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Original Article: Clinical Investigation

Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia

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Objectives: To compare the efficacy and safety of silodosin and tamsulosin in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) by a randomized crossover method.

Methods: BPH patients with the complaint of LUTS were included in this study, and 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' administration of tamsulosin, followed by 4 weeks' administration of silodosin). No drug withdrawal period was provided when switching the drug.

Results: In the first treatment period, both drugs significantly improved the International Prostate Symptom Score total score, but the improvement by silodosin was significantly superior to that by tamsulosin. After crossover treatment, significant improvement was observed only with silodosin treatment. Moreover, intergroup comparison of changes revealed that silodosin showed significant improvement of straining and nocturia with first and crossover treatments, respectively, compared with tamsulosin. Silodosin also significantly improved quality of life (QOL) score in both treatment periods, while tamsulosin significantly improved QOL score only in the first treatment period. The most frequent adverse drug reaction was ejaculatory disorder with silodosin; however, the incidence of dizziness with silodosin was similar to that with tamsulosin.

Conclusions: In BPH/LUTS patients, silodosin exhibits excellent efficacy in improving subjective symptoms in both initial and crossover treatment, and it appears to improve the QOL of patients.

Key words: benign prostatic hyperplasia, crossover treatment, lower urinary tract symptoms, silodosin, tamsulosin hydrochloride.

Introduction

Currently, for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH/LUTS), α1-adrenoreceptor (α1-AR) antagonists (α_1-blockers) are widely used as first-line therapy.[1,2] Recent studies have revealed that α1-AR can be subclassified into three subtypes: α1A, α1B, and α1D, and it has been reported that contraction of the human prostate is regulated mainly via the α1A-AR subtype.[3,4] On the other hand, α1B-AR is mainly located in the vascular smooth muscle and regulates cardiac compensatory mechanisms and blood pressure, especially in the elderly.[4–6] Agents with a high degree of selectivity for α1A-AR should thus have beneficial effects on the symptoms associated with BPH and less effect on blood pressure, as occurs with non-selective α1-AR antagonists.[7,8]

Silodosin is a selective α1A-AR antagonist developed by Kissei Pharmaceutical Co., Ltd. (Matsumoto, Japan), and was confirmed to have higher selectivity for the α1A subtype than the α1B subtype in a binding experiment using human α1 receptor subtypes.[9,10] In a study using isolated human prostate and mesenteric artery, silodosin was found to be more uroselective (more selective for prostate than vessels) than either tamsulosin or prazosin.[5] Such selectivity for prostatic and urethral tissues compared with vascular tissue has also been observed in several animal models.[11,12] In fact, in a phase III study performed in Japan, the superiority of silodosin at 8 mg/day (4 mg/dose, twice daily) compared with a placebo was confirmed.[13] In that study, silodosin significantly improved symptoms and quality of life (QOL) compared with the placebo, and the incidence of adverse events, such as dizziness, was almost the same as

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those in the placebo and tamsulosin groups. Although tamsulosin is an α1-AR antagonist widely used throughout the world, there have been few comparative studies of the efficacy of silodosin and tamsulosin in clinical practice, other than the preceding phase III trial, which confirmed only the non-inferiority of silodosin to tamsulosin at 0.2 mg/day (0.2 mg/dose, once daily).

Accordingly, we compared the efficacy and safety of silodosin and tamsulosin in LUTS patients with BPH by a randomized crossover method.

Methods

This study was performed with the approval of an Institutional Review Board in each participating center including Tokai University (Approval no. 06-27). Prior to the start of the study, we provided a full explanation of it to subjects, and enrolled only those who consented to participate in it.

BPH/LUTS patients who newly visited the participating centers from May 2006 to July 2007 were enrolled. BPH was diagnosed based on International Prostate Symptom Score (IPSS), ultrasonographic observation, and objective findings. The inclusion criteria were as follows: IPSS ≥8 points; QOL score ≥ 3 points; prostate volume measured by ultrasonographic method ≥ 20 mL; void volume ≥ 100 mL; and maximal urinary flow rate (Qmax) < 15 mL/s. Patients who met any of the following criteria were excluded: patients who had already used any α_1-blocker for the treatment of hypertension; patients who were taking vardenafil hydrochloride hydrate; and patients otherwise judged by an attending physician to be inappropriate. Patients who had previously taken any α_1-blocker for the treatment of BPH but had not taken it during the 2-month period before the study were included.

After obtaining informed consent, the patients were randomly divided into two groups: the silodosin-preceding group or the tamsulosin-preceding group. Patients in the silodosin-preceding group were administered silodosin at 8 mg/day (4 mg/dose, twice daily) for 4 weeks, followed by 4 weeks' administration of tamsulosin at 0.2 mg/day (0.2 mg/dose, once daily). Patients in the tamsulosin-preceding group were administered tamsulosin at 0.2 mg/day (0.2 mg/dose, once daily) for 4 weeks, followed by 4 weeks' administration of silodosin at 8 mg/day (4 mg/dose, twice daily). In this study, considering the half-life of each drug (silodosin: about 10 h;[14] tamsulosin: about 12 h[15]) and the benefits of treatment in patients, no drug withdrawal period was provided when the drug was changed, and drugs were thus continuously administered for a total of 8 weeks.

The following three populations were to be considered in the statistical analysis:

Intention-to-treat (ITT) population: The ITT population consisted of all randomized patients who took at least one medication. Efficacy-evaluable (per protocol [PP]) population: The PP population was a subset of the ITT population in which IPSS was measured at all the prescribed points (before administration and after 4 and 8 weeks of administration) and there were no major protocol violations. This was the primary population for all efficacy analyses. Safety population: The safety population consisted of all randomized patients who had taken at least one medication. Demographic parameters and all efficacy variables were to be analyzed in the PP population.

The primary end-point of evaluation for efficacy was the change in total IPSS from baseline; secondary end-points were changes in objective parameters (Qmax, residual urinary volume, blood pressure, and heart rate) and evaluation of subjective symptoms, for example, IPSS voiding and storage subscores and QOL score. The symptom scores were measured before administration of the drug and 1, 2, 4, 6 and 8 weeks after initiation of administration (the objective parameters were measured before administration and 4 and 8 weeks after initiation of administration).

Changes from baseline after the initiation of administration (first treatment: before administration and 4 weeks after initiation of administration; crossover treatment: 4 and 8 weeks after initiation of administration) were evaluated by paired *t*-test. Differences between the groups were examined using the unpaired *t*-test. Values are the mean ± standard deviation (SD), and findings of $P < 0.05$ were considered significant. Statistical analyses were performed with SAS 9.1.3 for Microsoft Windows (SAS Institute Inc., NC, USA). We investigated adverse drug reactions throughout the study period in both groups. We also conducted a questionnaire survey to determine which of the drugs patients wished to continue after completion of the study period, including reasons for selection of drugs.

Results

Ninety-seven 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 had missing values for measurements, such as IPSS at one or more time points, and were therefore excluded from efficacy analysis. Finally, 34 patients in the silodosin-preceding group and 31 patients in the tamsulosin-preceding group were evaluated for efficacy comparison (PP population). Demographic parameters of each treatment group are shown in Table 1. Of the demographic characteristics, including objective parameters, only heart rate differed significantly between the two treatment groups. Other parameters, such as IPSS subscore (voiding symptoms, storage symptoms, individual symptom scores) and blood pressure, were not significantly different between the two groups.

In a crossover analysis of the change in total IPSS (primary end-point), there was no significant difference in

Table 1 Baseline characteristics of patients

Parameters	Silodosin-preceding group	Tamsulosin-preceding group	*P*-value
Age (years)	68.2 ± 8.6 (34)	70.1 ± 8.9 (31)	NS
Prostate volume (mL)	41.3 ± 25.3 (33)	37.8 ± 16.3 (31)	NS
IPSS total score	16.6 ± 5.2 (34)	18.2 ± 5.8 (31)	NS
QOL score	4.9 ± 0.9 (34)	4.9 ± 0.9 (31)	NS
Maximal urinary flow rate (mL/s)	9.4 ± 3.5 (29)	9.7 ± 4.4 (29)	NS
Residual urine volume (mL)	96 ± 102 (24)	97 ± 113 (27)	NS

Data represents the mean ± standard deviation. Numbers in parenthesis indicates number of subjects. Statistical analyses were performed by unpaired *t*-test. IPSS, International Prostate Symptom Score; NS, not significant; QOL, quality of life.

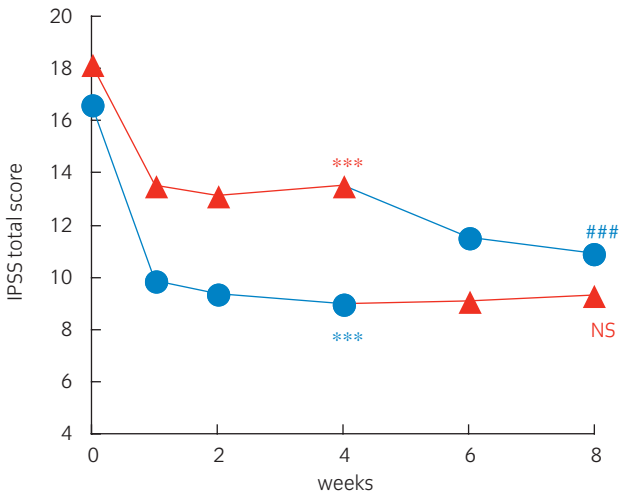

Fig. 1 The time-course of changes in International Prostate Symptom Score (IPSS) total score. ***$P < 0.001$ *vs* pre, ###$P < 0.001$ *vs* 4 weeks (paired *t*-test). NS, not significant. Silodosin (–●–); Tamsulosin (–▲–).

carry-over effect but there was a significant difference in period effect. We therefore used a standard between-group comparison method for the following analyses.

IPSS total score 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 to prior drug treatment (Fig. 1). 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, while 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: $P < 0.01$).

Similar changes were observed in subscores of IPSS, that is, voiding symptoms, storage symptoms, and post-micturition symptoms. Silodosin significantly improved subscores regardless of the period of administration, while tamsulosin significantly improved them only after the first treatment period (Table 2). Significant improvement from baseline was also observed in all seven symptoms of the IPSS after administration of silodosin and in five items (incomplete emptying, frequency, intermittency, weak stream, and nocturia) after administration of tamsulosin in the first treatment period. In the crossover treatment period, further significant improvement was observed in five items (incomplete emptying, frequency, urgency, straining, and nocturia) with silodosin treatment, while no significant improvement was observed in any items with tamsulosin treatment (Table 2). Intergroup comparison of changes revealed that silodosin yielded significant improvement of straining and nocturia with first and crossover treatments, respectively, compared with tamsulosin (Figs 2,3).

The results of QOL score were similar to those for IPSS. Silodosin significantly improved QOL score in both treatment periods, while tamsulosin significantly improved QOL score only in the first treatment period (Table 2). Moreover, silodosin showed significant improvement of QOL score in both treatment periods (first treatment: $P < 0.05$; crossover treatment: $P < 0.05$) compared with tamsulosin.

Maximal urinary flow rate 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 (Table 2). 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 first treatment; a significant decrease from baseline was observed only with silodosin, with no significant improvement with either drug after crossover treatment (Table 2). Systolic blood pressure was significantly decreased from baseline after administration of first silodosin treatment and heart rate was significantly increased with crossover tamsulosin treatment, but neither of these changes was clinically problematic. No other significant changes were observed in blood pressure or heart rate.

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

Table 2 Changes in subjective symptoms and objective parameters in each group

Parameters	Group	Pretreatment	4 weeks after	8 weeks after	Pre *vs* 4 weeks	4 weeks *vs* 8 weeks
IPSS total score	S-T	16.6 ± 5.2 (34)	9.0 ± 4.0 (34)	9.3 ± 4.8 (34)	$P < 0.001$	NS
	T-S	18.2 ± 5.8 (31)	13.5 ± 6.3 (31)	10.9 ± 5.9 (31)	$P < 0.001$	$P < 0.001$
Voiding symptoms	S-T	8.0 ± 4.1 (34)	4.1 ± 2.7 (34)	4.4 ± 3.2 (34)	$P < 0.001$	NS
	T-S	8.5 ± 3.3 (31)	6.1 ± 3.2 (31)	5.2 ± 3.3 (31)	$P < 0.001$	$P < 0.05$
Storage symptoms	S-T	6.2 ± 3.1 (34)	3.7 ± 2.1 (34)	3.8 ± 2.0 (34)	$P < 0.001$	NS
	T-S	7.5 ± 3.6 (31)	5.8 ± 3.2 (31)	4.5 ± 2.9 (31)	$P < 0.001$	$P < 0.01$
Incomplete emptying	S-T	2.5 ± 1.7 (34)	1.1 ± 1.4 (34)	1.1 ± 1.1 (34)	$P < 0.001$	NS
	T-S	2.3 ± 1.5 (31)	1.7 ± 1.2 (31)	1.1 ± 1.1 (31)	$P < 0.05$	$P < 0.01$
Frequency	S-T	2.5 ± 1.5 (34)	1.5 ± 1.1 (34)	1.5 ± 1.0 (34)	$P < 0.001$	NS
	T-S	2.8 ± 1.6 (31)	2.2 ± 1.4 (31)	1.7 ± 1.3 (31)	$P < 0.01$	$P < 0.05$
Intermittency	S-T	2.4 ± 1.8 (34)	1.2 ± 1.2 (34)	1.2 ± 1.3 (34)	$P < 0.001$	NS
	T-S	2.6 ± 1.6 (31)	1.8 ± 1.3 (31)	1.5 ± 1.3 (31)	$P < 0.001$	NS
Urgency	S-T	1.5 ± 1.6 (34)	0.9 ± 1.0 (34)	0.9 ± 1.1 (34)	$P < 0.05$	NS
	T-S	1.9 ± 1.5 (31)	1.6 ± 1.4 (31)	1.2 ± 1.2 (31)	NS	$P < 0.01$
Weak stream	S-T	3.6 ± 1.5 (34)	2.2 ± 1.5 (34)	2.5 ± 1.7 (34)	$P < 0.001$	NS
	T-S	3.8 ± 1.4 (31)	2.7 ± 1.3 (31)	2.4 ± 1.6 (31)	$P < 0.001$	NS
Straining	S-T	2.0 ± 1.7 (34)	0.7 ± 1.0 (34)	0.8 ± 1.1 (34)	$P < 0.001$	NS
	T-S	2.1 ± 1.6 (31)	1.6 ± 1.5 (31)	1.3 ± 1.2 (31)	NS	$P < 0.05$
Nocturia	S-T	2.1 ± 1.4 (34)	1.3 ± 0.8 (34)	1.4 ± 1.0 (34)	$P < 0.001$	NS
	T-S	2.7 ± 1.3 (31)	2.0 ± 1.1 (31)	1.6 ± 1.0 (31)	$P < 0.001$	$P < 0.05$
QOL score	S-T	4.9 ± 0.9 (34)	3.2 ± 1.4 (34)	3.3 ± 1.4 (34)	$P < 0.001$	NS
	T-S	4.9 ± 0.9 (31)	4.0 ± 1.0 (30)	3.3 ± 1.4 (31)	$P < 0.001$	$P < 0.001$
Maximum flow rate	S-T	9.4 ± 3.5 (29)	11.3 ± 4.9 (33)	10.9 ± 4.3 (30)	$P < 0.05$	NS
	T-S	9.7 ± 4.4 (29)	11.6 ± 6.0 (31)	12.2 ± 5.3 (29)	$P < 0.01$	NS
Residual urine volume	S-T	95.8 ± 102.4 (24)	48.7 ± 62.9 (26)	50.8 ± 54.7 (25)	$P < 0.05$	NS
	T-S	97.3 ± 113.3 (27)	83.8 ± 111.3 (28)	101.6 ± 123.6 (25)	NS	NS

Data represents the mean ± standard deviation. Numbers in parenthesis indicates number of subjects. Statistical analyses were performed by paired *t*-test. IPSS, International Prostate Symptom Score; NS, not significant; QOL, quality of life; S-T, silodosin-preceding group; T-S, tamsulosin-preceding group.

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 and whose status could not be confirmed, silodosin was continuously administered to all patients. Other adverse reactions included diarrhea/soft stool in two patients, dizziness in two patients, staggering in two patients, and sense of abdominal fullness, sense of fullness of the stomach, and drug eruption in one patient each. 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.

In the questionnaire conducted after completion of the study, 27 of 58 patients who answered wished to continue silodosin and 25 patients wished to continue tamsulosin. In the silodosin-preceding group, the reason for selection of silodosin was "excellent effect" in 12 cases; and those of tamsulosin were "excellent effect" in six cases, "easy to take" in four cases, "fewer adverse effects" in two cases, and "others" in two cases. On the other hand, the reasons for selection of tamsulosin were "excellent effect" in five cases, "easy to take" in two cases, "fewer adverse effects" in three cases, and "others" in one case, and that for selection of silodosin was "excellent effect" in 15 cases in the tamsulosin-preceding group. In total, the reason for selection of silodosin was "excellent effect" in all cases; and reasons for selection of tamsulosin were "excellent effect" in 40% of cases, "easy to take" in 24%, and "fewer adverse effects" in 20%.

Discussion

BPH is a disease that impairs QOL, and satisfactory progress in the early stage of treatment is considered one of the important elements of treatment. In an attempt to mirror

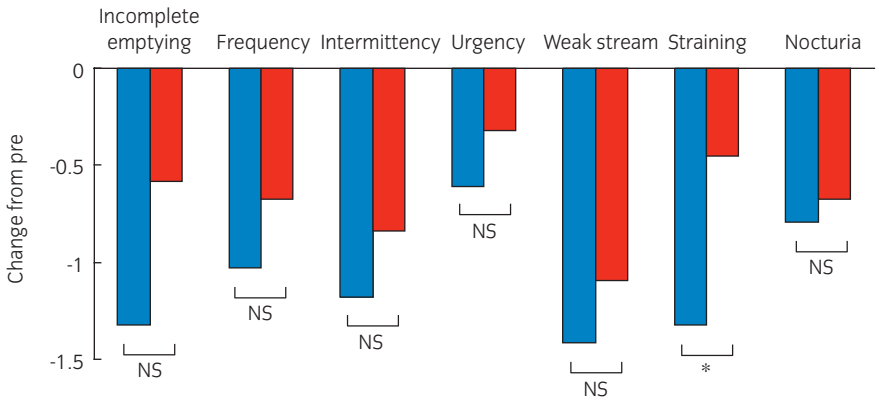

Fig. 2 Change from baseline of International Prostate Symptom Score in first treatment period. Asterisk indicates the significant difference ($P < 0.05$) between groups (unpaired *t*-test). NS, not significant. Silodosin (■); Tamsulosin (■).

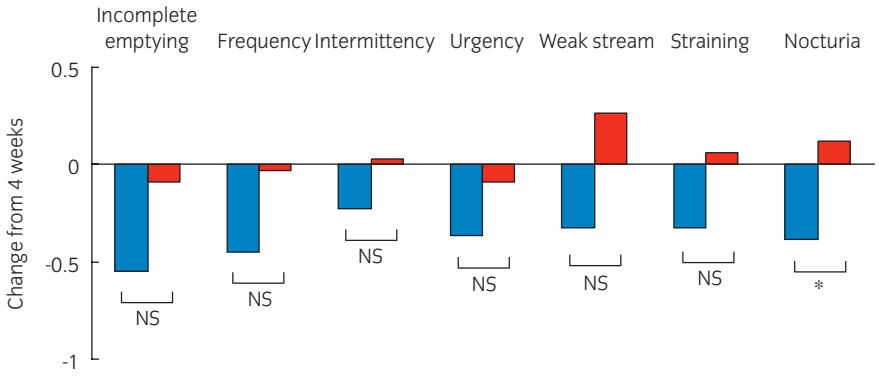

Fig. 3 Change from baseline of International Prostate Symptom Score in crossover treatment period. Asterisk indicates the significant difference ($P < 0.05$) between groups (unpaired *t*-test). Silodosin (■); Tamsulosin (■).

the actual conditions of usage in clinical practice, we compared the efficacy and safety of silodosin and tamsulosin, two types of α1 blockers, after 4 weeks' administration in BPH/LUTS patients by a crossover design without a drug withdrawal period.

Silodosin significantly improved IPSS total score after both the first and crossover treatment periods. Tamsulosin significantly improved IPSS in the first treatment, but no further improvement was observed in crossover treatment with silodosin. Regardless of the period of administration, the improvement with silodosin was superior to that with tamsulosin, suggesting that silodosin will improve the symptoms of BPH from the early stage of administration both in new patients and those who have previously received tamsulosin. In the Japanese phase III study of silodosin,[13] significant improvement of IPSS compared with placebo was observed from the first week of administration, suggesting the finding of improvement from the early stage in the present study. Moreover, in the same trial, silodosin yielded significant improvement of IPSS compared not only to placebo but also to tamsulosin in the second week of administration, and this difference in efficacy was sustained until 12 weeks. In particular, at the end of first treatment (after 4 weeks), the extent of symptom improvement by each drug was almost the same in the present study and the prior phase III trial. The efficacy of silodosin and tamsulosin were thus considered confirmed in this study, although it included neither a placebo group nor a large number of patients compared with the phase III double blind study.

It has been reported that there are increasing numbers of BPH/LUTS patients who wish to be treated for not only voiding symptoms but also storage symptoms, such as nocturia.[16,17] In this study, silodosin significantly improved storage and post-micturition symptoms in addition to voiding symptoms in both the first and crossover treatment periods. Furthermore, it significantly improved nocturia, which among LUTS markedly affects QOL, regardless of the period of administration. Moreover, silodosin significantly improved not only symptoms but also QOL scores from the early stage of administration in both treatment periods. Taken together, these findings suggested that silodosin improved patient satisfaction by improving a wide range of symptoms, including nocturia. This appears to reflect the rating by patients of an "excellent effect" as the reason for selection of silodosin.

Qmax significantly improved in each group after the treatment with the preceding drug but no further improvement was observed after the changeover. As to the residual urine, significant improvement was observed in the silodosin-preceding group but no significant improvement was observed in the tamsulosin-preceding group. The reason why no improvement was observed due to any drug in the latter group is not clear but more patients in the tamsulosin-preceding group demonstrated the change of 100 mL or

more in residual urine, indicating the influence of dispersion, etc. between individual cases. Therefore, if based on objective findings, including Qmax, it is considered that the difference in effect between these two drugs was not clearly observed.

The incidence of ejaculatory disorder was higher in the silodosin than in the tamsulosin group. This may have been due to the pharmacological effect of silodosin, that is, its α1A blocking activity. In fact, according to a phase III double-blind study in the USA,[18] ejaculatory disorders were observed in 28% of the patients after administration of silodosin at 8 mg once-daily. In addition to retrograde ejaculation due to inhibition on the contraction of the bladder neck, the involvement of inhibition on the contraction of seminal vesicle and vas deferens is also reported in regard to the mechanism of ejaculatory disorder,[19] and the expression of α1A receptor is confirmed in these tissues. Moreover, a clinical trial of tamsulosin in the USA found that tamsulosin induces abnormal ejaculation in some American patients (8.4% at 0.4 mg daily and 18.1% at 0.8 mg daily).[20,21] It is therefore not considered an adverse reaction specific to silodosin, and has been shown to be reversible with discontinuation of drug administration.[19,22]

Besides ejaculation disorder, other adverse drug reactions, such as diarrhea, were also reported in the silodosin-preceding group, and the overall rate of adverse drug reactions in this group was higher than that in the tamsulosin-preceding group. These reactions, however, were all mild, and resolved or were relieved with either continuation or discontinuation of treatment. On the other hand, the incidences of dizziness with silodosin and tamsulosin were comparable, and no clinically problematic change in blood pressure was observed with silodosin treatment.

In conclusion, silodosin, a selective α1A-adrenoceptor antagonist, exhibited excellent efficacy in improving subjective symptoms regardless of period of administration, and appears to improve QOL in patients with BPH/LUTS.

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Editorial Comment

Editorial Comment to Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia

A-blockers represent the first-line drug treatment of men with moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).[1] Indirect comparisons between α-blockers and limited direct comparisons demonstrate that the efficacy seems to be similar across all α-blockers. The newest entry in the class is silodosin. *In vitro* studies have indicated that silodosin has the greatest selectivity for the α1A adrenoceptor among all clinically used α-blockers.[2] A recent review of the available data reported that silodosin is significantly more effective than placebo in controlling LUTS and at least as effective as tamsulosin.[3] In addition, it is significantly more effective than tamsulosin in inducing simultaneous improvement of bothersome LUTS, such as incomplete emptying, frequency, and nocturia. Pooled data also showed that silodosin is safe with excellent cardiovascular tolerability, whereas retrograde ejaculation is the most common (21.5%) adverse event (AE) presented.[3]

Miyakita *et al.* evaluated the efficacy and safety of silodosin and tamsulosin in a randomized crossover fashion.[4] It was found that the efficacy of silodosin in improving symptoms was superior to that of tamsulosin in both initial and crossover treatment. Intergroup comparison of changes demonstrated that silodosin yielded significant improvement in straining and nocturia compared with tamsulosin. Similarly, silodosin significantly improved quality of life (QOL) score in both treatment periods, while tamsulosin significantly improved QOL score only in the first treatment period. Interestingly, the incidence of AE in the silodosin group was eight times (16.5%) higher compared to the AE rate for tamsulosin patients (2.1%).

These results are very interesting but they should be interpreted with caution as the number of patients included in the present study was rather low, while in addition there was a remarkable attrition rate (only 67% of the patients were finally evaluated).

What do we need in the future? More randomized controlled studies with a larger number of patients and longer follow-up are required to draw solid conclusions on the efficacy and safety of silodosin in comparison with tamsulosin. It would also be interesting to evaluate the impact of silodosin on patients suffering from LUTS who did not respond to previous treatment with other α-blockers.

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