Movement Disorders
CLINICAL PRACTICE

LETTER: PUBLISHED ARTICLE

Expanding Clinical Experience With Istradefylline in *ADCY5*-Related Movement Disorder: A Case With No Benefit

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We read with great interest the case report by Miyamoto et al. describing successful treatment with istradefylline in a patient with *ADCY5*-related movement disorder.[1] Together with earlier reports of caffeine efficacy[2] and recent evidence supporting theophylline,[3] their report represents an important first clinical observation expanding the A2A receptor antagonist therapeutic repertoire in *ADCY5*-related disorders. Given the extremely limited clinical experience with istradefylline, we report a contrasting case that may help inform expectations for this treatment.

Our patient is a 15-year-old female with the same heterozygous de novo R418W *ADCY5* mutation characterized by generalized chorea, dystonia, orofacial dyskinesia, and truncal hypotonia. Despite achieving independent ambulation in early childhood, her progressive movement disorder resulted in loss of walking ability and wheelchair dependence by age 9. Additional features include paroxysmal nocturnal dyskinesias, swallowing dysfunction, and poor weight gain. Multiple previous treatments, including caffeine, showed no benefit.

Istradefylline was initiated at 20 mg daily and increased to 40 mg daily after 1 month, as described by Miyamoto et al.[1] After 6 months at 40 mg daily, we observed no improvement in paroxysmal dyskinesias, baseline movement disorder, or functional status. No adverse effects occurred. The medication was discontinued after this trial period.

While Miyamoto et al.[1] reported sustained improvement over 21 months, our patient showed no response despite having the same *ADCY5* mutation and similar clinical features, though perhaps more severe functional impairment. Notably, our patient also failed to respond to caffeine. In the retrospective series by Méneret et al., one patient with the R418W mutation similarly showed no benefit from caffeine,[2] raising the question of whether response to A2A receptor antagonists may be heterogeneous in *ADCY5*-related disorders.

The preclinical evidence supporting A2A receptor antagonists in *ADCY5*-related movement disorders is compelling. Tänzler et al. demonstrated that caffeine, theophylline, and istradefylline all reduced cAMP levels in *ADCY5* R418W mutant cells, with istradefylline showing the most pronounced effect based on its superior A2A receptor affinity.[4] More recently, a retrospective case series of 12 patients treated with theophylline reported substantial clinical efficacy, with 92% demonstrating significant improvements in movement disorder symptoms.[3] Yet our clinical experience suggests that cellular efficacy may not always translate to clinical benefit, or that response may depend on factors we do not yet understand, such as disease severity, age at treatment initiation, mutation-specific effects, or other genetic or environmental modifiers.

Notably, our patient subsequently achieved significant clinical improvement with bilateral globus pallidus internus deep brain stimulation, supporting its consideration for cases refractory to medications.[5]

With only two reported cases of istradefylline use in *ADCY5*-related movement disorders and limited medication availability in many countries, we believe documenting both positive and negative outcomes, together with long-term efficacy data, is essential. We encourage clinicians to report their experiences with A2A receptor antagonists to help identify potential predictors of treatment response in *ADCY5*-related movement disorders.

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Financial Disclosures and Conflicts of Interest

Author disclosures are available in the Supporting Information.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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Supporting Information

Supporting information may be found in the online version of this article.

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