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Istradefylline, an adenosine A_{2A} receptor antagonist, for patients with Parkinson's Disease: A meta-analysis

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ABSTRACT

Objectives: To assess the efficacy and safety of istradefylline as an adjunct to levodopa in patients with Parkinson's Disease (PD).

Methods: In this study, we searched the Cochrane Library, MEDLINE, Embase, China Academic Journal Full-text Database (CNKI), China Biomedical Literature Database (CBM), Chinese Scientific Journals Database (VIP), and Wanfang Database. The quality of included studies was strictly evaluated. Data analyses were performed by the Cochrane Collaboration's RevMan5.0 software.

Results: Five randomized controlled trials (RCTs) were included. The result showed a significant reduction of the awake time per day spent in the OFF state and improvement of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III in the ON state when receiving istradefylline compared with patients receiving placebo. There was no significant difference between the istradefylline 20 mg and the istradefylline 40 mg groups in the UPDRS Part III in the ON state (WMD = 1.27, 95% CI [−0.40, 2.95]). The results showed significant differences in dyskinesia (RR = 1.63, 95% CI [1.16, 2.29]) compared to istradefylline 40 mg with placebo. There was no significant statistical difference with regard to other adverse events.

Conclusions: The present study showed that istradefylline is safe and effective as an adjunct to levodopa in patients with PD. Future large-scale, higher-quality, long-treatment, and placebo-controlled trials are needed.

1. Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine producing neurons in the substantia nigra, leading to major motor function impairments such as bradykinesia, rigidity, and tremors [1]. It is the most common neurodegenerative disease after Alzheimer's disease, which affects at least six million people worldwide [2]. Of all the available antiparkinsonian drugs, the dopamine precursor L-dopa remains the most effective and major drugs for relieving PD symptoms, with the most rapid onset of action, the fewest side effects and the lower cost in the short term treatment [3,4]. However, L-dopa administration due to its short-acting drug characteristic [5], combined with the disease progression, leads to motor fluctuations [6,7]. The number of individuals afflicted by PD is expected to double by 2030 [8]. Therefore, this requires new effective antiparkinsonian therapies to PD management, especially for long-term treatment.

Antagonists of the adenosine receptor subtype A_{2A} had shown efficacy in antiparkinsonian activities in rodents and nonhuman primate models [9–11]. Istradefylline (KW-6002; (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione, produced by Kyowa Hakko Kogyo) is a selective adenosine A_{2A} receptor antagonist, which has a 12 nmol/L human binding affinity constant (Ki) in human brain [12,13]. Istradefylline reverses motor impairments in neurotoxin-induced parkinsonism experimental models in rodents and in non-human primates [14,15].

Recently, istradefylline is being applied more and more frequently to patients with PD, but its effectiveness and safeness lack systematic evidence. This meta-analysis is based on RCTs to evaluate the efficacy and safety of istradefylline in patients with PD.

2. Patients and methods

2.1. Inclusion and exclusion criteria

2.1.1. Type of studies

All randomized trials tested the effect of istradefylline use for patients with PD.

2.1.2. Type of participants

Eligible patients were at least 20 years old, met the United Kingdom Parkinson's Disease Society Criteria (UKPDSC) [16], with a modified Hoehn and Yahr Stage [17] 2 to 4 in the OFF state, and had an average of at least 2 h per 24 h of OFF time. In addition, patients had to be treated with at least 3 doses/day (if 2 or more were a sustained-release formulation) of levodopa for at least 1 year and had been on a stable PD

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Table 1
Basic characteristics of the patients in five RCTs.

Study	Pourcher (2011)			Mizuno (2010)			Hauser (2008)		LeWitt (2008)		Stacy (2008)	
Group	Istrade-1	Istrade-2	Placebo	Istrade-1	Istrade-2	Placebo	Istrade-1	Placebo	Istrade-2	Placebo	Istrade-1	Placebo
Age (years)	64 (9.8)	63 (9.3)	63 (8.3)	65.1 (7.2)	63.7 (8.6)	65.0 (7.0)	63 (9.5)	64 (10.2)	63 (9)	64 (10)	65.0 (9.59)	63.0 (12.05)
Male (%)	103 (69.1)	100 (65.8)	97 (64.2)	50 (43.5)	55 (44.4)	45 (38.1)	76 (66.1)	77 (67.0)	77 (59.7)	40 (60.6)	104 (63.8)	54 (70.1)
Time since diagnosis (years)	8.9 (4.6)	8.5 (4.6)	9.1 (5.1)	8.037 (4.076)	8.089 (4.048)	8.338 (4.826)	10.0 (5.5)	8.8 (4.4)	9.3 (4.7)	9.3 (5.1)	9.24 (5.275)	8.69 (5.002)
Time since onset of motor complications (years)	3.7 (3.4)	3.4 (3.2)	3.7 (3.5)	3.167 (2.499)	3.126 (2.884)	3.506 (3.015)	4.0 (3.7)	3.6 (3.3)	3.3 (2.5)	3.6 (3.2)		
The daily OFF time per day (h)	6.7 (2.2)	6.9 (2.3)	6.7 (2.1)	6.79 (2.86)	6.55 (2.48)	6.43 (2.71)	6.7 (2.8)	6.5 (2.1)	6.4 (2.7)	6.2 (2.5)	5.72 (2.502)	6.31 (2.591)
UPDRS Part III subscale score (ON state)	22.3 (11.3)	21.9 (11.5)	22.7 (11.8)	21.0 (10.6)	21.1 (11.0)	20.6 (9.2)	23.9 (11.3)	22.8 (11.2)	17.7 (11.1)	18.0 (11.2)	17.6 (9.82)	16.2 (8.80)
Daily dosage of levodopa (mg)	602 (357)	645 (407)	718 (394)	407.0 (113.1)	415.3 (159.2)	426.3 (143)	652 (370.6)	631 (356.7)	560 (291)	589 (301)		
Dopaminergic agonist use	136 (91.3)	138 (90.8)	135 (89.4)	110 (95.7)	114 (91.9)	105 (89.0)	103 (89.6)	104 (90.4)	116 (89.9)	51 (77.3)	149 (91.4)	71 (92.2)
Entacapone use	70 (47.0)	65 (42.8)	63 (41.7)	22 (19.1)	16 (12.9)	15 (12.7)	55 (47.8)	47 (40.9)	53 (41.1)	27 (40.9)	67 (41.1)	27 (35.1)
Amantadine use	38 (25.5)	39 (25.7)	37 (24.5)	43 (37.4)	39 (31.5)	45 (38.1)	37 (32.2)	34 (29.6)	35 (27.1)	20 (30.3)	46 (28.2)	23 (29.9)
Selegiline use	18 (12.1)	18 (11.8)	27 (17.9)	57 (49.6)	67 (54.0)	62 (52.5)	13 (11.3)	13 (11.3)	24 (18.6)	9 (13.6)	25 (15.3)	13 (16.9)

Data are mean(SD) or n(%) istrade-1: istradefylline (20 mg); istrade-2: istradefylline (40 mg).

medication regimen for at least 4 weeks before the study. The individuals were excluded if they had received previous treatment with istradefylline.

2.1.3. Type of interventions

The inclusion criteria for the meta-analysis were RCTs which tested the effect of istradefylline for patients in PD in comparison with placebo.

2.1.4. Outcome

The primary endpoint was the change of the awake time per day spent in the OFF state from baseline to endpoint. The secondary outcome was the change in UPDRS Part III score (Motor Subscale). The adverse events were drug-related treatment emergent adverse events (TEAEs), dyskinesia, nausea and constipation.

2.2. Search strategy

We searched MEDLINE (1966–2011/10), the Cochrane Library (2011/10 issue), Embase (1974–2011/10), CNKI (1994–2011/10), CBM (1978–2011/10), VIP (1989–2011/10), and Wanfang Database (1999–2011). The search terms used included: istradefylline, KW-6002, an adenosine A_{2A} receptor antagonist, Parkinson's Disease, parkinsonism, parkinsonismus and PD. We also searched the references of all primary studies in all academic journals.

2.3. Data extraction

Data were extracted by two of us (Chen and Wang). From included trials, we recorded the journal, the first author, the study design, the intervention, the outcome, the country, etc.

2.4. Quality assessment of RCTs

After reviewing all trials, we identified five original trials. The basic information of the patients in each study is shown in Table 1. We also evaluated the quality of every study according to their randomization method, blinding and follow-up. The criteria were cited from the Cochrane Collaboration guidelines (Table 2).

2.5. Statistical analysis

We extracted and pooled data using Review Manager 5.0 software. We showed outcomes with continuous as weighted mean difference (WMD) or standardized mean difference (SMD) and for dichotomous as relative risk (RR), with 95% confidence intervals (CI), and with chi-square statistic to assess the extent of inconsistency. Data analysis was performed using the fixed-effect model with no significant heterogeneity or using a random-effect model with significant heterogeneity. Subgroup analyses were intended to explore important clinical differences among trials.

3. Result

3.1. Search result

The electronic search yielded 186 trials from Embase, 64 from PubMed, 7 from the Cochrane Library, 5 from Chinese Scientific Journals Fulltext Database, and 3 trials from China Journal Fulltext Database, and 9 trials from Wanfang Database. Seven RCTs were identified. After reading each article, only five [18–22] of them fulfilled the inclusion criteria (Fig. 1).

Table 1 contains the basic information on randomization methods, sample sizes, ITT, intervention, and follow-up. Two studies [20,21] pointed out that the randomization was done with a randomization schedule. Double-blind trials were described in all studies. All of the