 5, total UPDRS Part III score; 6, on state on Modified H & Y [mH&Y] scale; 7, off state on mH&Y scale; 8, pattern of concomitant anti-PD drugs; 9, duration of PD; 10, duration of motor complication; 11, L-dopa dosage; and 12, L-dopa-equivalent dose). The results are presented in Table 1.

Off Time Reduction

The reduction in off time as the primary efficacy outcome was associated with istradefylline treatment, and the effectiveness was significantly greater in patients aged ≥65 years (OR, 2.65). Patients with higher baseline off time showed a significantly greater reduction of off time with the 40- versus 20-mg/d dose of istradefylline or a lower baseline off time. The effect of istradefylline at 40 mg/d on off time reduction was most favorably observed in patients with ≥8 hours of daily off time at baseline (OR, 6.68).

Other Efficacy Endpoints

The influence of istradefylline 40 mg/d on the increase in Good on time was significantly greater in patients aged ≥65 years (OR, 2.88). Female sex (OR, 1.65) and higher baseline of UPDRS Part III score (OR, 2.79) were identified as factors associated with favorable improvement in UPDRS Part III score following istradefylline treatment. Female sex (OR, 1.71), absence of baseline dyskinesia (OR, 2.27), treatment with L-dopa + anti-PD medications including amantadine (OR, 2.28), and baseline mH&Y stage (off state) ≥3 (OR, 3.50) were identified as factors associated with favorable improvement UPDRS Part II score (off state) following treatment with istradefylline. An mH&Y stage (off state) ≥3 (OR, 1.89) and absence of baseline dyskinesia (OR, 2.27) were associated with an improvement in CGI-I score following treatment with istradefylline (dosages of istradefylline are described in Table 1).

Discussion

Our analysis revealed that the effects of istradefylline on off time were more favorable in patients aged ≥65 years. Istradefylline elicited significant increases in Good on time. Similar to the results for off time, age ≥65 years was significantly associated with a more
favorable trend in Good on time. This age group accounted for 57% of patients in our analysis. However, although the number of patients aged ≥65 versus <65 years was balanced, this does not reflect the real-world setting, in which the overwhelming majority of PD patients are elderly.1 Thus, istradefylline may be useful as adjunct therapy in terms of the off time reduction/Good on time increase for the majority of PD patients.

Patients with longer off time at baseline were more likely to have favorable outcomes, but the reason for this is not clearly understood given that there were no significant differences in baseline l-dopa dose or l-dopa-equivalent dose in this subpopulation; therefore, these patients may have not received maximal treatment benefits owing to dose limitations related to dopaminergic side effects. As an important secondary outcome, UPDRS Part III also indicated that baseline score ≥20 was associated with more favorable outcomes. This suggests that the effects of istradefylline are more easily detected in terms of wearing-off, but also motor dysfunction in a wide therapeutic window (ie, patients with longer baseline off time or higher baseline UPDRS Part III score).

It has been suggested that adenosine A2A receptors abrogate the dopamine D2 receptor-mediated inhibitory influence on the indirect pathway.12 When A2A receptors are blocked, the normal function of D2 receptors on the pathway is restored. Thus, the efficacy of A2A receptor antagonists may depend on individual patient variability in the extent to which excitability of indirect pathway can be regulated by D2 receptors. This proposed dopamine D2 receptor-mediated “therapeutic window” may be supported by a monkey study, in which combination treatment of istradefylline with threshold dopaminergic therapy elicited remarkable and significant improvement in efficacy in an MPTP model,13 although this needs clarification in clinical studies.

Sex was an influential factor, given that more favorable improvements in UPDRS Part III and Part II (off state) were observed in female patients. Although male sex is a risk factor for PD,14 no reports have found sex differences for the pharmacology or toxicology of istradefylline. We found a difference in mean body weight between sexes (female, 49.40 kg; male, 62.56 kg) in the istradefylline-treated arms. Thus, istradefylline exposure in the body (mg/kg) may be higher in female than male patients; hence, being female could be more favorable for improvement in UPDRS Parts II and III, although this remains to be investigated with a larger sample size.

The multivariate logistic regression analysis indicated that baseline mH&Y (off state) ≥3 and lack of dyskinesia at baseline were associated with more favorable CGI-I outcomes. Dyskinesia at baseline may influence the effect of istradefylline on improvements in CGI-I, given that dyskinetic movement affects the impression of drug efficacy.15

This study identified some demographic factors associated with favorable istradefylline treatment outcomes. These results suggest the potential for personal optimization of therapy using the same drug in different patients who desire different clinical efficacy outcomes: (1) Patients aged ≥65 years can expect more favorable effects on motor fluctuations without troublesome dyskinesia; (2) patients with a wider therapeutic window at baseline in daily off time and UPDRS Part III score can expect more favorable effects on off time reduction and improvement of UPDRS Part III score; (3) patients with a higher mH&Y stage can expect more favorable effects in UPDRS Part II score and CGI-I improvement; and (4) patients without pre-existing dyskinesia can expect more favorable effects with istradefylline in terms of CGI-I and UPDRS Part II off state (activities of daily living).

Limitations of this pooled analysis include the enrollment of only Japanese patients and the relatively short duration of each study.

In conclusion, istradefylline exerts an effect on the wearing-off phenomenon in Japanese PD patients treated with l-dopa. This analysis also suggested favorable pairings between patient factors and clinical endpoints, providing useful information for patient selection and prognostic indicators for particular characteristics. Our findings provide the first insight into adenosine A2A receptor antagonist-based personalized PD therapy, tailored according to its desired outcomes in individual clinical subtypes, without considering a patient’s genetic background.

Acknowledgments: We thank Chihiro Nosaka and Mayumi Saki, of Kyowa Kirin Co., Ltd., for their analysis support and writing support. We also thank Clare Cox, PhD, of Edanz Medical Writing, for providing medical writing support, which was funded by Kyowa Kirin Co., Ltd.

References
1. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson’s disease: a systematic review and meta-analysis. Mov Disord 2014;29:1583–1590.
2. Fahn S. How do you treat motor complications in Parkinson’s disease: medicine, surgery, or both? Ann Neurol 2008;64(Suppl.):S56–S64.
3. Titova N, Chaudhuri KR. Personalized medicine in Parkinson’s disease: time to be precise. Mov Disord 2017;32:1147–1154.
4. Kalia LV, Brochton JI, Fox SH. Novel nondopaminergic targets for motor features of Parkinson’s disease: review of recent trials. Mov Disord 2013;28:131–144.
5. Jenner P, Mori A, Hauser R, Morelli M, Fredholm BB, Chen JF. Adenosine, adenosine A2A antagonists, and Parkinson’s disease. Parkinsonism Relat Disord 2009;15:406–413.
6. Mori A, LeWitt P, Jenner P. The story of Istradefylline – the first approved A2A antagonist for the treatment of Parkinson’s disease. In: Morelli M, Simola N, Wardas J, eds. The Adenosinergic System: a Non-dopaminergic Target in Parkinson’s Disease (Current Topics

1486 Movement Disorders, Vol. 35, No. 8, 2020
1. Uchida S, Soshiroda K, Okita E, et al. The adenosine A2A receptor antagonist, istradefylline enhances the anti-parkinsonian activity of low doses of dopamine agonists in MPTP-treated common marmosets. Eur J Pharmacol 2015;747:160–165.

14. Shulman LM, Bhat V. Gender disparities in Parkinson’s disease. Expert Rev Neurother 2006;6:407–416.

15. Goetz CG, Stebbins GT, Chung KA, et al. Which dyskinesia scale best detects treatment response? Mov Disord 2013;28:341–346.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.