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Clinical Efficacy of Istradefylline for Depression in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a common movement disorder with a wide range of non-motor symptoms. Depression is one of these symptoms; however, its pathomechanism and management remains to be elucidated. We evaluated of istradefylline (ISD), a first selective adenosine A_{2A} receptor antagonist, for the treatment of depression in PD.

Method: This was an open-labeled, prospective study that enrolled 15 PD patients (Men 8, Women 7) with motor fluctuations who fully filled UK PD society brain bank clinical diagnostic criteria. We added ISD 20 mg/day for 4 weeks followed with 40 mg/day for next 4 weeks on the preceding anti-parkinsonian medications. We evaluated Patient Health Questionnaire (PHQ-9) and Unified PD Rating Scale (UPDRS) part III (on state) at baseline and 8 weeks follow-up.

Results: 14 patients completed the evaluations. PHQ-9 scores improved in 5 patients (responder). PHQ-9 scores of responders at baseline were higher than those of non-responders; however, there was no significant difference. Furthermore, there were no significant differences in UPDRS part III, age, onset, duration, daily levodopa dose, and levodopa equivalent dose at baseline among both groups. UPDRS part III scores improved in both groups; however, there was also no significant difference between them.

Conclusion: ISD could have efficacy to depression in some PD patients.

Keywords: Parkinson's disease; Non-motor symptoms; Depression; Istradefylline; Adenosine A_{2A} antagonist

Introduction

A selective adenosine A_{2A} receptor antagonist, istradefylline (ISD), is the one of novel drugs for Parkinson's disease (PD). The clinical efficacy of ISD for motor fluctuations in advanced PD patients was proved [1-5]; however, its efficacy for non-motor features in PD has not been elucidated well. We conducted an open-labeled, prospective clinical study to evaluate efficacy of ISD for depression in PD patients.

Patients and Methods

We enrolled 15 patients (Men 8, Women 7; aged 60 - 79 years; **Table 1**) with idiopathic PD with motor fluctuations. All the patients fully filled UK PD society brain bank clinical diagnostic criteria [6]. We enrolled patients who had been stable (no drug adjustments needed) on anti-parkinsonian drugs for 4 weeks prior to study. We added ISD 20 mg/day for 4 weeks followed with 40 mg/day for next 4 weeks on the previous anti-parkinsonian drugs. We evaluated Patient Health Questionnaire (PHQ-9) [7] and Unified PD Rating Scale (UPDRS) part III scores (on state) [8] at baseline and 8 weeks follow-up. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively. The results were presented as mean values ± standard deviation (SD). Wilcoxon t-test and Mann-Whitney U-test were used to compare the clinical values. A p-value < 0.05 was considered as statistically significant. We excluded patients with dementia or major depression.

This study was approved by the Review Board of Tokushukai Medical Alliance and all the patients provided written

informed consent in accordance with the Declaration of Helsinki before enrollment.

Table 1 Demography of patients (LED: Levodopa Equivalent Dose).

No.	Age (y.o.)	Sex	Onset (y.o.)	Duration (months)	PHQ-9	UPDRS part III (on state)	L-dopa (mg)	LED (mg)
1	70	M	53	214	9	14	400	712
2	79	M	71	103	14	18	500	690
3	76	F	73	31	10	17	150	150
4	68	F	63	56	9	10	500	734
5	78	M	70	99	6	18	600	1049
6	72	M	57	184	11	35	400	774
7	76	F	62	164	4	19	450	600
8	62	F	59	45	9	48	300	399
9	71	M	64	82	5	17	200	306
10	79	F	67	150	5	15	300	488
11	66	M	61	63	1	21	200	266
12	63	M	60	30	2	18	100	140
13	76	M	71	69	18	39	200	300
14	60	F	57	37	0	9	100	175
15	77	F	57	238	6	37	450	450

Results

14 patients completed the evaluations because one patient withdrew due to hallucination (No.12). No patient was administered any antidepressants from 4 weeks prior to study to the end-point. PHQ-9 scores showed no significant improvement totally (from 7.6 ± 4.8 to 7.8 ± 4.6, p=0.591); however, PHQ-9 scores improved in 5 of 14 patients (responder). Although there was no significant difference, the PHQ-9 scores of responders seemed higher than those of non-responders (10.2 ± 4.8, 6.2 ± 4.5, p=0.204). Furthermore, there were no significant differences in age, onset, duration of PD; UPDRS part III, daily levodopa dose, and levodopa equivalent dose (LED) [9] between responders and non-responders at baseline **(Table 2).** On the other hand, UPDRS part III scores improved significantly (from 22.6 ± 12.0 to 8.7 ± 6.9, p=0.002). UPDRS part III scores improved in both groups; however, there was no significant difference between them (-18.0 ± 12.7, -11.7 ± 8.5, p=0.439).

Table 2 Characteristics of responder and non-responder at baseline.

Variables	Responder	Non-responder	p-value
PHQ-9	10.2 ± 4.8	6.2 ± 4.5	0.204*
Age (y.o.)	70.6 ± 5.9	73.0 ± 6.6	0.337**
Onset (y.o.)	66.0 ± 5.8	61.7 ± 6.4	0.171**
Duration (months)	56.2 ± 20.6	132.9 ± 75.1	0.094**
UPDRS part III	26.2 ± 16.4	20.7 ± 9.4	0.549*
L-dopa (mg)	270.0 ± 140.0	377.8 ± 154.3	0.279**
LED (mg)	377.8 ± 218.2	578.2 ± 268.2	0.229**
*Wilcoxon t-test; **Mann-Whitney U-test			

Discussion

PD is a progressive neurodegenerative disorder manifested by a broad spectrum of motor and non-motor features. Non-motor symptoms include autonomic dysfunction, cognitive/ neurobehavioral disorders, sensory abnormalities, and sleep disorders [10]. Depression is one of the frequent non-motor symptoms in PD and could suffer under the influence of quality of life; however, the pathomechanism and management are discussed.

ISD is the first therapeutic agent targeting adenosine A_{2A} receptors in the central nervous system, which was approved as the anti-parkinsonian agent in 2013. The efficacy on the reduction of daily off-time was shown in several randomized controlled, double blinded, multicenter trials [**1-5**]. In addition, the normalization of the striatal A_{2A} receptor-upregulations and the effect to A_{2A} receptors in nucleus accumbens were suggested to have relations with antidepressant-like effects of A_{2A} receptor antagonist in rodent models [11-13].

ISD was reported to show prominent effects in some PD patients and younger or female patients without excessive daytime sleepiness were suggested as better candidates [14]. In this study, ISD was effective for subclinical, less than moderately severe depression in some PD patients. Moreover, the clinical efficacy of ISD for depression in PD seemed not to be influenced by the improvement of motor function.

This study included three limitations. The size of study was so small that it might have powered insufficiently to detect a statistical significance and lead to be falsely negative. And we could not rule out the placebo effects because this study was an open-labeled. Furthermore, we used only PHQ-9 to evaluate depression in this study. PHQ-9 is a useful screening scale depression; however, it has limitations in identifying depression [15]. In future, we need randomized-controlled study with more patients and longer follow-up periods, and with more than one scale for depression to elucidate the effect of ISD for depression in PD.

Conclusion

ISD could improve depression in some PD patients.

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Conflicts of Interest

There are no conflicts.

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