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Research Article

Safety and efficacy of tamsulosin 0.4 mg as an initial dose in 1,219 Korean patients with moderate to severe lower urinary tract symptoms: data from a phase IV study

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ABSTRACT

Background: An initial dose of tamsulosin 0.2 mg is frequently prescribed for Asian men. We investigated the safety and efficacy of tamsulosin 0.4 mg as the initial dose in Korean men with moderate to severe lower urinary tract symptoms (LUTSs) in everyday clinical practice.
Materials and methods: A phase IV study was conducted in South Korea. Eligible patients were prescribed tamsulosin 0.4 mg for 6 months. We excluded patients with previous exposure to LUTS drugs and patients with an international prostate symptom score (IPSS) < 8.
Results: The mean total IPSS, storage subscore, voiding symptoms subscore, and quality of life significantly decreased from 18.0, 10.8, 7.2, and 3.8 to 12.8, 7.5, 5.3, and 2.6, respectively, after 6 months of treatment. The number of nocturia episodes significantly decreased from 3.0 to 2.2 in patients who reported at least 2 nocturia events at baseline. A mean reduction in the IPSS was quantitatively equivalent in all age groups. The mean reduction in the IPSS was greater in the IPSS ≥ 20 group than in the IPSS < 20 group (mean reduction in the total IPSS: −2.6 in the IPSS < 20 group; −9.4 in the IPSS ≥ 20 group). All treatment-emergent adverse events were mild. The most frequently recorded treatment-emergent adverse event was dizziness, which was reported in 22 patients (1.8%).
Conclusion: Treatment of LUTS with tamsulosin 0.4 mg as the initial dose for 6 months in Korean men was effective in improving LUTS and showed a favorable safety profile in a real-life setting.

1. Introduction

Lower urinary tract symptoms (LUTSs) are highly prevalent in men, and the prevalence increases with age, reaching up to 80% among men in their 80s.[1,2] Guidelines for non-neurogenic male LUTS recommend alpha-adrenergic blockers, 5α-reductase inhibitors, beta-3 agonists, and muscarinic receptor antagonists as medical treatment options.[3,4]

Alpha-adrenergic blockers relieve bladder outlet obstruction by decreasing the tonic contraction of prostatic smooth muscle and bladder neck smooth muscle, and they have the advantage of rapidly reducing male LUTS; these blockers show significant efficacy over placebo within hours to days.[5,6] Tamsulosin has preferential selectivity for the α1A receptor in the prostate. It has been reported that vasodilating effects are less common with tamsulosin.[7]

The initial dose of tamsulosin for male LUTS differs between Western countries and Asian countries, including South Korea, Japan, Taiwan, and China. The initial dose of tamsulosin in Western countries is 0.4 mg, while an initial dose of 0.2 mg is frequently prescribed and recommended for Asian men with LUTS.[8] Recent studies have reported that increasing the dose of tamsulosin to 0.4 mg is effective and safe in Asian men with LUTS who do not respond to an initial dose of 0.2 mg tamsulosin.[9–12] However, it is still unclear whether tamsulosin 0.4 mg as the initial dose is effective and safe in Asian men with LUTS. To the best of our knowledge, only one randomized clinical, double-blind, phase 3 trial has been reported thus far.[13] In that study, which was conducted in South Korea, tamsulosin 0.4 mg as an initial treatment showed favorable efficacy and tolerability and was more effective than tamsulosin 0.2 mg. However, the study was limited by the

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shortcomings inherent to many randomized controlled trials (RCTs): a small number of participants selected under strict inclusion and exclusion criteria. In turn, the results might not be generalizable to clinical practice.

Therefore, we conducted this study to investigate the safety and efficacy of tamsulosin 0.4 mg as the initial dose in Korean men with moderate to severe LUTS using a large cohort of men seeking medical attention in everyday clinical practice.

2. Patients and method

2.1. Study design

From July 2017 to August 2021, a prospective, multicenter, single-arm, non-interventional, open, phase IV study was conducted in 69 centers in South Korea (study number: HM-TAM-OS-02). The study was approved by the ethics committees of each center and carried out in accordance with the Declaration of Helsinki. All patients gave their written informed consent before beginning any investigational procedure.

This phase IV study included males who were 19 years of age or older and complained of LUTS. The exclusion criteria were as follows: (1) hypersensitivity to the active substance or to any of the excipients; (2) history of orthostatic hypotension or syncope; (3) severe hepatic impairment; (4) any other condition that rendered the patient unable to complete the study or increased the risk to the patient or which prevents optimal participation in achieving the objectives of the study; (5) subjects with contraindications to tamsulosin.

At screening, anthropometric measurements were taken, current smoking and current drinking status were evaluated, and the patient's history was taken. Eligible patients were prescribed single pills of tamsulosin 0.4 mg for 6 months. The international prostate symptom score (IPSS) questionnaire was administered at baseline, after 3 months, and after 6 months of treatment.

The safety population (SAF) was defined as patients who took at least one dose of tamsulosin 0.4 mg. The full analysis set (FAS) was defined as patients who took at least one dose of tamsulosin 0.4 mg, completed the IPSS evaluation at baseline, and completed at least one additional IPSS evaluation.

A total of 4,692 patients were enrolled in this phase IV study. Among them, patients with previous therapeutic exposure to tamsulosin, other alpha-adrenergic blockers, or other drugs for LUTS, including anticholinergics, beta-3 agonists, and 5 alpha-reductase inhibitors (n = 2976), were excluded. After the exclusion of the aforementioned patients, 1,716 patients were enrolled in the naive LUTS drug group. We then excluded patients who did not undergo safety assessment (n = 344), who did not take tamsulosin 0.4 mg after prescription (n = 30), who took part in multiple clinical trials (n = 7), and for other reasons (n = 2). Additionally, we excluded patients with IPSS $\leq$ 7 (n = 114) in this analysis to evaluate the safety and efficacy of tamsulosin 0.4 mg as the initial dose in Korean men with moderate to severe LUTS.[14] Finally, 1,219 patients were allocated to SAF, and 1,121 patients were allocated to FAS.

The primary endpoint was the mean change in total IPSS from baseline. The secondary endpoints of our study were as follows: (1) changes in IPSS voiding symptoms subscore (IPSS questionnaire no. 1, 3, 5, 6), IPSS storage symptoms subscore (IPSS questionnaire no. 2, 4, 7), and IPSS quality of life (QoL) (IPSS questionnaire no. 8); (2) changes in IPSS total score, IPSS voiding symptoms subscore, IPSS storage symptoms subscore, and IPSS QoL according to age group ($\leq$64, 65–74, $\geq$75); (3) changes in IPSS total score, IPSS voiding symptoms subscore, IPSS storage symptoms subscore, and IPSS QoL according to symptom severity (IPSS < 20, IPSS $\geq$ 20); (4) changes in the mean number of nocturia episodes assessed by the number 7 IPSS questionnaire in patients with $\geq$2 nocturia/night at baseline; (5) the rate of treatment-emergent adverse events (TEAEs). Any TEAE reported spontaneously by the patients or observed by the investigator during clinical examination was recorded. Paired t tests and chi-square tests were used to compare frequencies and proportions among groups using SAS (version 9.2, SAS Institute, Inc., Cary, NC, USA). A P value <0.05 was considered statistically significant.

The Institutional Review Board (IRB) of Nowon Eulji Hospital approved this research (Approval No.: 2023-02-010).

3. Results

3.1. Baseline characteristics

A total of 1219 patients were treated with tamsulosin 0.4 mg and included in SAF. Finally, 1121 patients were included in the FAS. Table 1 shows the baseline patient characteristics. In the FAS population, the mean age and mean BMI were 65.7 years and 24.4 kg/m^2, respectively (Table 1). The mean IPSS total score, voiding symptoms subscore, storage symptoms subscore, and QoL score were 18.0, 10.8, 7.2, and 3.8, respectively. The percentage of patients with severe symptoms (IPSS, total $\geq$20) and the number of nocturnal voids $\geq$2 were 37.2% and 72.9%, respectively.

3.2. Efficacy results

Total IPSS, IPSS storage subscore, IPSS voiding subscore, and IPSS QoL decreased significantly after 3 and 6 months of 0.4 mg

Table 1
Characteristics of patients

	SAF population (n = 1219)	FAS population (n = 1121)
Age (years)		
N	1219	1121
Mean (SD)	65.7 (9.2)	65.7 (9.2)
Age		
<65, n (%)	559 (45.9)	509 (45.4)
65–75, n (%)	433 (35.5)	404 (36.0)
≥75, n (%)	227 (18.6)	208 (18.6)
BMI (kg/m^2)		
N	812	751
Mean (SD)	24.4 (2.7)	24.4 (2.7)
Current drinking		
Yes, n (%)	419 (34.4)	384 (34.3)
No, n (%)	491 (40.3)	454 (40.5)
Unknown, n (%)	309 (25.3)	283 (25.2)
Current smoking		
Yes, n (%)	203 (16.7)	190 (16.9)
No, n (%)	699 (57.3)	640 (57.1)
Unknown, n (%)	317 (26.0)	291 (26.0)
IPSS, total		
N	1219	1121
Mean (SD)	18.1 (6.6)	18.0 (6.6)
IPSS, storage symptoms		
N	1219	1121
Mean (SD)	10.9 (4.7)	10.8 (4.7)
IPSS, voiding symptoms		
N	1219	1121
Mean (SD)	7.2 (3.3)	7.2 (3.3)
IPSS, QoL		
N	1218	1120
Mean (SD)	3.8 (1.1)	3.8 (1.1)
Severity of symptoms		
IPSS total score <20, n (%)	758 (62.2)	704 (62.8)
IPSS total score ≥20, n (%)	461 (37.8)	417 (37.2)
Number of voids, nocturnal		
<2, n (%)	337 (27.6)	304 (27.1)
≥2, n (%)	882 (72.4)	817 (72.9)

BMI, body mass index; FAS, full analysis set; IPSS, international prostate symptom score; SAF, safety population.

Table 2
IPSS at each visit and change from baseline in the FAS population

	IPSS, total	IPSS, voiding	IPSS, storage	QoL
Baseline				
N	1121	1121	1121	1120
Mean (SD)	18.0 (6.6)	10.8 (4.7)	7.2 (3.3)	3.8 (1.1)
3 months				
N	1108	1108	1108	1109
Mean (SD)	13.6 (6.9)	7.9 (4.7)	5.7 (3.2)	2.9 (1.2)
Change from baseline at 3 months				
N	1108	1108	1108	1109
Mean (SD)	−4.5 (6.8)	−3.0 (4.8)	−1.5 (3.0)	−0.9 (1.3)
*P**	<0.01	<0.01	<0.01	<0.01
6 months				
N	887	887	887	887
Mean (SD)	12.8 (7.2)	7.5 (4.7)	5.3 (3.2)	2.6 (1.2)
Change from baseline at 6 months				
N	887	887	887	887
Mean (SD)	−5.0 (7.6)	−3.3 (5.3)	−1.7 (3.3)	−1.2 (1.4)
*P**	<0.01	<0.01	<0.01	<0.01

FAS, full analysis set; IPSS, international prostate symptom score.
* Paired t test.

tamsulosin treatment (Table 2). The mean reduction in total IPSS was 4.5 ± 6.8 (25.0% reduction) after 3 months and 5.0 ± 7.6 (27.8% reduction) after 6 months. The mean reduction in the IPSS voiding subscore was 3.0 ± 4.8 (27.8% reduction) after 3 months and 3.3 ± 5.3 (30.6% reduction) after 6 months. The mean reduction in the IPSS storage subscore was 1.5 ± 3.0 (20.8% reduction) after 3 months and 1.7 ± 3.3 (23.6% reduction) after 6 months. Finally, the IPSS QoL score decreased significantly after 3 and 6 months of treatment (mean decrease of 0.9 ± 1.3 at 3 months; 1.2 ± 1.4 at 6 months). The number of nocturia events in patients with ≥2 episodes of nocturia per night at baseline was significantly reduced (0.6 ± 1.1 events at 3 months; 0.8 ± 1.3 events at 6 months) (Table 3).

The mean reduction in IPSS was quantitatively equivalent in all age groups (Table 4). The IPSS QoL score also decreased similarly in all age ranges. The mean decrease in IPSS total score from baseline to study end in the age ≤64, 65–74, and ≥75 groups was 5.0 ± 7.1, 5.0 ± 8.2, and 5.0 ± 7.8, respectively. The IPSS QoL score also significantly decreased from 3.8 ± 1.2 at baseline to 2.6 ± 1.3 at the study end in the age ≤64 group, from 3.7 ± 1.2 at baseline to 2.6 ± 1.2 at the study end in the age 65-74 group, and from 3.5 ± 1.3 at baseline to 2.5 ± 1.2 at the study end in the age ≥75 group (Table 4).

Table 3
The number of nocturia events at each visit and the change from baseline in patients with ≥2 episodes of nocturia per night in the FAS population

	The number of nocturnal voids
Baseline	
N	817
Mean (SD)	3.0 (1.0)
3 months	
N	809
Mean (SD)	2.4 (1.2)
Change from baseline at 3 months	
N	1108
Mean (SD)	−0.6 (1.1)
*P**	<0.01
6 months	
N	633
Mean (SD)	2.2 (1.2)
Change from baseline at 6 months	
N	633
Mean (SD)	−0.8 (1.3)
*P**	<0.01

FAS, full analysis set.
* Paired t test.

Table 4
IPSS, total at each visit and change from baseline in the FAS population after stratification according to age and severity of symptoms

	Age group (years)			Severity of symptoms	
	≤64	65–74	≥75	IPSS < 20	IPSS ≥ 20
Baseline					
N	509	404	208	704	418
Mean (SD)	17.7 (6.1)	18.3 (7.0)	18.1 (6.8)	13.8 (3.3)	25.2 (4.1)
3 months					
N	505	397	206	695	413
Mean (SD)	13.0 (6.7)	13.9 (7.0)	14.3 (7.4)	11.2 (5.5)	17.5 (7.3)
Change from baseline at 3 months					
N	505	397	1108	695	413
Mean (SD)	−4.7 (6.4)	−4.5 (7.3)	−3.9 (7.1)	−2.6 (5.6)	−7.7 (7.5)
*P**	<0.01	<0.01	<0.01	<0.01	<0.01
6 months					
N	392	332	163	571	316
Mean (SD)	12.5 (7.0)	13.1 (7.3)	13.0 (7.2)	11.2 (6.2)	15.7 (7.9)
Change from baseline at 6 months					
N	392	332	163	571	316
Mean (SD)	−5.0 (7.1)	−5.0 (8.2)	−5.0 (7.8)	−2.6 (6.4)	−9.4 (7.7)
*P**	<0.01	<0.01	<0.01	<0.01	<0.01

FAS, full analysis set; IPSS, international prostate symptom score.
* Paired t test.

The mean reduction in IPSS was greater in the IPSS ≥ 20 group than in the IPSS < 20 group (Table 4). The mean reduction in total IPSS was 2.6 ± 6.4 (18.8% reduction) after 6 months in the IPSS < 20 group. The mean reduction in total IPSS was 9.4 ± 7.7 (37.3% reduction) after 6 months in the IPSS ≥ 20 group. In the IPSS < 20 group, the IPSS voiding subscore, IPSS storage subscore, and QoL significantly decreased from 8.2 ± 3.1 to 6.5 ± 4.1, from 5.6 ± 2.4 to 4.7 ± 0.9, and from 3.4 ± 1.0 to 2.4 ± 1.2, respectively, corresponding to a 20.7% reduction, 16.1% reduction, and 29.4% reduction, respectively. In the IPSS ≥ 20 group, the IPSS voiding subscore, IPSS storage subscore, and QoL significantly decreased from 15.3 ± 3.1 to 9.2 ± 5.1, 9.8 ± 2.9 to 6.5 ± 3.5, and 4.5 ± 0.9 to 3.0 ± 1.3, respectively, corresponding to a 39.9% reduction, 33.7% reduction, and 33.3% reduction, respectively.

3.3. Safety

The incidence of TEAEs in SAF was 83 (6.8%), and 43 (3.5%) patients discontinued the treatment because of TEAEs. All TEAEs were mild. The most frequently recorded TEAE was dizziness, reported in 22 patients (1.8%). Other treatment-related TEAEs that occurred at a frequency of ≥3 in patients were “orthostatic hypertension” (0.3%), “headache” (0.2%), “erectile dysfunction” (0.2%), “ejaculatory disorder” (0.2%), and “pruritis” (0.2%) (Table 5).

A total of 332 patients in SAF discontinued the treatment, and the main reasons were lost to follow-up (n = 201), TEAEs (n = 43), and patient decision (n = 32).

4. Discussion

The aim of our study was to evaluate the efficacy and safety of tamsulosin 0.4 mg as an initial treatment in Korean male patients with moderate to severe LUTS. Overall, initial treatment of LUTS with tamsulosin 0.4 mg for 6 months significantly improved LUTS assessed by IPSS, regardless of age and LUTS severity. Additionally, treatment with 0.4 mg tamsulosin for 6 months significantly reduced the number of nocturnal voids in patients with nocturia ≥2 at baseline. Finally, all TEAEs were mild.

In the CombAT study, the mean change in IPSS from baseline to 6 months was 4.4 for tamsulosin 0.4 mg.[15] Network meta-analysis showed that the reduction in the total IPSS score from baseline

Table 5
Frequency of patients with ≥3 TEAEs in SAF

	All patients	Age group (years)		
	(N = 1219)	<65 (N = 559)	65-75 (N = 433)	≥75 (N = 227)
Subjects with TEAEs	83 (6.8)	49 (8.8)	20 (4.6)	14 (6.2)
Nervous system disorders				
Dizziness	22 (1.8)	19 (3.4)	2 (0.5)	5 (2.2)
Headache	3 (0.2)	15 (2.7)	2 (0.5)	5 (2.2)
Reproductive system and breast disorders				
Ejaculation disorder	3 (0.2)	3 (0.5)	0 (0.0)	0 (0.0)
Erectile dysfunction	3 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)
Vascular disorders				
Orthostatic hypotension	4 (0.3)	1 (0.2)	2 (0.5)	1 (0.4)
Skin and subcutaneous tissue disorders				
Pruritus	3 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)

SAF, safety population; TEAEs, treatment-emergent adverse events.
TEAEs are displayed as number of subjects (percentage of subjects).

for tamsulosin (dose range 0.2 mg to 0.8 mg) was 5.52 (95% CI: −8.85 to −2.19).[16] Although the patient characteristics are different from those in previous studies, the mean reduction in IPSS in FAS in our study was 5.0, a total IPSS reduction similar to that in a previous meta-analysis[16] and a well-designed RCT.[15] Our data confirmed that tamsulosin 0.4 mg as an initial treatment is also effective in Korean male patients with moderate to severe LUTS.

In our study, in the group with IPSS ≥ 20, the mean reduction in total IPSS was greater than that in the IPSS<20 group. A previous RCT using alfuzosin reported a greater reduction in the total IPSS score in patients with a higher IPSS at inclusion.[17] When 0.4 mg of tamsulosin was administered as an initial treatment in Korean patients with moderate to severe LUTS, it was confirmed that patients with more severe symptoms showed greater symptom reduction.

The mean reduction in total IPSS in the group with severe LUTS (IPSS ≥ 20) in our study was 9.4, which was similar to the reduction in a previous RCT using tamsulosin 0.4 mg as the initial dose in South Korea (−9.59).[13] A previous RCT also reported a high IPSS at baseline (total IPSS: 20), which indicated severe LUTS. An approximately 9-point reduction in total IPSS might be expected in Korean patients with severe LUTS after 6 months of treatment with tamsulosin 0.4 mg as an initial dose according to our results and a previous RCT.[13]

We found that the mean number of nocturia episodes decreased from 3.0 to 2.2 per night after 6 months of treatment with tamsulosin 0.4 m, corresponding to a reduction of 0.8 episodes. Our results are in accordance with those that treatment with 0.4 mg of tamsulosin in patients with nocturia not responding to 0.2 mg reduced nocturia from 2.71 to 1.98 per night.[10] It has been reported that alpha adrenergic blockers ameliorate the function of bladder storage by increasing bladder blood flow and/or inhibiting urethral afferent activity.[18,19] Therefore, it could be reasonably speculated that tamsulosin 0.4 mg increased nocturnal bladder capacity and sequentially reduced nocturia. We confirmed that 0.4 mg of tamsulosin as an initial treatment is effective in reducing nocturia in Korean patients with moderate to severe LUTS and nocturia ≥2 at baseline.

Scant data are available concerning the efficacy of alpha-adrenergic blockers, especially tamsulosin, in male LUTS patients aged ≥75 years. In a phase IV observational study with alfuzosin,[20] the quantitative reduction in total IPSS was similar for LUTS between the age group ≥75 and the age group <75. Another phase IV observational study with silodosin[21] also reported no significant difference in the percentage of responders (decrease ≥25% in the total IPSS) between the age group ≥75 and the age group <75. In our study, the mean reduction in IPSS was quantitatively equivalent in all age groups. We confirmed that tamsulosin 0.4 mg as the initial dose in Korean male LUTS patients is effective regardless of age.

A total of 6.8% of patients experienced TEAEs. The most common TEAE was dizziness (1.8%). In a previous RCT using tamsulosin 0.4 mg, dizziness was reported in 1.29%,[13] 3%,[22] and 5%[23] of patients. These results are similar to our findings. It has been reported that a higher incidence of dizziness is associated with doxazosin and terazosin than with tamsulosin,[24] and a previous RCT demonstrated that there were no significant differences in the incidence of dizziness between 0.2 and 0.4 mg of tamsulosin as the initial dose.[13] Nevertheless, care should be taken when tamsulosin 0.4 mg as the initial dose is prescribed in patients who are vulnerable to dizziness, considering that the most common TEAE was dizziness in our study.[25–27]

In this study, TEAEs were assessed by age group. There was a trend the incidence of TEAEs was higher in the age group of <65. However, the number of TEAEs concerning dizziness, headache, and sexual dysfunction was too small to compare the incidence of TEAEs between age groups.

The limitations of the study need to be mentioned. Our study is limited by the lack of a control group, lack of data on uroflowmetry, postvoid residual urine volume, prostate-specific antigen, prostate volume, and lack of data on sexual activity. In particular, the lack of data on sexual activity might hamper the exact investigation of ejaculatory dysfunction induced by tamsulosin 0.4 mg. Nevertheless, our study would be informative for both physicians and patients because the data are derived from a large multi-institutional phase IV clinical trial, which mimics real-world practice.

In conclusion, treatment of LUTS with tamsulosin 0.4 mg as the initial dose for 6 months in Korean men is effective and safe in a real-life setting.

Conflicts of interest

M.P. is an employee of Hanmi Pharmaceutical Co., Ltd. J.H.L., Y.W.P., and T.K.Y. have no conflicts of interest to declare.

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