

Istradefylline: A novel agent in the treatment of “off” episodes associated with levodopa/carbidopa use in Parkinson disease

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Abstract

The current gold standard for treatment of Parkinson disease (PD) is levodopa/carbidopa (L/C), but long-term treatment frequently results in motor complications, such as wearing-off and motor fluctuations (eg, dyskinesia, “on-off” phenomenon). Istradefylline is a new drug with a unique pharmacologic profile that was approved by the FDA for use as adjunctive treatment to L/C in adult patients with PD experiencing “off” episodes. The drug was shown to reduce “off” time in 4 randomized, double-blind, placebo-controlled studies. The most common adverse effects are dyskinesia, dizziness, constipation, nausea, hallucinations, and insomnia. Unlike many drugs that treat PD, istradefylline is a nondopaminergic drug that exerts its effects via adenosine A_{2A} receptor antagonism. The major drug interactions involve inhibitors or inducers of CYP3A₄ as well as tobacco smoking via induction of CYP1A₁. Istradefylline is taken once daily as a 20- or 40-mg dose, except in cases involving drug interactions or hepatic impairment. The cost of the drug is relatively expensive, which has implications for Medicare and private insurance coverage. Istradefylline is an alternative option to dopaminergic drugs such as dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors as an adjunct to L/C in patients with motor fluctuations, but clinical use will further define its role in treatment of PD.

Keywords: istradefylline, Parkinson disease, adenosine A_{2A} receptor antagonists

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Background

Parkinson disease (PD) is a complex neurodegenerative movement disorder that is estimated to affect 572 out of every 100 000 people aged 45 years and older.¹ The

pathophysiology of PD involves loss of dopaminergic neurons in the substantia nigra (SN). The current gold standard for treatment of PD is levodopa/carbidopa (L/C), which essentially serves to replace lost dopamine in the CNS. Unfortunately, long-term treatment with L/C can result in motor complications, such as wearing-off symptoms (diminishing effects before it is time for the next dose), dyskinesia (unintended, involuntary, and uncontrollable movements), and “on-off” phenomenon (sudden changes in movement control for variable durations).² It is estimated that over one-half of PD patients will develop motor complications within 5 to 10 years of initiating L/C therapy.³ Other well-known drugs in treatment of PD in such circumstances include dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase B (MAO-B) inhibitors;

TABLE: Efficacy trials⁶⁻⁹ that led to FDA approval

Study	Design	Patients Enrolled	Randomization	Results ^a
LeWitt et al ⁶ (2008)	Randomized, double-blind, placebo-controlled trial 12-wk duration 23 North American sites	Levodopa-treated PD patients with “off” time ≥ 2 hr/d	Istradefylline 40 mg/d = 130 Placebo = 66	Placebo = -4.0% Istradefylline = -10.8% (<i>P</i> = .007) Placebo = -0.64 hr Istradefylline = -1.79 hr (<i>P</i> = .006)
Hauser et al ⁷ (2008)	Randomized, double-blind, placebo-controlled trial 12-wk duration 26 American sites	Levodopa-treated PD patients with “off” time ≥ 3 hr/d	Istradefylline 20 mg/d = 116 Placebo = 115	Placebo = -5.0% Istradefylline = -9.3% (<i>P</i> = .03) Placebo = -0.9 hr Istradefylline = -1.6 hr (<i>P</i> = .03)
Mizuno et al ⁸ (2010)	Randomized, double-blind, placebo-controlled trial 12-wk duration 47 Japanese sites	Levodopa-treated PD patients with “off” time ≥ 2 hr/d	Istradefylline 20 mg/d = 119 Istradefylline 40 mg/d = 125 Placebo = 119	Placebo = -0.66 hr Istradefylline 20 mg/d = -1.31 hr (<i>P</i> = .013) Istradefylline 40 mg/d = -1.58 hr (<i>P</i> < .001)
Mizuno et al ⁹ (2013)	Randomized, double-blind, placebo-controlled trial 12-wk duration 44 Japanese sites	Levodopa-treated PD patients with “off” time ≥ 2 hr/d	Istradefylline 20 mg/d = 123 Istradefylline 40 mg/d = 124 Placebo = 126	Placebo = -0.23 hr Istradefylline 20 mg/d = -0.99 hr (<i>P</i> = .003) Istradefylline 40 mg/d = -0.96 hr (<i>P</i> = .003)

PD = Parkinson disease.

^aMean change in daily time spent in off state from baseline to endpoint.

unfortunately, the dopaminergic effects of these drugs can cause motor fluctuations (eg, dyskinesia) as well as serious adverse effects (eg, psychosis) in patients.⁴ There is still a need for additional treatments for PD owing to the complexity of the disease and paucity of curative treatment options.

Adenosine receptors found throughout the CNS are thought to play a role in the development of PD; however, the mechanisms behind this are not completely understood.⁴ Several adenosine receptor antagonists have been developed and studied in PD patients, but the principal one is istradefylline.⁵ Approved in the United States in August 2019, istradefylline is the first adenosine receptor antagonist labeled for use in PD.⁵ Its novel mechanism of action may lend it a unique place in therapy. The goal of this concise review is to provide clinicians with an overview of istradefylline in treatment of “off” episodes associated with L/C use in PD.

Efficacy

The FDA approval of istradefylline was based on results from 4 randomized, double-blind, placebo-controlled trials (Table).⁶⁻⁹ All 4 trials examined reduction of daily awake “off” time (percentage or hours) as the primary endpoint over a 12-week period, and istradefylline reduced “off” time by approximately 1 to 2 hours in these trials. Furthermore, a recently published pooled analysis¹⁰ of 8

randomized, placebo-controlled, double-blind phase 2b/3 studies (including the studies in the Table) showed that istradefylline significantly improved “off” time as well as “on” time without troublesome dyskinesia relative to placebo. However, some placebo-controlled studies^{11,12} have failed to show efficacy of istradefylline in PD, including a phase-3 trial examining istradefylline as adjunctive therapy to L/C in PD patients with motor-response complications to reduce “off” time and a trial that studied istradefylline as monotherapy for improving motor symptoms in early PD. Notably, the FDA initially denied approval of istradefylline in 2008 owing to the relatively modest clinical benefit shown in trials involving the entire PD population. Additional trials were completed, and the subsequent submission for FDA approval was limited to patients with “off” episodes to better highlight the clinical efficacy of istradefylline.⁵

Regarding long-term effects, an open-label study showed that istradefylline produced an enduring reduction in “off” time in L/C-treated patients over a 52-week period.¹³ Experimental models suggest that targeting adenosine A_{2A} receptors may address some of the neuropsychiatric complications of PD, including cognitive impairment, depression, and excessive daytime sleepiness.¹⁴ Of interest, an open-label trial demonstrated the efficacy of istradefylline for treatment of mood disorders in PD that was independent of improvement of motor symptoms.¹⁵

Adverse Effects

Istradefylline was generally well tolerated in clinical trials. In fact, treatment discontinuation due to adverse effects was similar between istradefylline 20 mg/d, istradefylline 40 mg/d, and placebo (5%, 6%, and 5%, respectively).¹⁶ The most common adverse effect of istradefylline was dyskinesia. The pooled rate of dyskinesia was 15% in patients receiving 20 mg/d, 17% in those receiving 40 mg/d, and 8% in those receiving placebo.¹⁶ However, dyskinesia as a treatment-emergent effect of istradefylline is difficult to distinguish from L/C-related dyskinesia as a result of increased “on” time.¹³ Authors of a meta-analysis¹⁷ concluded that istradefylline might worsen dyskinesia compared with placebo, but publication bias could have contributed to this effect. Other common adverse effects occurring at a frequency greater than that of placebo were dizziness, constipation, nausea, hallucinations, and insomnia.¹⁶ Regarding long-term safety, a 52-week open-label study¹³ of 308 patients revealed the occurrence of adverse effects such as dyskinesia (21.4%), contusion (10.4%), constipation (9.4%), visual hallucination (8.8%), decreased weight (7.1%), and insomnia (5.2%). The overall lack of severe side effects with istradefylline has been compared with that of caffeine, given the molecules’ shared antagonism of adenosine A_{2A} receptors.⁵ The absence of severe adverse effects from istradefylline may be attributed to its lack of direct dopaminergic activity.¹³

Pharmacology/Pharmacokinetics

Istradefylline is believed to exert its antiparkinsonian effects through adenosine A_{2A} receptor antagonism.^{18,19} How the pathogenesis of PD is related to increased expression of these receptors in the striatum or SN is unknown.¹⁹ It is thought that antagonism of these receptors regulates GABAergic neurotransmission in the basal ganglia rather than affecting the dopaminergic system.¹⁹ In PD, dopaminergic cell degeneration in the SN affects the ability of the nigrostriatal tract to provide normal inhibition of an indirect pathway that is located between the striatum and globus pallidus. Blockade of striatal adenosine A_{2A} receptors on medium spiny neurons in the indirect pathway decreases excessive pathway activation.¹⁸ Istradefylline has not demonstrated any appreciable effects on other neurotransmitter receptors, including dopamine, acetylcholine, serotonin, and norepinephrine, decreasing the risks of undesirable off-target effects.²⁰

Istradefylline is administered orally. Under fasting conditions, T_{max} is approximately 4 hours. There are clinically insignificant changes in pharmacokinetic parameters if the drug is taken with a high-fat meal. The apparent volume of distribution is approximately 557 L, and plasma protein binding is approximately 98%. Metabolism of the drug is

primarily via CYP1A1 and CYP3A4. The mean elimination half-life ($t_{1/2}$) is approximately 83 hours; therefore, steady-state is reached within 2 weeks of once-daily dosing. Moderate hepatic impairment can result in more than a 3-fold increase in steady-state exposure (area under the concentration-time curve [AUC_{0-24h}]) of the drug, but renal impairment does not affect pharmacokinetics of the drug.¹⁸

Drug Interactions

Of importance, there is no drug interaction between istradefylline and L/C.²¹ The most clinically relevant drug interactions with istradefylline involve drugs that either strongly induce or inhibit CYP3A4.¹⁸ For example, oral steady-state rifampin 600 mg/d decreased the $t_{1/2}$ of istradefylline from 94.8 to 31.5 hours in a crossover study²² involving healthy subjects who took single 40-mg doses. In another study,²⁰ CYP3A4 inhibitors increased the istradefylline AUC_{SS} at steady-state by 35%. Additionally, smoking can affect istradefylline serum concentrations via induction of CYP1A1. Smoking decreased the istradefylline AUC at steady-state by 38%.²⁰ Istradefylline was a weak inhibitor as well as weak inducer of CYP3A4 when tested *in vitro*.¹⁶ It was a weak inhibitor for P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OCT2, MATE1, and MATE2-K when tested *in vitro*.¹⁶

Dosing

Although L/C is often dosed up to 3 or 4 times daily, istradefylline is administered as a once-daily tablet.¹⁶ The current dosing recommended for istradefylline is 20 mg PO once daily, with a maximum dose of 40 mg daily based on patient response and tolerability.¹⁶ In 1 published trial,²³ there was only a very modest difference in efficacy between the 20-mg/d and the 60-mg/d dosages. Overall, doses between 20 and 40 mg/d of istradefylline resulted in clinically meaningful “off” time, when analyzing results from controlled clinical trials, and FDA approval for these 2 doses subsequently followed (see the Table). A maximum dose of 20 mg/d of istradefylline is recommended in patients taking concomitant strong CYP3A4 inhibitors; however, it is recommended to avoid taking istradefylline with known strong CYP3A4 inducers.¹⁶ In patients who smoke more than 20 cigarettes a day, dosing of istradefylline is recommended at 40 mg/d.¹⁶ Renal dose adjustments are not recommended based on available data, but a maximum dose of 20 mg/d is recommended in patients with moderate hepatic impairment (Child-Pugh Class B) and istradefylline should be avoided in cases of severe hepatic impairment.¹⁶

Cost Considerations

While istradefylline has shown benefit in treatment of PD, medication cost may be a barrier to some patients using

this new agent. Currently, the medication is only available as a brand name product (Nourianz, Kyowa Kirin, Inc). The average wholesale price unit of either 20-mg or 40-mg tablets is \$63 (\$5670 for package size of 90 tablets; same price for both dosage strengths), which is substantially higher than drugs in other classes that are available generically, such as ropinirole (approximately \$14 for 12-mg extended-release tablet [maximum dose 24 mg/d]), entacapone (approximately \$5 for 200-mg tablet [maximum dose 1600 mg/d]), and rasagiline (approximately \$25 for 1-mg tablet).²⁴ Istradefylline may likely be a non-preferred drug that requires prior authorization in many commercial insurance plans. Moreover, Medicare prescription drug plans (Part D) do not generally cover istradefylline.²⁵ The manufacturer offers a co-pay card program for those who are commercially insured and a patient assistance program for those who are uninsured, but certain eligibility requirements and restrictions apply.²⁶

Place in Therapy

Based on current clinical data, istradefylline appears to be an appealing new option for patients with PD. Specifically, it is an alternative option to dopaminergic drugs such as dopamine agonists, MAO-B inhibitors, and COMT inhibitors as an adjunct to L/C in patients with motor fluctuations. Unfortunately, there are no head-to-head randomized controlled trials between istradefylline and drugs within these drug classes to assess the relative efficacy of reduction in “off” time. The 4 trials that led to FDA approval for istradefylline showed a mean reduction in daily “off” time relative to placebo of -0.75 hour for the 20-mg/d dose and -0.82 hour for the 40-mg/d dose.¹⁰ A previous meta-analysis²⁷ that assessed the efficacy of dopamine agonists, MAO-B inhibitors, and COMT inhibitors through indirect comparison (ie, because of a lack of head-to-head clinical trials) showed a reduction in daily “off” time relative to placebo of -1.54 hour, -0.93 hour, and -0.83 hour, respectively. However, indirect comparisons between istradefylline and these other drug classes may be susceptible to bias, so the results should be interpreted cautiously.

In addition to its efficacy, the overall safety profile appears comparable or better than other available agents used to treat PD, although more longitudinal research needs to be completed to confirm this. Istradefylline’s novel mechanism of action not only results in a lack of dopamine-related adverse effects but may also mitigate the risk of worsening dyskinesia commonly seen with dopaminergic agents.²⁸ However, potential benefits of treatment relative to alternative agents must be balanced against its cost when selecting optimal therapy for individual patients. Clinical experience with istradefylline will help identify its efficacy profile in relation to disease stage, patient population, and signs and symptoms of PD.²⁹

Finally, although istradefylline has potential benefits in terms of neuropsychiatric functioning of PD patients, more studies are needed to establish its role in this regard.^{14,30}

Conclusion

Istradefylline was recently approved by the FDA for treatment of PD. In randomized, double-blind, placebo-controlled studies, istradefylline decreased “off” time in patients taking L/C, and it was well tolerated. Its unique pharmacology includes antagonism of the adenosine A_{2A} receptor and lack of direct dopaminergic effects, which is potentially advantageous relative to other drugs that can be selected to treat patients with PD. However, the cost of therapy could be prohibitive in certain circumstances. Real-world use and additional research will further define its role in treatment of PD.

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