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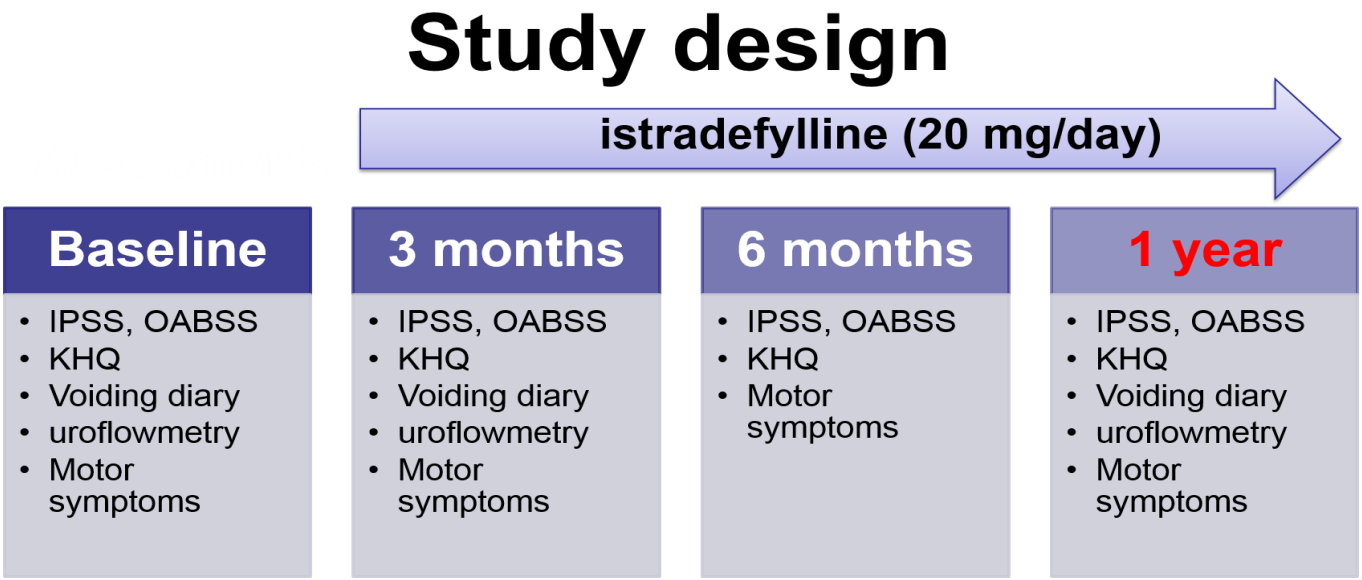
# ADENOSINE A2A RECEPTOR ANTAGONIST ISTRADEFYLLINE IMPROVES LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE IN A LONG-TERM PERIOD

Hypothesis / aims of study

In addition to motor symptoms, bladder dysfunction is a major clinical issue in patients with Parkinson's disease (PD). Anti-Parkinson treatments may influence bladder control in an unpredictable manner. Istradefylline, a novel non-dopaminergic selective adenosine A2A receptor antagonist, was approved in 2013. The adenosine receptor A2A is strongly expressed in the striatum, interacts with dopamine D2 receptors, and modulates dopamine transmission. Istradefylline improves wearing-off phenomena and is tolerated well by PD patients treated with levodopa. We previously reported that Istradefylline improved not only motor symptoms, but also lower urinary tract symptoms (LUTS) in patients with PD in a short-term period (ref. 1). However, the long-term effects of istradefylline for LUTS has not yet been clarified. The aim of this study was to determine the effects of 1 year istradefylline treatment on LUTS in PD patients.

Study design, materials and methods

We enrolled male 12 male PD patients. The mean of age of patients was 66 (61-80) years old, the Hoehn-Yahr stage was 2 (2-3), and disease duration was 9 (4-26) years. The effects of istradefylline (20 mg/day) on LUTS in PD patients with motor complications after 3, 6 months and 1 year of therapy were evaluated based on the International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), King's Health Questionnaire (KHQ) score, 3-day voiding diary, and urinary flow rate and post-voiding residual urine volume before and after its administration.




Results

Motor symptoms significantly improved after 1 year evaluating movement disorder rating scale ($P<0.01$). Significant improvements were also observed in the answers provided on urinary questionnaires after 1 year treatment (IPSS: 14.4 ± 7.6 vs. 8.5 ± 6.8, OABSS: 6.9 ± 2.8 vs. 5.5 ± 3.7; $P<0.05$) [breakdown: Table]. Data from the KHQ revealed that the domain of impact on life had significantly improved after 1 year treatment [Table]. And in 3-day voiding diary, nighttime urinary frequency (3.0 ± 1.6 vs. 2.4 ± 0.7; $P<0.05$). However, no significant changes were observed in the urinary flow rate (Qmax) or post-voiding residual urine volume (RU) between before and after 1 year administration of istradefylline (Qmax (ml/s): 10.7 ± 3.9 vs. 8.0 ± 2.8, RU (ml): 51.0 ± 60.0 vs. 40.5 ± 30.8).

No adverse urological effects were observed in any patient.

Interpretation of results

Central LUTS in patients with PD are OAB symptoms, characterized by urinary urgency and increases in daytime and night time urinary frequency [ref. 2]. LUTS are more likely to occur at more advanced stages of PD, and progressively deteriorate with the disease duration. Furthermore, LUTS 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 LUTS. Istradefylline effectively improved not only motor symptoms, but also LUTS in patients with PD in a long-term period.

Istradefylline does not have direct effects on dopaminergic mechanisms, which may provide anti-PD effects on motor and lower urinary tract. Not only IPSS and OABSS, but also KHQ significantly improved after 1year treatment. The mechanism responsible

for this improvement has not yet been elucidated, but may be related to the mechanism underlying the indirect impact of adenosine A2A receptor antagonists.

**International Prostate Symptom Score (IPSS)**

| Question | Baseline | 3 months | 6 months | 1 year |
|---|---|---|---|---|
| | Mean ± S.D. | | | |
| 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 |
| Strage symptoms (2+4+7) | 6.7 ± 3.3 | **4.2 ± 3.0 *** | 4.4 ± 1.9 | 4.5 ± 2.8 |
| Quality of life due to urinary symptoms | 4.4 ± 1.4 | **2.9 ± 1.8 *** | 3.2 ± 1.7 | **3.0 ± 2.0 *** |

**OverActive Bladder Symtoms Scores (OABSS)**

| Question | Baseline | 3 months | 6 months | 1 year |
|---|---|---|---|---|
| | Mean ± S.D. | | | |
| 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 |

**King's Health Questionnaire (KHQ)**

| KHQ domain score | Baseline | 3 months | 6 months | 1 year |
|---|---|---|---|---|
| | Mean ± S.D. | | | |
| 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 |

Significantly different from baseline (*P < 0.05 and ** P < 0.01)

## Concluding message

Istradefylline effectively improved not only motor symptoms, but also LUTS in patients with PD in a long-term period. And 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.

## References


1. 2016; 23: 893-894
2. 2006;21: 737-45


## Disclosures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