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# Long-term Outcome of Adenosine A2A Receptor Antagonist on Lower Urinary Tract Symptoms in Male Parkinson Disease Patients

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**Objectives:** In addition to motor symptoms, bladder dysfunction is a major clinical issue in patients with Parkinson disease (PD). Istradefylline is adenosine A2A receptor antagonist approved for PD patients with wearing-off symptoms. The aim of this study was to determine the long-term effects of istradefylline on lower urinary tract symptoms (LUTSs) in PD patients.

**Methods:** We enrolled 14 male PD patients. The mean age of patients was 73 years (61–77 years), the Hoehn-Yahr stage was 2 (2–3), and disease duration was 9 years (3–28 years). The effects of istradefylline (20 mg/d) on LUTSs in PD patients with motor complications after 3, 6, and 12 months of therapy were evaluated based on the International Prostate Symptom Score and Overactive Bladder Symptom Score before and after its administration.

**Results:** Motor symptoms significantly improved at 12 months' administration (Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale part III:  $30.0 \pm 12.9$  vs  $13.8 \pm 8.1$ ;  $P < 0.01$ ). Significant improvements were also observed in the answers provided on urinary questionnaires (International Prostate Symptom Score,  $14.4 \pm 7.6$  vs  $8.5 \pm 6.8$ ; Overactive Bladder Symptom Score,  $6.9 \pm 2.8$  vs  $5.5 \pm 3.7$ ;  $P < 0.05$ ). Nighttime urinary frequency and the percentage of the nocturnal urine volume also improved significantly at 3 months' administration ( $P < 0.01$ ).

**Conclusions:** Istradefylline effectively improved not only motor symptoms, but also LUTSs in patients with PD.

**Key Words:** istradefylline, lower urinary tract symptoms, overactive bladder, Parkinson disease

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Bladder dysfunction is a major clinical issue in patients with Parkinson disease (PD). The prevalence of lower urinary tract symptoms (LUTSs) characterized by urinary urgency, frequency, and incontinence was previously reported to be between 27% and 40%.<sup>1–3</sup> Bladder symptoms often appear once treatments for

PD have been initiated.<sup>1</sup> Anti-PD treatments may influence bladder control in an unpredictable manner.<sup>4</sup> These symptoms have a severe impact on the quality of life (QOL) of PD patients.<sup>5</sup> The adenosine receptor A2A is strongly expressed in the striatum, interacts with dopamine D<sub>2</sub> receptors, and modulates dopamine transmission. Istradefylline is a novel nondopaminergic selective adenosine A2A receptor antagonist. The Japanese phase 3 trial showed that 20 mg of orally administered istradefylline decreased the off-time. A recent study shows that adding istradefylline to low doses of L-DOPA and dopamine agonists is superior to the later use in PD patients treated with high doses of L-DOPA. It may be effective to administer istradefylline before the off symptoms progress.<sup>6</sup> We previously reported that istradefylline improved not only motor symptoms, but also LUTSs in patients with PD in a short-term period.<sup>7</sup> However, it currently remains unclear whether istradefylline is useful for the treatment of PD patients with LUTSs in the long-term real-world clinical settings. Therefore, the aim of this study was to determine the effects of 1-year istradefylline treatment on LUTSs in PD patients.

## METHODS

### Study Participants

In this prospective study, patients were invited consecutively from the Department of Neurology to participate between March 2015 and July 2015, regardless of the presence of LUTSs. Study exclusion criteria were any pelvic or urological abnormalities, bladder surgery, or disease that may affect bladder function. During this study, no changes to the type of rehabilitation or PD medication were required. The present study was approved by the Scientific Ethics Committee of Hokkaido University (#014-0342), and patients provided informed consent.

### Assessments

#### International Prostate Symptom Score, Overactive Bladder Symptom Score, King's Health Questionnaire

In order to analyze LUTSs and QOL, we used the International Prostate Symptom Score (IPSS), QOL score, and Overactive Bladder Symptom Score (OABSS) at baseline and 3 months, 6 months, and 1 year after the treatment (the data of 3 months were reported previously<sup>7</sup>). The IPSS is a 7-question questionnaire that assesses LUTSs in the storage (urgency episodes, nocturia, and increased daytime frequency) and voiding (incomplete emptying, a weak urinary stream, and straining at urination) phases. An additional question on the QOL score was evaluated. The IPSS is useful for detecting voiding dysfunctions in patients with PD.<sup>8</sup> Total IPSS scores range from 0 to 35, with greater scores indicating increasing symptom severity. The OABSS quantifies daytime frequency, nocturia, urgency, and urinary

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incontinence over a 1-week recall period.<sup>9</sup> Scores range from 0 to 15, with greater scores indicating increasing symptom severity. Question 3 of the OABSS measures urgency. The King's Health Questionnaire (KHQ-QOL) score was also calculated in the following 8 domains (Appendix 1, Supplemental Digital Content, <http://links.lww.com/CNP/A5>), using the formula shown in Appendix 2: General Health Perceptions, Impact on Life, Role Limitations, Physical Limitations, Social Limitations, Personal Relationships, Emotional Problems, and Sleep/Energy Disturbance, (Supplemental Digital Content, <http://links.lww.com/CNP/A5>). Symptom scores range from 0 to 100, with lower scores reflecting better KHQ-QOL.

### Voiding Diary

Patients also completed a 3-day voiding diary at baseline and 3 months and 1 year after the treatment. Patients recorded daytime and nighttime urinary frequencies, as well as voided volumes. The nocturnal polyuria index was defined as the nocturnal urine volume divided by the 24-hour volume. Nocturnal polyuria was also defined as a nocturnal urine volume exceeding 33% of the 24-hour urine output.

### Uroflowmetry and Residual Urine Volume

Measurements of the urinary flow rate and postvoiding residual urine volume using ultrasound were performed at baseline and 3 months and 1 year after the treatment.

### Scales for Outcomes in PD

Motor symptoms were assessed using the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at baseline and 3 months, 6 months, and 1 year after the treatment. The motor symptom test was performed at nearly the same time period with every clinic visit.

### Statistical Analyses

All data are shown as the mean  $\pm$  SD. GraphPad Prism (GraphPad Software, La Jolla, CA) was used for statistical analyses, which were conducted using the paired *t* test (parametric) or Wilcoxon signed rank test (nonparametric), with *P* < 0.05 being considered significant.

## RESULTS

Fourteen male patients were included, and 12 patients completed the study. One patient was unable to complete this study because of the adverse effects of istradefylline (the deterioration of dyskinesia), and the other patient was changed to another anti-PD drug because of the clinical condition. The mean age of our patients was 66 years (61–80 years), the Hoehn-Yahr stage was 2 (2–3), and disease duration was 9 years (4–26 years). The MDS-UPDRS parts I, II, and III were  $9.2 \pm 5.4$ ,  $13.8 \pm 7.3$ , and  $30.0 \pm 12.9$ , respectively.

### IPSS, QOL, and OABSS

In all patients (including those with the absence of LUTSs), statistical analyses revealed significant decreases in the IPSS total number (at 3 months, 6 months, and 1 year), QOL (at 3 months and 1 year), and OABSS total number (at 3 months and 1 year) after the treatment with istradefylline (Table 1). In patients with no or mild LUTSs or no OAB symptom (IPSS of <8 and OABSS urgency score [for question 3] of <2), no significant changes were noted in IPSS or OABSS total numbers after 1-year treatment (IPSS:  $5.3 \pm 2.9$  to  $4.7 \pm 4.6$ , OABSS:  $4.3 \pm 2.1$  to  $6.0 \pm 5.6$ ).

### Voiding Diary

Table 2 shows significant decreases in the nighttime voiding frequency (nocturia) in the 3-day voiding diary after 3 months of the treatment ( $3.0 \pm 1.6$  to  $2.0 \pm 0.9$ , *P* < 0.05). Significant decreases were also observed in nocturnal polyuria index ( $44.7 \pm 11.0$  to  $35.6 \pm 8.3\%$ , *P* < 0.05). However, 1 year after the treatment, these changes were not significant.

### Uroflowmetry and Residual Urine Volume

No significant changes were observed in the urinary flow rate or postvoiding residual urine volume between before and after the administration of istradefylline. The mean maximum urinary flow rates at baseline and 3 months and 1 year after the treatment were  $9.5 \pm 5.5$ ,  $10.4 \pm 4.0$ , and  $9.4 \pm 4.5$  mL/s, respectively, whereas residual urine volumes were  $23.0 \pm 47.2$ ,  $21.5 \pm 34.2$ , and  $45.4 \pm 31.0$  mL, respectively.

### King's Health Questionnaire

Data from the KHQ revealed that the 2 domains of personal relationships and incontinence severity measures had significantly improved at 3 months (*P* < 0.05 and *P* < 0.01, respectively). Role limitation at 3 and 6 months (*P* < 0.01 and *P* < 0.05, respectively) had significantly improved, whereas impact on life scores improved only after 1 year (*P* < 0.05) (Table 1).

### Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale

Motor symptoms were significantly better at 3 and 6 months and 1 year than at baseline (MDS-UPDRS part III:  $30.0 \pm 12.9$  vs  $10.9 \pm 7.1$ ,  $13.8 \pm 8.1$ , and  $13.5 \pm 7.0$ ; *P* < 0.01).

During this study, 2 patients developed slight dyskinesia, and 1 patient exhibited visual hallucination, which was so mild that the istradefylline administration was not discontinued. No adverse urological effects (such as urinary retention and urinary tract infection) were observed in any patient.

## DISCUSSION

The results of the present study demonstrate that long-term administration of istradefylline improves LUTSs in PD patients. Moreover, istradefylline did not aggravate LUTSs in PD patients without LUTSs. During this study, no adverse urological effects (such as urinary retention and urinary tract infection) were observed in any patient. Central LUTSs in patients with PD are overactive bladder (OAB) symptoms, characterized by urinary urgency and increases in daytime and nighttime urinary frequency.<sup>2</sup> Lower urinary tract symptoms are more likely to occur at more advanced stages of PD and progressively deteriorate with the disease duration. Furthermore, LUTSs become “unmasked” in patients with advanced PD. Prior to the treatment of motor symptoms, patients may be preoccupied with coping with motor symptoms and thus be less aware of bladder symptoms. When the severity of motor symptoms decreases with treatments, patients become more aware of LUTSs. In the present study, only 9 patients (64.3%) consulted a urologist prior to the administration of istradefylline, even among patients with moderate or severe LUTSs (IPSS of  $\geq 8$  and OABSS urgency score [for question 3] of  $\geq 2$  and a total OABSS of  $\geq 3$ ).

Previous studies reported that in contrast to motor dysfunction LUTSs are often nonresponsive to levodopa, suggesting that they occur through complex mechanisms. Therefore, add-on therapy is required in order to prioritize improvements in QOL.<sup>4,10</sup> Istradefylline, a nondopaminergic selective adenosine A2A receptor antagonist, does not have direct effects on dopaminergic

**TABLE 1.** International Prostate Symptom Score, OABSS, and KHQ Before and After the Treatment With Istradefylline

<b>IPSS</b>				
<b>Question</b>	<b>Baseline</b>	<b>3 Mo</b>	<b>6 Mo</b>	<b>1 y</b>
IPSS total	14.4 ± 7.6	9.5 ± 7.0*	8.7 ± 4.8*	8.5 ± 6.8*
1: Incomplete emptying	2.3 ± 2.0	0.5 ± 0.9*	1.2 ± 1.5*	0.7 ± 1.5*
2: Frequency	2.7 ± 1.4	1.7 ± 1.6	2.0 ± 1.2	2.1 ± 1.5
3: Intermittency	2.0 ± 1.9	1.6 ± 2.0	0.7 ± 1.2	1.3 ± 2.1
4: Urgency	2.1 ± 1.5	0.9 ± 1.3	0.8 ± 1.1	1.1 ± 1.2
5: Weak stream	2.5 ± 1.9	2.0 ± 2.0	1.7 ± 1.8*	1.1 ± 1.5†
6: Straining	0.8 ± 1.1	1.1 ± 1.0	0.7 ± 1.2	0.9 ± 0.9
7: Nocturia	1.7 ± 1.2	1.5 ± 0.9	1.5 ± 0.8	1.4 ± 1.0
Voiding symptoms (1 + 3 + 5 + 6)	7.6 ± 5.2	5.3 ± 4.5	4.4 ± 3.4	4.0 ± 4.4
Storage symptoms (2 + 4 + 7)	6.7 ± 3.3	4.2 ± 3.0*	4.4 ± 1.9	4.5 ± 2.8
QOL due to urinary symptoms	4.4 ± 1.4	2.9 ± 1.8*	3.2 ± 1.7	3.0 ± 2.0*
<b>OABSS</b>				
<b>Question</b>	<b>Baseline</b>	<b>3 Mo</b>	<b>6 Mo</b>	<b>1 y</b>
OABSS total	6.9 ± 2.8	4.3 ± 3.2*	5.9 ± 3.3	5.5 ± 3.7*
Daytime frequency	1.0 ± 0.4	1.0 ± 0.5	1.0 ± 0.5	0.8 ± 0.6
Nocturia	2.0 ± 1.0	1.0 ± 0.9*	2.0 ± 0.8	1.3 ± 1.0*
Urgency	2.5 ± 1.4	1.0 ± 1.5	2.0 ± 1.4	1.8 ± 1.6*
Urge urinary incontinence	1.0 ± 1.4	1.0 ± 1.4	1.0 ± 1.4	1.6 ± 1.6
<b>KHQ</b>				
<b>KHQ Domain Score</b>	<b>Baseline</b>	<b>3 Mo</b>	<b>6 Mo</b>	<b>1 y</b>
General health perception	52.5 ± 21.9	43.2 ± 16.2	56.3 ± 24.1	54.2 ± 20.9
Impact on life	60.0 ± 26.2	36.4 ± 27.7	44.4 ± 32.8	44.4 ± 29.6*
Role limitations	43.3 ± 26.3	22.7 ± 36.0*	29.2 ± 23.7†	26.4 ± 21.9
Physical limitations	41.7 ± 29.7	25.8 ± 31.9	25.0 ± 25.1	26.4 ± 18.1
Social limitations	32.1 ± 26.3	15.2 ± 27.3	25.0 ± 28.1	14.8 ± 21.4
Personal relationships	25.9 ± 26.5	7.4 ± 12.1*	13.6 ± 22.1	44.4 ± 28.9
Emotions	56.7 ± 31.1	31.1 ± 37.7	40.7 ± 34.9	31.5 ± 36.7
Sleep/energy	40.0 ± 34.4	21.7 ± 27.3	33.3 ± 33.3	29.2 ± 35.6
Incontinence severity measures	32.0 ± 22.3	16.0 ± 14.8†	23.9 ± 22.5	28.9 ± 28.3

Values are presented as mean ± SD.  
 \* $P < 0.05$ , significantly different from baseline.  
 † $P < 0.01$ , significantly different from baseline.

mechanisms, which may provide anti-PD effects on motor and lower urinary tract functions without adverse events.

We provided PD patients with detailed urinary questionnaires in order to survey LUTSs. A large number of studies have demonstrated that LUTSs have a significant impact on QOL measurements.<sup>5,11</sup> In the present study, both IPSS and OABSS significantly improved. This result is consistent with previous findings. Storage and voiding symptoms both significantly improved, with

the latter showing early improvements following the administration of the treatment. The mechanism responsible for this early improvement and lasting effect has not yet been elucidated but may be related to the mechanism underlying the indirect impact of adenosine A2A receptor antagonists. Further studies are needed in order to clarify this background mechanism. Previous studies on PD patients reported that the degeneration of dopaminergic neurons in the substantia nigra and subsequent loss of striatal

**TABLE 2.** Three Days Voiding Diary Before and After the Treatment With Istradefylline

	<b>Baseline</b>	<b>3 mo</b>	<b>1 y</b>
Voided volume/d, mL	1432.5 ± 642.0	1513.3 ± 382.0	1601.7 ± 320.4
Frequency/d, no. times	10.1 ± 3.0	9.1 ± 2.1	9.2 ± 1.7
Daytime frequency/d, no. times	7.1 ± 2.1	7.1 ± 1.7	6.8 ± 1.6
Nocturia/d, no. times	3.0 ± 1.6	2.0 ± 0.9*	2.4 ± 0.7
Nocturnal polyuria index, %	44.7 ± 11.0	35.6 ± 8.3*	40.0 ± 9.4

Values are presented as mean ± SD.

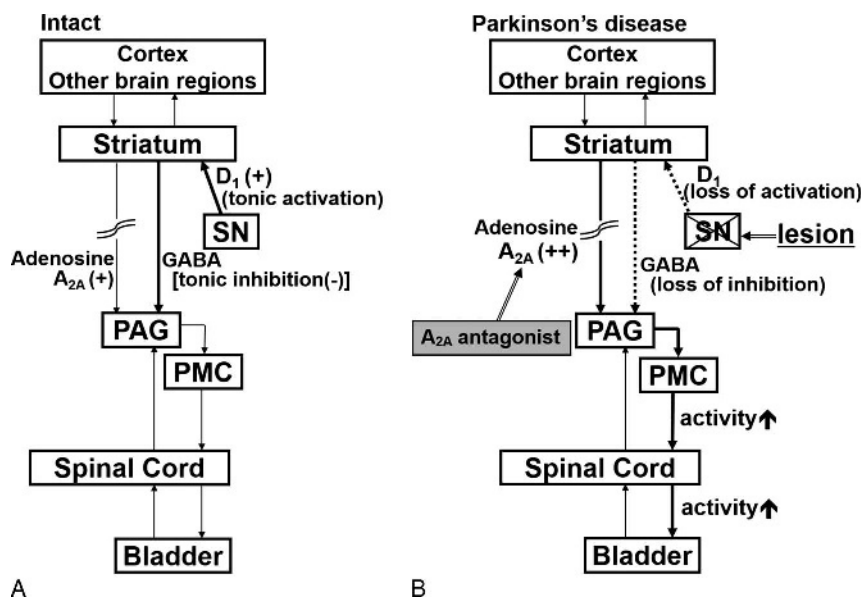
dopamine led to detrusor overactivity through an inability to activate D<sub>1</sub>-mediated tonic inhibition. In patients with PD, other mechanisms may include selective damage to inhibitory dopaminergic neurons.<sup>2</sup> We previously used a rat model of PD to examine the effects of an adenosine A<sub>2A</sub> receptor antagonist on the micturition reflex and found that its intravenous administration increased the intercontraction interval (inhibited the micturition reflex) in PD and sham rats, with inhibitory effects being stronger in PD rats.<sup>12</sup> These findings indicate that an adenosine A<sub>2A</sub> receptor-mediated excitatory mechanism is enhanced in the brain, thereby inducing bladder overactivity, and also that the inhibition of A<sub>2A</sub> receptors effectively suppressed bladder overactivity in the rat model of PD<sup>12-14</sup> (Fig. 1). As we represented in the hypothetical diagram (Fig. 1), dopaminergic neurons in the substantia nigra pars compacta are lost, which leads to the loss of dopamine D<sub>1</sub> receptor activation and facilitation of the spinobulbospinal pathway controlling the micturition reflex. The administration of adenosine A<sub>2A</sub> receptor antagonists may suppress the A<sub>2A</sub> receptor-mediated activation of the micturition reflex in order to reduce bladder overactivity in PD patients.

It has yet to be established whether adenosinergic mechanisms regulate LUTSs in patients with PD. In the present study, not only storage symptoms but also voiding symptoms were improved by the treatment with istradefylline. We also showed that objective urodynamic parameters were not significantly affected by this treatment even in long-term administration of adenosine A<sub>2A</sub> receptor antagonist. Discrepancies have been reported in LUTS studies. For example, objective findings such as the peak flow rate and residual urine volume did not correlate with IPSS and QOL scores, whereas each objective and subjective symptoms significantly improved after transurethral resection of the

prostate.<sup>15</sup> Istradefylline directly affects supraspinal lesions, which may ameliorate LUTSs without changing lower urinary tract functions. This function is preferable for other nonneurogenic OAB patients such as those with ischemic disease and multiple sclerosis. Moreover, the findings of an animal study<sup>12</sup> showed that istradefylline may suppress the adenosine A<sub>2A</sub> receptor-mediated excitatory adenosinergic mechanism in the spinal cord, caused by OAB in PD patients. Further studies are needed to examine how the adenosine A<sub>2A</sub> receptor modulates and ameliorates bladder overactivity in PD patients.

Quality of life is severely affected by nocturia.<sup>16-19</sup> Cornu et al<sup>20</sup> identified nocturnal polyuria as a cause of LUTSs (night-time urinary frequency). Furthermore, a recent study<sup>21</sup> demonstrated that nocturnal polyuria developed in PD patients and deteriorated LUTSs. However, the pathophysiology of nocturnal polyuria in PD patients currently remains unclear. Nocturnal polyuria is associated with decreases in daily changes in the secretion of antidiuretic hormone (ADH).<sup>22</sup> The secretion of pituitary hormones is controlled by hypothalamic hormones, which are directly and indirectly modulated by neurotransmitters such as dopamine, noradrenaline, and serotonin.<sup>23</sup> Tateno et al<sup>24</sup> reported that amantadine ameliorated nocturnal polyuria in patients with PD. They speculated that the effects of amantadine on dopamine, noradrenaline, and serotonin modulated the circadian secretion of ADH and ameliorated nocturnal polyuria in patients with PD. Istradefylline may also modulate the circadian secretion of ADH. However, long-term effect is not clear in the current study; further studies are needed in order to confirm this.

Anticholinergics are used to treat LUTSs in PD patients; however, many practitioners are well versed in the common adverse effects of dry mouth and constipation, other more serious



**FIGURE 1.** Hypothetical diagram showing neural mechanisms of bladder function in normal (intact) and PD. The micturition reflex is controlled by the spinobulbospinal pathway passing through the periaqueductal gray matter (PAG) in the midbrain and the pontine micturition center (PMC). This neural circuit is under the control of higher centers. A, In intact conditions, tonic activation (+) of dopaminergic neurons in the substantia nigra pars compacta (SN) activates dopamine D<sub>1</sub> receptors expressed on GABAergic inhibitory neurons in the striatum in order to inhibit the micturition reflex. At the same time, D<sub>1</sub> receptor stimulation suppresses the activity of adenosinergic neurons, which exert an excitatory effect on micturition via adenosine A<sub>2A</sub> receptors. B, In PD, dopaminergic neurons in the SN are lost, leading to the loss of dopamine D<sub>1</sub> receptor activation, which results in reduced activation of inhibitory GABAergic neurons in the striatum. At the same time, reduced D<sub>1</sub> receptor stimulation enhances the adenosinergic mechanism to stimulate adenosine A<sub>2A</sub> receptors, leading to facilitation of the spinobulbospinal pathway controlling the micturition reflex. Administration of adenosine A<sub>2A</sub> receptor antagonists could suppress A<sub>2A</sub> receptor-mediated activation of the micturition reflex to reduce bladder overactivity in PD. D<sub>1</sub> indicates dopamine D<sub>1</sub> receptor; GABA, γ-aminobutyric acid. Modified with permission from Yoshimura et al.<sup>14</sup>

problems of cognitive impairment. Moreover, polypharmacy in aged patient has increased in the past decade. From this aspect, adenosine A2A receptor antagonists are suitable agent as an “add-on” therapy for LUTSs in patients with PD.

The limitations of this study include the small number of patients treated and the absence of a placebo control. In the present study, we did not evaluate cognitive function at baseline or after the treatment, and thus, this warrants further examination.

## CONCLUSIONS

The results of the present study confirmed that adenosine A2A receptor antagonists are useful as a new pharmacological treatment for OAB in patients with PD in a long-term period.

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