Original Article: Clinical Investigation

Early efficacy of silodosin in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

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Objectives: To evaluate the early efficacy of the α_{1A}-adrenoceptor selective drug, silodosin, for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Methods: A total of 68 patients with an International Prostate Symptom Score (IPSS) of ≧8 and a Quality of Life (QOL) index of ≧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 of twice daily oral administration of 4 mg silodosin. Next, changes in IPSS subscores as well as voiding, storage, and post micturition symptoms were assessed. Changes in total IPSS based on symptom severity were also determined.

Results: Total IPSS and QOL index improved significantly from 19.38 ± 7.46, 4.68 ± 1.07 at baseline to 15.81 ± 7.40, 4.22 ± 1.30 at day 1. The subscores of voiding, storage, and post micturition symptoms were significantly decreased from 8.93 ± 3.95, 7.97 ± 3.88, and 2.49 ± 1.70 at baseline to 7.28 ± 4.09, 6.52 ± 3.47, and 2.02 ± 1.56 at day 1, respectively. This trend continued throughout the study. Regardless of severity, total IPSS were significantly decreased at day 1 and maintained throughout the study.

Conclusions: Silodosin may be considered a promising treatment for benign prostatic hyperplasia/lower urinary tract symptom patients.

Key words: α1-adrenoceptor antagonist, benign prostatic hyperplasia, quality of life, silodosin.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most prevalent diseases in elderly men. BPH causes not only voiding symptoms, but also storage symptoms and post-micturition symptoms such as the feeling of incomplete emptying. Not only may lower urinary tract symptoms (LUTS) suggestive of BPH restrict the patients' activities but they may also impair quality of life.

The first-line medication for BPH/LUTS is an α_1-adrenoceptor (α_1AR) blockade.[1,2] Initially, non-selective α_1AR blockers, terazosin and doxazosin, were used in the treatment of BPH/LUTS patients. Later, subtype selective $\alpha_{1A/D}$ AR blockers, tamsulosin and naftopidil, came into use in Japan; this was due to a lower incidence of adverse cardiovascular events in comparison with the non-selective drugs.[3–5] The short and long-term efficacy and safety of these drugs has been reported.[6–11] Tamsulosin ($\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$) and naftopidil ($\alpha_{1D} \geq \alpha_{1A} > \alpha_{1B}$) are more subtype selective drugs compared to terazosin and doxazosin ($\alpha_{1D} = \alpha_{1A} = \alpha_{1B}$).[2] Although it has been suggested that α_{1D} AR may provide a new therapeutic approach for controlling the storage symptoms in patients with BPH, the function of α_{1D} AR in the human detrusor has not been elucidated in clinical practice.[2,8,10]

Recently, the more selective α_{1A} AR drug, silodosin, has been used for BPH patients in Japan. Silodosin has been evaluated for improvement in subjective symptoms using the International Prostate Symptom Score (IPSS) in a 3-month[12] and a one-year period.[13] In this phase III study,[12] subjective symptoms of IPSS improved in the early stages of treatment, that is, at 1 and 2 weeks.

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The purpose of this study was to evaluate the early efficacy of silodosin in the treatment of BPH/LUTS patients. Additionally, we examined whether the α_{1A} AR selective drug could improve patients' subjective symptoms, both storage and voiding symptoms. Finally, we examined the possibility of early prediction for the efficacy of silodosin.

Methods

This study was performed at the Osaka University Hospital and six affiliated institutions between December 2006 and December 2007. Patients aged 45 years or older who complained of LUTS suggestive of BPH according to the judgment of a physician were recruited. The inclusion criteria of this study were an IPSS ≧ 8 and a Quality of Life (QOL) index of ≧2. Patients suffering from neurogenic bladder dysfunction, bladder neck contracture, urethral stricture, bladder calculus, severe bladder diverticulum, chronic bacterial prostatitis or active urinary tract infection were excluded. Patients with prostate cancer, a history of pelvic radiotherapy, prostatectomy or any other diseases affecting urinary function were excluded. Patients with clinically significant cardiovascular disease, severe renal dysfunction, severe hepatic illnesses (hepatic failure, fulminant hepatitis, cirrhosis, hepatic tumor, or jaundice) were excluded from this study. Patients receiving concomitant medication that is thought to have an affect on urinary function, such as α-AR antagonists, anti-cholinergic agents, antidepressants or anti-anxiety agents, or sex hormone agents, were also excluded. If the patients were receiving another α_1-AR blocker, it was necessary to withdraw from that drug at least one week prior to the study.

A total of 68 patients orally administered the usual dosage of 4 mg silodosin twice daily. The patient was handed a treatment diary on the first visit and modified IPSS and QOL index were recorded at Day 0 (baseline), 1, 2, 3, 4, 5, 6, 7, 14, and 28, respectively. The IPSS was

originally used for the evaluation of symptoms occurring within one month. We used a modified IPSS, in which we excluded the sentences 'over the past month' from the original sentences of the IPSS. The values for Day 0 to 7 are the symptoms for the day of observation. The values for Day 14 and Day 28 are the average of the observed values for the previous three days including the day of observation.

We evaluated the changes in IPSS and QOL index before and after each point of administration of silodosin. Then, we evaluated the subscores of IPSS, as voiding symptoms using the sum of the scores for intermittency, weak stream, and straining; storage symptoms using the sum of the scores for frequency, urgency, and nocturia; and post micturition symptoms using the score for feeling of incomplete emptying. We assessed changes in total IPSS based on the severity level of the IPSS or QOL index.

We evaluated the IPSS of Day 3, 7 and 28 to determine the prediction of efficacy of silodosin. Homma *et al*.[14] proposed four criteria for the efficacy of treatment in BPH as excellent (improvement of 75% IPSS), good (improvement of 50% IPSS), fair (improvement of 25% IPSS) and poor (less than 25% improvement). Because the number of cases was too small to divide into four categories in the current study, we defined a good responder as a patient with ≧25% improvement of total IPSS from pre-treatment (including excellent, good, fair in Ref. [15]) and a bad responder as a patient with <25% improvement (poor in Ref. [15]). We compared the number of good responders and bad responders at day 3, 7 and 28.

Adverse symptoms that were newly observed after the initiation of treatment were recorded on the information sheet with the day of onset, degree of symptom, severity level, outcome and causal association with silodosin. The clinical evaluation of the patients who discontinued the treatment was performed at the time of discontinuation.

All values are expressed as the mean ± standard deviation. Statistical comparisons before and after the administration were made using the Wilcoxon signed rank test. $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics included in this study are summarized in Table 1. The mean age of the 68 patients was 67.5 ± 8.0 years (range 48–92 years). Total IPSS was 19.38 ± 7.46. Subscores for voiding symptoms, storage symptoms, and post micturition symptoms were 8.93 ± 3.95, 7.97 ± 3.88, and 2.49 ± 1.70, respectively. QOL index was 4.68 ± 1.07. The number of patients with severe (IPSS ≧ 20) and moderate (IPSS 8–19) symptoms according to total IPSS were 36 and 32, respectively. The number of patients with severe (QOL index 5, 6) and moderate (QOL index 2–4) symptoms according to the QOL index were 39 and 29, respectively. The average calculated prostate volume was 32.6 ± 17.8 mL. The volume of mild (less than 20 mL), moderate (less than 50 mL) and severe (50 mL and more) prostate sizes was 15, 40 and 8 out of 63 cases, respectively.

The total IPSS improved from 19.38 ± 7.46 at baseline to 15.81 ± 7.40 at day 1 (Fig. 1). Symptom relief was very rapid and maintained throughout the study. The QOL index also improved from 4.68 ± 1.07 at baseline to 4.22 ± 1.30 at day 1 (Fig. 1). This trend continued throughout the study.

The subscores for voiding, storage, and post micturition symptoms were significantly decreased from 8.93 ± 3.95, 7.97 ± 3.88, and 2.49 ± 1.70 at baseline to 7.28 ± 4.09, 6.52 ± 3.47, and 2.02 ± 1.56 at day 1, respectively (Fig. 2). This improved throughout the study.

Table 1 Baseline characteristics of 68 patients

	n	Mean	SD
Age	68	67.5	8.0
IPSS			
Total	68	19.38	7.46
Severe (IPSS ≧ 20)	36		
Moderate (IPSS 8–19)	32		
Voiding symptoms		8.93	3.95
Storage symptoms		7.97	3.88
Post voiding symptoms		2.49	1.7
QOL index	68	4.68	1.07
Severe (5, 6)	39		
Moderate (2, 3, 4)	29		
Prostate volume	63	32.6	17.8
<20 mL	15		
<50 mL	40		
≧50 mL	8		

IPSS, International Prostate Symptom Score; QOL, quality of life; SD, standard deviation.

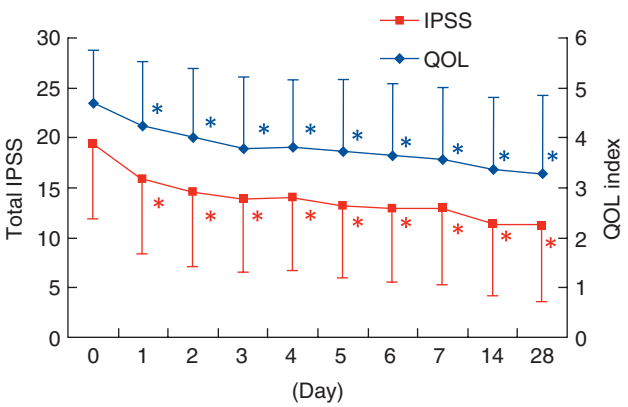

Fig. 1 The time-course of changes in the total International Prostate Symptom Score (IPSS) and quality of life (QOL) index. Asterisk indicates significantly different to Day 0 (before treatment) ($P < 0.05$).

Regardless of the severity of the total IPSS (Fig. 3) and QOL index (Fig. 4), total IPSS were significantly decreased at day 1 and were maintained throughout the study.

When we evaluated the efficacy of silodosin at day 28, 42 out of 68 patients (61.8%) were good responders and 26 patients (38.2%) were bad responders (Fig. 5). At day 3, a total of 31 patients (45.6%) out of 68 patients responded well to silodosin, while 37 patients (54.4%) had bad responses. Out of 31 good responders at day 3, 25 patients (80.6%) continued to respond well at day 28. Out of 37 bad responders at day 3, 20 patients (54.1%) continued to respond poorly at day 28. Therefore, the positive predictive value (PPV) at Day 3 was 80.6% and the negative predictive value (NPV) at Day 3 was 54.1%. At day 7, 42 out of 68 patients (61.8%) were good responders and 26 patients (38.2%) were bad responders. Out of 42 good responders at day 7, 33 patients (78.6%) continued to maintain a good response at day 28. Out of 26 bad responders at day 7, 17 patients (65.4%) continued to respond badly at day 28. Therefore, PPV at Day 7 was 78.6%, and NPV at Day 7 was 65.4%. Incidentally, while there was a total of 42 good responders and

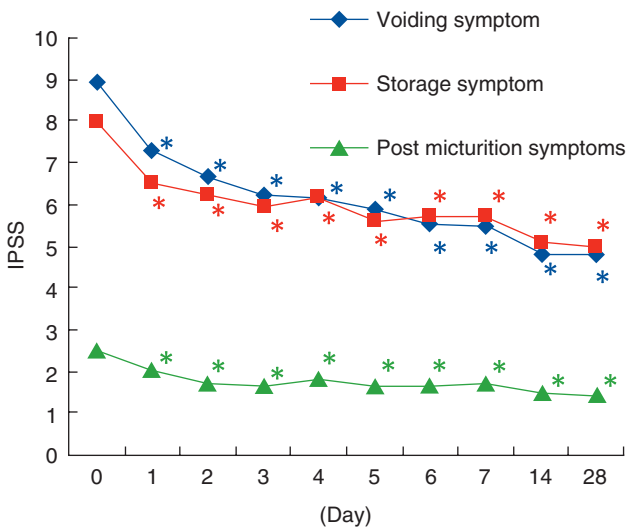

Fig. 2 The time-course of changes in the International Prostate Symptom Score (IPSS) subscores of voiding, storage, and post micturition symptoms. Asterisk indicates significantly different to Day 0 (before treatment) ($P < 0.05$).

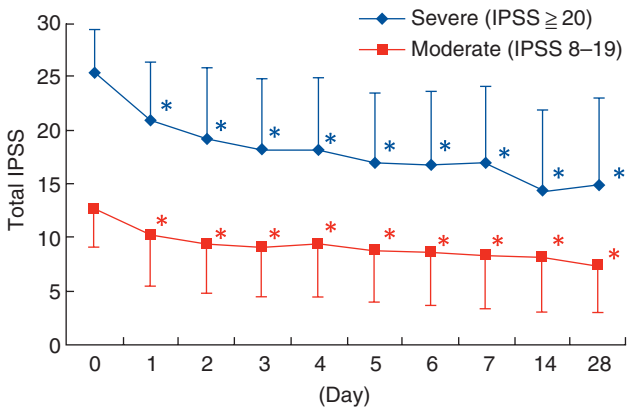

Fig. 3 The time-course of changes in the total International Prostate Symptom Score (IPSS) of patients with severe IPSS (IPSS ≧ 20) and moderate IPSS (IPSS 8–19) symptoms. Asterisk indicates significantly different to Day 0 (before treatment) ($P < 0.05$).

26 bad responders at day 7 and 28, we could not predict how the individual cases would respond to later treatment.

Adverse events occurred in six patients. The adverse events were comprised of abnormal ejaculation in two, diarrhea in two, tinnitus in one and lightheadedness in one. All of these adverse events resolved after ceasing the administration of silodosin.

Discussion

The purpose of this study was to evaluate the early efficacy of silodosin for the treatment of BPH/LUTS patients. Our results suggest that the selective α_{1A} AR blocker, silodosin, improves BPH/LUTS symptoms and QOL in a very short time. Moreover, not only voiding symptoms, but also storage and post micturition symptoms are improved by the selective α_{1A} AR blocker.

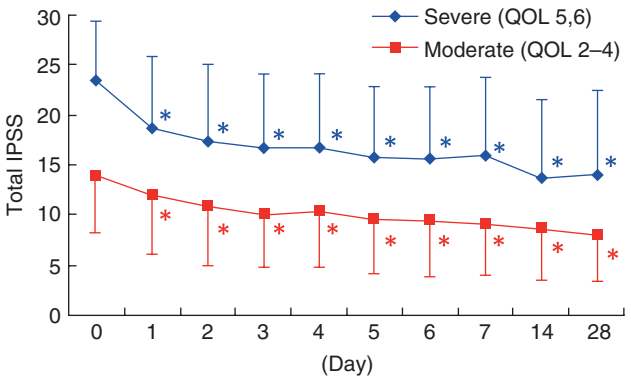

Fig. 4 The time-course of changes in the total International Prostate Symptom Score (IPSS) of patients with severe quality of life (QOL) (QOL 5, 6) and moderate QOL (QOL 2–4). Asterisk indicates significantly different to Day 0 (before treatment) ($P < 0.05$).

Patients suffering from BPH/LUTS can expect the early efficacy of treatment for their symptoms. One of the $\alpha_{1A/D}$ AR blockers, tamsulosin, has been reported in previous studies to significantly improve total American Urological Association scores and total QOL index after 4 days[15] and 1 week,[16] respectively. In an objective method with uroflowmetry, tamsulosin demonstrated a rapid onset of action (4 to 8 h) based on maximum flow rate (Qmax) after first administration.[16] The early efficacy of the drug can lead to better compliance to medication by patients. In the phase III study[12] of silodosin, subjective symptoms according to the IPSS improved within 1 week; however, there are no reports to examine the earlier effect of silodosin within 1 week. Our results show that silodosin improved the IPSS and QOL index after one day of administration. Unfortunately, we could not perform objective measurement by uroflowmetry. This study was performed at a real-life outpatient clinical practice and it was impossible to perform uroflowmetry on a daily basis. The phase III study[12] showed that Qmax and average flow rate (Qave) had improved after one month of silodosin administration.

There are some additional benefits beyond improvement to patient QOL. For example, one of the α_1AR blockers, tamsulosin, is used for the treatment of catheterized patients with acute urinary retention[17] because α_1AR blockers help to reduce bladder outlet resistance through their effects on the sympathetic tone of the bladder neck and prostatic stroma.[18] Tamsulosin significantly reduced the risk of acute urinary retention after attempts at early catheter removal following radical retropubic prostatectomy.[19] Tamsulosin may decrease the risk of voiding impairment after trans-rectal ultrasound sonography (TRUS)-guided prostate biopsy.[20] We would expect a similar effect of silodosin in patients suffering from voiding disorder.

There are three subtypes of α_1AR: α_{1A}, α_{1B} and α_{1D}. α_{1A} AR is the dominant receptor in the urethra[2] and α_{1D} is reported to be the dominant receptor in the detrusor[21] and spinal cord.[22] In the prostate, recent studies have shown that α_{1A}[23] and α_{1D} are dominant and that expression levels differ according to the individual.[24] Even though the efficacy of silodosin in relieving voiding symptoms is easily understood (it inhibits the sympathetic nervous signal in the prostate and urethra via α_{1A} AR) the mechanism through which silodosin relieves storage symptoms and post micturition symptoms has not been clearly elucidated. Tamsulosin and naftopidil, $\alpha_{1A/D}$ AR blockers, are efficient both for voiding and storage symptoms.[8] In the crossover comparison study on the therapeutic effects of these two drugs, tamsulosin was more effective than

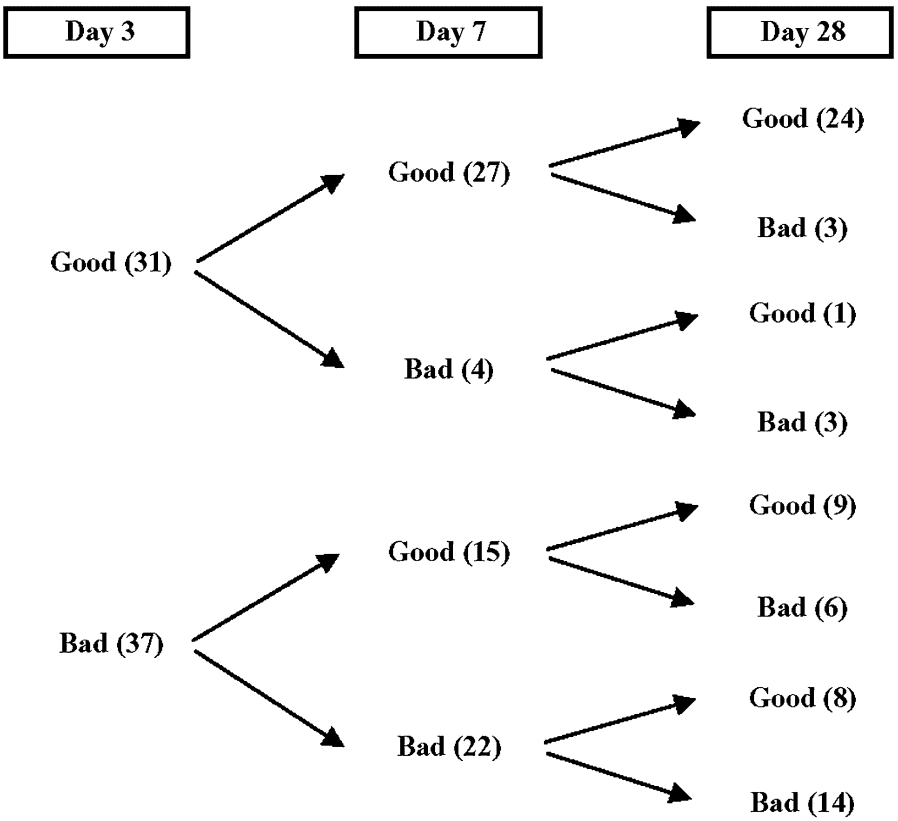

Fig. 5 The distribution of good responders (Good; ≧25% improvement in total International Prostate Symptom Score [IPSS] from the pre-treatment) and bad responders (Bad; <25% improvement) at day 3, 7 and 28.

naftopidil on intermittency, nocturia and QOL scores.[25] The other study showed that these two drugs caused no significant difference in voiding symptoms, total IPSS, or QOL index; however, relief of storage symptoms was significantly greater with naftopidil.[26] The expression level of the α_1-adrenoceptor subtype messenger ribonucleic acid (mRNA) in the prostate could be a predictor of the efficacy of subtype selective α_1-adrenoceptor antagonists in patients with BPH.[27] As the α_{1D} AR has dominant distribution in the detrusor, especially in the status of bladder outlet obstruction,[28] α_{1D} AR might be associated with the improvement of storage symptoms of LUTS patients. Moreover, animal experiments showed that the intrathecal administration of tamsulosin and naftopidil transiently abolished isovolumetric rhythmic bladder contraction in rats. The amplitude of bladder contraction after intrathecal injection was significantly decreased after injection of naftopidil, but was not altered by tamsulosin.[29] This effect of the α_{1D} AR on the spinal cord may be associated with the improvement of storage symptoms of LUTS patients. Although silodosin is the more highly selective drug for α_{1A}, it also had an affinity for α_{1D}. Therefore, the inhibition of α_{1D} AR may result in the improvement of storage symptoms. However, Nomiya *et al*. reported that the α_{1D} AR are not likely to be responsible for detrusor overactivity and storage symptoms in BPH/LUTS patients as the expression level of α_{1A} and α_{1D} mRNA in obstructed human bladders is very low.[30] Interestingly, Tatemichi *et al*. demonstrated that cystometry in the hormone treatment BPH rat model showed the detrusor overactivity only in male rats, not female rats and silodosin decreased the detrusor overactivity.[31] They suggested that the detrusor overactivity expression was responsible for increased urethral pressure and that the increased response, mediated by α_{1A}, occurred secondary to the hypertrophied prostate. Nevertheless, the elucidation of the roles of α_{1A} and α_{1D} AR in detrusor overactivity and storage symptoms in patients with BPH/LUTS will be needed for further investigations.

The interest in clinical use is whether the effect of silodosin is predictable in BPH/LUTS patients in early stages following the commencement of drug administration. When we evaluated the efficacy of silodosin at day 3, 31 out of 68 patients (45.6%) were good responders and 37 patients (54.4%) were bad responders. PPV at Day 3 and at Day 7 was 80.6% and 78.6%, respectively. As for the 80% of good responders at day 3 or day 7, we could predict the efficacy of silodosin at day 28. NPV at Day 3 and at Day 7, however, was 54.1% and 65.4%, respectively. This indicated that even in bad responses on day 3 or day 7, some patients' symptoms had improved by day 28. Therefore, we could not predict the bad responders at day 3 or day 7. From the phase III study,[13] the total IPSS gradually decreased until 52 weeks. Good responders in the early term tended to maintain the improvement of symptoms, but bad responders could not be predicted.

There were several limitations to this study. As the present study is not a placebo controlled randomized study, the placebo effect could not be eliminated. Our study resulted in a population that was slightly more severe (mean IPSS of 19.38) than that in the phase III studies (mean IPSS of 17.1). The tendency in this study was similar to the phase III study.[12] We did not perform frequency/volume chart or urodynamic studies. It is difficult to state the association of the improvement of subjective parameters, like the IPSS and QOL index, and objective parameters like uroflowmetry or pressure flow study. Further examination will be needed for these problems.

In conclusion, our results suggest that silodosin improves BPH/LUTS and QOL in a very short time. Silodosin may be considered a promising treatment for rapid improvement in BPH/LUTS patients.

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