Comparison of Silodosin versus Tadalafil in Patients with Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

Masaki YOSHIDA,1,∗ Hideki ORIGASA,2 and Narihito SEKI3

1Department of Urology, National Center for Geriatrics and Gerontology, Obu-City, Japan, 2Department of Biostatistics and Clinical Epidemiology, The University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan, and 3Department of Urology, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan

Objectives: To compare the efficacy and safety of silodosin versus tadalafil for treating lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH).

Methods: After informed consent, patients with LUTS/BPH were randomized in a 1:1 ratio to receive silodosin 8 mg/day or tadalafil 5 mg/day for 8 weeks (Period 1). Patients treated with tadalafil entered an exploratory phase and received silodosin or tadalafil for another 8 weeks. The primary efficacy endpoint was the change in the total International Prostate Symptom Score (IPSS) with Period 1 treatment.

Results: Both silodosin and tadalafil demonstrated statistically significant improvement in IPSS total symptom score, with a mean ± standard deviation change of −10.1 ± 6.4 (P < 0.0001) and −8.0 ± 6.3 (P < 0.0001), respectively. The former reduction was significantly greater than the latter (P = 0.0277). Adverse drug reactions occurred at a rate of 23.4% with silodosin and 8.4% with tadalafil. No serious adverse drug reactions were documented, suggesting that both drugs were well tolerated. Moreover, results of Period 2 showed that switching to silodosin from tadalafil achieved a faster onset of improvements in IPSS Quality of Life Index score and total Overactive Bladder Symptom Score.

Conclusions: Silodosin achieved significantly greater improvement than tadalafil, with a higher incidence of adverse drug reactions. The risk-benefit profiles obtained in this study will provide useful information for optimal pharmacological treatment of LUTS/BPH. Our results suggest that silodosin can be one of the first-line therapies for rapid and efficient relief in patients with LUTS/BPH.

Key words benign prostatic hyperplasia, lower urinary tract symptoms, randomized clinical trials, silodosin, tadalafil

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common cause of lower urinary tract symptoms (LUTS) in middle-aged and elderly men, and the incidence rate of LUTS associated with BPH (LUTS/BPH) increases with age until approximately 80.1 An epidemiological survey conducted in Japan suggests that more than 80% of males aged 60 years and older have LUTS.2 LUTS can be broadly grouped into: (i) storage symptoms, such as frequency, urgency, and nocturia, (ii) voiding symptoms, such as intermittency, weak stream, and straining, and (iii) postmicturition symptoms, such as a feeling of incomplete emptying and postmicturition dribble.3 Such symptoms interfere with the activities of daily living and decrease the quality of life (QoL) of patients with LUTS/BPH.4,5 For optimal management of LUTS/BPH, medications should be chosen based on age, disease progression, need for long-term management, and other clinical parameters.6

In 2011, the Japanese clinical guidelines for LUTS/BPH proposed α1-adrenoceptor antagonists (α1 blockers) as first-line drug therapy for LUTS/BPH.5 These agents reduce the α-adrenergic tone of the smooth muscle within the prostate and bladder neck, thereby relieving the bladder outlet obstruction. In 2014, tadalafil (phosphodiesterase type 5 [PDE-5] inhibitor) was approved in Japan for treating LUTS/BPH. The inhibition of PDE-5 leads to accumulation of cyclic guanosine monophosphate in the smooth muscles of the prostate and urethra, which causes their relaxation, resulting in alleviation of

∗Correspondence: Masaki Yoshida, MD, PhD, Department of Urology, National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu-City, Aichi 474-8511, Japan. Tel: +81-562-46-2311; Fax: +81-562-46-8329. Email: myoshida@ncgg.go.jp

Authorship Statement: The researchers listed above meet the ICMJE authorship criteria and certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Received 30 November 2016; revised 9 February 2017; accepted 1 March 2017
DOI: 10.1111/luts.12177

© 2017 The Authors. LUTS: Lower Urinary Tract Symptoms published by John Wiley & Sons Australia, Ltd. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
the symptoms of LUTS/BPH. Although several studies compared the effects of the α1 blocker tamsulosin and tadalafil, there was no randomized clinical trials that compared the selective α1 blocker silodosin and tadalafil. Therefore, we conducted a randomized clinical trial in patients with LUTS/BPH and compared the efficacy and safety of silodosin and tadalafil.

2. METHODS

2.1. Study design and participants

This prospective, multicenter, randomized, nonblind parallel-group study to compare the efficacy and safety of silodosin versus tadalafil for treating LUTS/BPH (University Hospital Medical Information Network Clinical Trials Registry No. UMIN000018743) was conducted between September 2015 and June 2016 in outpatient settings at eight urological departments and clinics in metropolitan areas of Japan. This study was conducted in accordance with the 1964 World Medical Association Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013), Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (joint regulatory notification released on 22 December 2014, by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare), and the International Committee on Harmonisation Good Clinical Practice guidelines. Prior to the initiation of the study, the protocol was reviewed and approved by an independent central institutional review board located in Tokyo, Japan (Adachi Kyosai Hospital Ethics Committee). All patients provided written informed consent before participating in the study.

The target sample size of this study was set at 90 subjects per treatment arm. Based on previous placebo-controlled clinical studies, the difference in the mean change of IPSS total symptom score between silodosin and tadalafil was estimated at 2.3. Assuming a standard deviation (SD) of 5.0 and 80% statistical power, 76 patients per treatment arm were necessary to demonstrate the superiority of silodosin over tadalafil at a 5% two-sided significance level. The target sample size was determined taking into consideration possible dropouts.

Inclusion criteria were: (i) male outpatients aged ≥60 years, (ii) diagnosis of BPH based on abdominal ultrasound or digital rectal examination, (iii) baseline (Week 0) conditions satisfying the following: total International Prostate Symptom Score (IPSS) ≥13, IPSS QoL Index score ≥3, prostate volume ≥20 mL, and postvoid residual urine volume ≤100 mL, (iv) 2 or more weeks of freedom or washout from any medications known to influence LUTS before enrollment, and (v) mental and physical capacity to understand and fill out the study questionnaires. Exclusion criteria were: (i) contraindications to silodosin or tadalafil, (ii) diagnosis of prostate cancer, (iii) possible presence of urinary infection or neurogenic bladder, (iv) use of silodosin or tadalafil within 12 weeks prior to enrollment, (v) use of an androgen or 5 α-reductase inhibitor within 24 weeks prior to enrollment, (vi) clinically significant cardiovascular, hepatic, or renal disorders, (vii) cataract surgery planned during the study period, and (viii) patients deemed to be ineligible for participation in the opinion of the investigator.

The study procedures are schematically presented in Figure 1. The therapy period of this study had two major phases, each lasting for 8 weeks. In Period 1, eligible patients were randomized in a 1:1 ratio to receive either silodosin 4 mg twice daily (arm S) or tadalafil 5 mg once daily (arm T). After the end of Period 1, arm S patients visited the study site for the end-of-study assessment, and arm T patients proceeded to exploratory Period 2, where they received either silodosin 4 mg twice daily (arm T-S) or tadalafil 5 mg once daily (arm T-T) according to the randomized assignments determined at their enrollment. The treatment assignment employed a dynamic randomization algorithm, with stratification for IPSS total symptom score (<20 versus ≥20) and age (<70 years versus ≥70 years).

2.2. Study endpoints and assessments

Study visits were scheduled at randomization (Week 0), completion of Period 1 (Week 8), and completion of Period 2 (Week 16) or early discontinuation. At the randomization visit, the following demographic and baseline characteristics were evaluated and documented: sex, age, height, weight, prostate volume, and clinical history, including disease duration, comorbid conditions, current medications, and previous and ongoing treatments for LUTS/BPH. At Week 8 and Week 16 visits, patients’ drug adherence, IPSS total symptom score, IPSS QoL Index score, Overactive Bladder Symptom Score (OABSS), and urodynamic parameters were determined. At Weeks 1, 2, 3, and 4 (Period 1) and Weeks 9, 10, 11, and 12 (Period 2), patients responded to the IPSS and OABSS questionnaires at home based on their micturition experience of the previous week.

The primary efficacy endpoint of this study was the change in IPSS total symptom score before and after Period 1 treatment. For exploratory purposes, changes in IPSS total symptom score with Period 2 treatment were also analyzed. Secondary efficacy endpoints included changes in IPSS voiding (Questions 3, 5, and 6), storage (Questions 2, 4, and 7), and postmicturition (Question 1) subscale scores, IPSS QoL Index score, OABSS total and subscale scores before and after Period 1 and Period 2 treatments. In addition, early changes were assessed at Weeks 1, 2, 3, and 4 of Period 1 treatment and Weeks 9, 10, 11, and 12 of Period 2 treatment. Uroflowmetry was also performed in each group at Weeks 0, 8, and 16. To evaluate the safety, all adverse events were monitored during the study. Adverse events and adverse drug reactions were coded using the Medical Dictionary for Regulatory Activities Version 19.0. An adverse drug reaction was defined as an adverse event for which a causal relationship to the study medication cannot be ruled out with certainty.
2.3. Statistical methods and analysis sets

Treatment effects on the efficacy endpoints were summarized for each arm using descriptive statistics (e.g., mean ± SD) and 95% confidence intervals (CIs) and tested for statistical significance using the paired t-test. Treatment effects were compared between the arms using the Student’s t-test. For exploratory analyses of the efficacy results, the proportions of patients whose IPSS total symptom score decreased (i.e., improved) by at least 25% from baseline (positive IPSS responders) were compared between the arms using Fisher’s exact test. To evaluate patients’ safety, reported adverse events, serious adverse events, and adverse drug reactions were analyzed by arm, and the incidence rates were compiled. All statistical tests were conducted at a two-sided significance level of 5%.

Efficacy was evaluated in a modified intention-to-treat (mITT) population that included all randomized patients but excluded those with major predefined protocol violations and those with no post-baseline efficacy data. The Period 2 mITT population comprised 47 arm T-S and 42 arm T-T patients. The Period 1 safety analysis set included 94 arm S and 95 arm T patients, and the Period 2 safety analysis set included 48 arm T-S and 42 arm T-T patients. The flow chart of study patients is schematically illustrated in Figure 2. The demographic and baseline characteristics of the Period 1 and Period 2 mITT patients are presented in Table 1. The baseline, demographic, and disease characteristics were well balanced across the treatment arms of Periods 1 and 2.

3. RESULTS

3.1. Participants

A total of 192 eligible patients provided informed consent to participate in the study and were randomized to treatment. At enrollment, 95 and 97 patients were assigned to arm S and arm T, respectively. Of the 97 patients of arm T, 49 and 48 patients were originally assigned to arm T-S and arm T-T, respectively. One arm S and 2 arm T patients withdrew from the study before any treatment. In addition, 1 arm S patient had no post-baseline visit data. Consequently, the Period 1 mITT population (efficacy analysis set) consisted of 93 arm S and 95 arm T patients. After completing Period 1, 5 arm T patients (all assigned to arm T-T) withdrew from the study before the start of Period 2 treatment. In addition, 1 arm T-S patient had no evaluable efficacy data for Period 2 treatment. As a result, the Period 2 mITT population comprised 47 arm T-S and 42 arm T-T patients. The Period 1 safety analysis set included 94 arm S and 95 arm T patients, and the Period 2 safety analysis set included 48 arm T-S and 42 arm T-T patients. The flow chart of study patients is schematically illustrated in Figure 2. The demographic and baseline characteristics of the Period 1 and Period 2 mITT patients are presented in Table 1. The baseline, demographic, and disease characteristics were well balanced across the treatment arms of Periods 1 and 2.

3.2. Period 1 efficacy

In Period 1, both silodosin and tadalafil demonstrated statistically significant improvement from baseline (Week 0) in IPSS total symptom score (primary endpoint), with a mean ± SD change of −10.1 ± 6.4 (P < 0.0001) and −8.0 ± 6.3 (P < 0.0001), respectively. The difference between silodosin and tadalafil was statistically significant (P = 0.0277). Silodosin and tadalafil achieved a statistically significant decrease in each IPSS symptom score as well as voiding and storage subscale scores (all Ps < 0.0001). Silodosin demonstrated a significantly greater decrease in the symptoms of incomplete emptying, weak stream, and nocturia than tadalafil (P = 0.0254, P = 0.0067, and P = 0.0387, respectively). Silodosin achieved numerically greater, but not statistically different, changes in the IPSS voiding and storage subscale
scores as compared to tadalafil. The proportions of positive IPSS responders were 78.7% (70/89) for silodosin and 69.6% (64/92) for tadalafil. These proportions were not statistically different from each other ($P = 0.1784$).

Changes in IPSS QoL Index score from baseline to the end of Period 1 treatment were statistically significant for silodosin and tadalafil (both $P < 0.0001$). Silodosin achieved significantly greater improvement than tadalafil ($P = 0.0032$).

Changes in total OABSS score from baseline (Week 0) to the end of Period 1 treatment (Week 8) were statistically significant for silodosin and tadalafil (both $P < 0.0001$). The difference between silodosin and tadalafil was statistically significant ($P = 0.0117$). Silodosin and tadalafil achieved a statistically significant decrease in each OABSS subscore from baseline (all $P s < 0.0001$ except for the arm T frequency subscore, for which $P = 0.0260$). Silodosin demonstrated a significantly greater decrease in nocturia and urgency subscores than tadalafil ($P = 0.0064$ and $P = 0.0293$, respectively). Silodosin exhibited numerically greater, but not statistically different, changes in other OABSS subscores as compared to tadalafil. The Period 1 efficacy results are summarized in Table 2.

Changes over time during Periods 1 and 2 in IPSS total symptom, IPSS QoL Index, and total OABSS scores are graphically illustrated in Figures 3–5, respectively. Silodosin and tadalafil demonstrated statistically significant improvements from baseline in IPSS total symptom, IPSS QoL Index, and total OABSS scores, starting after 1 or 2 weeks of treatment (Figs 3a, 4a, and 5a). Significantly greater improvements were observed for silodosin as compared to tadalafil in IPSS total symptom score at Week 4 ($P = 0.0212$) and in IPSS QoL Index score at Weeks 3 and 4 ($P = 0.0226$ and $P = 0.0119$, respectively).

Measurements of the maximum urine flow rate exhibited no significant change from baseline (Week 0) to the end of Period 1 treatment (Week 8) for tadalafil. However, silodosin achieved a statistically significant improvement
**TABLE 1.** Demographic and baseline characteristics of Periods 1 and 2 patients available for efficacy evaluation

| Study medication | Period 1 | Period 2 |
|------------------|----------|----------|
|                  | Silodosin | Tadalafil | Silodosin | Tadalafil |
| Sample size (n)  | 93        | 95        | 47        | 42        |
| Age (years)      | 70.5 [6.0] | 69.7 [5.8] | 69.2 [5.9] | 70.8 [5.8] |
| Patients aged <70 years (n) | 48        | 48        | 24        | 20        |
| Patients aged ≥70 years (n) | 45        | 47        | 23        | 22        |
| BMI (kg/m²)      | 23.5 [3.0] | 24.1 [2.8] | 23.8 [2.9] | 24.4 [2.5] |
| Duration of BPH (months) | 61.0 [58.2] | 59.9 [67.1] | 63.0 [79.3] | 54.6 [54.4] |
| Comorbidities/complications (n) | | | | |
| None             | 36        | 27        | 11        | 15        |
| ≥1               | 57        | 68        | 36        | 27        |
| Hypertension     | 29        | 28        | 14        | 10        |
| Hypertension     | 12        | 18        | 10        | 6         |
| Diabetes mellitus| 11        | 15        | 7         | 6         |
| Overactive bladder| 12        | 16        | 9         | 6         |
| IPSS total symptom score | 20.8 [5.0] | 20.9 [5.1] | 13.0 [6.1] | 12.1 [6.0] |
| Patients with IPSS total symptom score (n) | | | | |
| ≥20              | 50        | 54        | 7         | 4         |
| <20              | 43        | 41        | 40        | 38        |
| IPSS voiding subscore | 9.1 [3.2] | 9.7 [3.3] | 5.9 [3.7] | 5.9 [3.7] |
| IPSS storage subscore | 8.5 [2.7] | 8.2 [2.6] | 5.4 [2.3] | 4.7 [2.7] |
| IPSS QoL index score | 4.9 [0.8] | 4.9 [0.9] | 4.2 [1.3] | 3.8 [1.5] |
| Total OABSS score | 7.1 [2.9] | 6.4 [2.6] | 4.5 [2.0] | 4.0 [2.2] |
| Patients with OAB by OABSS score (n) | | | | |
| No               | 21        | 21        | 26        | 25        |
| Yes              | 72        | 74        | 21        | 17        |
| Prostate volume (mL) | 39.97 [17.14] | 39.16 [18.86] | 40.17 [22.78] | 37.99 [14.87] |
| Maximum urine flow rate (mL/sec) | 11.32 [5.93] | 12.04 [5.71] | 12.03 [6.29] | 12.42 [5.56] |
| Mean urine flow rate (mL/sec) | 4.75 [2.62] | 5.21 [2.70] | 5.42 [3.39] | 5.36 [2.70] |
| Postvoid residual urine volume (mL) | 23.38 [26.28] | 25.65 [25.01] | 34.38 [64.28] | 22.11 [30.41] |

Patients treated with tadalafil in Period 1 were randomized to receive either silodosin or tadalafil for another 8 weeks in Period 2. Results are summarized as mean [standard deviation], where appropriate. BMI, body mass index; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; OABSS, Overactive Bladder Symptom Score; OAB, overactive bladder symptoms; QoL, quality of life.

**TABLE 2.** Results of Period 1 efficacy evaluations

| Parameters                  | Silodosin | Tadalafil | Silodosin versus Tadalafil |
|-----------------------------|-----------|-----------|----------------------------|
|                             | n         | 95% CI     | P-value                    | n         | 95% CI     | P-value | P-value |
| IPSS total symptom score    | 89        | -10.1 [6.4] | <0.0001 | 92        | -8.0 [6.3] | <0.0001 | 0.0277 |
| IPSS symptom score †        |           |           |                       |           |           |         |         |
| Q1. Incomplete emptying     | 88        | -1.8 [1.7] | <0.0001 | 91        | -1.3 [1.3] | <0.0001 | 0.0254 |
| Q2. Frequency               | 89        | -1.6 [1.4] | <0.0001 | 92        | -1.3 [1.3] | <0.0001 | 0.2120 |
| Q3. Intermittency           | 87        | -1.4 [1.6] | <0.0001 | 92        | -1.3 [1.6] | <0.0001 | 0.4882 |
| Q4. Urgency                 | 86        | -1.4 [1.4] | <0.0001 | 89        | -1.2 [1.3] | <0.0001 | 0.3784 |
| Q5. Weak stream             | 88        | -1.8 [1.7] | <0.0001 | 92        | -1.2 [1.6] | <0.0001 | 0.0067 |
| Q6. Straining               | 79        | -1.3 [1.4] | <0.0001 | 92        | -1.1 [1.6] | <0.0001 | 0.3256 |
| Q7. Nocturia                | 88        | -1.0 [1.1] | <0.0001 | 92        | -0.7 [1.0] | <0.0001 | 0.0387 |
| IPSS voiding subscore       | 89        | -4.4 [3.6] | <0.0001 | 92        | -3.5 [3.9] | <0.0001 | 0.1266 |
| IPSS storage subscore       | 89        | -3.9 [2.9] | <0.0001 | 92        | -3.2 [2.7] | <0.0001 | 0.0732 |
| IPSS QoL index score        | 89        | -1.5 [1.4] | <0.0001 | 92        | -0.9 [1.3] | <0.0001 | 0.0032 |
| Total OABSS score           | 89        | -3.2 [2.7] | <0.0001 | 92        | -2.2 [2.6] | <0.0001 | 0.0117 |
| OABSS subscore              |           |           |                       |           |           |         |         |
| Q1. Frequency               | 86        | -0.3 [0.6] | <0.0001 | 87        | -0.2 [0.7] | <0.0001 | 0.2600 |
| Q2. Nocturia                | 88        | -0.9 [0.8] | <0.0001 | 92        | -0.5 [0.9] | <0.0001 | 0.0064 |
| Q3. Urgency                 | 88        | -1.4 [1.4] | <0.0001 | 90        | -0.9 [1.2] | <0.0001 | 0.0293 |
| Q4. Urinary incontinence    | 57        | -1.0 [1.4] | <0.0001 | 58        | -0.9 [1.2] | <0.0001 | 0.4721 |
| Maximum urine flow rate (mL/sec) | 80        | 2.04 [7.30] | 0.41 [6.66] | 0.0146 | 81        | 0.02 [5.98] | 1.30 [1.35] | 0.9719 | 0.0571 |
| Mean urine flow rate (mL/sec) | 80        | 0.78 [2.42] | 0.24 [1.32] | 0.0051 | 81        | 0.27 [2.57] | -0.29 [0.84] | 0.3404 | 0.2009 |
| Postvoid residual urine volume (mL) | 84        | 2.65 [5.14] | 4.76 [10.06] | 0.4794 | 90        | 3.65 [8.71] | 6.55 [13.86] | 0.4785 | 0.8753 |

†Q1 relates to a postmicturition symptom; Q3, Q5, and Q6 relate to voiding symptoms (grouped into the IPSS voiding subscale); and Q2, Q4, and Q7 relate to storage symptoms (grouped into the IPSS storage subscale). Changes from baseline (week 0) to the end of 8-week treatment are presented as mean [standard deviation]. CI, confidence interval; IPSS, International Prostate Symptom Score; OABSS, Overactive Bladder Symptom Score; QoL, quality of life.
from baseline ($P = 0.0146$). Similarly, silodosin achieved a statistically significant improvement in mean urine flow rate from baseline ($P = 0.0051$). Estimated postvoid residual urine volumes showed no statistically significant change from baseline with either study treatment. None of these urination parameters revealed statistically significant difference between silodosin versus tadalafil.

### 3.3. Period 2 efficacy (exploratory study)

Period 2 efficacy results of 8-week treatment are summarized in Table 3. In Period 2, both silodosin and tadalafil demonstrated statistically significant improvement from baseline (Week 8) to the end of treatment (Week 16) in IPSS total symptom score, with a mean $\pm SD$ change of $-3.0 \pm 5.1$ ($P < 0.0001$) and $-3.1 \pm 3.4$ ($P < 0.0001$), respectively. No statistically significant difference was noted between the treatments ($P = 0.8787$).

Silodosin and tadalafil showed statistically significant improvement from baseline (Week 8) to the end of treatment (Week 16) in IPSS QoL Index score (both $P < 0.0001$). No statistically significant difference was noted between the treatments ($P = 0.3746$). Both silodosin and tadalafil exhibited statistically significant
improvement from baseline to the end of treatment in total OABSS score ($P=0.0019$ and $P=0.0069$, respectively). No statistically significant difference was noted between the treatments ($P=0.5021$).

Changes over time in IPSS total symptom, IPSS QoL Index, and total OABSS scores from baseline (Week 8) during Period 2 treatment with silodosin and tadalafil are graphically illustrated in Figures 3b, 4b and 5b. Silodosin and tadalafil yielded IPSS total symptom scores significantly better than baseline, starting after 3 weeks of treatment. Statistically significant improvement from baseline in IPSS QoL Index score was seen after 2 weeks of treatment with silodosin and after 4 weeks with tadalafil. Total OABSS score showed statistically significant improvement from baseline after 3 weeks of treatment with silodosin and after 8 weeks with tadalafil. None of the above scores revealed a statistically significant difference between silodosin and tadalafil.
3.4. Safety

Adverse events and adverse drug reactions observed in Period 1 and Period 2 are summarized in Table 4. In Period 1, adverse events were reported in 26.6% of patients treated with silodosin, and in 12.6% of those treated with tadalafil. None of these adverse events were serious. Adverse drug reactions occurred more frequently with silodosin (23.4%) than tadalafil (8.4%). Nervous system disorders (i.e., dizziness and headache) and gastrointestinal disorders (i.e., soft feces) were reported in both arms. The following were reported in arm S only: orthostatic hypotension ($n = 2$), nasal congestion ($n = 4$), ejaculation disorder ($n = 6$), and retrograde ejaculation ($n = 5$). Three patients treated with silodosin and one patient with tadalafil prematurely discontinued the study during Period 1 due to adverse drug reactions.

In Period 2, adverse events were reported in 7.1% of patients of arm T-T. None of them were study-related. In contrast, adverse events were seen in 33.3% of patients of arm T-S, including one serious case each of intestinal obstruction and heat illness, the former of which led to premature discontinuation. In arm T-S, adverse drug reactions were documented at a rate of 27.1%, including gastrointestinal disorders in eight patients, ejaculation...
disorder and retrograde ejaculation in two patients each, and erectile dysfunction, dizziness, and dizziness postural in one patient each. One patient withdrew from the study due to adverse drug reaction.

4. DISCUSSION

We compared the effects of silodosin 4 mg twice daily and tadalafil 5 mg once daily on patients with LUTS/BPH. This study is the first head-to-head comparison of the efficacy and safety between silodosin and tadalafil. The primary efficacy variable, the mean change in IPSS total symptom score from baseline, showed a statistically significant improvement in both silodosin and tadalafil. The primary efficacy endpoint of silodosin was significantly greater than that of tadalafil.

In this study, the mean change from baseline in IPSS total symptom score of the silodosin group (−10.1) was greater than previous reports. In a placebo-controlled, 12-week clinical trial of silodosin 4 mg twice daily, Kawabe et al. reported a mean change of −8.3 in IPSS total symptom score from baseline. The difference was probably attributable to the fact that the mean baseline IPSS total symptom score of the silodosin group was greater in our study (20.9) than in those previous reports (16.4 to 18.7).

Silodosin also achieved a statistically greater improvement than tadalafil in IPSS QoL Index and total OABSS scores. The mean change in total OABSS score over 8 weeks was −3.2 for silodosin and −2.2 for tadalafil. As a value of −3 has been suggested as the minimal clinically important change on this subjective scale, the data suggest that silodosin offers clinically significant improvement for storage symptoms, as compared to tadalafil.

Regarding the differences in improvement in each variable of the IPSS and OABSS questionnaires between silodosin and tadalafil, improvements in IPSS incomplete emptying, weak stream and nocturia and OABSS nocturia and urgency scores of the silodosin group were significantly greater than those of the tadalafil group. In this study, silodosin, but not tadalafil, significantly improved the maximum and average urinary flow rate. The increased urinary flow rate might be related to the improvement of weak stream in the silodosin group. Urgency is the main symptom of overactive bladder. Improvement of OABSS urgency score was significantly greater in the silodosin group than in the tadalafil group. In IPSS, urgency similarly improved in both groups. However, the improvement was numerically greater in the silodosin group than in the tadalafil group. Although it has been reported that many action mechanisms contribute to the relief of overactive bladder symptoms by these drugs, the present data suggested that silodosin had superior efficacy for overactive bladder to tadalafil.
### TABLE 4. Adverse events and adverse drug reactions reported in patients treated with silodosin and tadalafil in Periods 1 and 2

| Adverse Drug Reactions by MedDRA System Organ Class and Preferred Term | Period 1 | Period 2 |
|---------------------------------------------------------------|---------|---------|
|                                                              | Silodosin, n = 94 | Tadalafil, n = 95 | Silodosin, n = 48 | Tadalafil, n = 42 |
| Adverse events                                                | 25 | 26.6 | 12 | 12.6 | 16 | 33.3 | 2 | 4.2 | 13 | 27.1 |
| Serious adverse events                                        | 22 | 23.4 | 8 | 8.4 | 2 | 4.2 | 1 | 2.1 |
| Adverse drug reactions                                        | 22 | 23.4 | 8 | 8.4 | 16 | 33.3 | 2 | 4.2 | 13 | 27.1 |
| Serious adverse drug reactions                                 | 22 | 23.4 | 8 | 8.4 | 16 | 33.3 | 2 | 4.2 | 13 | 27.1 |

**Effects of Silodosin and Tadalafil for LUTS/BPH**

Improvement of nocturia in the silodosin group was observed in both IPSS and OABSS. Nocturia is one of the storage symptoms, and many factors contribute to its pathophysiology. The reasons for the different effects of silodosin and tadalafil remain unclear. The different action mechanisms of the two drugs may contribute to the results. Further investigation is needed to clarify the difference.

We compared the changes in IPSS total symptom score from baseline with silodosin and tadalafil by age, prostate volume, urinary flow rate, and other variables, and no clearly difference was noted between the subgroups for either arm (data not shown).

In Period 2, tadalafil-treated patients were randomized to receive continued tadalafil therapy (T-T) or to switch to silodosin (T-S). Whereas both arms exhibited similar responses in terms of IPSS total symptom, IPSS QoL Index, and total OABSS scores, arm T-S showed a faster onset of action than arm T-T. In addition, these scores were further evaluated by subgroup analysis of patients whose baseline IPSS total symptom score was ≥ 13 (severe subgroup) (data not shown). The subgroup comparisons showed that the change over 8 weeks in IPSS total score was −4.3 ± 6.2 for arm T-S, a numerically greater, but not statistically significant, reduction than that for arm T-T (−3.4 ± 4.3). The total OABSS score also showed significantly greater improvement (P = 0.0338) in arm T-S (−1.5 ± 1.6), as compared to arm T-T (−0.4 ± 1.8). Period 2 results showed that switching to silodosin from tadalafil achieved faster improvements in symptoms and QoL, suggesting a possible benefit of switching to silodosin in patients with severe symptoms and in patients unresponsive to tadalafil.

The incidence rate of adverse drug reactions during Period 1 was 23.4% for silodosin, which was higher than that for tadalafil (8.4%). In Period 2, adverse drug reactions occurred at a rate of 27.1% for silodosin, and no adverse drug reactions were reported for tadalafil. No serious adverse drug reactions were documented with either medication. The similar incidence rates for silodosin between Periods 1 and 2 suggest that pretreatment with tadalafil does not adversely impact the safety profile of silodosin. The adverse drug reaction profiles documented in our study are comparable to those reported to date.

© 2017 The Authors. LUTS: Lower Urinary Tract Symptoms published by John Wiley & Sons Australia, Ltd.
We compared the incidence rates of adverse events and adverse drug reactions by age, prostate volume, urinary flow rate, and other variables. No clear differences were noted between subgroups with silodosin (data not shown).

Design limitations of this study deserve consideration in the interpretation of its results. First, this was a nonblinded study, although it involved randomization of participants by stratification for IPSS total symptom score and age. The nonblinded nature of this study could have allowed the patients’ expectations to influence their results. Second, Period 2 treatments were exploratory in nature. The smaller sample size considerably reduced the power of the tests. Despite these limitations, this study provided significant insight into the benefits and risks of the agents representing two major classes of drugs for LUTS/BPH management.

5. CONCLUSION

Silodosin demonstrated significantly greater improvements in IPSS total symptom, IPSS QoL, Index, and total OABSS scores than tadalafil, although it induced adverse drug reactions at a much higher rate. The risk-benefit profiles obtained in this study will provide useful information for optimal pharmacological treatment of LUTS/BPH. Our results suggested that silodosin can be one of the first-line therapies for rapid and efficient relief in patients with LUTS/BPH.

Acknowledgments

This study was sponsored by Kissei Pharmaceutical Co., Ltd., Nagano, Japan, and the authors designed the protocol in consultation with the sponsor. The following investigators participated in this study: Nobuaki Furugen, Yuji Kurooka, Shigeto Araki, Yasutada Onodera, Hiroaki Shiozawa, Yasunori Shishido, Yutaka Nagatomi, and Takahide Hosobe. We acknowledge the contributions of Mebix, Inc., a Tokyo-based contract research organization, whose responsibilities for this project included study site monitoring and auditing, data management, statistical analysis, and supporting final reporting.

Disclosure

Kissei provided consulting and lecture fees to Masaki Yoshida and Narihito Seki and consulting fees and research expenses to Hideki Origasa. To prevent funding bias, Kissei was not granted access to the data during the study, except for reports of serious adverse events from the study sites. The sponsor checked for possible clerical errors and editorial inaccuracies regarding the conflict of interest statements of the authors.

REFERENCES

1. Verhamme KM, Dieleman JP, Bleumink GS et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care—the Triumph project. Eur Urol 2002; 42: 323–8.
2. Homma Y, Kakizaki H, Gotoh M et al. [Epidemiologic survey on lower urinary tract symptoms in Japan.] J Neurogen Bladder Sys 2003; 14: 266–77. (In Japanese.)
3. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology in lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Urology 2003; 61: 37–49.
4. Okamura K, Usami T, Nagahama K, Maruyama S, Mizuta E. “Quality of life” assessment of urination in elderly Japanese men and women with some medical problems using International Prostate Symptom Score and King’s Health Questionnaire. Eur Urol 2002; 41: 411–9.
5. The Japanese Urological Association. Clinical Guidelines for Benign Prostatic Hyperplasia. Tokyo: Richill Medical Inc., 2011. (In Japanese.)
6. Oelke M, Bachmann A, Desxezaud A et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol 2013; 64: 118–40.
7. ZALUTIA Tablets 2.5 mg & 5 mg [package insert, in Japanese]. Tokyo: Nippon Shinyaku Co., Ltd., 2016. (3rd edn).
8. Oelke M, Giuliano F, Baygani SK, Melby T, Sontag A. Treatment satisfaction with tadalafil or tamsulosin vs placebo in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH): results from a randomised, placebo-controlled study. BJU Int 2014; 114: 568–75.
9. Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. Eur Urol 2012; 61: 917–25.
10. World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191–4.
11. The Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects. December 22, 2014. Ministry of Health, Labour and Welfare Web site. Provisional English translation. [Cited 10 Oct 2016.] Available from URL: http://www.mhlw.go.jp/file/06-Seisakujouhou-1060000-Daijinkankoukousigakuka/0000080278.pdf.
12. Takeda M, Nishizawa O, Imaoka T, Morisaki Y, Viktrup L, Tadafalil for the treatment of lower urinary tract symptoms in Japanese men with benign prostatic hyperplasia: results from a 12-week placebo-controlled dose-finding study with a 42-week open label extension. LUTS 2012; 4: 110–9.
13. Yokoyama O, Yoshida M, Kim SC et al. Tadafalil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a randomized placebo- and tamsulosin-controlled 12-week study in Asian men. Int J Urol 2013; 20: 193–201.
14. Takeda M, Yokoyama O, Lee SW, Murakami M, Morisaki Y, Viktrup L. Tadafalil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea. Int J Urol 2014; 21: 670–5.
15. Kawabe K, Yoshida M, Homma Y. Silodosin, a new α1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of phase III randomized, placebo-controlled, double-blind study in Japanese men. BJU Int 2006; 98: 1019–24.
16. Gotoh M, Homma Y, Yokoyama O, Nishizawa O. Responsiveness and minimal clinically important change in overactive bladder symptom score. Urology 2011; 78: 768–73.
17. URIEF Tablets 2 mg & 4 mg, URIEF OD Tablets 2 mg & 4 mg [package insert, in Japanese]. Nagano: Kissei Pharmaceutical Co., Ltd., 2016. (7th edn.)