Safety and Efficacy of 8-mg Once-daily vs 4-mg Twice-daily Silodosin in Patients With Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (SILVER Study): A 12-Week, Double-blind, Randomized, Parallel, Multicenter Study

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OBJECTIVE To show the noninferiority of silodosin 8-mg once-daily (QD) to 4-mg twice-daily (BID) in efficacy and safety in patients with lower urinary tract symptoms or benign prostatic hyperplasia in the Korean population.

METHODS A prospective, multicenter, double-blind, randomized, comparative study was conducted. A total of 532 male patients aged ≥50 years with lower urinary tract symptoms or benign prostatic hyperplasia were included. All patients received silodosin QD or BID for 12 weeks. The primary end point was the change from baseline in total International Prostate Symptom Score (IPSS) at 12 weeks. Adverse drug reactions, vital signs, and laboratory tests were recorded.

RESULTS A total of 424 patients were randomized to the silodosin QD or BID groups. These groups were not significantly different in baseline characteristics. The mean total IPSS change in QD group was not inferior to that in BID group (−6.70 and −6.94, respectively; 95% confidence interval, −0.88 to 1.36). The QD and BID groups did not significantly differ in the following: percentages of patients with ≥25% (63.41% and 67.82%, respectively; $P = .349$) or ≥4-point improvement in total IPSS (65.85% and 69.31%, respectively; $P = .457$), maximum urinary flow rate improvement ≥30% (47.32% and 40.59%, respectively; $P = .172$), changes in IPSS voiding subscore (-4.42 ± 4.93 and -4.65 ± 4.77; $P = .641$), IPSS storage subscore (-2.05 ± 3.07 and -2.52 ± 2.97; $P = .117$), quality of life (-1.19 ± 1.49 and -1.40 ± 1.42; $P = .136$), maximum urinary flow rate (3.55 ± 5.93 and 3.74 ± 6.79 mL/s; $P = .768$), International Continence Society male questionnaire score, Patient Goal Achievement Score, or Treatment Satisfaction Question. The 2 groups had similar frequencies of adverse drug reactions.

CONCLUSION QD administration of silodosin was not inferior to BID in efficacy. The 2 groups had similar adverse drug reaction profiles. UROLOGY 83: 875–881, 2014. © 2014 Elsevier Inc.

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Benign prostatic hyperplasia (BPH) is one of the most common diseases in men with an increasing prevalence rate with age.[1] A common clinical manifestation of BPH is the occurrence of lower urinary tract symptoms (LUTS) that affect quality of life (QoL) by interfering with normal daily activities.[2] Alpha-1-adrenoceptor blockers are a well-established and effective treatment for BPH related LUTS and are generally a first-line therapy.[3] Although nonselective α_1-adrenoceptor blockers increase the urinary flow rate and improve the symptoms in men with symptomatic BPH, they are associated with peripheral vasodilation-related adverse effects, such as postural hypotension, dizziness, and headache.[4-6] Thus, drugs with a high affinity for α_{1A}-adrenoceptors might be more prostate-specific and might maintain the therapeutic response in the treatment of symptomatic BPH with fewer effects on blood pressure and fewer cardiovascular side effects.[7] One such drug is silodosin.

Although the phase II trails in United States in patients with LUTS and BPH were showing that 8 mg per day was a reasonable clinical recommended dose of silodosin,[8] a phase III randomized confirmatory study verified the safety and efficacy of silodosin 8 mg per day.[9-11] Silodosin 4-mg twice-daily (BID) has been approved in Asian countries and widely used. However, an 8-mg once-daily (QD) administration of silodosin was developed to improve the convenience of dosing and provide an optimal 24-hour coverage.[8] Studies performed in healthy volunteers clearly demonstrated that silodosin QD possessed the appropriate pharmacokinetic and safety profiles. Based on the long half-life of elimination, approximately 13 hours after 7 days of dosing, of QD administration in the United States[8] and Europe,[12] the Food and Drug Administration and European Medicines Agency have approved the QD administration of silodosin.

Although studies have shown separately that the BID and QD administrations are effective and safe, the 2 different administrations have not been compared directly. This SILVER study has been aimed to verify whether silodosin QD is as effective and safe as silodosin BID in Korean patients with BPH and LUTS.

MATERIALS AND METHODS

Patients and Study Design

This randomized, prospective, double-blind, parallel-group, multicenter study was conducted in 14 hospitals in Korea. The study protocol was reviewed and approved by the institutional review board of each study center. The study was conducted according to the Declaration of Helsinki.

Men aged ≥50 years with LUTS associated with BPH were included. The inclusion criteria included a total International Prostate Symptom Score (IPSS) of ≥8, a QoL score of ≥3, a prostate volume measured by transrectal ultrasonography of ≥20 mL, and a maximum urinary flow rate (Q_{max}) of <15 mL/s. Patients with the following conditions were excluded: a postvoid residual urine volume (PVR) of ≥200 mL, history of prostatectomy, intrapelvic radiation therapy, prostate cancer or a prostate-specific antigen higher than 10 ng/mL, neurogenic bladder, active urinary tract infection, renal impairment, severe hepatic disorders, severe cardiovascular disease, a history of orthostatic hypotension, use of α-blockers in 2 weeks before baseline, or use of 5α-reductase inhibitors in 3 months before baseline.

The primary end point of the study was the change from baseline in the total IPSS at 12 weeks. The secondary end points were the percentages of patients with ≥25% or ≥4-point improvement in total IPSS or Q_{max} improvement ≥30%, changes in IPSS voiding subscore, IPSS storage subscore, QoL score, Q_{max} and International Continence Society (ICS) male questionnaire at 12 weeks, and Patient's Goal Achievement Score and Treatment Satisfaction Question at 12 weeks.

After completing a 14-day screening period, patients were randomized to receive oral silodosin with QD or BID administration for 12 weeks. The QD group was given 2 silodosin 4-mg capsules after breakfast, then 1 placebo capsule after dinner. The BID group was given 1 silodosin 4-mg capsule and 1 placebo capsule after breakfast, then 1 silodosin 4-mg capsule after dinner. Subjective symptoms were evaluated by determining the IPSS and QoL score at baseline, at 4 and 12 weeks. At the same point, the ICS male questionnaire was completed; drug compliance was recorded; uroflowmetry and PVR were conducted; vital signs (sitting and standing blood pressure, and pulse) were measured. Clinical laboratory tests such as hematology, blood chemistry, and urinalysis were performed at baseline and at 12 weeks of treatment. At 12 weeks, the Patient's Goal Achievement Score using a visual analog scale from 1 (unable to reach the goal) to 10 (reached the goal completely) was determined, and the Treatment Satisfaction Question regarding the level of satisfaction ('delighted', 'mostly satisfied', 'moderate', 'mostly dissatisfied', 'terrible') was recorded. All adverse events (AEs) and adverse drug reactions (ADRs) were recorded and assessed for severity and causal relationship.

Statistical Analysis

The total number of patients to be randomized was set at 200 per group to reject the null hypothesis that the 2 treatments were not equivalent with the following assumptions: a significance level of 2.5% (1-sided), test power of 80%, a noninferiority margin of 1.8 (change in total IPSS), standard deviation of 6.2, and a dropout rate of 10% after enrollment. The intent to treat (ITT) population included all randomized patients who received at least 1 dose of drug. The per protocol population included the patients who adhered to the visit schedules, did not take prohibited concomitant drugs, and met drug compliance rate of 70% or higher. The safety population included all patients who took the drug and produced assessment results.

The comparison of the changes from baseline in the total IPSS was estimated based on the adjusted means (with 95% confidence interval) obtained from the main analysis of the covariance model including terms for treatment and baseline values. All comparisons were performed by using chi-square test and Fisher's exact test for binary variables, and *t*-test or analysis of covariance for continuous variables. The significance of differences after the treatment was analyzed by using paired *t*-test or Wilcoxon's signed rank test. All statistical analyses were performed by using SAS statistical software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Demographics

Between August 2010 and November 2011, 424 patients were randomized to receive silodosin QD (n = 215) or