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REVIEW ARTICLE

The belated US FDA approval of the adenosine A_{2A} receptor antagonist istradefylline for treatment of Parkinson's disease

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Abstract
After more than two decades of preclinical and clinical studies, on August 27, 2019, the US Food and Drug Administration (FDA) approved the adenosine A_{2A} receptor antagonist Nourianz® (istradefylline) developed by Kyowa Hakko Kirin Inc., Japan, as an add-on treatment to levodopa in Parkinson's disease (PD) with "OFF" episodes. This milestone achievement is the culmination of the decade-long clinical studies of the effects of istradefylline in more than 4000 PD patients. Istradefylline is the first non-dopaminergic drug approved by FDA for PD in the last two decades. This approval also provides some important lessons to be remembered, namely, concerning disease-specific adenosine signaling and targeting subpopulation of PD patients. Importantly, this approval paves the way to foster entirely novel therapeutic opportunities for adenosine A_{2A} receptor antagonists, such as neuroprotection or reversal of mood and cognitive deficits in PD and other neuropsychiatric diseases.

Keywords Adenosine · A2A receptor · Parkinson's disease · istradefylline · KW6002 · clinical trial · safety · therapy

Adenosine A_{2A} receptors in Parkinson's disease: preclinical basis

Motor deficits characteristic of PD involve an over-activation of the striatopallidal pathway of the dorsal striatum due to a lack of dopamine signaling, which is the main brake of this pathway [75]. Notably, adenosine A_{2A} receptors ($A_{2A}R$) have a strikingly high density in dopamine D_2 receptor (D_2R)-containing striatopallidal neurons in rodents, non-human primates and humans. $A_{2A}R$ agonists inhibit striatal D_2R binding, D_2R-mediated neurotransmitter release and immediate early gene expression [25], possibly through $A_{2A}R$-D_2R heteromers [7]. This unique co-localization and antagonistic interaction between $A_{2A}R$ and D_2R in striatopallidal neurons together with the ability of $A_{2A}R$ to control glutamatergic terminals driving striatal circuits [67] provide a strong anatomical and molecular basis for striatal $A_{2A}R$ to integrate dopamine and glutamate signals [70] modulating striatal synaptic plasticity [20, 26], thus justifying the motor and possibly cognitive benefits of $A_{2A}R$ antagonists in PD [69, 70].

Since the 1980s, medicinal chemistry has generated antagonists with high affinity (K_D of low nM) and selectivity (> 100–200-fold over other adenosine receptor subtypes) for the human variants of the $A_{2A}R$ [55]. Several $A_{2A}R$ antagonists with largely different core structures (see Fig. 1) including istradefylline, preladenant and tozadenant were developed and tested in preclinical and clinical studies for the treatment of PD [36]. Indeed, since the early 1990s, mounting experimental findings have demonstrated the motor enhancement effect of $A_{2A}R$ antagonists, alone or synergizing with L-DOPA and D_2R agonists, in rodents [63] and non-human primates [38] by acting at striatopallidal $A_{2A}R$. These preclinical studies have confirmed the validity of $A_{2A}R$ as a novel target for PD treatment and prompted the clinical studies as a leading non-dopaminergic therapeutic target in PD.

Clinical development of $A_{2A}R$ antagonists

Several $A_{2A}R$ antagonists have been developed and tested in humans. Overall, since 2001, more than 25 clinical trials were conducted to evaluate the safety and clinical efficacy of $A_{2A}R$ antagonists in PD patients; among these, eight double-blind, placebo-controlled, phase IIb and III trials of istradefylline

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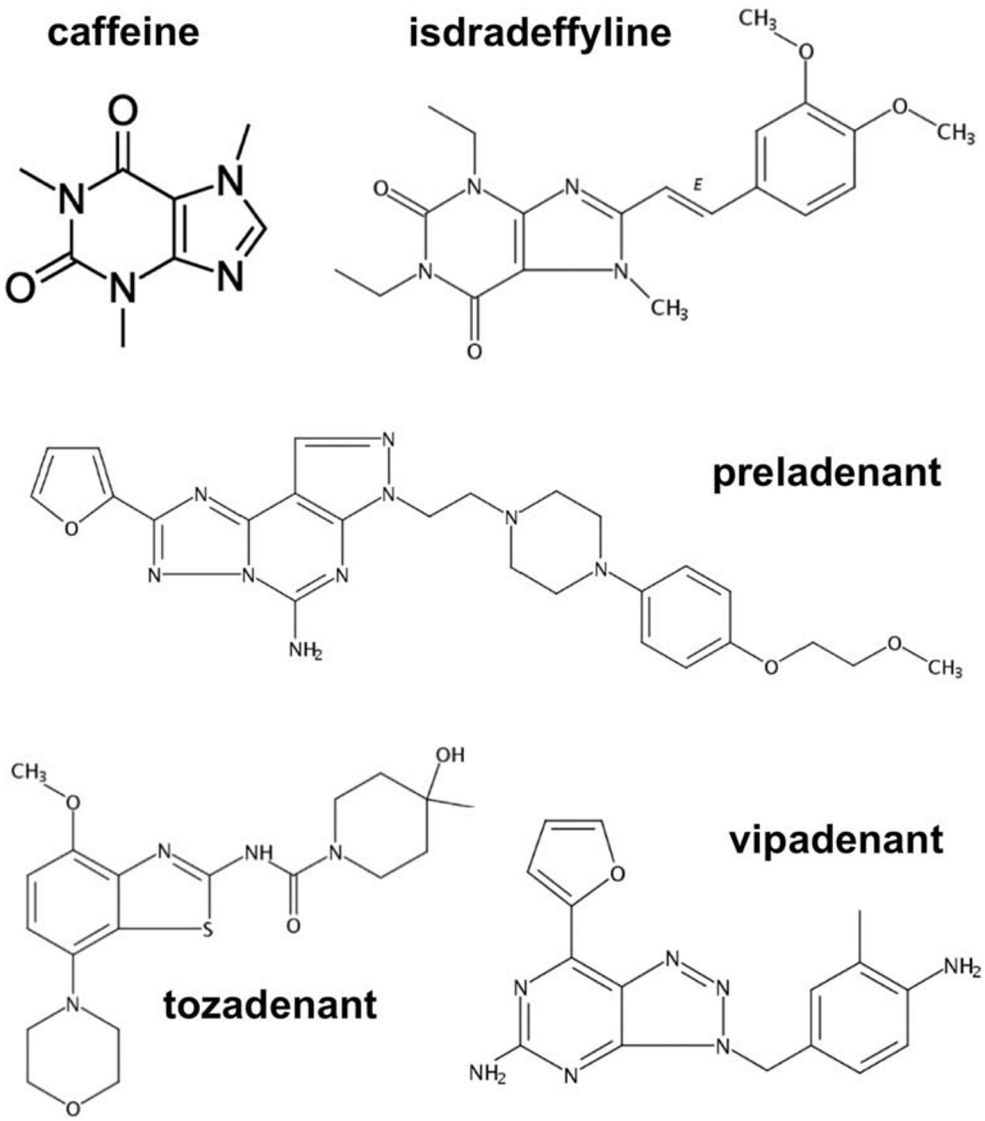

Fig. 1 Chemical structures of different antagonists of adenosine A_{2A} receptors tested in humans

(KW-6002, > 4000 PD patients), one phase IIb trial with preladenant (SCH 420814, 253 PD patients) and one phase IIb trial with tozadenant (337 PD patients) all reported motor benefits in advanced PD patients as an add-on therapy with L-DOPA [4, 31, 32, 40]. There is a single report of another $A_{2A}R$ antagonist vipadenant, which only shows the occupation between 74 and 94% of $A_{2A}R$ in human brain regions (including putamen) at a dose of 2.5 mg (saturation obtained at 100 mg) and no description of effects in PD patients [5].

Istradefylline is a xanthine derivative developed by Kyowa Hakko Kirin Inc., with a relatively high affinity for $A_{2A}R$ (K_D = 10–20 nM) and selectivity towards A_1R (100 times selective), when compared with preladenant (SCH 420814) first developed by Schering-Plough Corp. and then acquired by Merck & Co Inc., which has a higher affinity (K_D of 0.9 nM) and a higher selectivity for $A_{2A}R$ (1000 times versus A_1R). Preladenant belongs to a different chemical family and has a larger molecular weight than istradefylline, which may become a liability due to a more limited bioavailability. Furthermore, pharmacokinetic studies of preladenant in human volunteers reported a moderate to high coefficient of variation across different doses [19]. In fact, despite some positive results in an initial phase IIb trial with long-term treatment with preladenant (5–10 mg/kg, twice a day) [23, 31], two subsequent phase III trials failed to show the clinical efficacy of preladenant to significantly decrease "OFF" time compared with placebo either in conjunction with L-DOPA treatment [33] or in monotherapy [74]. However, this conclusion is blurred by the parallel lack of efficacy of the active control rasagiline, suggesting that issues of study design may have affected these particular trials that lead to the suspension of the preladenant program by Merck & Co Inc.

Long history of istradefylline development

The detailed description of the clinical trials with istradefylline has been provided in several previous reviews [14, 42, 60, 79, 83] and meta-analyses [66]. These clinical IIb and III trials involving a total of > 4000 PD patients [including studies in Japan [44, 53, 54], in North America in 2003–2007 [30, 46, 73], one study in North America in 2016 (NCT02610231) and one study in Europe], showed a relatively modest but significant motor benefit, namely, a reduction of the average "OFF" time by ~ 1.7 h compared to the "optimal" L-DOPA dose regimen [36]. However, the US FDA initially considered in 2008 that this modest motor benefit was not sufficient to support the clinical utility of istradefylline for PD. To address this efficacy issue, additional PD clinical trials with istradefylline in Japan were undertaken to show consistent motor benefits, leading to the approval of istradefylline for treatment of PD in Japan in March 2013 [22]. Additionally, an interim analysis of a post-marketing surveillance study in Japan with 476 PD patients showed that istradefylline effectively reduces "OFF" time symptoms and improves motor dysfunction in 44.7% and 48.5% of patients, with a mean decrease of the UPDRS Part III score from 33.7 to 30.3 at the end of the study and a physician's global assessment of drug as effective in 61.3% of patients [76]. Furthermore, a single-arm, open-label, prospective, multicentre study also showed that istradefylline treatment improves gait deficits and sleepiness in PD patients [35, 51] and corrects postural deformities in a small number of PD patients [27].

Finally, after reviewing the data from 5 pivotal clinical trials (including 3 phase III and 2 phase IIb trials, all using as the primary endpoint the change in the subjects' percentage of their daily awake time spent in the "OFF" state and the PD patient diary as the primary data), the US FDA considered istradefylline to be effective selectively for PD with "OFF" episodes (total 1143 PD participants with "OFF" episodes) as an add-on treatment to L-DOPA/carbidopa. As a result, on August 27, 2019, the US FDA has granted approval for Nourianz® (istradefylline) to be used as adjunctive treatment to L-DOPA in adult patients with PD experiencing "OFF" episodes (see https://www.kyowakirin.com/media_center/news_releases/2016/e20161213_01.html). This is an important milestone in PD drug development, providing PD patients with a novel non-dopaminergic once-a-day oral treatment option in conjunction with L-DOPA for PD.

Safety profile of $A_{2A}R$ antagonists

Notably, these clinical IIb and III trials with istradefylline showed a very consistent safety profile in > 4000 advanced PD patients [31, 37]. The most common adverse reactions for patients taking istradefylline are non-troublesome dyskinesia, dizziness, constipation, nausea, hallucination and insomnia. The post-market surveillance study similarly showed that long-term treatment with istradefylline in a real-world setting for PD patients is generally well tolerated, with the most common adverse reactions being dyskinesia and hallucination [76]. Importantly, potential side effects related to different biological roles of $A_{2A}R$, such as the control of the immune-inflammatory system [72], sleep [45] and vascular tone [71], are not evident in clinical trials, which noted the absence of insomnia, hypertension or increased infection rates [31, 37, 76]. This general lack of side effects of istradefylline is entirely consistent with the general safety associated with the widespread use of the non-selective adenosine receptor antagonist caffeine in moderate doses in 70% of the human population, with striking benefits of increasing healthspan on ageing [41].

This safe profile of istradefylline is in sharp contrast to the recent report that tozadenant (an $A_{2A}R$ antagonist from a different chemical class of istradefylline) has unfortunately resulted in the death of 5 patients in a clinical phase III trial involving 409 participants [10]. The causes of death were identified as drug-induced agranulocytosis, a process resulting from drug- or hapten-induced formation of antibodies against neutrophil membrane glycoproteins, leading to neutrophil destruction. This was never observed with istradefylline but has been reported to occur for multiple other drugs such as dipyrone, diclofenac, calcium dobesilate, spironolactone, carbamazepine, clozapine, sulfamethoxazole, trimethoprim, antithyroid drugs or β-lactam antibiotics. Thus, additional experiments are required to determine if the complications associated with tozadenant are either related to its particular chemical structure or might instead involve $A_{2A}R$.

Lessons learned from istradefylline drug development

This long history of istradefylline development offers several important lessons for future adenosine-related and PD-related drug development. As noted above, a large number of phase IIb–III trials have demonstrated that istradefylline affords relatively mild motor benefits but with noted safety profile. It is surprising that these fundamental clinical features desired for any drug (efficacy, even if moderate, and safety) were not valued to merit US FDA approval. In fact, the initial submission (in 2007) of istradefylline targeting the entire PD population in 5 studies involving a total ~ 3500 patients was unsuccessful. This US FDA decision for this disapproval was largely based on the opinion that "the efficacy data of istradefylline was not sufficient to support its clinical utility". The final submission in 2018 selected 1134 patients from the total 4000 participants from all 7 phase III trials with istradefylline: the selection of only PD patients with "OFF" episodes allowed to highlight the clinical efficacy of

istradefylline, thus leading to the approval of istradefylline by US FDA. The critical difference between these two submissions is the selection of only 1134 PD patients with "OFF" episodes to better highlight the clinical efficacy of istradefylline. This shows, once again, that the selection of specific patient subpopulations who are most responsive to the tested drug is critical for a successful demonstration of the clinical efficacy of a drug. Additional factors contributing to this substantially delayed approval by the US FDA include regulatory delays, corporate mergers (Kyowa Hakko Kogyo is now Kyowa Hakko Kirin) and formulation issues related to the fact that KW-6002 can isomerize in solution when exposed to light.

As the main pharmacological targets of caffeine are adenosine receptors, particularly $A_{2A}R$ as revealed by genetic knockout studies [50, 81], it is highly possible that a different pattern of caffeine consumption in human populations may affect their response to drugs targeting adenosine receptor due to their pharmacokinetic and pharmacodynamic (PK/PD) interaction with caffeine. Indeed, PK/PD analysis shows that caffeine ingestion at a dose equivalent to regular human consumption (2–4 cups of coffee) can affect $A_{2A}R$ agonist-induced myocardial perfusion imaging [77] and reduces the efficacy of adenosine in the treatment of paroxysmal supraventricular tachycardia [6]. Thus, it is somewhat surprising that several clinical phase III trials with $A_{2A}R$ antagonists in advanced PD patients apparently did not consider monitoring and recording the consumption of caffeine [24, 30–33, 40, 44, 46, 51, 73]. We proposed [14] that sufficient information on caffeine intake should always be incorporated into any clinical trial of $A_{2A}R$-based therapies.

Development of next generation of $A_{2A}R$ antagonists

As the patent life of istradefylline is coming to an end (expected in 2024, with a new formulation), Kyowa Hakko Kirin has strategically developed a second generation of $A_{2A}R$ antagonists, namely, KW-6356, which has a longer patent life (https://www.kyowakirin.com/media_center/news_releases/2018/e20180820_01.html). However, very limited information is available on the pharmacological profile of KW-6356, with regard to its affinity and selectivity for $A_{2A}R$ or its pharmacokinetics. It has only been publicized that a multicentre, randomized, double-blind, placebo-controlled, phase IIb study involving 168 participants (NCT03703570) is ongoing to evaluate the effect of KW-6356 on motor symptoms in PD. Interestingly, a monotherapy for de novo PD patients is being pursued with KW-6356, and it was reported that both a low and a high dose of KW-6356 reduce motor dysfunction scores compared with placebo (NCT02939391). Thus, KW-6356 monotherapy is apparently well tolerated (no major safety issues were observed) and effective in the treatment of motor symptoms in early/de novo PD patients.

Novel prospects offered by istradefylline approval for PD treatment

Neuroprotective effects of $A_{2A}R$ antagonists in PD

Since 2000, at least five large prospective studies, initially from the Honolulu Heart Program [64], followed by the Health Professionals Follow-Up Study and the Nurses' Health Study – involving 47,351 men and 88,565 women [3], by the Finnish Mobile Clinic Health Examination Survey [65] and by the NeuroGenetics Research Consortium [62], have firmly established a relationship between increased caffeine consumption and a decreased risk of developing PD [2]. The neuroprotective potential of caffeine and $A_{2A}R$ antagonists (reviewed in [17]) is further substantiated by animal studies demonstrating a neuroprotective effect of both the pharmacological and genetic blockade of $A_{2A}R$ in animal models of PD [13, 38] as well as stroke [12], traumatic brain injury [47], epilepsy [9], spinocerebellar ataxia [28] or Alzheimer's disease [8]. However, the lack of sensitive biomarkers for PD progression and the lack of proper clinical trial designs to uncover neuroprotective effects in the face of the slow progression of PD and relatively short (usually < 52 weeks) clinical trial periods have hindered testing this critically important issue. With the US FDA approval of istradefylline, phase IV clinical studies of istradefylline in PD patients will allow long-term monitoring of the disease course to evaluate possible neuroprotective effects of istradefylline on PD progression.

Pro-cognitive effects of $A_{2A}R$ antagonists in PD

PD is primarily characterized by cardinal motor symptoms, but cognitive dysfunction also occurs both in the early and later stages of the disease process [11]: ~30% of PD patients have dementia, and an additional 25% of non-demented PD patients develop mild cognitive impairments that are characterized by fronto-striatal cognitive deficits such as alterations in executive function, attention, working and episodic memory. These early cognitive deficits are particularly troubling to patients and reduce their quality of life. Currently, there is no effective treatment for mild cognitive impairments in PD. Recent preclinical studies in rodents and non-human primates demonstrated that $A_{2A}R$ antagonists not only enhance working memory [84], reversal learning [59], set-shifting [52], goal-directed behaviour [49] and Pavlovian conditioning [80] in normal animals but also reverse working memory impairments in animal models of PD [43] and Huntington's

disease [48], traumatic brain injury [57] as well as Alzheimer's disease [21]. Thus, $A_{2A}R$ may represent a novel therapeutic target for improving cognitive impairments in PD, as heralded by the improvement of cognitive performance by caffeine in PD patients [15]. However, the effect of istradefylline on cognition was not considered in the clinical trials testing $A_{2A}R$ antagonists in PD patients. With the approval of istradefylline, it will now be possible to evaluate the ability of $A_{2A}R$ antagonists to reverse cognitive deficits in PD patients in clinical phase IV trials.

Mood normalizing effects of $A_{2A}R$ antagonists in PD

PD patients often display mood-related alterations [68], typified by the occurrence of anxiety and depressive-like disorders in ~40% of patients since early stages of the disease [78]. $A_{2A}R$ function impacts on several psychiatric symptoms [18] with $A_{2A}R$ over-activation bolstering anxiety and depressive-like behaviour [16] and $A_{2A}R$ blockade preventing and reverting repeated stress-induced depressive-like behaviour in rodents [39]. Furthermore, $A_{2A}R$ polymorphisms are correlated with the incidence of anxiety [34] and depression [58]. Notably, recent studies in PD patients showed that caffeine intake reduces the severity of the mood domains in the Mini-Mental State Examination [15] and istradefylline improves the scores of Snaith-Hamilton Pleasure Scale Japanese (SHAPS-J) version, of the Apathy scale and of the Beck Depression Inventory independently of its effects on motor symptoms [56]. The approval of istradefylline will now allow detailing in phase IV clinical trials the expected benefits of $A_{2A}R$ antagonists on different psychiatric symptoms afflicting PD patients.

Opportunities to develop personalized treatments with $A_{2A}R$ antagonist, based on caffeine genetics

Selecting the population of patients for clinical trials is always critical to a successful outcome of the trials. This includes selecting homogenous populations of PD patients who are most responsive to the treatment with $A_{2A}R$ antagonists, according not only to specific clinical features (such as with defined "OFF" episodes) but also to genetic variability (i.e. single nucleotide polymorphisms) of $A_{2A}R$. The genetic studies related to caffeine sensitivity offer a unique opportunity for "personalized medicine" by identifying useful pharmacogenetic markers for predicting individual responses to caffeine in PD populations in clinical trials. During the last two decades, many genetic studies have been carried out to determine a possible genetic basis for the known human individual variation in caffeine response [82]. Genome-wide association and interaction studies have revealed associations between: (i) an Adora2a variant (rs7165183and rs5996696) and a reduced risk of PD [61]; (ii) a stronger coffee-PD association and slow metabolizers of caffeine with homozygous carriers of the CYP1A2 polymorphisms [1]; and (iii) polymorphism rs4998386 and neighbouring SNPs in GRIN2A and heavy coffee drinkers with the reduced risk of developing PD [29]. As caffeine and $A_{2A}R$ antagonists share a common target and elimination mechanisms, these findings raise the exciting possibility of predicting individual responses to caffeine (and possibly other adenosine receptor antagonists) and selection of patient subpopulations by caffeine genetic polymorphisms of these associated alleles identified (such as CYP1A1, CYP1A2, Adora2a, NRCAM and GRIN2A).

Concluding remarks

The US FDA approval on August 2019 of the $A_{2A}R$ antagonist istradefylline (Nourianz®) as an add-on treatment to levodopa in PD patients with "OFF" episodes is a milestone achievement in adenosine research and PD drug development; in fact, istradefylline is the first $A_{2A}R$ therapeutic drug and the first non-dopaminergic drug approved by US FDA in the last two decades for PD treatment. While multiple factors contributed to substantially delay US FDA approval, the important lessons learned from this belated approval is that the selection of defined patient subpopulations who are most responsive to the tested drug is critical for a successful demonstration of the clinical efficacy of the drug. Importantly, this approval opens new avenues to foster entirely novel therapeutic opportunities for $A_{2A}R$ antagonists, such as neuroprotection and reversal of mood and cognitive deficits in PD.

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Compliance with ethical standards

Conflict of Interest Dr. Jiang-Fan Chen declared no conflict of interest.

Competing interests R.A. Cunha is a scientific consultant to ISIC – Institute for Scientific Information on Coffee.

Ethical approval This article does not contain any studies with participants or animals performed by either of the authors.

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