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Differences between Istradefylline Responders and Non-Responders in Parkinson's Disease

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Abstract

Background: Istradefylline is a selective adenosine A2A receptor antagonist approved for Parkinson's disease (PD) patients with wearing-off symptoms. The Japanese phase III trial showed that 20 mg of orally administrated istradefylline decreased the Off-time. However, istradefylline showed prominent effects in some patients and no benefits in others. We examined the differences in characteristics between responders and non-responders who received 8 weeks of 20 mg/day istradefylline. **Methods:** Thirty-one patients were enrolled (age, 65.4 [SD 10.4] years; disease duration, 10.4 [SD 6.1] years; daily levodopa dosage, 553.2 [SD 228.7] mg; frequency of levodopa consumption, 4.7 [SD 1.5] times; levodopa equivalent dose, 811.2 [SD 307.5] mg). **Results:** There were significant differences ($p < 0.05$) in sex (male/female: 5/16, 6/4), age (62.9 (SD 10.4), 70.6 (SD 8.0) years), age at onset (51.9 (SD 12.3), 61.5 (SD 10.5) years old), age at dyskinesia onset (57.9 (SD 8.8), 67.6 (SD 7.2), and Epworth sleepiness scale scores (4.5 (SD 2.7), 11.2 (SD 6.7), $p < 0.01$) for the responders and non-responders, respectively. There were no differences in disease duration, On-time, Off-time, Unified Parkinson's disease Rating scale scores, daily levodopa dose, levodopa equivalent dose, cumulative levodopa dose, or coffee intake. **Conclusions:** Younger or female patients who are not excessively sleepy during daytime are better candidates for the istradefylline therapy.

Keywords

Parkinson's Disease, Istradefylline, Adenosine A2A Receptor Antagonist, Wearing-Off, Sleepiness

1. Introduction

Current treatments for Parkinson's disease (PD) are based on dopamine replacement therapy, including L-3, 4-dihydroxyphenylalnine (levodopa, L-DOPA),

dopamine agonists (DA), monoamine oxidase B inhibitors (MAOB-I), and cathechol-O-methyltransferase inhibitors (COMT-I). Istradefylline is a selective antagonist of the adenosine A2A receptor, and has been approved for use in PD with regard to anti-parkinsonian effects in patients with wearing-off symptoms [1]. A recent phase III trial demonstrated that the oral administration of istradefylline (20 mg) reduced off time in patients, while 40 mg of istradefylline improved part III of the Unified Parkinson's disease Rating scale (UPDRS) during on-phase [2]. However, the clinical results were inconsistent. While istradefylline demonstrated prominent effects in a number of patients; others experienced little or no benefit. Therefore, to elucidate the epidemiological differences between istradefylline responders and non-responders, a retrospective analysis was performed.

2. Methods and Materials

2.1. Patients

Patients with PD were recruited according to the following specifications: 1) patients were diagnosed on the basis of the UK PD Brain Bank criteria [3]; 2) patients were medicated with levodopa and experienced wearing off; 3) patients featured a rating between 0 and 4 on the modified Hoehn and Yahr (H&Y) scale during the on-phase; and 4) patients wanted to reduce their off-phase disability and received 20 mg/day of istradefylline once in the morning in A.Y.'s outpatient clinic at the Juntendo University Koshigaya hospital between October 2013 and October 2015. Participants were excluded based on the following criteria: 1) patients experienced Parkinsonism due to diseases other than PD; 2) patients were diagnosed with other serious diseases, malignant tumors, or adverse events caused by drugs. All patients provided informed consent prior to the data collection. This study was approved by the Juntendo Koshigaya Hospital Institutional Ethics Committee.

2.2. Evaluations

Upon initiation of istradefylline (baseline) treatment and after the 8th week visit, patients were examined according to the UPDRS [4], Epworth sleepiness scale (ESS), [5] on time and off time, and sleeping time, which were recorded in an on/off hourly diary for one week. Responders were evaluated according to the criteria: "very much improved," "much improved," and "minimally improved," while non-responders were defined as "no change" and "worsened" using the Patients Global Impression of Improvement.

2.3. Statistical Analysis

We compared the two groups by using either t-test or χ^2-test using SPSS (Version 20.0). Two-sided statistical tests were used and the significance level was set at 0.05.

3. Results

The epidemiological characteristics of 31 Japanese patients (male 11, female 20)

Table 1. Patient characteristics at baseline and the 8th week.

	Baseline		8th week		*p*
	Mean	Std. Deviation	Mean	Std. Deviation	
Age	65.4	10.3			
Disease duration (years)	10.4	6.1			
Daily levodopa (mg)	553.2	228.7			
Frequency of the levodopa consumption	4.7	1.5			
Levodopa equivalent dose (mg)	811.2	307.5			
Unified Parkinson's disease Rating scale					
Total	32.1	24.2	28.5	21.4	0.030*
Part II	8.3	7.2	6.9	5.7	0.015*
Part III	19.4	16.9	17.2	15.3	0.107
Part IV	3.9	1.9	3.7	2.6	0.897
On time (hours)	12.0	3.4	14.0	3.4	0.008**
Off time (hours)	5.3	3.1	3.1	2.8	0.007**
Epworth sleepiness scale	7.0	5.6	6.1	5.3	0.458

*$p < 0.05$, **$p < 0.01$.

are displayed in Table 1. Istradefylline significantly increased On-time ($p < 0.01$), and decreased Off-time ($p < 0.01$), total UPDRS ($p < 0.05$), and UPDRS part II ($p < 0.05$) in patients with PD associated motor complications. Twenty one patients were responsive to istradefylline, while 10 patients did not demonstrate any therapeutic benefit. One patient who experienced auditory hallucinations was included in the non-responder group. The dyskinesia severity score (UPDRS) increased from 1 to 2 in several of the responders (n = 2). Other responders experienced slight euphoria (n = 2). Subsequent analysis identified significant differences in the baseline characteristics of responders (n = 21) and non-responders (n = 10) with regard to sex, age, age at onset, age at dyskinesia onset, and ESS (Table 2). No differences were detected in disease duration or daily levodopa dosage. The ESS of non-responders was improved by istradefylline treatment, but was not significant. Regression analysis of changes in On- or Off-time did not indicate any correlations, and logistic regression analysis demonstrated that the odds ratio for non-responders was 1.519 (95% confidence interval 1.021 - 2.261, p = 0.039) in ESS. No correlation was detected between the effects of istradefylline and the therapeutic combination of DA, COMT-I, selegiline, and zonisamide. In the non-responder group, with the exception of one patient with hallucinations, no improvements were detected after istradefylline treatment with 40 mg.

4. Discussion

This study demonstrated the therapeutic efficacy of istradefylline with regard to increasing On-time and reducing Off-time, and UPDRS-ADL (part II) score

Table 2. Clinical differences of responders and non-responders to istradefylline.

	Responders		Non-responders		*p*
Sex (Male: Female) n	5	16	6	4	0.049*
	Mean	Std. Deviation	Mean	Std. Deviation	*p*
Age at onset	51.9	12.3	61.5	10.5	0.043*
Age at examination	62.9	10.4	70.6	8.0	0.049*
Disease duration (year)	9.1	6.2	9.1	6.2	0.429
Age at onset of wearing off	59.3	11.0	65.6	9.4	0.127
Wearing off duration (year)	3.7	3.7	4.1	4.7	0.774
Age at onset of dyskinesia	57.9	8.8	67.6	7.2	0.025*
Dyskinesia duration (year)	4.2	4.3	3.7	5.6	0.468
Daily cups of coffee	1.1	1.2	0.5	0.6	0.105
Daily levodopa (mg)	538.1	254.9	585.0	168.4	0.414
Levodopa cumulative dose (g)	1163.5	1141.4	1023.7	1453.9	0.772
Levodopa equivalent dose (mg) [6]	802.5	320.1	829.4	294.7	0.825
Frequency of the levodopa	4.6	1.4	4.9	1.7	0.569
On time (hour)	11.8	3.6	10.0	3.7	0.236
Off time (hour)	5.3	3.6	7.1	2.1	0.216
Sleeping time (hour)	6.8	1.9	6.9	2.3	0.886
Total UPDRS	29.2	22.4	35.4	26.1	0.744
UPDRS part II	7.9	7.3	9.6	7.1	0.617
UPDRS part III	16.9	15.6	21.3	18.4	0.763
UPDRS part IV	3.5	1.8	4.0	2.0	0.337
Epworth sleepiness scale	4.5	2.7	11.2	6.7	0.001**
The change from the baseline					
On time (hour)	2.8	3.5	0.0	0.6	0.073
Off time (hour)	−2.8	3.6	−0.3	0.9	0.105
Total UPDRS	−3.9	7.0	−2.9	6.1	0.744
UPDRS part II	−1.2	2.4	−1.7	1.9	0.617
UPDRS part III	−2.6	6.5	−1.7	5.0	0.763
UPDRS part IV	−0.3	0.9	0.6	2.0	0.337
Epworth sleepiness scale	0.0	1.8	−1.8	4.7	0.231

UPDRS: Unified Parkinson's disease Rating scale, *$p < 0.05$, **$p < 0.01$.

without affecting sleepiness. The majority of anti-parkinsonian drugs produce sleepiness in patients, excluding anti-cholinergics, amantagine, and selegiline; however, istradefylline maintains the level of sleepiness. Significant differences were detected between responders and non-responders in relation to sex, age, age at onset, and ESS. The study found no differences between the groups with

regard to disease duration, daily or cumulative levodopa dose, duration of baseline On- or Off-time, or the age at the onset of wearing off. In addition, no differences were detected in the duration of dyskinesia between the two groups; however, the onset of dyskinesia was earlier than that of wearing off in responders. This might relate to the increase in putamen adenosine A_{2A} receptors observed in PD patients with dyskinesia [7].

Caffeine is an adenosine A_{2A} antagonist that induces wakefulness via pre adenosine A_{2A} receptors [8]. In the present study, the level of sleepiness correlated with the effects of istradefylline; therefore, patients who maintain sleep control might be suitable for istradefylline therapy.

Patients with PD demonstrate adenosine A_{2A} receptor up-regulation in lymphocyte membranes compared to healthy subjects [9]. No differences in A_{2A} receptor parameters were detected in relation to age, age at onset, or disease duration strata. Patients with a greater density of A_{2A} receptors were more likely to experience motor complications [9]. In the present study, earlier onset of dyskinesia correlated with the effectiveness of istradefylline; however, the duration of dyskinesia was unrelated. Accordingly, the daily levodopa dose, levodopa equivalent dose, and the levodopa cumulative dose were not linked to the effectiveness of the adenosine A_{2A} antagonist istradefylline in this study.

Previous studies did not identify increased responsiveness to istradefylline in female patients with PD. The adenosine A_{2A} receptor antagonist ATL 444 demonstrated reduced sensitivity in male compared to female rats [10]. However, the mechanisms underlying sex-related differences in adenosine A_{2A} receptor sensitivity were not identified, although ovarian hormones are reported to increase the sensitivity of the D2/A2A receptor system in females [11]. The efficacy on the reduction of daily Off-time shown in four of the five randomized controlled, double blinded, multicenter trials (**Table 3**) [12] [13] [14] [15]. A Japanese phase III trial that included more female subjects than the western trial demonstrated

Table 3. Off-time change from baseline of the randomized multicenter trials of Istradefylline.

			Placebo			20 mg				40 mg			
		n	Mean age (SD)	Male %	Change of OFF time (hours)	Mean age (SD)	Male %	Change of OFF time (hours)	*p*-value	Mean age (SD)	Male %	Change of OFF time (hours)	*p*-value
LeWitt PA. *et al.* [12]	2008	196	64 (10.0)	60.6	−0.64	–	–	–	–	63 (9.0)	59.7	−1.79	0.006
Hauser RA. *et al.* [13]	2008	231	64 (10.2)	67.0	−0.9	63 (9.5)	66.1	−1.6	0.03	–	–	–	–
Pourcher E. *et al.* [14]	2012	584	63 (8.3)	64.2	−1.3	64 (9.8)	69.1	−1.1	–	63 (9.3)	65.8	−1.5	0.529 (overall)
Mizuno Y. *et al.* [15]	2010	363	65.0 (7.6)	38.1	−0.66	65.1 (7.2)	43.5	−1.31	0.013	63.7 (8.6)	44.4	−1.58	<0.001
Mizuno Y. *et al.* [2]	2013	373	65.8 (8.6)	47.2	−0.23	66.1 (8.6)	33.3	−0.99	0.003	65.7 (9.0)	52.0	−0.96	0.003

a reduction in daily Off-time in the istradefylline group [2]. In a western Phase III trial, KW-6002-US-018, a reduction in Off-time was −1.3 hours in the placebo group, and it was −1.1 hours in the 20 mg of istradefylline group [14], and their baseline characteristics were similar to the present study, excluding those regarding race and sex. Although, other two Western studies including the same ratio of sex, showed the efficacy on the reduction of Off-time [12] [13] (**Table 3**).

This study featured several limitations. Primarily, the present study featured a small population; therefore, a larger study will be required to validate these results. Second, this was an open study, and it was not possible to rule out the placebo effect. In addition, the previous Japanese phase III trial revealed a 0.28 h increase in On-time, and a 0.23 h reduction in Off-time in the placebo group, therefore, additional effects need to be explored to elucidate this [2]. The placebo effects in female subjects are described in one report, which stated that female subjects with both lower dispositional anxiety and cortisol levels showed the largest vasopressin-induced modulation of placebo effects [16]. However, Shetty *et al*. analyzed the placebo effects in PD from 22 reports and a DATATOP study and found no correlation with age and gender [17]. In addition, Goetz *et al*. reported that gender, age, disease duration, and baseline disability score did not influence the likelihood of improvement in association with placebo treatment [18].

5. Conclusion

In summary, our results cannot deny placebo effects; however, this study suggests that younger or female patients who are not excessively sleepy during the daytime are better candidates for istradefylline therapy.

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