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ORIGINAL RESEARCH ARTICLE

Post-Marketing Surveillance of Silodosin in Patients with Benign Prostatic Hyperplasia and Poor Response to Existing Alpha-1 Blockers: The SPLASH Study

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Abstract

Objectives Our objective was to investigate the effectiveness and safety of silodosin in patients with benign prostatic hyperplasia (BPH) who switched to silodosin from another α_1 blocker because of inadequate response.

Methods This was a prospective observational study conducted at 715 medical facilities in Japan in patients with BPH who received an α_1 blocker other than silodosin for at least 3 months but had experienced unsatisfactory treatment outcomes. Patients completed questionnaires, including the International Prostate Symptom Score (IPSS), quality of life (QOL) score and Overactive Bladder Symptom Score (OABSS) at baseline (time of switching) and after 3 months of treatment with silodosin.

Results Overall, 3355 patients were assessed for safety and 3144 patients for effectiveness. Mean ± standard deviation age was 73.1 ± 8.2 years, and most patients had been receiving tamsulosin (53.6%) or naftopidil (45.5%) before silodosin. Silodosin was well tolerated, with an overall incidence of adverse drug reactions of 8.1% and no unexpected safety signals. Significant improvements were observed after switching to silodosin in all effectiveness outcome measures, including total IPSS, all IPSS subscale scores, QOL score, total OABSS, all OABSS subscale scores and residual urine volume. Significant improvements in total IPSS were seen in patients who had been receiving tamsulosin or naftopidil before switching and in almost all other patient subgroups, with the exception of patients with mild symptoms (total IPSS ≤ 7) at baseline.

Conclusions This post-marketing analysis indicates that switching to silodosin from tamsulosin or naftopidil significantly improved symptoms associated with BPH, and silodosin was well tolerated in Japanese patients.

Key Points

A prospective observational study was conducted in Japan to investigate the effectiveness and safety of silodosin in patients with benign prostatic hyperplasia.

Silodosin showed favorable safety profiles and significant improvement in Japanese patients, including International Prostate Symptom Scores, quality of life scores and Overactive Bladder Symptom Scores.

1 Introduction

Silodosin (Urief®, Kissei Pharmaceutical Co. Ltd. and Daiichi Sankyo Co. Ltd.) is a selective α_{1A} blocker developed in Japan and has been on the market since May 2006. Two post-marketing surveys (a drug use results survey [1] and a specified drug use results survey [2]) were conducted after launch, followed by the submission of a reexamination application in April 2014, and the results were reported in June 2015.

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The number of patients with benign prostatic hyperplasia (BPH) is expected to increase in Japan, which is becoming a super-aging society. As a result, physicians will be seeing more patients with BPH with age-related progression of symptoms and prolonged periods of treatment and will need to select the optimal drug based on the background of each individual patient. Currently in Japan, α_1 blockers, including silodosin, are recommended in the Clinical Guidelines for BPH in Japan as a first-line drug therapy for lower urinary tract symptoms (LUTS) associated with BPH [3], but selection of an α_1 blocker depends on the preference of each physician. Furthermore, clinical evidence about switching between α_1 blockers is currently limited.

A pooled analysis of the earlier post-marketing surveys [1, 2] with silodosin included an assessment of patients with a treatment history of α_1 blockers other than silodosin and a low degree of satisfaction (quality of life (QOL) score ≥ 3 points) who switched to silodosin [4]. The results suggested that the voiding symptom score of the International Prostate Symptom Score (IPSS) was an influential factor on the effectiveness of silodosin in LUTS associated with BPH.

SPLASH (Study on patients' QOL by changing medication to silodosin in men with BPH) was a post-marketing surveillance study designed to identify an appropriate patient profile for switching to silodosin. It was a prospective observational study to complement the pooled analysis of the two earlier post-marketing surveys and included the Overactive Bladder Symptom Score (OABSS) in addition to the IPSS and QOL score evaluations included in the previous analyses.

The survey was conducted in accordance with good post-marketing study practice in Japan.

2 Methods

2.1 Study Population

The study population was selected from among patients with BPH who had not experienced satisfactory outcomes with α_1 blockers other than silodosin in routine clinical practice and according to the following inclusion criteria: patients who (1) had not received silodosin previously, (2) gave consent to change their medication from their current α_1 blocker to silodosin, (3) had been using another α_1 blocker other than silodosin for at least 3 months and (4) were evaluated using the face scale questionnaire before the start of silodosin administration. Exclusion criteria were patients who (1) had a QOL score of ≤ 2 before the start of silodosin administration and/or (2) had started treatment with a 5α-reductase inhibitor within 6 months before the start of silodosin administration.

Patients were enrolled using a prospective central registration method through an online system. The enrollment period was for 1 year from 1 November 2014 to 31 October 2015, and the observation period was set for 3 months. The targeted number of patients for the survey was 3000.

2.2 Survey Items

Basic information collected in the study included patient background, administration status of silodosin, and drug therapy history for LUTS other than silodosin (including prior or concomitant therapies).

Patients were also asked to complete a symptoms checklist before the start of administration and at 3 months after the start of administration (or at the final evaluation) so we could understand the patients' LUTS. The IPSS, the QOL score, and the OABSS were obtained through the symptoms checklist. In addition, residual urine volume was measured before the start of administration and at 3 months after the start of administration (or at the final evaluation) as an objective outcome measure.

Safety data collected in the study included the occurrence of adverse events (AEs) and the likely causal relationship with silodosin in the case of onset of an AE.

2.3 Statistical Analysis

Baseline demographic and clinical information was summarized using descriptive summary statistics, including frequency for categorical variables and mean ± standard deviation (SD) for continuous variables.

For the safety assessment, the incidence of adverse drug reactions (ADRs), defined as AEs for which a causal relationship with silodosin could not be ruled out, was calculated for the whole cohort and in specific patient subgroups based on background factors. ADRs were classified according to the preferred terms in the Medical Dictionary for Regulatory Activities-Japanese, version 19.0.

Effectiveness was assessed as the change from baseline in the overall cohort and in subgroups based on the α_1 blocker (tamsulosin or naftopidil) administered prior to silodosin.

The impact of background factors on the incidence of ADRs was assessed using the chi-squared test and Fisher's exact test, depending on the data properties. To compare the effectiveness measurements before and after administration, a one-sample *t*-test was used. The two-tailed significance level was set at 5%.

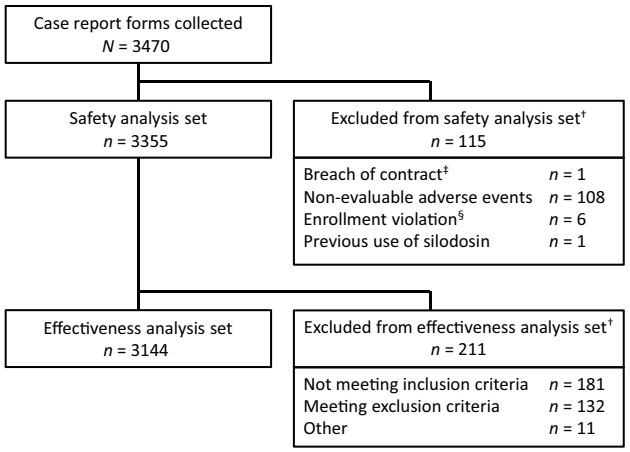

Fig. 1 Patient disposition. †Patients may be included more than once if they were excluded for more than one reason. ‡Patients who received silodosin outside the contract period. §Patients who were not registered within the registration period

3 Results

3.1 Case Description

Figure 1 shows the patient disposition in the study. A total of 3470 case report forms were obtained from 715 medical facilities across Japan. Of those, 115 cases were excluded for reasons such as breach of contract, non-evaluable AEs, enrollment violations, and previous use of silodosin, leaving 3355 cases for the safety analyses. An additional 211 patients were excluded (not meeting inclusion criteria, meeting exclusion criteria, and other), leaving 3144 patients for the effectiveness analyses.

3.2 Patient Background

Baseline demographics and clinical characteristics of the patients in the safety cohort ($n = 3355$) are shown in Table 1. Most patients (46.1%) were aged ≥ 70 and < 80 years, and the mean age was 73.1 ± 8.2 years. The disease duration with the highest proportion was ≥ 3 years (48.9%). The most administered α_1 blockers before silodosin were tamsulosin (53.6%) and naftopidil (45.5%), and other concomitant drugs used to treat LUTS included 5α-reductase inhibitor (9.9%), anticholinergics (8.5%), β_3 agonist (7.0%) and phosphodiesterase 5 (PDE5) inhibitor (2.1%). Based on the total IPSS, most patients had moderate (56.1%) or severe (31.9%) symptoms, with only 8.4% having mild symptoms, and the mean total IPSS was 16.6 ± 6.7. The QOL score showed moderate or severe impairment in 63.3% and 33.6% of patients, respectively, and the mean QOL score was 4.2 ± 0.9. Total OABSS scores were in the mild category for 51.5% of

Table 1 Baseline demographics and clinical characteristics (safety analysis set)

Items and categories	Patients[a] ($n = 3355$)
Age (years)	
< 50	14 (0.4)
≥ 50 and < 60	166 (4.9)
≥ 60 and < 70	871 (26.0)
≥ 70 and < 80	1545 (46.1)
≥ 80	759 (22.6)
Non-elderly patients: < 65	485 (14.5)
Elderly patients: ≥ 65	2870 (85.5)
Mean ± SD	73.1 ± 8.2
BMI (kg/m^2)	
< 18.5	85 (2.5)
≥ 18.5 and < 25.0	1339 (39.9)
≥ 25.0 and < 30.0	546 (16.3)
≥ 30.0	46 (1.4)
Unknown/unlisted	1339 (39.9)
Mean ± SD	23.45 ± 3.05
Prostate volume (mL)	
< 40	1881 (56.1)
≥ 40	1083 (32.3)
Unknown/unlisted	391 (11.7)
Mean ± SD	38.42 ± 20.19
BPH duration	
< 3 months	15 (0.4)
≥ 3 months and < 1 year	612 (18.2)
≥ 1 year and < 3 years	945 (28.2)
≥ 3 years	1640 (48.9)
Unknown/unlisted	143 (4.3)
PSA (ng/mL)	
≤ 4.0	2305 (68.7)
> 4.0 and ≤ 10.0	659 (19.6)
> 10.0	93 (2.8)
Unknown/unlisted	298 (8.9)
Mean ± SD	3.377 ± 16.940
Complications	
No	1235 (36.8)
Yes[b]	2117 (63.1)
Hypertension	1263 (37.6)
Dyslipidemia	476 (14.2)
Diabetes mellitus	415 (12.4)
Gout	38 (1.1)
Hyperuricemia	181 (5.4)
Heart disorder	314 (9.4)
Unknown/unlisted	3 (0.1)
α_1 Blockers used before silodosin	
Tamsulosin	1799 (53.6)
Naftopidil	1525 (45.5)
Other	19 (0.6)

Table 1 (continued)

Items and categories	Patients[a] ($n=3355$)
Concomitant drugs for LUTS other than α_1 blockers	
No	2195 (65.4)
Yes[b]	1160 (34.6)
Anticholinergics	285 (8.5)
5α-Reductase inhibitor	331 (9.9)
PDE5 inhibitor	69 (2.1)
β_3 Agonist	234 (7.0)
Total IPSS	
Mild: 0–7	281 (8.4)
Moderate: 8–19	1883 (56.1)
Severe: 20–35	1070 (31.9)
Mean ± SD	16.6 ± 6.7
QOL score	
Mild: 0–1	1 (0.0)
Moderate: 2–4	2125 (63.3)
Severe: 5–6	1128 (33.6)
Mean ± SD	4.2 ± 0.9
Total OABSS	
Mild: ≤ 5	1728 (51.5)
Moderate: 6–11	1349 (40.2)
Severe: ≥ 12	134 (4.0)
Mean ± SD	5.6 ± 3.0
Residual urine volume (mL)	
< 50	1361 (40.6)
≥ 50 and < 100	497 (14.8)
≥ 100	332 (9.9)
Unknown/unlisted	1165 (34.7)
Mean ± SD	52.4 ± 64.7

BMI body mass index, *BPH* benign prostatic hyperplasia, *IPSS* International Prostate Symptom Score, *LUTS* lower urinary tract symptoms, *OABSS* Overactive Bladder Symptom Score, *PDE* phosphodiesterase, *PSA* prostate-specific antigen, *QOL* quality of life, *SD* standard deviation

[a]Data are presented as n (%) or mean ± SD

[b]Patients may be included more than once if they had more than one condition or were taking more than one concomitant medication

patients, moderate for 40.2%, and severe for 4.0%, with a mean total OABSS of 5.6 ± 3.0.

3.3 Safety

3.3.1 Incidence of Adverse Drug Reactions (ADRs)

The overall incidence of ADRs and those that occurred in five or more patients are described in Table 2. Of the 3355 patients included in the safety analysis, 271 patients developed an ADR (8.1%). ADRs occurring in ≥ 0.5% of patients included ejaculation disorder (1.5%), retrograde ejaculation (1.4%), diarrhoea (1.0%), dizziness (0.9%), and nasal congestion (0.5%).

Table 2 Incidence of adverse drug reactions

ADRs	Safety analysis set ($n=3355$)
Number of patients developing ≥ 1 ADR	271
Number of ADRs reported	306
Incidence of ADRs (%)	8.1
Specific ADRs occurring in ≥ 5 patients, *n* (%)	
Ejaculation disorder	52 (1.5)
Retrograde ejaculation	47 (1.4)
Diarrhoea	35 (1.0)
Dizziness	31 (0.9)
Nasal congestion	18 (0.5)
Faeces soft	13 (0.4)
Dizziness postural	11 (0.3)
Thirst	7 (0.2)
Abdominal discomfort	6 (0.2)
Pollakiuria	6 (0.2)
Orthostatic hypotension	5 (0.1)
Urinary incontinence	5 (0.1)

ADRs adverse drug reactions

3.3.2 Serious ADRs

Two patients developed serious ADRs: haematemesis ($n=1$) and urinary retention ($n=1$). The patient with haematemesis died, and the investigator physician could not determine whether this was causally related to silodosin as the details of the death were unspecified. The urinary retention resolved after transurethral resection of the prostate; the investigator physician determined the causal relationship with silodosin as "unlikely".

3.3.3 Incidence of ADRs Based on Patient Background Factors

The incidence of ADRs based on patient background factors is described in Table 3. The age-specific incidence of ADRs was 17.1% in non-elderly (aged < 65 years) and 6.6% in elderly (aged ≥ 65 years) patients, with a significant difference between groups ($P<0.0001$). The incidence of ADRs did not differ significantly between patients who used concomitant drugs for LUTS other than α_1 blockers (7.6%) and those who did not (8.3%; $P=0.4644$). Among patients who were taking concomitant therapy for LUTS, ADRs occurred in 7.7% of those taking anticholinergics, 6.9% of those taking a 5α-reductase inhibitor, 10.1% of those taking a PDE5 inhibitor, and 5.6% of those taking a β_3 agonist.

Table 3 Incidence of adverse drug reactions in patient subgroups according to background factors

Items and categories	*n*	ADRs, n (%)	*p* value
All patients	3355	271 (8.1)	
Age (years)			
<50	14	3 (21.4)	<0.0001 (Chi-squared)
≥50 and <60	166	36 (21.7)	
≥60 and <70	871	104 (11.9)	
≥70 and <80	1545	102 (6.6)	
≥80	759	26 (3.4)	
Non-elderly patients: <65	485	83 (17.1)	<0.0001 (Fisher)
Elderly patients: ≥65	2870	188 (6.6)	
Concomitant drugs for LUTS other than α_1 blockers			
No	2195	183 (8.3)	0.4644 (Fisher)
Yes	1160	88 (7.6)	
Anticholinergics	285	22 (7.7)	
5α-Reductase inhibitor	331	23 (6.9)	
PDE5 inhibitor	69	7 (10.1)	
β_3 Agonist	234	13 (5.6)	

ADR adverse drug reaction, *LUTS* lower urinary tract symptoms, *PDE* phosphodiesterase

3.4 Effectiveness

3.4.1 Improvement in International Prostate Symptom Score (IPSS)

Overall, 1972–2510 patients in the effectiveness analysis set ($n=3144$) had data for each symptom of the IPSS before and after the administration of silodosin, and the value for those symptoms was not 0 (Table 4). The mean total IPSS value before silodosin administration was 16.6 ± 6.7 but improved to 12.5 ± 6.4 after silodosin treatment ($P<0.0001$). The voiding symptom score, the storage symptom score, and seven other symptoms in the IPSS questionnaire also showed significant improvements with silodosin treatment ($P<0.0001$). Significant improvements in the mean total IPSS and all IPSS subscale scores were seen during silodosin therapy, regardless of whether patients had been receiving tamsulosin or naftopidil ($P<0.0001$) prior to switching to silodosin.

3.4.2 Improvement in Quality of Life Score

The aggregated data for the 2527 patients in the effectiveness analysis set ($n=3144$) who had paired QOL scores before and after silodosin administration are shown in Table 4. The mean QOL scores before and after administration were 4.2 ± 0.9 and 3.0 ± 1.3, respectively, indicating a significant improvement ($P<0.0001$). In the subgroups of patients who had received an α_1 blocker (tamsulosin or naftopidil) prior to silodosin treatment, similar significant improvements in the mean QOL were seen after switching ($P<0.0001$).

3.4.3 Improvement in Overactive Bladder Symptom Score

Between 1117 and 2474 patients in the effectiveness analysis set ($n=3144$) had data for each OABSS symptom before and after the administration of silodosin and a value for those parameters that was not 0 (Table 4). The mean total OABSS was 5.7 ± 2.9 at baseline and 4.5 ± 2.7 after silodosin, indicating a significant improvement ($P<0.0001$). All four symptoms of the OABSS showed a significant improvement from baseline with silodosin ($P<0.0001$). Significant improvements from baseline in total OABSS and all OABSS subscale scores were also seen in patients who had switched from tamsulosin or naftopidil ($P<0.0001$).

3.4.4 Improvement in Residual Urine Volume

In the effectiveness analysis set, 1399 of the 3144 patients had residual urine volume data at baseline and after the administration of silodosin (Table 4). The mean residual urine volume at baseline was 55.0 ± 68.6 mL, decreasing to 37.8 ± 49.7 mL during silodosin treatment ($P<0.0001$). Similar reductions (improvements) in residual urine volume were seen in patients who had previously used tamsulosin or naftopidil before switching to silodosin ($P<0.0001$).

3.4.5 Improvement in the Total IPSS According to Patient Background Factors

The aggregated data of the total IPSS before and after the administration of silodosin according to patient background factors are shown in Table 5. The mean total IPSS showed significant improvement during silodosin treatment in almost

Table 4 Changes in IPSS, QOL score, OABSS, and residual urine volume before and after silodosin administration

Items	All patients					α_1 Blockers used prior to administration of silodosin									
						Tamsulosin					Naftopidil				
	n	Before administration	After administration	Change	*p* value[a]	*n*	Before administration	After administration	Change	*p* value[a]	*n*	Before administration	After administration	Change	*p* value[a]
Total IPSS	2510	16.6±6.7	12.5±6.4	−4.1±6.0	<0.0001	1356	16.5±6.8	12.3±6.6	−4.2±6.2	<0.0001	1147	16.8±6.5	12.7±6.3	−4.1±5.7	<0.0001
IPSS voiding symptoms score[b]	2459	7.7±3.7	5.8±3.7	−2.0±3.4	<0.0001	1327	7.7±3.8	5.7±3.7	−2.0±3.5	<0.0001	1125	7.7±3.7	5.8±3.6	−1.9±3.3	<0.0001
IPSS storage symptoms score[c]	2495	6.9±3.1	5.3±2.8	−1.6±2.7	<0.0001	1344	6.8±3.2	5.2±2.8	−1.7±2.8	<0.0001	1144	7.0±3.1	5.4±2.8	−1.6±2.5	<0.0001
Incomplete emptying	2158	2.6±1.5	1.8±1.3	−0.7±1.5	<0.0001	1158	2.5±1.4	1.8±1.3	−0.7±1.5	<0.0001	995	2.6±1.5	1.9±1.3	−0.7±1.5	<0.0001
Frequency	2367	2.7±1.4	2.1±1.3	−0.6±1.4	<0.0001	1278	2.7±1.4	2.1±1.3	−0.6±1.5	<0.0001	1084	2.7±1.4	2.2±1.3	−0.6±1.4	<0.0001
Intermittency	2125	2.7±1.5	2.0±1.5	−0.7±1.5	<0.0001	1148	2.7±1.5	2.0±1.5	−0.6±1.6	<0.0001	970	2.7±1.5	2.0±1.4	−0.7±1.5	<0.0001
Urgency	2070	2.3±1.4	1.7±1.3	−0.6±1.4	<0.0001	1112	2.3±1.4	1.6±1.3	−0.6±1.5	<0.0001	952	2.3±1.4	1.7±1.2	−0.6±1.4	<0.0001
Weak stream	2426	3.4±1.4	2.5±1.5	−0.9±1.6	<0.0001	1310	3.5±1.4	2.5±1.6	−0.9±1.6	<0.0001	1109	3.4±1.4	2.6±1.5	−0.8±1.6	<0.0001
Straining	1972	2.5±1.5	1.9±1.4	−0.6±1.6	<0.0001	1061	2.5±1.5	1.9±1.4	−0.6±1.6	<0.0001	905	2.5±1.5	1.9±1.5	−0.6±1.6	<0.0001
Nocturia	2428	2.5±1.2	2.0±1.0	−0.6±1.0	<0.0001	1303	2.5±1.1	1.9±1.0	−0.6±1.0	<0.0001	1118	2.6±1.2	2.0±1.0	−0.5±1.0	<0.0001
QOL score	2527	4.2±0.9	3.0±1.3	−1.3±1.3	<0.0001	1367	4.2±0.9	2.9±1.3	−1.3±1.4	<0.0001	1153	4.2±0.9	3.0±1.2	−1.2±1.3	<0.0001
Total OABSS	2474	5.7±2.9	4.5±2.7	−1.1±2.3	<0.0001	1333	5.6±2.9	4.4±2.7	−1.2±2.4	<0.0001	1134	5.7±2.9	4.6±2.7	−1.1±2.1	<0.0001
Frequency	1951	1.0±0.4	0.9±0.4	−0.1±0.6	<0.0001	1047	1.0±0.4	0.9±0.4	−0.1±0.6	<0.0001	898	1.0±0.4	0.9±0.5	−0.1±0.6	<0.0001
Nocturia	2403	2.2±0.8	1.8±0.8	−0.4±0.7	<0.0001	1288	2.2±0.8	1.8±0.8	−0.4±0.8	<0.0001	1108	2.2±0.8	1.9±0.8	−0.4±0.7	<0.0001
Urgency	1977	2.4±1.3	1.8±1.3	−0.6±1.4	<0.0001	1063	2.4±1.3	1.8±1.3	−0.6±1.5	<0.0001	908	2.4±1.4	1.9±1.3	−0.5±1.3	<0.0001
Urinary incontinence	1117	1.7±1.2	1.3±1.2	−0.4±1.3	<0.0001	598	1.8±1.2	1.3±1.2	−0.5±1.3	<0.0001	517	1.7±1.2	1.3±1.1	−0.4±1.2	<0.0001
Residual urine volume (mL)	1399	55.0±68.6	37.8±49.7	−17.2±53.9	<0.0001	750	55.1±70.7	37.6±48.9	−17.5±55.6	<0.0001	643	54.6±66.1	37.7±50.6	−16.8±52.0	<0.0001

Data are presented as mean±standard deviation unless otherwise indicated

IPSS International Prostate Symptom Score, *OABSS* Overactive Bladder Symptom Score, *QOL* quality of life

[a]One-sample *t*-test

[b]Intermittency + weak stream + straining

[c]Frequency + urgency + nocturia

Table 5 Changes in total IPSS before and after silodosin administration in patient subgroups according to background factors

Items and categories	*n*	Before administration	After administration	Change	*p* value[a]
All patients	2510	16.6 ± 6.7	12.5 ± 6.4	−4.1 ± 6.0	< 0.0001
Age (years)					
< 50	8	13.3 ± 6.0	9.5 ± 6.8	−3.8 ± 5.0	0.0706
≥ 50 and < 60	114	17.2 ± 7.0	12.8 ± 6.7	−4.4 ± 5.1	< 0.0001
≥ 60 and < 70	652	16.6 ± 6.7	12.4 ± 6.4	−4.2 ± 5.9	< 0.0001
≥ 70 and < 80	1153	16.5 ± 6.6	12.2 ± 6.2	−4.3 ± 6.1	< 0.0001
≥ 80	583	16.9 ± 6.8	13.2 ± 6.9	−3.7 ± 5.9	< 0.0001
Non-elderly patients: < 65	350	16.6 ± 6.8	12.2 ± 6.5	−4.3 ± 5.7	< 0.0001
Elderly patients: ≥ 65	2160	16.7 ± 6.7	12.5 ± 6.4	−4.1 ± 6.0	< 0.0001
BMI (kg/m^2)					
< 18.5	61	15.4 ± 6.5	12.3 ± 6.2	−3.1 ± 5.0	< 0.0001
≥ 18.5 and < 25.0	1035	16.6 ± 6.7	12.5 ± 6.6	−4.1 ± 6.0	< 0.0001
≥ 25.0 and < 30.0	425	16.7 ± 7.0	12.6 ± 6.6	−4.1 ± 6.4	< 0.0001
≥ 30.0	37	15.8 ± 7.6	11.5 ± 7.2	−4.2 ± 7.4	0.0013
Unknown/unlisted	952	16.8 ± 6.6	12.5 ± 6.2	−4.3 ± 5.8	< 0.0001
Prostate volume (mL)					
< 40	1376	16.3 ± 6.6	12.4 ± 6.3	−3.9 ± 6.0	< 0.0001
≥ 40	837	17.1 ± 6.8	12.7 ± 6.3	−4.4 ± 6.2	< 0.0001
Unknown/unlisted	297	16.8 ± 7.0	12.3 ± 7.2	−4.6 ± 5.2	< 0.0001
BPH duration					
< 3 months	0	–	–	–	–
≥ 3 months and < 1 year	447	16.2 ± 6.5	12.1 ± 6.5	−4.1 ± 5.9	< 0.0001
≥ 1 year and < 3 years	711	16.5 ± 6.8	11.9 ± 6.2	−4.6 ± 6.0	< 0.0001
≥ 3 years	1257	16.7 ± 6.7	12.9 ± 6.4	−3.8 ± 5.9	< 0.0001
Unknown/unlisted	95	18.9 ± 7.1	13.6 ± 7.8	−5.3 ± 6.3	< 0.0001
PSA (ng/mL)					
≤ 4.0	1720	16.6 ± 6.6	12.5 ± 6.3	−4.1 ± 5.9	< 0.0001
> 4.0 and ≤ 10.0	495	16.4 ± 6.5	12.0 ± 6.2	−4.4 ± 6.2	< 0.0001
> 10.0	70	17.2 ± 7.9	14.0 ± 7.8	−3.2 ± 6.7	0.0001
Unknown/unlisted	225	17.3 ± 7.2	12.8 ± 7.5	−4.5 ± 5.8	< 0.0001
α_1 Blockers used prior to silodosin					
Tamsulosin	1356	16.5 ± 6.8	12.3 ± 6.6	−4.2 ± 6.2	< 0.0001
Naftopidil	1147	16.8 ± 6.5	12.7 ± 6.3	−4.1 ± 5.7	< 0.0001
Other	12	17.3 ± 6.3	13.3 ± 5.5	−3.9 ± 3.9	0.0051
Concomitant drugs for LUTS other than α_1 blockers					
Anticholinergics	226	16.8 ± 6.5	13.6 ± 6.6	−3.2 ± 5.1	< 0.0001
5α-Reductase inhibitor	244	15.3 ± 6.5	12.4 ± 6.4	−2.9 ± 5.9	< 0.0001
PDE5 inhibitor	50	20.3 ± 6.8	15.2 ± 5.0	−5.1 ± 5.8	< 0.0001
β_3 Agonist	171	17.1 ± 6.8	13.3 ± 6.2	−3.8 ± 5.9	< 0.0001
Total IPSS					
Mild: 0–7	207	5.7 ± 1.4	6.7 ± 4.3	1.0 ± 4.4	0.0014
Moderate: 8–19	1465	13.8 ± 3.3	10.8 ± 4.9	−3.0 ± 4.8	< 0.0001
Severe: 20–35	838	24.3 ± 3.6	16.9 ± 6.7	−7.4 ± 6.5	< 0.0001
QOL score					
Mild: 0–1	0	–	–	–	–
Moderate: 2–4	1647	14.6 ± 5.9	11.4 ± 5.9	−3.2 ± 5.6	< 0.0001
Severe: 5–6	863	20.4 ± 6.6	14.5 ± 7.0	−5.9 ± 6.3	< 0.0001
Total OABSS					
Mild: ≤ 5	1312	14.0 ± 5.8	10.9 ± 5.7	−3.1 ± 5.4	< 0.0001
Moderate: 6–11	1079	19.2 ± 6.3	13.9 ± 6.4	−5.2 ± 6.1	< 0.0001
Severe: ≥ 12	96	24.4 ± 6.3	17.8 ± 9.0	−6.6 ± 8.8	< 0.0001

Table 5 (continued)

Items and categories	*n*	Before administration	After administration	Change	*p* value[a]
Residual urine volume (mL)					
< 50	1059	16.0 ± 6.4	12.2 ± 6.3	−3.7 ± 5.9	< 0.0001
≥ 50 and < 100	387	17.6 ± 7.0	12.6 ± 6.6	−5.0 ± 6.8	< 0.0001
≥ 100	256	17.4 ± 6.9	12.8 ± 6.3	−4.6 ± 6.2	< 0.0001
Unknown/unlisted	808	16.8 ± 6.8	12.7 ± 6.6	−4.1 ± 5.5	< 0.0001

Data are presented as mean ± standard deviation unless otherwise indicated

BMI body mass index, *BPH* benign prostatic hyperplasia, *IPSS* International Prostate Symptom Score, *LUTS* lower urinary tract symptoms, *OABSS* Overactive Bladder Symptom Score, *PDE* phosphodiesterase, *PSA* prostate-specific antigen, *QOL* quality of life

[a]One sample t-test

all subgroups containing at least 50 patients ($P < 0.001$); the only exception was the group with mild symptoms (total IPSS ≤ 7) at baseline.

4 Discussion

The clinical guidelines for BPH in Japan recommend α_1 blockers as a first-line drug therapy for BPH [3]. Although silodosin has been compared with tamsulosin or naftopidil in crossover or parallel studies [5–7], evidence concerning the effect of switching between α_1 blockers is currently limited. We expected that this survey would demonstrate the specific patient characteristics suitable for switching to silodosin from other α_1 blockers and the effect of the switching.

As for the safety profile, the incidence of ADRs with silodosin was 8.1% in this post-marketing surveillance, indicating a slightly lower rate compared with the aggregated results (11.3%) [8] in the previous post-marketing surveys [1, 2]. ADRs that occurred at an incidence of ≥ 0.5% included ejaculation disorder, retrograde ejaculation, diarrhoea, dizziness, and nasal congestion. No new safety signals were identified, as all of the common ADRs in our analysis were consistent with those in the previous surveys.

Consistent with the previous post-marketing surveys, the incidence of ADRs was significantly higher in non-elderly patients (17.1%) than in elderly patients (6.6%). A total of 271 patients developed ADRs, and the most common ADRs were ejaculation disorder ($n = 52$) and retrograde ejaculation ($n = 47$), events that are likely to be more frequent in non-elderly patients as shown in previous post-marketing data. The age-related incidence of ADRs based on 10-year increments was also investigated, and the result indicated a lower incidence of ADRs with more advancing age, as has been shown previously.

Since silodosin was launched, a number of new therapeutic agents for overactive bladder (OAB) and BPH have become available, including anticholinergics, 5α-reductase inhibitor, PDE5 inhibitor, and β_3 agonist. The incidence of ADRs in patients taking these agents concomitantly with silodosin (7.6%) was not significantly different from that in silodosin recipients not taking concomitant BPH therapy (8.3%). The incidence of ADRs according to the type of concomitant drugs was as follows: anticholinergics 7.7%; 5α-reductase inhibitor 6.9%; PDE5 inhibitor 10.1%; and β_3 agonist 5.6%. Although the incidence of silodosin ADRs was slightly higher with concomitant use of a PDE5 inhibitor than with other drug classes, the number of patients receiving this combination was small ($n = 69$). Therefore, more data from a larger cohort of patients are needed.

As for the effectiveness profile, the mean change in total IPSS after switching to silodosin was −4.1 ± 6.0, indicating a significant improvement in symptoms. Furthermore, significant improvements were observed in all effectiveness outcome measures, including the seven symptoms of the IPSS, the IPSS voiding symptom score, the IPSS storage symptom score, the QOL score, the total OABSS, the four symptoms of the OABSS, and residual urine volume. Similar improvements were observed in patients who had previously received tamsulosin or naftopidil before switching to silodosin, indicating no difference depending on the types of prior therapeutic drugs. The results suggested that switching to silodosin, which has high α_{1A}-receptor selectivity, could be a treatment option for patients with a low level of satisfaction with the treatment.

With the exception of patients who had mild symptoms (total IPSS ≤ 7) at baseline, significant improvements in total IPSS were seen after switching in all subgroups containing at least 50 patients. Thus, switching to silodosin improved the total IPSS in most patients, regardless of background factors. Patients whose symptoms were of mild severity in the total IPSS during their initial α_1 blocker treatment did not show further improvement after switching to silodosin. Therefore, total IPSS at the time of switching can be a predictor of the effect of the switching.

This study was conducted to investigate the effectiveness and safety of silodosin in patients with BPH who had not achieved satisfactory symptom control with other α_1 blockers in routine clinical practice. The results confirmed the safety of silodosin, consistent with previous post-marketing

surveys such as the drug use results survey, and showed there was no increase in the incidence of ADRs with the use of any type of concomitant drug for LUTS treatment. Moreover, significant improvements in effectiveness were observed in all outcome measures, including the IPSS, the QOL score and OABSS.

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Compliance with Ethical Standards

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Conflict of interest Hiroshi Takahashi, Shinichi Kubono, Takehiko Taneyama, and Kiyotoshi Kuramoto are employees of and hold stock options in Kissei Pharmaceutical Co., Ltd. Hideki Mizutani is an employee of and holds stock options in Daiichi Sankyo Co., Ltd. Noriko Tanaka is an employee of Daiichi Sankyo Co., Ltd. Masaki Yoshida has received grants from Astellas Pharma Inc.; consulting fees from Kyorin Pharmaceutical Co. Ltd. and Kissei Pharmaceutical Co. Ltd.; support for travel to meetings for the study, manuscript preparation and other purposes from Astellas Pharma Inc., Kyorin Pharmaceutical Co. Ltd., Kissei Pharmaceutical Co. Ltd. and Hisamitsu Pharmaceutical Co. Inc.; fees for participation in review activities from Astellas Pharma Inc., Kyorin Pharmaceutical Co. Ltd., Kissei Pharmaceutical Co. Ltd. and Hisamitsu Pharmaceutical Co. Inc.; payment for writing or reviewing the manuscript from Astellas Pharma Inc., Kyorin Pharmaceutical Co. Ltd., Kissei Pharmaceutical Co. Ltd. and Hisamitsu Pharmaceutical Co. Inc.; and payment for lectures, including service on speakers bureaus, from Astellas Pharma Inc., Kyorin Pharmaceutical Co. Ltd., Kissei Pharmaceutical Co. Ltd. and Hisamitsu Pharmaceutical Co. Inc.

Data availability The datasets generated and analysed during the current study are not publicly available because our dataset includes identified individual participants data.

Research involving human participants This survey was conducted in accordance with good post-marketing study practice in Japan.

Informed consent According to good post-marketing study practice in Japan, informed consent was not required for this post-marketing study. As such, informed consent was not obtained from individual participants included in the study.

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