This section contains papers from Japan, Austria, the UK, and joint papers from France, Denmark, Switzerland, Australia and the USA. A wide variety of lower urinary tract topics is covered, from BPH to overactive bladder and urodynamic stress incontinence.

Silodosin, a new α_{1A}-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men

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OBJECTIVE

To verify the efficacy and safety of the new α_{1A}-adrenoceptor-selective antagonist silodosin compared with tamsulosin and placebo in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

PATIENTS AND METHODS

This randomized, double-blind, placebo-controlled study was conducted at 88 centres in Japan. Men aged ≥50 years with an International Prostate Symptom Score (IPSS) of ≥8, a quality-of-life (QoL) score of ≥3, a maximum urinary flow rate (Q_{max}) of <15 mL/s, a prostate volume of ≥20 mL and a postvoid residual urine volume of <100 mL were eligible for enrolment. Patients were randomized to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily, or placebo, for 12 weeks. The primary endpoint was the change in IPSS from baseline. Safety was assessed by adverse events, physical examination, vital signs and laboratory tests.

RESULTS

In all, 457 patients were randomized (silodosin 176, tamsulosin 192 and placebo 89). The change in the total IPSS from baseline in the silodosin, tamsulosin and placebo groups was −8.3, −6.8 and −5.3, respectively. There was a significant decrease in the IPSS vs placebo in the silodosin group from 1 week. In the early-stage comparison, silodosin showed a significant decrease in IPSS vs tamsulosin at 2 weeks. The change in QoL from baseline was −1.7, −1.4 and −1.1 in the silodosin, tamsulosin and placebo groups, respectively; silodosin showed a significant improvement in the QoL score vs placebo. In the subgroup of patients with severe symptoms (IPSS ≥20) silodosin also gave a significantly better improvement than placebo (−12.4 vs −8.7). The incidence rates of adverse events and drug-related adverse events were, respectively, 88.6%, 82.3% and 71.6% and 69.7%, 47.4% and 36.4%, respectively. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred more often in the silodosin than in the tamsulosin group (22.3% vs 1.6%).

However, only five men (2.9%) discontinued treatment for abnormal ejaculation.

CONCLUSION

Silodosin was generally effective in the absence of obtrusive side-effects. This study suggests that silodosin is clinically useful for treating LUTS associated with BPH.

KEYWORDS

α_{1A}-adrenoceptor-selective antagonist, silodosin, tamsulosin, BPH, phase III, randomized, double-blind, placebo-controlled

INTRODUCTION

There are ever more patients with LUTS associated with BPH and consequently the awareness of this problem has grown significantly. The causes of LUTS associated with BPH include mechanical compression of the urethra due to hyperplasia of prostatic tissue (mechanical obstruction), and increased urethral resistance induced by smooth muscle tension associated with increased activity of sympathetic nerves in the LUT, including prostatic tissue, posterior urethra and bladder neck (functional obstruction) [1].

Treatments for LUTS associated with BPH include pharmacotherapy using α_1-adrenoceptor (AR) antagonists (α_1-blockers) and antiandrogen preparations, principally in moderate to mild cases, and surgical therapy such as TURP for severe cases [1,2]. As α_1-blockers rapidly improve subjective symptoms by improving functional obstruction, they are widely used as first-choice drugs for the pharmacological treatment of LUTS resulting from BPH [1,2].

Smooth muscle tone in the bladder neck and prostate is mainly regulated by α_{1A}-AR [3,4]. Blockade of these receptors can cause smooth muscle relaxation in these areas, resulting in improved symptoms and urinary flow rates. On the other hand, α_{1B}-AR are largely located on vascular smooth muscle and antagonising the activity at these receptors can cause relaxation of this tissue, and decrease cardiac compensation mechanisms involved in regulating blood pressure [5,6]. Therefore, agents with high selectivity for the α_{1A}-subtype AR should have beneficial effects on the symptoms associated with BPH and minimal effects on blood pressure, as occurs with nonselective α_1-AR antagonists.

Silodosin (KMD-3213) is a new, highly selective α_{1A}-AR antagonist developed by Kissei Pharmaceutical Co., Ltd (Matsumoto, Japan). The selectivity of silodosin towards α_{1A}-AR vs α_{1B}-AR subtype was reported to be 38 times higher than that of tamsulosin hydrochloride in studies using Chinese hamster ovary cells expressing three human α_1-AR subtypes, indicating a high selectivity of silodosin for the LUT, where α_{1A}-AR is the predominant subtype [7]. *In vivo* comparative studies with tamsulosin and prazosin showed that silodosin produces favourable 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 [8,9].

As 8 mg/day (given as 4 mg twice daily) was considered a reasonable clinical recommended dose of silodosin, based on the results of phase II trials of 4- vs 8-mg doses conducted in patients with LUTS associated with BPH, a phase III randomized confirmatory study was planned and conducted to verify the safety and efficacy of silodosin 8 mg/day. The objectives of this study were to verify that silodosin was better than placebo and to establish that it was not inferior to tamsulosin, the standard α_1-blocker used in patients with BPH. Based on the efficacy and safety results of a dose-finding study conducted in Japanese patients [10], the usual therapeutic dose of tamsulosin recommended in Japan is 0.2 mg/day, and this regimen was adopted in the present study.

PATIENTS AND METHODS

This randomized, double-blind, placebo-controlled study was conducted at 88 centres in Japan, in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study protocol was reviewed and approved by the institutional review boards of each study centre before its inception. All patients provided written informed consent to participate before study entry.

The men included were ≥50 years old, outpatients and had LUTS associated with BPH, the latter diagnosed based on a DRE or ultrasonographic findings. Inclusion criteria were a total IPSS of ≥8, an associated quality-of-life (QoL) score of ≥3, prostate volume (measured by transabdominal ultrasonography or TRUS) of ≥20 mL, a maximum urinary flow rate (Q_{max}) of <15 mL/s with a voided volume of ≥100 mL and a residual urine volume of <100 mL. Patients were excluded if they had received antiandrogen preparations for 1 year before the study or had a prostatectomy, intrapelvic radiation therapy or prostatic hyperthermia (transurethral microwave hyperthermia or transurethral needle ablation). Patients who had prostate cancer or suspected prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, severe bladder diverticulum, active UTI requiring medical treatment, renal impairment (serum creatinine ≥2.0 mg/dL) and other complications considered likely to affect micturition, were excluded, as were those with severe hepatic disorders, severe cardiovascular disease and a history of orthostatic hypotension.

After completing 7-day 'washout' and 7-day observation periods, patients were randomized to receive oral silodosin 4 mg twice daily, tamsulosin 0.2 mg/day or placebo twice daily for 12 weeks. At the end of the washout period and at 1, 2, 4, 8 and 12 weeks during the treatment period subjective symptoms (IPSS and QoL scores) and medication compliance were recorded, and uroflowmetry and physical examinations (blood pressure and heart rate) conducted. Clinical laboratory tests (haematology, blood chemistry and urine analysis) were conducted at the start of the observation period and at 4 and 12 weeks of treatment. All adverse events were recorded and assessed for severity and causal relationship with taking the investigational products.

The primary endpoint of evaluation for efficacy was the change in the total IPSS from baseline; secondary endpoints were change in Q_{max}, urodynamics and evaluation of subjective symptoms, e.g. the IPSS voiding and storage scores and QoL score. Values are shown as the mean (SD) unless otherwise stated.

The target sample size was 170, 170 and 85 men in the silodosin, tamsulosin and placebo groups, respectively. A two-stage closed

procedure was used to verify that silodosin was better than placebo and not inferior to tamsulosin, as shown by the change in total IPSS from baseline; superiority over placebo was verified by a two-sided *t*-test, and that it was not inferior to tamsulosin by the non-inferiority test with margin-Δ (1.0). Safety (adverse events, physical examinations, vital signs and laboratory tests) was assessed among three treatment groups using Fisher's exact method.

RESULTS

In all, 457 patients were enrolled and randomized to receive silodosin (176), tamsulosin (192) or placebo (89). One patient in the silodosin group was excluded from the full analysis set due to protocol violation. The baseline characteristics of three groups are shown in Table 1. There were no significant differences among the three groups in baseline characteristics, except for the QoL score. Therefore, an adjusted analysis by baseline QoL score was used for the primary endpoint.

The results of the primary outcome measure are shown in Fig. 1; the change in total IPSS from baseline was −8.3 (6.4), −6.8 (5.7) and −5.3 (6.7) in the silodosin, tamsulosin and placebo groups, respectively. As shown in Table 1, there were significantly greater decreases with silodosin than placebo from 1 week after starting treatment. In the early-stage comparison, silodosin elicited a significantly larger decrease in IPSS than did tamsulosin at 2 weeks. The mean (95% CI) intergroup differences in the total IPSS between silodosin and placebo, and between silodosin and tamsulosin, were −3.0 (−4.6, −1.3) and −1.4 (− 2.7, −0.2), respectively, thus confirming that silodosin was better than placebo and not inferior to tamsulosin (both $P < 0.001$). Furthermore, the adjusted analysis of the QoL score (analysis of covariance, setting the QoL score to covariance-adjusted deviation) to eliminate patient background bias, as noted during the observation period, also confirmed these findings.

The results of the secondary outcome measures are also shown in Table 1. The change in QoL score from baseline was −1.7 (1.4), −1.4 (1.3) and −1.1 (1.2) in the silodosin, tamsulosin and placebo groups, respectively. Silodosin was significantly better than placebo in QoL score ($P = 0.002$). Silodosin also showed significant improvements in voiding and storage symptoms over placebo. In addition to significant effects in patients with moderate symptoms (IPSS 8–19), silodosin also showed significant improvements in total IPSS over placebo in patients with severe symptoms (IPSS ≥20). The change in Q_{max} from baseline was 2.24 (3.96), 2.95 (4.64) and 2.42 (5.50) mL/s in the silodosin, tamsulosin and placebo groups, respectively, showing an improvement in all three groups compared with baseline values, with no significant difference detected among the groups. However, it is known that Q_{max} depends on the voided volume at measurement [11,12]. In the present study, there were large changes in voided volume before and after treatment in some men, and these patients' data could potentially affect the overall evaluation of the change in Q_{max}. Therefore, the change of Q_{max} was compared among the three treatment groups in the overall subgroup of patients with a change in voided volume of <50% before and after treatment. In this *post hoc* investigation, the change in Q_{max} from baseline was 1.70 (3.31), 2.60 (3.98) and 0.26 (2.21) mL/s in the silodosin, tamsulosin and placebo groups, respectively, and silodosin was significantly ($P = 0.005$) better than placebo in improving Q_{max}.

The incidence rates of adverse events were 88.6%, 82.3% and 71.6% in the silodosin, tamsulosin and placebo groups, respectively. Intergroup comparisons showed that adverse events were significantly ($P < 0.001$) more frequent in the silodosin than in the placebo group. Adverse events are also summarized in Table 1. The incidence rates of drug-related adverse events were 69.7%, 47.4% and 36.4% in the three groups, respectively, showing a significantly ($P < 0.001$) higher frequency of adverse events in the silodosin than in the placebo and tamsulosin groups. Adverse events resulting in withdrawal occurred in 18 (10.2%), 11 (5.7%) and four (4.5%) patients in the silodosin, tamsulosin and placebo groups, respectively. All of these adverse events resolved after discontinuing treatment. The most common adverse event in the silodosin group was abnormal ejaculation. However, only five men (2.9%) discontinued treatment due to abnormal ejaculation. There were no clinically significant differences of systolic/diastolic blood pressure or heart rate between the silodosin and tamsulosin groups.

DISCUSSION

BPH frequently causes bothersome LUTS, e.g. urinary frequency, urgency, nocturia, slow stream and sensation of incomplete bladder emptying [1,2]. α_1-blockers are prescribed as the first-choice medication, based on the hypothesis that these drugs inhibit α_1-AR-mediated contraction of prostatic smooth muscle and thereby rapidly relieve BOO [1,2]. Among α_1-AR subtypes it was shown that α_{1A}-AR are mainly involved in constriction due to sympathetic nerves in the LUT [13]. Therefore, clinicians should preferentially prescribe drugs that are highly selective towards the LUT. Silodosin is a novel selective α_{1A}-AR antagonist expected to have high selectivity towards the LUT.

In this phase III double-blind study, silodosin was better than placebo and not inferior to tamsulosin, as verified by the reduction in total IPSS. The difference in the change in total IPSS between the silodosin and tamsulosin groups was −1.4 (95% CI, −2.7, −0.2). Based on this result, it is considered that silodosin at 4 mg twice daily is at least as effective as tamsulosin at 0.2 mg/day, the recommended clinical dose in Japan and other Asian countries.

The further analysis of secondary outcome measures for IPSS to characterize the efficacy of silodosin showed a marked improvement in subjective symptoms in the silodosin group in the early stage of treatment, i.e. at 1 and 2 weeks. This early improvement in patients' symptoms indicates that silodosin has good clinical utility. Silodosin was not only effective in reducing voiding symptoms but also in reducing storage symptoms. In addition, the change in QoL score from baseline was significantly different between the silodosin and placebo groups ($P = 0.002$; two-sample *t*-test). These results suggest that silodosin elicits an excellent improvement in subjective symptoms.

The subgroup analysis of total IPSS, by defining severe cases as patients with a baseline total IPSS of ≥20, suggested that silodosin is useful in severe, mild and moderate cases for improving subjective symptoms. Patients with severe LUTS can show significant decreases in QoL, and surgical procedures such as TURP are often considered when pharmacotherapy is unsuccessful [1,2]. However, as silodosin produced a significant improvement in

TABLE 1 Baseline demographic characteristics, the efficacy measures, and adverse events

Variable	Silodosin	Tamsulosin	Placebo	P	
Number of patients	175	192	89		
Mean (SD):					
Age, years	65.4 (7.0)	65.6 (7.0)	65.0 (6.9)	0.835	
Total IPSS	17.1 (5.7)	17.0 (5.7)	17.1 (6.1)	0.968	
QoL score	4.9 (0.8)	4.7 (0.8)	4.7 (0.8)	0.018	
Prostate volume, mL	36.0 (16.9)	35.7 (14.4)	35.2 (16.0)	0.449	
Q_{max}, mL/s	9.89 (2.72)	9.43 (2.79)	9.96 (2.65)	0.169	
Residual urinary volume, mL	28.1 (28.3)	29.0 (27.3)	28.0 (28.0)	0.766	
Efficacy outcome measures:				P*	P†
Mean (SD):					
Change in total IPSS at week 1	−3.4 (4.2)	−2.7 (4.1)	−1.2 (3.4)	<0.001	0.110
Change in total IPSS at week 2	−4.9 (4.9)	−3.7 (4.4)	−2.2 (4.1)	<0.001	0.011
IPSS voiding symptoms					
Baseline	10.8 (4.1)	10.8 (4.2)	10.9 (4.4)		
Change	−5.8 (4.6)	−4.8 (4.1)	−3.8 (4.8)	<0.001	0.023
IPSS storage symptoms					
Baseline	6.4 (3.0)	6.2 (2.9)	6.3 (2.8)		
Change	−2.5 (2.9)	−2.1 (2.6)	−1.5 (2.6)	<0.006	0.106
n/N (%) patients with ≥25% improvement in IPSS	133/174 (76.4)	126/192 (65.6)	45/89 (50.6)	<0.001	0.028
Mean (SD):					
IPSS in severe (IPSS ≥20) patients					
Baseline	23.9 (3.6)	23.9 (3.3)	24.9 (3.8)		
Change	−12.4 (7.3)	−10.1 (6.1)	−8.7 (8.4)	0.044	0.063
IPSS in moderate (IPSS 8–19) patients					
Baseline	13.9 (3.2)	13.8 (3.1)	13.7 (3.0)		
Change	−6.3 (4.9)	−5.3 (4.9)	−3.8 (5.3)	0.001	0.105
QoL score					
Baseline	4.9 (0.8)	4.7 (0.8)	4.7 (0.9)		
Change	−1.7 (1.4)	−1.4 (1.3)	−1.1 (1.2)	0.002	0.052
Q_{max}‡					
Baseline	9.88 (2.75)	9.41 (2.81)	10.18 (2.72)		
Change	1.70 (3.31)	2.60 (3.98)	0.26 (2.21)	0.005	0.063
Adverse events§; clinical symptoms, n (%)					
Abnormal ejaculation	39 (22.3)	3 (1.6)	0		
Upper respiratory tract infection	33 (18.9)	53 (27.6)	17 (19.1)		
Thirst	18 (10.3)	7 (3.6)	4 (4.5)		
Loose stool	16 (9.1)	7 (3.6)	5 (5.6)		
Diarrhoea	12 (6.9)	13 (6.8)	5 (5.6)		
Urinary incontinence	11 (6.3)	11 (5.7)	0		
Dizziness	9 (5.1)	14 (7.3)	4 (4.5)		
Adverse events§; laboratory test values, n/N (%)					
Elevated triglyceride	44/175 (25.1)	42/192 (21.9)	18/88 (20.5)		
Elevated C-reactive protein	22/175 (12.6)	32/192 (16.7)	13/88 (14.8)		
Elevated γ-glutamyl transpeptidase	13/175 (7.4)	7/192 (3.6)	6/88 (6.8)		
Urinary sediment abnormality	12/173 (6.9)	13/192 (6.8)	7/87 (8.0)		
Elevated total cholesterol	9/175 (5.1)	6/192 (3.1)	2/88 (2.3)		
Glycosuria	9/175 (5.1)	16/192 (8.3)	6/88 (6.8)		

**Silodosin vs placebo; †silodosin vs tamsulosin; ‡values from the subgroup analysis of patients with a change of voided volume from baseline of <50%; §adverse events reported in >5% of patients in the silodosin group are shown.*

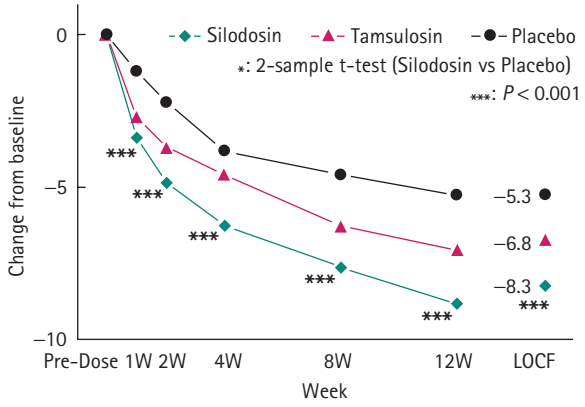

FIG. 1.
The time-course of changes in the total IPSS.

subjective symptoms in the present severe cases, it is suggested that this drug might elicit improvements even in patients who could be candidates for surgical therapy.

There were no significant cardiovascular effects, including syncope, in the silodosin group, thus supporting the hypothesis that high α_{1A}-AR selectivity is not associated with blood pressure effects that are typically seen with nonselective α_1-AR agents. However, abnormal ejaculation was common in patients in the silodosin group. This adverse effect might also be related to the high α_{1A}-AR selectivity of this drug. Functional studies and binding assays showed that the α_{1A}-subtype predominates in the bladder neck, vas deferens and seminal vesicles [14]. Furthermore, pharmacological investigation confirmed that the contraction of human vas deferens is mediated by α_{1A}-AR [15]. Hence blockade of α_{1A}-AR by silodosin might have caused abnormal ejaculation, as observed in the present study.

Although the incidence rate of abnormal ejaculation associated with silodosin therapy was 22.3% in the study, only 2.9% of patients discontinued due to this adverse event. In patients with LUTS associated with BPH, sexual dysfunction is common [14]. Schou *et al.* [16] reported that in a survey of 261 patients with BPH, those who considered abnormal ejaculation as a major problem accounted for only 6%. Emberton *et al.* [17] also reported that among 2989 patients who had a prostatectomy, only 156 patients (5.2%) considered retrograde ejaculation bothersome. Furthermore, Scarpa [18] indicated that among 877 patients with BPH, abnormal ejaculation was not considered as problematic as erectile dysfunction. Therefore, in patients with LUTS that impairs QoL, abnormal ejaculation seems generally not to be considered a highly bothersome symptom, and this might be supported by the low discontinuation rate for this symptom in the present study.

To date, several α_1-blockers with very high α_{1A}-AR selectivity have been developed [19–23]. However, the efficacy and safety profiles have not been confirmed clinically in patients with BPH. Silodosin is the first agent with very high α_{1A}-AR selectivity to show clinical efficacy for LUTS associated with BPH. It could be useful to compare published data on the affinity and selectivity of α_{1A}-selective antagonists to α_1-AR subtypes [7,19–23]. Whereas silodosin has a high affinity for α_{1A}-AR (pKi 10.44) in addition to very high selectivity for the α_{1A}-AR (583 times more selective for α_{1A} than α_{1B}), these compounds do not have high affinity for α_{1A}-AR (pKi 7.71–9.80). From these results, high selectivity is possibly important to avoid adverse reactions such as hypotension, but to achieve good efficacy a strong receptor affinity might also be required.

In conclusion, silodosin, a novel α_{1A}-AR selective antagonist, was effective in general in the absence of obtrusive side-effects. This study provides clear evidence in support of the clinical usefulness of silodosin in the treatment of LUTS associated with BPH.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **AR**, adrenoceptor; **Q_{max}**, maximum urinary flow rate; **QoL**, quality-of-life (score).