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Role of istradefylline for treating Parkinson's disease

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Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission: 15 / 2 / 2019

ABSTRACT

This report evaluated the efficacy and safety of istradefylline in Parkinson's disease patients with wearing-off symptoms and dyskinesia. Parkinson's disease (PD) is the second-most common neurodegenerative disorder after Alzheimer's disease. It slowly progressive neurodegenerative disease results from reduction of dopaminergic activity in nigrostriatal pathway. Istradefylline is non-dopaminergic, selective adenosine A2a receptor antagonist for the treatment of Parkinson's disease (PD) in patients with wearing-off symptoms and dysknisia with levodopa (L-DOPA) therapy. Istradefylline safety was assessed by the incidence of treatment emergency adverse effects (TEAEs) and drug-related TEAEs. Effectiveness was assessed off-time, off-time symptoms, ON-time with dyskinesia and ON-time without dyskinesia. The change in daily OFF time duration was significantly reduced in the istradefylline 20 mg/day and istradefylline 40 mg/day groups. In the long term study that conducted in 2015 the most frequently TEAE was nasopharyngitis, and the most frequently drug-related TEAE was dyskinesia compared with the the study conducted between 2009 and 2011. istradefylline administered as adjunctive therapy to levodopa was safe and produced a sustained reduction in off time and further improved motor functions during on state in advanced Parkinson's Disease (PD) patients.

INTRODUCTION

Parkinson's disease (PD) is the second-most common neurodegenerative disorder after Alzheimer's disease. It slowly progressive neurodegenerative disease results from reduction of dopaminergic activity in nigrostriatal pathway[1].

The Parkinson is not the same for everyone, each person has unique and different symptoms. It affects about 4 million people worldwide, and this number is expected to double by the year 2030[2]. The stages of PD depend on both severity of movement symptoms and how much the disease affects a person's daily activities[3]. The causes of PD stay unknown may be due to combination of genetic and environmental factors[3].

The most part of the brain that is affected is located within the brain stem called substantia nigra. It's formed of group of cells responsible for produce a dopamine. Dopamine is a neurotransmitter responsible for sending out massage from substantia nigra to other parts of brain to control movement of body, where it's not enough the motor symptoms of PD will develop[1]. Due to dying or damaging of the cells that produce dopamine Primary motor symptoms of PD appear, include tremor (shaking), slowness of movement, muscle stiffness (rigidity) and impaired balance. Most people with PD also have non-motor symptoms may come before motor symptoms and PD diagnosis by years. The people with disease are at high risk of dementia[2].

Since the 1970, the treatment of PD is levodopa along with a periphral dopamine decarboxylase inhibitors that prevent periphral metabolism of levodopa but long-term levodopa use often causes motor complications such as dyskinesia and wearing-off symptoms. Management of PD still represent a challenge, especially when motor complications are present[1].

Istradefylline (ISD) is a nondopaminergic, selective adenosine A2 receptor antagonist, because of the lack of effects on dopamine receptors and dopamine-metabolizing enzymes. It is a new drug treats the symptoms of PD in combination with levodopa[3]. The purpose of this report was to evaluate the incidence of treatment emergency adverse effects and to identify unexpected TEAEs, as well as factors potentially affecting the safety and effectiveness of the long-term use of istradefylline as an adjunct to L-DOPA.

MATERIALS AND METHODS

The key exclusion criteria included a history of neurosurgery for PD, transcranial magnetic stimulation for PD, dementia, pregnant or lactating women, women planning to have children, and prior istradefylline exposure[3]. This study conducted between 2009 and 2011 by Mizuno, Y. and Kondo, T. at 44 investigative Japanese sites. The total patients are 373 that were selected randomly. The patients divided into 3 groups are 109 placebo, 111 istradefylline 20 mg/day, and 115 istradefylline 40 mg/ day all of the 3 groups completed 12 weeks of treatment[3]. During the 4 weeks prior to randomization the antiparkinsonian drugs were not changed. The dosages of antiparkinsonian drugs reduced only for Treatment Emergent Adverse Events (TEAEs)[3].

The primary efficacy variable was the difference between the total hours of awake time per day spent in daily OFF time. The secondary efficacy variables included change in percentage of awake time per day spent in the daily OFF time, change in percentage of awake time per day spent in the daily ON time and change in total hours of awake time per day spent in the daily ON time[3].

Whereas, In the long term study that conducted in 2015 by Kondo, T. and Mizuno, Y., the number of patients were 313 obtained from 44 investigative Japanese sites as we mentioned study conducted between 2009 and 2011. This long term study included 2 phases, 1 to 4-week double-blind transition phase and 52-week open-label phase. The patients in double-blind transition phase received the same treatment that administered at the 12-week study (study conducted between 2009 and 2011), namely, placebo, istradefylline 20 mg or 40 mg once daily. All patients received istradefylline once a day for 52 weeks at the first their dosage were 20 mg/d in the open-label phase. The dosage of istradefylline was increased to 40 mg/d after 4 weeks if the patient's clinical response was considered to unsatisfactory and there were no safety concerns[4].

The dose of istradefylline was reduced to 20 mg/d after 8 weeks if unwanted effects had occurred. The dose of concomitant antiparkinsonian drugs was constant as far as possible for about week 8. The TEAEs were based on body weight, vital signs, symptoms, laboratory results and other data[4]. Efficacy variable included the change in

daily ON time and daily OFF time compared with that at first study. In the first study the patients were placed in 3 groups: group one (placebo), group two (istadefylline 20 mg/d) and group 3 (istradefylline 40 mg/d) and patients who received one dose of this study were included in safety analysis set[4].

RESULTS

Fewer men were included in the istradefylline 20 mg/day group about 40/120 (33.3%), most of patients about 75 (61.0%) used concomitant selegiline in the istradefylline 40 mg/day group; and fewer subjects used concomitant entacapone in the placebo group about 52 (42.3%). Other demographics and characteristics had compared in (Table 1)[3].

The changes for primary efficacy (daily OFF time) are placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were 20.23, 20.99, and 20.96 hours, respectively[3].

The changes for secondary efficacy variable showed daily ON time without dyskinesia for placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were 0.26, 1.09, and 1.08 hours, respectively. The percentages of patients who were "Much improved" plus "Very much improved" at end point for placebo, istradefylline 20 mg/day, and istradefylline 40 mg/day were 10.7%, 20.8%, and 28.7%, respectively[3].

TEAEs occurred in 51.6% of patients that treated with placebo, 65.0% of patients that treated with istradefylline 20 mg/day and 59.7% of patients that treated with istradefylline 40 mg/day. One patient treated with placebo died on day 19[3].

In the long term study the 313 patients, 308 patients received open-label treatment. Five patients discontinued during the double-blind transition phase. 77 patients (group 1, 27; group 2, 28; group 3, 22) discontinued prematurely, and 231 patients (group 1, 73; group 2, 73; group 3, 85) completed this long-term study. In week 4, of the 297 patients who were receiving istradefylline, 165 received an increased dosage of 40 mg/d. The dosage was reduced from 40 mg/d to 20 mg/d in 10 patients, in week 8. Of the 231 patients that completed 52 weeks of treatment, 81 of them were receiving 20 mg/d istradefylline, and the other 150 were receiving 40 mg/d in week 52[4].

TABLE 1. Demographic and baseline

Characteristic	Placebo (n = 123)	Istradefylline 20 mg/day (n = 120)	Istradefylline 40 mg/day (n = 123)
Age (y), mean (SD)	65.8 (8.6)	66.1 (8.6)	65.7 (9.0)
Male, n (%)	58 (47.2%)	40 (33.3%)	64 (52.0%)
BMI, mean (SD), kg/m^2	22.17 (3.59)	22.34 (3.40)	22.37 (3.65)
Time since diagnosis (y), mean (SD)	7.990 (4.453)	7.301 (4.206)	7.730 (4.547)
Time since onset of motor complications (y), mean (SD)	3.432 (3.470)	3.183 (2.759)	3.258 (3.009)
Daily OFF time			
Mean (SD), h	6.31 (2.47)	6.55 (2.72)	5.97 (2.45)
Mean (SD), %	38.91 (14.80)	40.59 (16.19)	36.92 (15.10)
Daily ON time			
Without dyskinesia (h), mean (SD)	8.53 (2.84)	7.93(3.38)	8.50(3.54)
With dyskinesia (h), mean (SD)	1.35(2.50)	1.57(2.75)	1.83(3.30)
With nontroublesome dyskinesia (h), mean (SD)	0.94 (1.95)	1.00 (1.71)	1.13(2.03)
With troublesome dyskinesia (h), mean (SD)	0.41 (1.11)	0.58 (1.63)	0.69 (1.75)
Without troublesome dyskinesia (h), mean (SD)	9.47 (2.54)	8.93 (2.86)	9.64 (2.82)
UPDRS Part I subscale score, mean (SD)	1.1 (1.5)	1.2 (1.4)	1.0 (1.4)
UPDRS Part II subscale score (ON state), mean (SD)	5.9 (5.2)	5.3 (5.2)	5.3 (5.0)
UPDRS Part II subscale score (OFF state), mean (SD)	14.7 (7.7)	14.9 (7.5)	15.4 (8.1)
UPDRS Part III subscale score (ON state), mean (SD)	21.6 (11.6)	21.3 (10.8)	20.7 (11.0)
UPDRS Part IV subscale score, mean (SD)	4.7 (2.0)	5.1 (2.2)	5.0 (2.4)
Daily dosage of prior levodopa (mg), mean (SD)	425.4 (146.4)	430.8 (156.5)	420.5 (131.8)
Concomitant antiparkinsonian medications, n (%)			
Dopamine agonists	112 (91.1%)	103 (85.8%)	103(83.7%)
Anticholinergic agents	20 (16.3%)	12 (10.0%)	19(15.4%)
Selegiline	57 (46.3%)	52 (43.3%)	75 (61.0%)
Entacapone	52 (42.3%)	63 (52.5%)	68(55.3%)
Amantadine	49 (39.8%)	41 (34.2%)	44 (35.8%)
Zonisamide	17 (13.8%)	13 (10.8%)	20 (16.3%)

Mizuno, Y. and Kondo, T. (2013). Adenosine A2a receptor antagonist istradefylline reduces daily OFF time in PD

The mean daily dosage of levodopa in the first study was 416.3mg/d in group 1, 424.3 mg/d in group 2 and 422.7 mg/d in group 3. Additional dopamine agonists were taken by 90.0%, 89.1% and 83.2% of patients in groups 1,2 and 3 respectively[4].

Treatment Emergency Adverse Effect was 93.0% in group 1 and 85.6% in group 2/3 (88.0% in total). The most frequently TEAEs in group 1 were dyskinesia (25.0%) and nasopharyngitis (25.0%), followed by visual hallucination (11.0%), contusion (9.0%), and weight decrease (8.0%). In group 2/3 were most frequently TEAEs were nasopharyngitis (24.0%), followed by dyskinesia (19.7%), contusion (11.1%), constipation (10.6%), and visual hallucination (7.7%)[4].

The incidence of drug-related TEAEs was 57.0% and 45.2% in groups 1 and 2/3 respectively. The most frequently drug-related TEAE was dyskinesia was 21.0% in group 1 and 17.3% in group 2/3[4]. There are no deaths were reported but the serious TEAEs were reported by 12.0% and 13.0% in groups 1 and 2/3 respectively[4].

TEAEs that led to discontinuation of treatment occurred in 13.0% of group 1 and 5.3% of group 2/3. No difference was observed in the safety profile between group 1 and group 2/3, and no clinically abnormalities were noted in physical examinations, laboratory parameters and signs[4].

In group 1, the mean change in the daily off time in week 2 and in group 2, it remained at similar levels between weeks 2 and 4 but the mean change occurs between weeks 2 and 52 in group 3.

Discussion

In the long term study that conducted in 2015 the most frequently TEAE was nasopharyngitis by 25.0% in group 1 and, 24.0% in group 2/3, and the most frequently drug-related TEAE was dyskinesia (group 1, 21.0%; group 2/3, 17.3%)[4]. In 4 patients the most frequent serious adverse event was spinal compression fracture. Femoral neck fracture, gastric ulcer haemorrhage and colonic polyp were reported in 2 patients each[4]. Whereas, In the study conducted between 2009 and 2011 ,12 nasopharyngitis as a TEAE occurred in 8.7% of patients in the placebo, 8.1% of patients in the istradefylline 20 mg/d, and 5.6% of patients in the istradefylline 40 mg/d groups[3]. However, the investigators considered the all events of nasopharyngitis were unrelated to istradefylline. an increase in reports of nasopharyngitis in the long-term study (study that conducted in 2015) seems likely to be a result of the longer observation period in compare with the 12 weeks (first study). No patients experienced severe dyskinesia, and All events of dyskinesia were mild to moderate in severity. All of the patients received istradefylline in combination with levodopa for the entire studies so the occurrence of dyskinesia as a TEAE could not be distinguished from levodopa-related dyskinesia[4].

In the study conducted between 2009 and 2011 on advanced PD patients, dyskinesia as a drug-related TEAE occurred in 4.0% of patients in the placebo, 12.2% of patients in istradefylline 20 mg/d, and 12.1% of patients inistradefylline 40 mg/d groups[3]. Ports of dyskinesia in the long-term study seems likely to be a result of disease progression or the longer observation period (52 vs 12 weeks). Serious adverse events were observed in 2 patients receiving placebo that are toxicity to various agents and breast cancer in situ, in 6 patients receiving istradefylline 20 mg/day there are 8

events; gait disturbance, neuralgia, radius fracture, sciatica, parkinsonism, delirium, bile duct cancer and pneumonia bacterial and in 6 patients receiving istradefylline 40 mg/day there are 6 events; gastric ulcer, rectal cancer, myocardial infarction, pneumonia aspiration,bronchitis and hallucination. All events resolved and there are no clinically meaningful changes from baseline were observed in laboratory results, ECG, body weight and vital signs[3].

In both studies the most of the reported treatment emergent adverse effects (TEAEs) were mild to moderate in severity were not dose dependent. In the long-term study, the most frequently reported drug-related TEAE was dyskinesia and the most frequently reported TEAE was nasopharyngitis but in the first study, the most frequently reported drug-related TEAE and TEAE were both dyskinesia which occurred with a higher incidence in patient treated with istradefylline than with placebo[4]. Serious adverse events were observed in 2 patients receiving placebo that are toxicity to various agents and breast cancer in situ, in 6 patients receiving istradefylline 20 mg/day there are 8 events; gait disturbance, neuralgia, radius fracture, sciatica, parkinsonism, delirium, bile duct cancer and pneumonia bacterial and in 6 patients receiving istradefylline 40 mg/day there are 6 events; gastric ulcer, rectal cancer, myocardial infarction, pneumonia aspiration, bronchitis and hallucination. All events resolved and there are no clinically meaningful changes from baseline were observed in laboratory results, ECG, body weight and vital signs[3].

Group 1 switched from placebo to istradefylline in the study that conducted in 2015 and showed a reduction in mean daily off time in week 2, which was maintained up to week 52. Group 2/3 both received istradefylline in both studies, and also showed reduced mean daily off time until week 52[4]. The effectiveness of istradefylline in reducing of daily OFF time had not affected by sex or age[3]. Off time reduction was better in group 2/3 compared with that in group 1 in all the study period until week 52[4].

In the study conducted between 2009 and 2011, Istradefylline 20 and 40 mg/day significantly increased in daily ON time without dyskinesia compared with placebo[3]. No one of the groups showed an increase in daily on time with dyskinesia[4].

These data showed that istradefylline effected in Parkinson disease patients with wearing-off symptoms for at least 52 weeks.

Conclusion

This report demonstrates that istradefylline administered as adjunctive therapy to levodopa was safe and produced a sustained reduction in off time and further improved motor functions during on state in advanced PD patients, thus showing a nondopaminergic drug that can be added to any existing PD therapy.

Future work

In this report we had wondered about some questions that we didn't find their answers, one of them mode of action of istradefylline that may be can help in other questions like the causes of side effects and we hope create studies that will be limit the progression of the disease and not only minimize the symptoms.

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