Early Efficacy of Tamsulosin Versus Terazosin in the Treatment of Men With Benign Prostatic Hyperplasia: A Randomized, Open-Label Trial

Perinchery Narayan, MD[*]
Michael P. O'Leary, MD[†]
Giora Davidai, MD[‡]

[*]*North Florida Research Institute, Inc., North Florida Urology Associates, Gainesville, Florida*
[†]*Department of Surgery, Harvard Medical School, and Division of Urology, Brigham and Women's Hospital, Boston, Massachusetts*
[‡]*Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut*

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ABSTRACT

Background: We evaluated the efficacy and tolerability of tamsulosin versus terazosin in patients with signs and symptoms of benign prostatic hyperplasia (BPH).

Methods: Patients (N = 1,993) were randomized to tamsulosin (0.4 mg/day) or terazosin (5 mg/day, following titration). The primary efficacy endpoint was total American Urological Association Symptom Index (AUA-SI) score after 4 days of treatment. Secondary endpoints were score changes on measures of BPH symptoms and other clinical assessments made at 6 time points through study-end (Day 57).

Results: In the efficacy-evaluable tamsulosin population (n = 905), statistically and clinically significant improvement (25.3%) in mean total AUA-SI score after 4 days of treatment was shown; this was not seen in the terazosin population (n = 884; improvement: 18.1%). Adjusted mean change in total AUA-SI score after 4 days was –4.8 for tamsulosin and –3.4 for terazosin ($P < .001$). Twenty-three of the 42 secondary efficacy endpoint score comparisons also were statistically significant in favor of tamsulosin; the other 19 numerically favored tamsulosin. Dizziness and somnolence were reported significantly more often (each, $P \leq .001$) in the terazosin group (12.1% and 3.0%, respectively) than in the tamsulosin group (5.5% and 0.9%, respectively). Tamsulosin was associated with fewer discontinuations due to adverse events (4.3%, versus 6.6% for terazosin).

Conclusions: Reduction in BPH symptom severity was significantly greater after 4 days of treatment with tamsu-

losin than with terazosin, indicating a more rapid onset of clinical action. Tamsulosin was well tolerated, with fewer adverse events associated with reduced blood pressure (BP).

INTRODUCTION

The α_1-adrenoceptor antagonists are the first-line medical therapy for treating lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).[1] These agents inhibit prostatic smooth muscle contraction caused by sympathetic nervous system stimulation, which contributes to characteristic LUTS.

Doxazosin, terazosin, alfuzosin, and tamsulosin are 4 α_1-adrenoceptor antagonists approved in the United States for treatment of BPH. These agents differ in α_1-adrenoceptor subtype selectivity and, by extension, cardiovascular effects.[2,3] Doxazosin, terazosin, and alfuzosin are equally selective for α_{1A} and α_{1B}. Tamsulosin is selective for α_{1A} and α_{1D} and has low affinity for α_{1B}.[3] To avoid vascular-tissue–associated side effects, doxazosin and terazosin are initiated at a low dose, which may have the effect of delaying the onset of clinical efficacy.[4-7] Tamsulosin, however, needs no dose titration, achieving therapeutic effect rapidly.[2,3,6] Tamsulosin has been reported to significantly improve BPH symptom scores and quality-of-life measures after 1 week and peak urinary flow within 4 to 8 hours of administration.[8] Therefore, the aim of the present study, which compared the early onset of symptom relief and the tolerability of tamsulosin versus terazosin, was to document the speed of clinical symptom relief.

METHODS

This 11-week, randomized, open-label, multicenter, parallel-design study compared the early symptomatic improvement in patients with BPH and moderate-to-severe LUTS treated with tamsulosin hydrochloride capsules 0.4 mg/day or terazosin hydrochloride capsules 5 mg/day (after titration). The terazosin 5-mg dose is most commonly prescribed in clinical practice.[9] During a 3-week placebo lead-in period, nonmatching placebo capsules were administered in a manner similar to that used during the active treatment phase.

The trial was based on findings in men aged 45 years or older with a diagnosis of BPH and a total American Urological Association Symptom Index (AUA-SI) score of 13 or more at 3 initial visits.[10] All patients provided informed written consent. Exclusion criteria included allergy to any α_1- or nonspecific α- or β-adrenergic receptor blocking agents, first-dose hypotension with an α-adrenergic receptor blocker, other significant urologic disease, a prostate-specific (PSA) level greater than 4.0 mg/mL, or other significant laboratory abnormalities.

At each study site, patients were randomized in a 1 to 1 ratio, using a blinded randomization, to tamsulosin or terazosin. Terazosin dosing began at 1 mg from Day 1 to Day 8, increased to 2 mg at Day 8, and to 5 mg from Day 15 to Day 57. One capsule of study drug was taken orally half an hour after dinner (tamsulosin) or at bedtime (terazosin) starting the evening of Day 1. Compliance was assessed at each visit by capsule count. Evaluations preceded study drug administration.

The primary efficacy endpoint was the mean change in total AUA-SI score from baseline (Day 1) to Day 5 (after 4 days of dosing). Secondary endpoints—mean change in total AUA-SI score at Day 5, AUA Bother Score Index[11] and BPH Impact Index[11] from baseline, and Investigator's Global Assessment—were completed at Days 5, 8, 15, 19, 22, and 57. Tamsulosin-treated patients completed a patient assessment at their last visit.

A safety assessment was used to

evaluate adverse changes in physical examination (including digital rectal examination of the prostate) and electrocardiographic findings, sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings, heart rate, and clinical laboratory results (hematology, chemistry [including PSA], and urinalysis) from baseline (Day 1) to Day 57.

Changes in total AUA-SI score from baseline to Day 5 were analyzed using analysis of covariance (ANCOVA) with center, treatment, and center-by-treatment interaction as terms of the model and baseline total AUA-SI score as the covariant. The mean change in total AUA-SI score from baseline to each postbaseline assessment was analyzed using analysis of variance (ANOVA), with baseline AUA severity, center, treatment, and interaction of treatment and baseline AUA severity as terms of the model.

AUA symptom subscores, total AUA Bother Score Index, and total BPH Impact Index score were analyzed using ANCOVA, with center, treatment, and baseline score as covariants. Additional ANOVA models for the analyses of total AUA Bother Score Index and total BPH Impact Index score included adjustment for baseline severity and interaction of treatment and baseline AUA severity.

Treatment-related differences in safety results and comparisons of baseline demographic and clinical data were analyzed using the Fisher's Exact Test, Cochran-Mantel-Haenszel test, or ANOVA. Statistical significance was established at $P \leq .05$.

The intent-to-treat (ITT) population consisted of patients who took at least 1 dose of a study drug and for whom at least 1 on-treatment efficacy assessment was recorded. In the efficacy-evaluable (EFF) population, a total AUA-SI score was obtained on Day 5 and participants took at least 1 dose of an active treatment drug. The EFF population was used for the primary efficacy analysis. All other efficacy analyses were performed in the ITT population.

Patients missing data for the total AUA-SI score at Day 5 were excluded from the primary efficacy analysis. A last-observation-carried-forward technique was used to estimate missing data for the secondary efficacy parameters.

RESULTS

Of 1,993 patients enrolled at 79 sites, 1,983 received study medication. No significant between-group differences existed at baseline (Table 1).

In the ITT population (n = 1,975), 1,789 patients constituted the EFF population. Ninety percent of treated patients (1,784 of 1,983) completed the study. The most common reason for discontinuation was adverse events (5.6%; n = 111).

Total AUA Symptom Index Score

After 4 days of treatment, the tamsulosin group demonstrated a clinically and statistically significant difference in total AUA-SI score in favor of tamsulosin. The tamsulosin group had a mean change in total AUA-SI score of –4.8, compared with –3.4 for the terazosin group, after 4 days of dosing ($P < .001$); this represents a 41.2% improvement in tamsulosin over terazosin. In the tamsulosin group, the mean change represented a clinically significant 25.3% decrease in BPH symptoms.[12] The 18.1% decrease in BPH symptoms in the terazosin group did not reach clinical significance.

After 4 days of treatment, tamsulosin demonstrated a significant advantage over terazosin in terms of total AUA-SI score in the ITT population; adjusted mean changes were –5.1 and –3.8 ($P < .001$) for tamsulosin- and terazosin-treated patients, respectively. This

Table 1. Demographic and Clinical Characteristics of the Safety-evaluable Patients

Parameter	Treatment Group: Tamsulosin n (%)*		Treatment Group: Terazosin n (%)		*P* Value†
Total patients	1,002		981		
Age (yr)					
Mean	61.7		61.7		0.947
SE	0.27		0.30		
Age distribution					
<45 yr	5	(0.5)	6	(0.6)	0.679
45-54 yr	239	(23.9)	245	(25.0)	
55-64 yr	362	(36.1)	345	(35.2)	
65-74 yr	317	(31.6)	293	(29.9)	
>74 yr	79	(7.9)	92	(9.4)	
Race					
White	937	(93.5)	914	(93.2)	0.582
Black	54	(5.4)	59	(6.0)	
Asian	11	(1.1)	8	(0.8)	
Weight (lb)‡					
Mean	195.2		194.0		0.442
SE	1.11		1.13		
Hypertensive status					
Hypertensives	311	(23.7)	292	(22.9)	0.784
Uncontrolled	90	(6.9)	81	(6.4)	
Controlled	221	(16.8)	211	(16.6)	
Normotensives	691	(52.6)	689	(54.1)	
Severity of disease					
AUA symptom score distribution					
Mild (0-7)	1	(0.1)	0		0.244
Moderate (8-19)	605	(60.4)	621	(63.3)	
Severe (20-35)	396	(39.5)	360	(36.7)	
Total AUA symptom score					
Mean	19.0		18.9		0.645
SE	0.16		0.16		
Total AUA bother score					
Mean	13.6		13.8		0.608
SE	0.18		0.19		
Total BPH Impact Index					
Mean	5.1		5.2		0.381
SE	0.09		0.09		

SE indicates standard error; AUA, American Urological Association; and BPH, benign prostatic hyperplasia.
*All percentages are based on the total number of patients in the safety population within each treatment group.
†From analysis of variance with center and treatment in the model for noncategorical parameters age, weight, total AUA symptom score, total AUA bother score, and total BPH Impact Index. For categorical parameters (race, hypertensive status, severity of disease, and age category), the Cochran-Mantel-Haenszel test stratified by center was performed.
‡Weight obtained for 1001 tamsulosin-treated patients and 979 terazosin-treated patients.

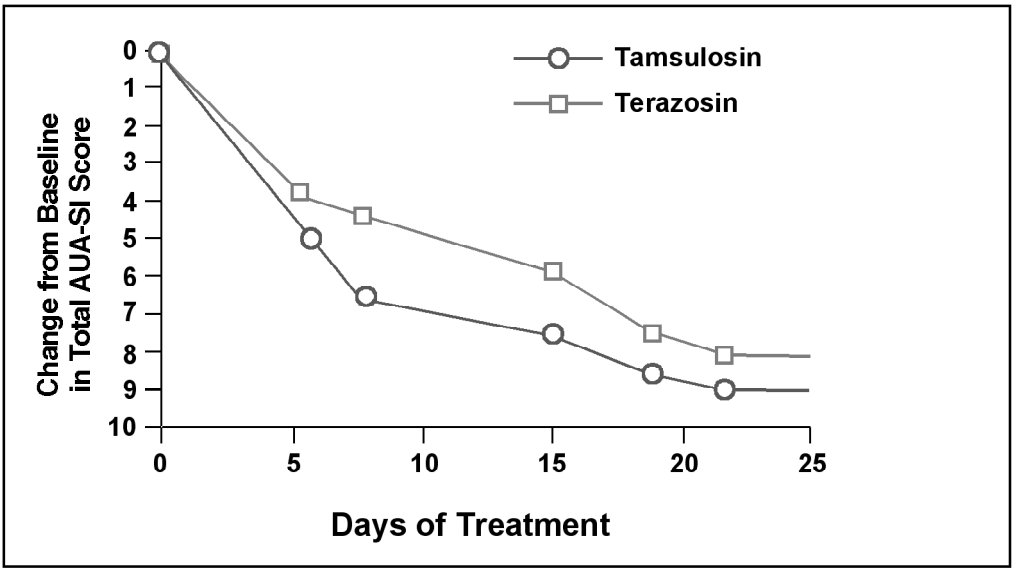

Figure 1. Early treatment effect. American Urological Association Symptom Index scores decreased over 25 days of treatment with tamsulosin or terazosin in the intent-to-treat population from baseline values of 19.0 for tamsulosin and 18.9 for terazosin. The differences between treatment groups were significant through Day 22 ($P < .001$ through Day 15; $P < .010$, Days 19 and 22). AUA-SI = American Urological Association Symptom Index.

difference remained significant to Days 8 through 22 ($P < .010$) (Figure 1).

Tamsulosin was significantly more effective than terazosin through Day 15 in patients with moderate BPH symptoms. The adjusted mean change in total AUA-SI score after 4 days of treatment was –3.5 for tamsulosin-treated versus –2.9 for terazosin-treated patients ($P = .026$); at Day 8, it was –4.8 and –3.7, respectively ($P = .001$); and at Day 15, –5.4 and –4.6, respectively ($P = .014$).

Tamsulosin was significantly more effective than terazosin in patients with severe BPH symptoms (defined as total AUA-SI score 20-35). The adjusted mean change in total AUA-SI score after 4 days of treatment was –6.6 for tamsulosin-treated patients versus –4.8 for terazosin-treated patients ($P < .001$). This significant difference between treatment groups was apparent at Days 5 through 22.

Other Efficacy Assessments

AUA Symptom Index subscales (Table 2) showed significant differences between groups in AUA obstructive symptom score at Days 8 and 15 and in AUA irritative symptom score at Days 15 and 19. Thereafter, the between-group differences favored tamsulosin but were not statistically significant.

Changes from baseline in total AUA Bother Score Index showed statistically significant improvement favoring tamsulosin through Day 22 and tended to favor tamsulosin thereafter. Changes from baseline in total BPH Impact Index showed statistically significant improvement favoring tamsulosin through Day 15 and at Day 22 and tended to favor tamsulosin thereafter. A higher proportion of patients treated with tamsulosin versus terazosin reported that their symptoms "markedly improved," "improved," or "slightly improved" throughout the trial, according to the Investigator's Global Assessment.

At the final visit, 76.9% (n = 767) of tamsulosin-treated patients rated their active treatment as "highly favorable" or "favorable". Those who had taken tera-

Table 2. Changes from Baseline in Selected AUA Symptom Index Subscales (ITT population)*

	Day						
	1 Baseline	5	8	15	19	22	57
AUA Obstructive Score							
Tamsulosin	10.6 (0.13)† [997]§	-3.1 (0.11) [991]	-3.9 (0.12)‡ [997]	-4.3 (0.12)‡ [997]	-4.9 (0.12) [997]	-5.3 (0.13) [997]	-5.1 (0.13) [997]
Terazosin	10.5 (0.13) [978]	-2.2 (0.11) [973]	-2.7 (0.12) [978]	-3.5 (0.12) [978]	-4.4 (0.12) [978]	-4.8 (0.13) [978]	-5.0 (0.13) [978]
AUA Irritative Symptom Score							
Tamsulosin	8.3 (0.08) [997]	-1.7 (0.08) [986]	-2.2 (0.08) [996]	-2.6 (0.08)‡ [997]	-3.0 (0.08)‡ [997]	-3.2 (0.09) [997]	-3.3 (0.09) [997]
Terazosin	8.4 (0.08) [978]	-1.4 (0.08) [974]	-1.7 (0.08) [978]	-2.1 (0.08) [978]	-2.7 (0.09) [978]	-2.9 (0.09) [978]	-3.2 (0.09) [978]
Total AUA Bother Score							
Tamsulosin	13.6 (0.18) [997]	-3.0 (0.14)‡ [991]	-4.1 (0.15)‡ [997]	-4.9 (0.15)‡ [997]	-5.6 (0.16)‡ [997]	-6.1 (0.16)‡ [997]	-6.2 (0.17) [997]
Terazosin	13.8 (0.19) [978]	-2.1 (0.14) [971]	-2.9 (0.15) [978]	-3.6 (0.15) [978]	-4.8 (0.16) [978]	-5.4 (0.16) [978]	-5.9 (0.17) [978]
BPH Impact Index							
Tamsulosin	5.1 (0.09) [997]	-1.1 (0.07)‡ [994]	-1.4 (0.07)‡ [997]	-1.6 (0.07)‡ [997]	-1.8 (0.07) [997]	-2.0 (0.07)‡ [997]	-2.1 (0.08) [997]
Terazosin	5.2 (0.09) [978]	-0.7 (0.07) [976]	-1.0 (0.07) [978]	-1.2 (0.07) [978]	-1.6 (0.07) [978]	-1.7 (0.07) [978]	-1.9 (0.08) [978]
Investigators Global Assessment							
Tamsulosin		71.2‖ [978]	79.1 [974]	83.6 [958]	84.9 [947]	86.8 [935]	86.2 [989]
Terazosin		60.4 [963]	66.7 [953]	77.7 [941]	84.8 [921]	86.8 [904]	88.0 [961]

AUA indicates American Urological Association; ITT, intent-to-treat; and BPH, benign prostatic hyperplasia.

*A negative value represents improvement in symptoms (eg, AUA obstructive symptom score) or in patients' perception of the effect of urinary symptoms on quality of life (eg, BPH Impact Index).

†Mean (standard error of the mean).

‡ Statistically significant difference between treatment groups ($P \leq .05$).

§ Brackets indicate number of patients.

‖Percentage of patients markedly improved, improved, and slightly improved from baseline.

zosin or doxazosin for BPH prior to study entry (78 of 162, 48.1%) reported a "shorter" or "much shorter" time to onset of symptom relief with tamsulosin.

Safety Evaluations

Treatment-Emergent Adverse Events (TEAEs). Table 3 summarizes TEAEs reported by 5% or more of patients. The percentage of patients with TEAEs did not differ between the 2 treatment groups. Most TEAEs were mild to moderate.

TEAEs of special interest due to their association with α-adrenoceptor antagonists, such as dizziness and somnolence, were reported significantly more often (each, $P \leq .001$) with terazosin (12.1% and 3.0%, respectively) than with tamsulosin (5.5% and 0.9%, respectively). Rates of ejaculation failure and ejaculation disorder were low, but significantly greater (each, $P < .001$) for tamsulosin than for terazosin, 2.1% and 3.7% versus 0% and 0.3%, respectively.

TEAEs led to a discontinuation rate of 5.4% (108 of 1,983) of all patients, and the rate was lower with tamsulosin (4.3%; 43 of 1002) than with terazosin (6.6%; 65 of 981). Dizziness was reported as the reason for discontinuation of

Table 3. Treatment-emergent Adverse Events (TEAEs)*

Parameter	Treatment Group† Tamsulosin n (%)		Terazosin n (%)		*P* Value‡
Total patients	1,002		981		
Patients with any TEAE	541	(54.0)	545	(55.6)	0.474
Headache	67	(6.7)	84	(8.6)	0.127
Fatigue	25	(2.5)	53	(5.4)	0.001
Dizziness	55	(5.5)	119	(12.1)	< 0.001
Rhinitis	55	(5.5)	61	(6.2)	0.504
Upper respiratory tract infection	59	(5.9)	57	(5.8)	1.000

*Reported by ≥ 5% of patients evaluable for safety in either treatment group.
†Percentages are based on the total number of patients in the safety population within each treatment group.
‡The overall incidence of adverse events was compared using the Cochran-Mantel-Haenszel test stratified by center. The incidence of adverse events that occurred in at least 5% of patients in either treatment group was compared using the Fisher's Exact Test (two-tailed).

therapy by most patients (1.3%; n = 26), including patients taking tamsulosin (0.6%; n = 6) and terazosin (2.0%; n = 20). Small percentages of patients discontinued treatment because of ejaculation disorder (tamsulosin, 0.5%, n = 5; terazosin, 0%), ejaculation failure (tamsulosin, 0.1%, n = 1; terazosin, 0%), and impotence (tamsulosin, 0.2% [n = 2]; terazosin, 0.3% [n = 3]).

Serious Adverse Events (SAEs). Thirty-four SAEs were reported by 28 patients, including 13 taking tamsulosin (1.3%) and 15 taking terazosin (1.5%). Investigators judged the SAEs in the tamsulosin group to be unrelated to study medication, whereas 3 SAEs in patients receiving terazosin (cerebrovascular disorder, supraventricular tachycardia, and syncope) were judged as treatment related. Five patients taking tamsulosin and 6 taking terazosin discontinued treatment because of SAEs.

Vital Signs. Terazosin reduced SBP, DBP, and heart rate more than tamsulosin, most obviously by Day 19, by which time terazosin was fully titrated to 5 mg. The greater decrease in BP in terazosin-treated patients compared with tamsulosin-treated patients was consistent irrespective of patients' baseline hypertension status. Between-group differences in heart rate were not clinically or statistically significant.

The 3 deaths in this study (tamsulosin, 2 patients; terazosin, 1 patient) were not considered related to study medication. There were no other clinically significant changes in physical examination findings or laboratory values.

DISCUSSION

Earlier BPH symptom relief with tamsulosin, as indicated by total AUA-SI score, was demonstrated in this study of the α_1-adrenoceptor antagonists tamsulosin and terazosin in the treatment of LUTS due to BPH. Clinically and statistically significant improvement in total AUA-SI score followed 4 days of tamsulosin treatment. The rapid reduction in symptom severity with tamsulosin may increase compliance in clinical practice.

Although terazosin may be titrated to 10 mg/day, the 5-mg dose represents as many as half of all prescriptions.[9] This may reflect physician reluctance to pre-

scribe the 10-mg dose owing to concern about an increased incidence of adverse events at that dose.

The change from baseline (Visit 3) to Visit 4 (Day 5) in the total AUA-SI score demonstrated by the tamsulosin group establishes clinically meaningful, early reduction in symptom relief following 4 days of dosing. Additionally, analyses of secondary efficacy assessments demonstrated consistently that the tamsulosin group, particularly for those patients with severe BPH at baseline, showed early relief and improvement in the symptoms of BPH relative to the terazosin group.

The TEAEs associated with terazosin were probably perceived as more annoying to the patients who received it, as evidenced by the higher discontinuation rate in this group. The strong patient satisfaction with tamsulosin reported in the previous studies[12,13] is echoed in the current study, in which about 80% of tamsulosin-treated patients rated their overall experience with the agent as highly favorable or favorable.

Research into tamsulosin's mechanism of action has demonstrated antagonism at both α_{1A}- and α_{1D}-receptor subtypes. Terazosin is a non–subtype-selective α_1-antagonist.[3] The α_{1A}-adrenoceptor subtype mediates smooth muscle contraction of the prostate and bladder neck; α_{1B}, vascular smooth muscle contraction; and α_{1D}, detrusor muscle contraction and sacral spinal cord innervation.[14-16] The low incidence of dizziness and hypotension with tamsulosin may be attributable to the relative lack of α_{1B}-receptor antagonism. Additionally, the α_{1D}-receptor may affect a bladder-related filling component of LUTS, whereas α_{1A} addresses voiding symptoms.[15] Further studies will be necessary to determine the clinical significance of receptor subtype selectivity.

CONCLUSION

After only 4 days of dosing, significantly greater relief of signs and symptoms of BPH occurred with tamsulosin than with terazosin. Tamsulosin affected SBP and DBP less than terazosin throughout the period of study and irrespective of BP status at baseline. Tamsulosin was well tolerated, effective, and appeared to be better tolerated than terazosin, with fewer cardiovascular adverse events likely to be associated with reduced BP. Fewer tamsulosin patients than terazosin patients discontinued treatment because of TEAEs.

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