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Review Article

New clinical evidence of silodosin, an α_{1A} selective adrenoceptor antagonist, in the treatment for lower urinary tract symptoms

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Abbreviations & Acronyms
α_1-AR = α_1-adrenoceptor
α_{1A}-AR = α_{1A}-adrenoceptor
AE = adverse effects
BOO = bladder outlet obstruction
BOOI = bladder outlet obstruction index
BPH = benign prostatic hyperplasia
CI = confidence interval
CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome
DE = disorders of ejaculation
GRA = global response assessment
HR-QOL = health-related quality of life
IPSS = International Prostate Symptom Score
ITT = intention to treat
LOCF = last observation carried forward
LUTS = lower urinary tract symptoms
LUTS/BPH = lower urinary tract symptoms associated with benign prostatic hyperplasia
mRNA = messenger ribonucleic acid
NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index
P_{det}•Q_{max} = detrusor pressure at maximal flow
PI = prostate implantation
PP = per protocol
PVR = post-void residual urine
Q_{max} = maximal flow rate
RE = retrograde ejaculation
SF-12 = Medical Outcomes Study Short Form 12
SIL + EjD = silodosin-treated group with ejaculation disorder
SIL – EjD = silodosin-treated group without ejaculation disorder
TEAE = treatment emergent adverse effects.

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Abstract: Lower urinary tract symptoms associated with benign prostatic hyperplasia are highly prevalent in older men. Pharmacological treatment is the first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia. The first choice in the pharmacological treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia is the α_1-adrenoceptor antagonists. Many α_1-adrenoceptor antagonists are available in the world. Silodosin is an α_1-adrenoceptor antagonist developed by Kissei Pharmaceutical, and has a specific selectivity for the α_{1A}-adrenoceptor subtype. By antagonizing α_{1A}-adrenoceptor in the prostate and urethra, silodosin causes smooth muscle relaxation in the lower urinary tract. As a result of the high affinity for the α_{1A}-adrenoceptor than for the α_{1B}-adrenoceptor, silodosin minimizes the propensity for blood pressure-related adverse effects caused by blockade of α_{1B}-adrenoceptor. The efficacy and safety of silodosin for treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia was first reported by Japanese investigators in 2006. At present, silodosin is used in many countries. In the present review, we summarize the new clinical evidence for lower urinary tract symptoms associated with benign prostatic hyperplasia and introduce the data supporting the new clinical indications of silodosin.

Key words: α_{1A} adrenergic receptor subtypes, α_1-adrenoceptor antagonists, benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), silodosin.

Introduction

BPH is one of the most common diseases in men, with an increasing prevalence rate with age.[1,2] BPH is a histological diagnosis characterized by the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[3,4] This disease clinically manifests as LUTS. LUTS can be classified into three categories: storage, voiding and postmicturition symptoms.[5] Current strategies for treating men with LUTS/BPH depend on the severity of the symptoms and include watchful waiting, pharmacological management, minimally invasive therapies and surgery.[2,3,6,7]

Three types of α_1-AR subtypes (α_{1A}, α_{1B} and α_{1D}) are found in human tissue.[8] The α_{1A} subtype (located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra) mediates contraction of the smooth muscle in these tissues.[9,10]

Over the past 20 years, α_1-AR antagonists have become the primary first-line therapy for LUTS/BPH. A number of α_1-AR antagonists (alfuzosin, doxazosin, terazosin, tamsulosin, naftopidil) have been approved for the treatment of BPH in the world. Early α_1-AR antagonists were non-selective for subtypes and were associated with blood pressure-related AE, such as orthostatic hypotension. Tamsulosin has relative selectivity for the α_{1A}- and α_{1D}-subtypes, and naftopidil has relative selectivity for the α_{1D}-subtype. The subtype-selective α_1-AR antagonists might contribute to reducing AE of cardiovascular systems.

As α_{1A}-AR mediates contraction of the smooth muscle of the human prostate, it has been suggested that treatment of BPH with a highly selective α_{1A}-AR is likely to have excellent efficacy and be associated with fewer cardiovascular AE. Silodosin (KMD-3213) is a highly selective α_{1A}-AR antagonist developed by Kissei Pharmaceutical (Matsumoto, Japan). The selectivity of silodosin towards α_{1A}-AR versus α_{1B}-AR subtype was reported to be 38-fold higher than that of tamsulosin in studies using Chinese hamster ovary cells expressing three human α_1-AR subtypes, showing a high selectivity of silodosin for the lower urinary tract, where α_{1A}-AR is the predominant subtype.[11] *In vivo* comparative studies with tamsulosin and prazosin showed that silodosin produces favorable uroselectivity, as determined by the ratio between the dose required to inhibit intraurethral pressure and that to decrease blood pressure in rat and dog models.[12,13]

More than 5 years have passed since the first report of the clinical efficacy and safety for treatment of LUTS/BPH by Kawabe *et al.*[14] At present, silodosin is available in many countries.[15] In the revised clinical guideline for BPH in Japan,[16] silodosin had a Grade A recommendation for treatment. We have reviewed the recent new clinical reports of silodosin for evaluation of the efficacy and safety.

New clinical data of silodosin for treatment of LUTS/BPH

New randomized controlled trials in the USA, Europe and Taiwan

Several phase III studies of silodosin for the treatment of LUTS/BPH were carried out in the USA,[17] Europe[18] and Taiwan.[19] The main results are summarized in Tables 1, 2 and 3, including the results of a Japanese study.[14]

Two USA clinical studies that evaluated the efficacy and tolerability of silodosin 8 mg once daily in men with BPH were described individually, and were pooled and reported. Both were 12-week, multicenter, randomized, double-blind, placebo-controlled trials.[17] Once daily dosing of 8 mg was different to twice daily dosing in Japan. The two studies enrolled patients aged ≥50 years who had an IPSS ≥ 13, a Q_{max} between 4 and 15 mL/s, and a postvoid residual volume of <250 mL. The studies had a 4-week placebo run-in period; patients with a >30% decrease in IPSS or a >3 mL/s increase in Q_{max} at the end of this period were excluded from subsequent randomization. The enrolled men showed an average IPSS score of 21.2–21.4 points and a Q_{max} between 8.4–9.0 mL/s. After treatment with silodosin, the IPSS improvements were 6.3 and 6.5 versus 3.4 and 3.6 improvements in the placebo group, respectively, and the flow rate improvements were 2.2 and 2.9 versus 1.2 and 1.9 mL/s, respectively. Of 923 patients, 466 received silodosin and 457 received placebo. After 3–4 days of treatment, patients

Table 1 Main results in phase III clinical trials in United States, Taiwan and Japan

Study	Patients (*n*)	Total IPSS, mean (SD)		IPSS (voiding symptoms) mean (SD)		IPSS (storage symptoms) mean (SD)		Q_{max} mean (SD), mL/s	
		Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Marks *et al.*[17]									
Silodosin 8 mg/day	466	21.3 (5.1)	−6.4 (6.63)*	12 (3.6)	−4.0 (4.31)*	9.3 (2.6)	−2.3 (2.93)*	8.7 (2.60)	2.6 (4.43)*
Placebo	457	21.3 (4.9)	−3.5 (5.84)	12 (3.5)	−2.1 (3.76)	9.3 (2.5)	−1.4 (2.99)	8.9 (2.80)	1.5 (4.36)
Yu *et al.*[19]									
Silodosin 8 mg/day	87	19.3 (4.5)	−10.6 (5.1)	12.1 (3.3)	−7.1 (3.8)	7.1 (3.1)	−3.5 (2.2)	10.3 (2.8)	0.9 (4.2)
Tamsulosin 0.2 mg/day	83	19.8 (4.5)	−10.0 (5.1)	13.0 (3.3)	−6.7 (3.9)	6.9 (3.1)	−3.3 (2.2)	10.6 (2.8)	1.4 (4.2)
Kawabe *et al.*[14]									
Silodosin 8 mg/day	175	17.1 (5.7)	−8.3 (6.4)*	10.8 (4.1)	−5.8 (4.6)*	6.4 (3.0)	−2.5 (2.9)*	9.88 (2.75)	1.70 (3.31)
Tamsulosin 0.2 mg/day	192	17.0 (5.7)	−6.8 (5.7)	10.8 (4.2)	−4.8 (4.1)	6.2 (2.9)	−2.1 (2.6)	9.41 (2.81)	2.60 (3.98)
Placebo	89	17.1 (6.1)	−5.3 (6.7)	10.9 (4.4)	−3.8 (4.8)	6.3 (2.8)	−1.5 (2.6)	0.18 (2.72)	0.26 (2.21)

*Significant difference versus placebo. Marks *et al.*[17]: Two USA clinical studies to evaluate the efficacy and tolerability of silodosin 8 mg once daily in men with BPH were carried out individually, and pooled. Then, the data were reported in Marks *et al.*[17]

Table 2 Main results in phase III clinical trials in Europe[18]

Group	No. patients	Total IPSS			IPSS (voiding symptoms)		IPSS (storage symptoms)		Q_{max} (mL/s)	
		Baseline Mean (SD)	Change from baseline	Difference *vs* placebo (95% CI)	Change from baseline	Difference *vs* placebo (95% CI)	Change from baseline	Difference *vs* placebo (95% CI)	Change from baseline	Responder (%)
Silodosin (8 mg/day)	371	19 (4)	−7.0	−2.3 [−3.2, −1.4]*	−4.5	−1.7* [−2.2, −1.1]	−2.5	−0.7* [−1.1, −0.2]	3.77	46.6
Tamsulosin (0.4 mg/day)	376	19 (4)	−6.7	−2.0 [−2.9, −1.1]*	−4.2	−1.4* [−2.0, −0.8]	−2.4	−0.6* [−1.1, −0.2]	3.53	46.5
Placebo	185	19 (4)	−4.7	–	−4.7	–	−1.8	–	2.93	40.5

*Significant difference versus placebo. Responder of Q_{max} was defined as an increase from baseline ≥30%.

receiving silodosin versus the placebo achieved a significant improvement in total IPSS, and storage and voiding subscores. The mean ± SD change from baseline in total IPSS was −4.2 ± 5.3 for silodosin versus −2.3 ± 4.4 for placebo. Differences (silodosin *vs* placebo) in IPSS and subscores increased by week 12 ($P < 0.0001$). Mean change from baseline in Q_{max} was greater ($P < 0.0001$) with silodosin (2.8 ± 3.4) than placebo (1.5 ± 3.8). Differences remained significant ($P < 0.001$) through week 12. The most common AE was (mostly mild) RE (silodosin 28.1% of patients, placebo 0.9%). Few patients treated with silodosin (2.8%) discontinued because of RE. The proportions of patients with orthostatic hypotension were similar for silodosin (2.6%) and placebo (1.5%).

The report suggested that silodosin was safe and well tolerated. RE was the most common drug-related AE, but it rarely resulted in the discontinuation of treatment. In addition, silodosin had a low incidence of orthostatic hypotension and was associated with few events of dizziness. The rapid onset of clinical efficacy would make it a useful option for the treatment of patients with LUTS/BPH.

An open-label extension study was also reported with the primary objective to assess the safety.[20] A total of 435 (65.8%) of 661 participants completed the study and 431 (65.2%) experienced 924 AE. No serious AE occurred that the investigators considered as drug-related. Of the 34% who discontinued the study, AE were responsible for 14.1% and lack of efficacy for 8.8%. Because of α_{1A} selectivity profile, although dizziness and orthostasis side-effects were noted in less than 3% of patients for each, an increase in ejaculatory dysfunction was observed. The most common AE observed in this trial was retrograde and/or altered ejaculation in 31.1% of de novo-treated patients and 9.6% of previously-treated patients.

Disorders relating to ejaculation observed in patients with silodosin are not life-threatening. In patients with LUTS/BPH, sexual dysfunction is common.[21] Schou *et al*.[22] reported that in a survey of 261 patients with BPH, those who considered abnormal ejaculation as a major problem accounted for just 6%. Scarpa showed that among 877 patients with BPH, abnormal ejaculation was not considered to be as problematic as erectile dysfunction.[23] Therefore, in patients with LUTS that impairs QOL, abnormal ejaculation seems generally not to be considered as a highly bothersome symptom.

However, in the younger sexually active men, the problem of ejaculation might be very bothersome. It is suggested that informed consent of the side-effect would be necessary in prescribing this drug for such patients.

In Europe, a multicenter double-blind, placebo- and active-controlled parallel group clinical study was carried out.[18] After a wash-out phase of 14 days and a 4-week single-blind placebo run-in period, participants who met the selection criteria were randomly assigned (2:2:1) to 12-week

Table 3 Adverse effects of silodosin compared with tamsulosin and placebo in four phase III studies[14,17–19]

Adverse effects	Silodosin (%)	Tamsulosin (%)	Placebo (%)
Ejaculatory disorders (Retrograde ejaculation)	9.7–28.1	1.0–2.1	0–1.1
Upper respiratory tract infection	18.9	27.6	19.1
Thirst	10.3	3.6	4.5
Loose stool	9.1	3.6	5.6
Urinary incontinence	6.3	5.7	0
Diarrhea	2.6–6.9	6.8	5.6
Dizziness	3.2–7.8	2.9–7.3	4.5
Orthostatic hypotension	2.6	–	1.5
Headache	2.4–5.5	2.9	0.9–4.7
Discontinued the study due to TEAE	2.1–10.7	1.0–5.7	1.6–4.5
Discontinued the study due to ejaculatory disorders	1.3–2.9	0.3	0

treatment with silodosin 8 mg, tamsulosin 0.4 mg or placebo, given once daily. Men aged 50 years and over with LUTS (defined by a stable IPSS total score 13 points and over), BOO (defined by a Q_{max} between 4 and 15 mL/s, with a minimum voided volume of 125 mL).

A total of 1228 patients were screened; 955 were randomized to receive silodosin 8 mg (381), tamsulosin 0.4 mg (384) or placebo (190), respectively. The primary end-point was the evaluation of the IPSS; the secondary end-points were a subanalysis of urinary storage and voiding symptoms, QOL, and Q_{max}. Treatment responders were defined as 25% decrease in IPSS and 30% increase in Q_{max} from baseline. In the primary end-points, superiority of silodosin and tamsulosin treatments versus placebo was observed with highly statistically significant differences at all weeks ($P < 0.001$), both in the ITT (difference from placebo −2.3 and −2.0, respectively) and PP population (difference from placebo −2.2 and −1.9, respectively). In all three treatment groups, the percentage of IPSS responders progressively increased from baseline to week 12. At study end, 66.8% and 65.4% of the patients receiving silodosin or tamsulosin were responders respectively, compared with 50.8% in the placebo group. The differences versus placebo were highly significant ($P < 0.001$) for both active compounds, whereas the comparison between silodosin and tamsulosin did not show a statistically significant difference.

The same results as previous studies were obtained from the analysis of the subscore of urinary storage and voiding symptoms, when compared with the placebo Only in the nocturia subscore did silodosin have an advantage over tamsulosin, which was not statistically significant ($P = 0.095$ for tamsulosin *vs* placebo; $P = 0.314$ for silodosin *vs* tamsulosin; $P = 0.013$ for silodosin *vs* placebo). However, there was no significant difference in Q_{max} (responders 46.6% silodosin, 46.5% tamsulosin and 40.5% placebo; responders had a reduction >30% from baseline) between the two active drugs and the placebo. There was also no difference between the two drugs for the QOL parameter, whereas both were better than the placebo.

The AE for the three groups were 34.9% for silodosin, 28.9% for tamsulosin and 24.2% for placebo, and the disturbances to ejaculatory function were significantly higher in the group treated with silodosin (14.2%) than in that treated with tamsulosin (2.1%) or placebo (1.1%). When analyzing cardiovascular AE, no statistically significant differences were found in laboratory parameters, vital signs and electrocardiograms for silodosin and tamsulosin when compared with placebo. There were significant greater variations in blood pressure and heart rate for silodosin than tamsulosin when compared with placebo.

In Taiwan, a 12-week, randomized, double blind, multicenter study was carried out.[19] Men aged 40 years and more with an IPSS of 13 and more, a QOL score of 3 and more, a prostate volume of 20 mL and more, and Q_{max} of less than 15 mL/s with a voided volume of 100 mL and more were enrolled. The primary efficacy measure was the mean change from baseline to end-point in IPSS. The non-inferiority margin of the IPSS change was set at 1.0. Secondary efficacy measures included change in Q_{max} and QOL score.

The mean difference (silodosin minus tamsulosin) in IPSS change from baseline was −0.60 (95% confidence interval: −2.15 to 0.95), inferring the non-inferiority of silodosin to tamsulosin. The mean changes in the Q_{max} and QOL score from baseline were comparable between the groups (both, $P < 0.05$).

Although patients receiving silodosin had a significantly higher incidence of abnormal ejaculation (9.7% *vs* tamsulosin 1.0%, $P < 0.009$), just 1.9% discontinued treatment. Tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure (-4.2 mmHg, within-group $P < 0.004$) relative to the negligible change of silodosin (–0.1 mmHg, within-group $P = 0.96$).

Table 4 Effects of disorders of ejaculation on clinical efficacies of silodosin

Study	Japanese study[24]			American study[25]		
	Silodosin		Placebo	Silodosin		Placebo
	+DE	–DE		+DE	–DE	
Baseline data						
No. patients	39	136	89	131	335	457
Age	60.9 (6.9)†	66.6 (6.5)	65.0 (6.9)	60.8 (6.28)†‡	66.1 (8.20)	64.7 (8.06)
IPSS						
Total score	18.3 (5.3)	16.8 (5.8)	17.1 (6.1)	22.2 (5.01)	21.0 (5.14)	21.3 (4.91)
Storage subscore	9.4 (2.60)	9.3 (2.59)	9.3 (2.51)			
Voiding subscore	12.8 (3.38)	11.7 (3.59)	12.0 (3.53)			
QOL	5.0 (0.8)	4.9 (0.9)	4.7 (0.9)	4.1 (1.05)	3.9 (1.05)	4.0 (1.07)
Change from baseline at LOCF						
IPSS						
Total score	–11.8 (6.5)†‡	–7.2 (6.0)	–5.3 (6.7)	–7.2 (7.23)‡	–6.1 (6.36)‡	–3.5 (5.84)
Storage subscore	–2.9 (3.1)	–2.4 (2.9)	–1.5 (2.6)	–2.6 (3.15)‡	–2.2 (2.84)‡	–1.4 (2.66)
Voiding subscore	–9.9 (4.4)†‡	–4.9 (4.2)	–3.8 (4.8)	–4.6 (4.59)‡	–3.8 (4.19)‡	–2.1 (3.76)
QOL	–2.2 (1.6)†‡	–1.5 (1.3)	–1.1 (1.2)	–1.0 (1.35)‡	–0.8 (1.29)‡	–0.4 (1.14)

†Significantly different from the comparable value of silodosin group without DE ($P < 0.05$). ‡Significantly different from the comparable value of placebo group ($P < 0.05$). Each value shows the average, and the value of the parenthesis is standard deviation.

Thus, the authors concluded that silodosin can be considered an effective and safe treatment for LUTS/BPH.

Effects of disorders of ejaculation on clinical efficacies of silodosin

Silodosin for treatment of BPH symptoms was analyzed to examine the relationship between treatment efficacy and occurrence of abnormal ejaculation, using a Japanese phase III study.[24] The SIL + EjD showed a larger change in total IPSS than the SIL – EjD (difference: –4.36 [95% CI –6.44 to –2.27]) and the placebo group (difference –6.29 [95% CI –8.44, –4.14]; Table 4). When the treatment success rate using a 25% reduction in the total IPSS category was measured, the success rate in SIL + EjD was higher than in SIL – EjD and placebo. There were no significant differences in adverse drug reactions rates other than ejaculation disorder. Discontinuation rates between SIL + EjD and SIL – EjD were similar. The authors conclude that ejaculation disorder caused by silodosin is associated with very large improvements in LUTS. Patients with ejaculation disorder might have larger symptomatic improvements without incremental risk for AE.

A similar study was reported, using two phase III studies from the USA.[25] Silodosin-treated patients were stratified by the absence or presence of RE. Of the 466 patients treated with silodosin, 131 (28%) patients reported RE and 335 (72%) patients did not; four of the 457 patients receiving placebo (0.9%) reported RE. Most "RE" events in patients (110/134; 82%) treated with silodosin were reported as "orgasm with absence of seminal emission." Silodosin-treated patients with and without RE showed significant improvement in IPSS, Q_{max} and QOL versus placebo ($P < 0.02$). Patients with RE versus patients without RE showed greater improvement, but there were not statistically significant differences ($P > 0.05$). For patients with RE, the odds of achieving an improvement of 3 and more points in IPSS, and 3 mL/s and more in Q_{max} by study end were 1.75-fold those for patients without RE ($P = 0.0127$). The absence of seminal emission might predict superior treatment efficacy of silodosin in individual patients.

Urodynamic effects of silodosin

Urodynamic effects of silodosin were evaluated in two Japanese studies using pressure flow studies. Yamanishi *et al.*[26] treated 36 patients with LUTS/BPH and carried out pressure flow studies at baseline and at 3 months, noting a decrease in the P_{det}•Q_{max} from 80.6 to 48.6 cmH_2O and a decrease in the BOOI from 70.2 to 32.6 ($P < 0.0001$ for both).

In a similar study, Matsukawa *et al.*[27] treated 57 patients with silodosin 8 mg for 4 weeks, and carried out pressure flow studies before and after. They found a decrease in P_{det}•Q_{max} (cmH_2O) from 72.5 to 51.4, and in the BOOI from 60.6 to 33.8 ($P < 0.0001$). The detailed results of both studies are shown in Table 5. These findings are particularly

Table 5 Urodynamic effects of silodosin for treatment of BPH/LUTS; changes in urodynanic parameters before and after treatment

Study	Yamanishi *et al*.[25]		Matsukawa *et al*.[27]	
	Before	After†	Before	After‡
No. patients	36	25	51	51
Uroflowmetry				
Q_{max} (mL/s)	6.7 (3.0)	8.4 (3.5)§	8.4 (3.8)	11.5 (4.7)§
PVR (mL)	169.9 (119.5)	94.0 (90.1)§	63 (48.8)	33 (27.6)§
No. patients	35	29	51	51
Pressure flow study				
First desire to void (mL)	193.1 (105.5)	230.3 (99.9)	113 (50.2)	140 (49.6)§
Maximum cystometiric capacity (mL)	356.1 (139.6)	409.1 (122.2)§	239 (99.2)	275 (90.1)
Detrusor pressure at Q_{max} (cmH_20)	80.6 (37.8)	48.6 (25.3)§	72.5 (26.6)	51.4 (17.9)§
BOOI	70.2 (38.1)	32.6 (29.2)§	60.6 (28.9)	33.8 (20.4)§

In both studies, silodosin 4 mg capsules was administered orally twice daily for a total of 8 mg daily. The measurements of parameters were carried out at 3 months† or 4 weeks ‡ after treatment; §significantly different from the comparable value before treatment ($P < 0.05$). Each value shows the average, and the value of the parenthesis is standard deviation.

remarkable, as meta-analyses of urodynamic studies using other α_1-blocking agents had failed to show a significant effect on the parameters.[28,29]

Other important clinical studies

Miyakita *et al*. reported the comparison of the efficacy and safety of silodosin and tamsulosin in patients with LUTS/BPH by a randomized crossover method.[30] BPH was diagnosed based on IPSS, ultrasonographic observation and objective findings. The inclusion criteria were IPSS ≥ 8 points; QOL score ≥ 3 points; prostate volume measured by ultrasonographic method ≥ 20 mL; void volume ≥ 100 mL; and Q_{max} < 15 mL/s. The patients were randomly divided into two groups: a silodosin-preceding group (4 weeks of twice-daily administration of silodosin at 4 mg, followed by 4 weeks of once-daily administration of tamsulosin at 0.2 mg) or a tamsulosin-preceding group (4 weeks of tamsulosin administration, followed by 4 weeks of silodosin administration). The symptom scores were measured before administration of the drug and 1, 2, 4, 6 and 8 weeks after the start of administration (the objective parameters were measured before administration, and 4 and 8 weeks after administration).

A total of 97 patients were enrolled in the study; 46 patients were assigned to the silodosin-preceding group and 51 patients to the tamsulosin-preceding group (ITT and safety population). Several patients were excluded as a result of missing values for measurements. Finally, 34 patients in the silodosin-preceding group and 31 patients in the tamsulosin-preceding group were evaluated for efficacy comparison (PP population).

IPSS total score (primary end-point) significantly improved from baseline to after administration with both silodosin and tamsulosin in the first treatment period. However, in the crossover treatment period, only silodosin yielded further significant improvement compared with prior drug treatment. Change in IPSS total score after administration of the first drug was −7.7 ± 5.9 for silodosin and −4.6 ± 5.4 for tamsulosin, whereas change after crossover was −2.6 ± 3.8 for silodosin and 0.3 ± 4.3 for tamsulosin, with a significant difference between drugs in both administration periods (first treatment $P < 0.05$; crossover treatment $P < 0.01$).

In the secondary end-points, similar changes were observed in voiding symptoms, storage symptoms and post-micturition symptoms of IPSS. Silodosin significantly improved QOL score in both treatment periods, whereas tamsulosin significantly improved QOL score only in the first treatment period. Furthermore, silodosin showed significant improvement of QOL score in both treatment periods compared with tamsulosin (first treatment $P < 0.05$; crossover treatment $P < 0.05$). Q_{max} was significantly improved from baseline with both silodosin and tamsulosin in the first treatment period; however, no significant change was observed with either drug in the crossover treatment period. The change in residual urinary volume was −48.6 ± 104.1 mL after administration of silodosin and −11.9 ± 83.0 mL after administration of tamsulosin in the first treatment; a significant decrease from baseline was observed only with silodosin, with no significant improvement with either drug after crossover treatment.

Adverse drug reactions were observed in 16 of 97 patients (16.5%) after administration of silodosin, and two of 97

patients (2.1%) after administration of tamsulosin. The most frequently observed adverse drug reaction to silodosin was ejaculatory disorder in seven patients (7.2%). Except for two patients who did not visit during the study, silodosin was continuously given to all patients. The adverse drug reaction to tamsulosin was mild dizziness in two patients. All of these adverse drug reactions were mild and resolved or were relieved in all patients with continued administration or dose reduction or withdrawal.

The authors concluded that silodosin showed better efficacy in improving subjective symptoms and improvement of QOL regardless of period of administration compared with tamsulosin in patients with LUTS/BPH.

Watanabe *et al*. also reported the comparison of silodosin and tamuslosin in Japanese patients with BPH using a randomized cross-over study.[31] The primary end-point was the patient-reported outcomes. The patients were randomly assigned to either the tamuslosin–silodosin group (tamsulosin 0.2 mg orally once daily for 4 weeks then silodosin 4 mg orally twice daily for 4 weeks) or the silodosin–tamuslosin group (silodosin 4 mg orally twice daily for 4 weeks then tamsulosin 0.2 mg orally once daily for 4 weeks). In total, 102 patients (mean age 70.3 years) were enrolled and 84 ($n = 42$ per group) completed the study. There was a significant difference in the proportion of patients who preferred tamuslosin or silodosin.

The patients who preferred tamsulosin was 70.2% (59/84 patients) and those who preferred silodosin was 21.4% (18/84 patients). Among the reasons for preferring either drug, the most frequent response was "good efficacy" over twice as many patients selected tamsulosin over silodosin for that reason. Many patients also preferred tamsulosin for reasons of no/few AE or prefer once daily treatment. Incidence of AE was significantly lower with tamsulosin (3/91 patients; 3.3%) than with silodosin (25/88 patients; 28.4%).

The authors concluded that it is important to consider patients' opinions and drug preferences when treating BPH, because this condition affects QOL. The study showed that even among the α_1-blockers developed to treat BPH, there are large differences in patients' preferences between the drugs. The authors believed that patients' choices are determined by factors that include therapeutic efficacy, AE and ease of administration.

To evaluate the early efficacy of silodosin, Takao *et al*.[32] carried out a 28-day, open-label, uncontrolled study to evaluate the efficacy of silodosin 4 mg twice a daily during the early stages of treatment. A total of 68 BPH patients (67.5 $\pm$ 8.0 years) with IPSS $\geq$ 8 and QOL index $\geq$ 2 were included. Changes in the IPSS and QOL index were evaluated before and after 1, 2, 3, 4, 5, 6, 7, 14 and 28 days administration of 4 mg silodosin. Next, changes in IPSS subscores (voiding, storage and postmicturition symptoms) were assessed. Changes in total IPSS based on symptom severity were also determined.

Improvements were observed regardless of the severity of total IPSS and QOL scores at baseline. IPSS subscores for voiding, storage and postmicturition symptoms were significantly decreased, from 8.93 $\pm$ 3.95 to 7.28 $\pm$ 4.09, from 7.97 $\pm$ 3.88 to 6.52 $\pm$ 3.47, and from 2.49 $\pm$ 1.70 to 2.02 $\pm$ 1.56, respectively, at day 1 (all, $P < 0.05$). These improvements were reported to be significant throughout the study. Patients with $\geq$25% improvement in total IPSS were classified as good responders, and those with <25% improvement were classified as bad responders. At day 3, 31 of 68 patients (45.6%) were considered good responders, of whom 25 (80.6%) continued to be good responders at study end. At day 7, 42 patients (61.8%) were good responders; 33 of these patients (78.6%) had maintained a good response at day 28. Conversely, 37 of 68 patients (54.4%) were poor responders at day 3, and 20 of these patients (54.1%) continued to be poor responders at study end. At day 7, 26 patients (38.2%) were poor responders, of whom 17 (65.4%) remained poor responders at day 28. Therefore, the positive predictive value of a response at days 3 and 7 was 80.6% and 78.6%, respectively, and the negative predictive value at days 3 and 7 was 54.1% and 65.4%.

AE were documented in six patients (8.8%). These events consisted of two reports of abnormal ejaculation, two reports of diarrhea, one report of tinnitus and one report of lightheadedness. All AE resolved after the discontinuation of silodosin. The study suggested that silodosin showed the fast onset of the efficacy in the treatment of LUTS/BPH.

Other clinical possibilities of silodosin

Abacterial CP/CPPS

Prostatitis-like symptoms are relatively popular in adult men, with an estimated prevalence in North America ranging from 2.2% to 9.7%.[33,34] At least 90% of all cases of chronic prostatitis seem to be CP/CPPS.[35] CP/CPPS is characterized by urogenital pain and various LUTS in the absence of urinary tract infection,[35] and the associated symptoms can be debilitating.[36–38] It has been reported that CP/CPPS is associated with impairment of disease-specific, as well as general mental and physical HRQOL.[39] Although there are many available treatment options, none has consistently shown efficacy in clinical studies.[39] One of the drugs is α_1-AR antagonists. It has been suggested that α_1-AR antagonists improve CP/CPPS-associated LUTS and pain by improving voiding functions.[40]

There are a number of randomized, placebo controlled, phase II studies of terazosin, alfuzosin and tamsulosin showing promising efficacy.[41–43] In addition, a systematic review and meta-analysis of data from 11 CP/CPPS randomized placebo controlled studies showed that the use of α_1-blockers provided a statistically significant clinical ben-

efit.[44] However, two multicenter, randomized, placebo controlled studies included in this analysis, one of tamsulosin and the other a large study of alfuzosin, failed to show significant symptom improvement in patients with CP/CPPS.[45,46]

Nickel *et al*. evaluated the efficacy and safety of two doses of silodosin (4 and 8 mg once daily) compared with placebo in patients with moderate to severe abacterial CP/CPPS not previously treated with α_1-AR antagonists for this condition.[47] This study was a 12-week, multicenter, double-blind, placebo controlled, phase II study. The primary end-point was a change from baseline to week 12 in NIH-CPSI total score. Secondary end-points included safety; change from baseline in the NIH-CPSI pain, urinary and HRQOL subscores; and change from baseline in SF-12 physical and mental component scores. In addition, responder analyses were carried out for GRA and NIH-CPSI at week 12. GRA responders were defined as participants who indicated markedly or moderately improved on the 7-point GRA scale. NIH-CPSI responders were defined as participants who had a decrease of 6 or more points in the NIH-CPSI total score.

Patients were randomized 1:1:1 to receive 4 or 8 mg silodosin, or placebo once daily with food at breakfast for 12 weeks. Baseline parameters were assessed after a 4-week screening period. Patients completed the NIH-CPSI and subscales, GRA scale and pain medication use surveys at baseline, and at weeks 4, 8 and 12 of the study. SF-12 was completed at baseline and at study end (week 12 or time of discontinuation).

Of 151 patients (mean age 48 years), 52 received 4 mg silodosin, 45 received 8 mg silodosin and 54 received placebo. Silodosin 4 mg was associated with a significant decrease in total NIH-CPSI (-12.1 ± 9.3) *vs* placebo (-8.5 ± 7.2, $P = 0.0224$), including a decrease in urinary symptoms (-2.2 ± 2.7, placebo -1.3 ± 3.0, $P = 0.0102$) and QOL (-4.1 ± 3.1, placebo -2.7 ± 2.5, $P = 0.0099$). The 4 mg silodosin also significantly increased SF-12 physical component scores (4.2 ± 8.1, placebo 1.7 ± 9.0, $P = 0.0492$). Neither dose of silodosin had a significant effect on the NIH-CPSI pain scores or SF-12 mental component scores versus placebo. During global response assessment 56% of patients receiving 4 mg silodosin versus 29% receiving placebo reported moderate or marked improvement ($P = 0.0069$). Increasing the dose of silodosin to 8 mg resulted in no incremental treatment effects.

Overall, 51.7% of patients in this study experienced at least one AE, and 33.1% experienced AE considered by the investigator to be related to a study drug. The most common drug-related AE was RE, which showed a dose-dependent incidence profile. The percentage of patients with drug-related AE was greater in the 8 mg silodosin group than in the 4 mg silodosin group. Except for RE, the incidence of drug-related AE with 4 mg silodosin was similar to that with placebo. The percentages of patients who discontinued study participation because of a drug-related AE were 13.3% for 8 mg silodosin, 5.8% for 4 mg silodosin and 1.9% for placebo.

The authors concluded that silodosin 4 mg relieved symptoms and improved QOL in men with CP/CPPS, but its efficacy requires confirmation in additional studies.

Efficacy for LUTS after prostate cancer brachytherapy

Tsumura *et al*. compared the efficacy of three α-AR antagonists; naftopidil, tamsulosin and silodosin for treatment of LUTS after brachytherapy with ^{125}I PI for prostate cancer in Japanese men.[48] This study was a single-institution, prospective randomized controlled trial. Patients were randomized and prescribed either naftopidil, tamsulosin or silodosin. Treatment was started one day after PI and continued for 1 year. The primary end-points for efficacy evaluation were the changes in IPSS and PVR. The secondary efficacy variables were changes in voiding and storage symptoms score of IPSS from baseline to set points during the study (1, 3, 6 and 12 months).

A total of 212 patients were evaluated in this study. The assigned patients to naftopidil, tamsulosin and silodosin were 71, 70 and 71, respectively. The mean changes in the total IPSS at 1 month after treatment with naftopidil, tamsulosin and silodosin groups were +10.3, +8.9 and +7.5, respectively. There were significantly greater decreases with silodosin than naftopidil at 1 month in the total IPSS. The mean changes in the PVR at 6 months were +14.6, +23.7 and +5.7 mL in the naftopidil, tamsulosin and silodosin groups, respectively. Patients with silodosin showed a significant improvement in the PVR at 6 months versus tamsulosin. The mean changes in the IPSS voiding score at 1 month in the naftopidil, tamsulosin and silodosin groups were +6.5, +5.6 and +4.5, respectively. Silodosin showed a significant improvement in the IPSS voiding score at 1 month versus naftopidil. The study showed that silodosin had a greater improvement of LUTS after treatment with PI than other two drugs in patients with prostate cancer.

Treatment for ureteral stone

It has been shown that α-AR predominate in the human ureter. Therefore, the use of α-AR antagonists is advocated in the management of ureteral colic secondary to ureteral stones.[49] It was suggested that the blockage of α_1-AR antagonists in the ureter leads to decreased ureteral peristaltic activity with a consequent loss of ureteral pressure and an increase in fluid transport ability.[50,51] It has been shown that selective α-AR antagonists increase the ureteral pressure gradient around the obstructed ureter by increasing the bolus of urine above the stone and decreasing the ureteral pressure

below the stone.[52] This might facilitate stone passage by increased urine flow. In addition, α_1-AR antagonists seem to decrease the frequency of phasic peristaltic contractions in the ureter and decrease the frequency of ureteral colic, leading to decreased analgesic requirement and use.[53,54]

Several publications exist in the literature regarding the successful use of tamsulosin (α_{1A} and α_{1D} subtype selective antagonist) in patients with urinary tract stone diseases.[53,55–61]

Itoh *et al*. previously showed that three types of α_1-AR mRNA (α_{1a}-, α_{1b}-, and α_{1d}-) are expressed in the human ureter, and that of these three types, the α_{1d}-subtype was predominant.[62] Using a receptor-binding assay, Sigala *et al*. also reported that these three types of α_1-AR proteins were present in the human ureter.[63] Recently, Sasaki *et al*. reported the characterization of the contractile functions of the α_1-AR subtypes present in the human ureter.[64] In that study, the authors showed that among α_1-AR, the α_{1A} subtype played the major role in contraction in the human ureter.

Based on the reports, Itoh *et al*. carried out a prospective randomized study to evaluate the effects of silodosin, as a medical expulsive therapy for ureteral stones.[65] A total of 187 male patients referred for the management of symptomatic unilateral ureteral stone of less than 10 mm were randomly divided into two groups: group A (92 patients), who were instructed to drink 2000 mL of water daily; and group B (95 patients), who received the same instruction and were also prescribed silodosin (8 mg/daily) for a maximum of 8 weeks. Expulsion rate, mean expulsion time and need for analgesics were evaluated. Overall mean expulsion time was 15.19 ± 7.14 days for group A and 10.27 ± 8.35 days for group B ($P = 0.0058$). In patients with distal ureteral stones, the time was 13.40 ± 5.90 and 9.29 ± 5.91 days, respectively ($P = 0.012$). For stones of 1–5 mm diameter, the mean expulsion time was 14.28 ± 6.35 and 9.56 ± 8.45 days, respectively ($P = 0.017$). For stones of 6–9 mm diameter, the stone expulsion rate was 30.4% and 52.2% ($P = 0.036$), and the mean expulsion time was 21.00 ± 9.9 and 11.33 ± 8.31 days, respectively ($P = 0.038$). This was the first report on silodosin for the management of ureteral stones. The authors concluded that silodosin might have significant potentiality as a medical expulsive therapy for ureteral stones.

Now, to evaluate spontaneous stone passage without the need for emergency department visits, hospital admissions, surgical intervention or other interventional procedures for 4 weeks, a double-blind, placebo-controlled study of silodosin to facilitate urinary stone passage is ongoing in the USA.

Conclusion

Silodosin is a selective α_{1A}-AR antagonist that was approved for the treatment of LUTS/BPH. In new clinical studies, silodosin was associated with significant improvements in both storage and voiding symptoms, as well as improvement in measures of QOL. The clinical improvements were observed early in the course of treatment. The efficacy was also confirmed by the objective urodynamic studies.

Silodosin was generally well tolerated and was associated with minimal cardiovascular AE. Ejaculation disorder, which is a class effect of α_{1A}-AR antagonists, was the most common silodosin-associated AE, but resulted in treatment withdrawal in only a limited number of patients.

Further randomized clinical trials are required to confirm the efficacy and safety for additional indications of silodosin.

Conflict of interest

MY is a consultant for Kissei Pharma and had speaker honorarium for Kissei Pharma and Astellas Pharma. YH is a consultant for Kissei Pharma and Astellas Pharma, and had speaker honorarium for Kissei Pharma and Astellas Pharma. Other authors report no conflicts of interest.

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