Long-Term Efficacy and Safety of Tamsulosin for Benign Prostatic Hyperplasia

Perinchery Narayan, MD, FACS,* Hari Siva Gurunadha Rao Tunuguntla, MD, MS, MCh†

*North Florida Research Institute, Gainesville, FL, †Department of Urology, University of California, Davis School of Medicine, Sacramento, CA

The treatment approach for recent benign prostatic hyperplasia has changed since the recent introduction of medical therapies with evidence-based efficacy. The choice of treatment to achieve symptom relief must take into account factors such as clinical benefits, potential for morbidity, probable long-term efficacy, and costs. α_1-Adrenergic receptor antagonists are the primary therapy for patients with benign prostatic hyperplasia presenting with lower urinary tract symptoms and are used by 80% of physicians as the first-line agent to treat this common condition in the aging male. Tamsulosin has been available in the United States since 1997 and has demonstrated its efficacy. Of patients completing 6 years of treatment, 80.7% demonstrated consistent positive response with extremely low incidence of orthostasis, the response being greatest during the first year and largely maintained over the following 5 years.
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Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) are common among older men, with approximately 25% of men over 40 suffering from LUTS. The prevalence of this condition rises with age.[1] Histologic evidence of the disease is noted in 8% of men in their 30s, the prevalence of which rapidly increases to over 70% after age 60.[2] With an aging of the US population, the number of men with BPH is likely to increase, creating a

greater demand for effective and enduring treatments. Besides watchful waiting and surgery, current medical therapies to treat LUTS/BPH include α_1-adrenergic receptor antagonists (terazosin, doxazosin, tamsulosin, and alfuzosin), 5α-reductase inhibitors such as finasteride and dutasteride, and phytotherapy. The treatment approach for BPH has changed since the recent introduction of medical therapies with evidence-based efficacy. Physicians choosing treatment to achieve symptom relief must take into account factors such as the clinical benefits, potential for morbidity, probable long-term efficacy, and costs.

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Most of the information on the efficacy (symptom relief and increase in urine flow) and side effects of medical therapy comes from clinical trials performed in urological practice, which are crucial in obtaining data regarding the efficacy and safety of medication. In addition, information on the long-term efficacy of treatment, such as reduction of complications related to BPH (eg, acute urinary retention), safety, and tolerability, is important, and this information will be all the more significant in the future because of the aging of American men. The number of men demanding treatment for LUTS will increase, while healthcare budgets will most likely remain relatively restricted.

α_1-Adrenergic receptor antagonists are the main treatment for patients with BPH presenting with LUTS and are used by 80% of physicians as the first agent to treat this common condition in the aging male.[3] Use of α-blockers in BPH is based on research showing that prostate smooth muscle mediates bladder outlet obstruction via the α-adrenergic receptor–mediated mechanism. α-Blockers relax prostatic smooth muscle, thereby improving BPH-related symptoms. Three subtypes of α receptors exist: α_{1A}, α_{1B}, and α_{1D}. α_{1A} Composes 70% of the human prostatic receptors, but this percentage may actually increase to 80% in patients with BPH. Twenty-seven of 30 clinical trials have confirmed Caine's observation that α-blockers are effective for BPH treatment.[4]

Tamsulosin has been available in the United States since 1997 and has demonstrated its efficacy in the treatment of BPH.[5–7] It has a 20- to 38-fold greater affinity for α_{1A}-adrenergic receptors than for α_{1B} receptors. This α_{1A} subtype adrenergic receptor selectivity is considered to be responsible for tamsulosin's low cardiovascular side effects and lack of interaction with antihypertensives.[8,9] It was the first drug developed specifically to treat only LUTS due to BPH.

Other articles in this supplement have dealt with the short-term efficacy of tamsulosin; in this article, the long-term (up to 6 years) efficacy, safety, and tolerability of the agent will be our focus.

Historical Background

In 1995, Lepor reported on the results of two placebo-controlled, randomized U.S. trials of 0.4 mg and 0.8 mg of tamsulosin daily for symptomatic BPH in 1488 patients for 13 weeks and noted significant improvement in symptoms with the 0.4 mg dose over placebo. There was no increase in adverse cardiovascular events, including episodes of orthostatic hypotension, in the treatment arm when compared to controls.[10] The subsequent pivotal double-blind tamsulosin studies have shown the efficacy and safety of 0.4 mg tamsulosin once daily for up to 1 year,[5–7] and a recently published extension study by Narayan and Lepor demonstrated similar results for up to 2 years.[10]

In 1996, Chapple and associates reported on the meta-analysis of two different double blind, randomized, controlled, 12-week European trials of tamsulosin administered once daily at a dose of 0.4 mg.[8] Patients were defined as responders or nonresponders based on an improvement in overall Boyarsky symptom score of 25%, or a 30% improvement in the maximum flow rate, or an improvement above 3 mL/sec in flow rate. A group of 382 treated patients were matched with a control group of 193 patients; the overall response rate using these criteria was 32% for treated patients versus 20% for controls. Boyarsky symptom scores were reduced by an average of 3.3 points in the tamsulosin arm versus 2.4 points in the control arm. There were no significant changes in heart rate or blood pressure in the treatment arm versus control.[8] An open-label extension of this trial by Schulman and associates[11] confirmed sustained efficacy at 60 weeks of treatment and revealed that 21% of treated

There was no increase in adverse cardiovascular events including episodes of orthostatic hypotension in the treatment arm.

Table 1
Baseline Characteristics of Patients in the European Long-Term Study

No. pts	516
Mean age (range): No. white (%) No. other (%)	63.5 ± 8.1 (42–83) 509 (99) 7 (1)
Mean kg wt ± SD (No. pts)	77.6 ± 10.3 (514)
Mean cm ht ± SD (No. pts)	174.6 ± 6.5 (513)
Mean digital rectal examination g prostate size ± SD (No. pts)	33.1 ± 19.8 (328)
Mean ultrasound mL prostate vol ± SD (No. pts)	36.6 ± 19.8 (328)
Mean ng/mL PSA ± SD (No. pts)	3.8 ± 4.2 (457)
Mean Boyarsky symptom score ± SD (No. pts)	9.6 ± 3.0 (511)
Mean mL/sec max urinary flow ± SD (No. pts)	10.1 ± 3.2 (491)

Adapted with permission from Schulman et al.[13]
PSA, prostate-specific antigen.

patients reported adverse events related to the medication. The most common side effect was dizziness (5.3%), followed by retrograde ejaculation (4.5%). Side effects frequently associated with nonspecific α_1-blockers, such as rhinitis, asthenia, and postural hypotension, occurred in fewer than 2% of treated patients.[11]

Subsequently, Schulman and the European Tamsulosin Study Group presented an update on 516 patients treated with tamsulosin 0.4 mg for an average of 2 years.[12,13] A decrease in Boyarsky symptom scores was reported in 75% of treated patients, and an increase in maximum flow rate of over 30% was demonstrated in up to 30% of patients. No dose titration schedule was necessary, and at 2-year follow-up the most common side effects remained dizziness and abnormal ejaculation, with dizziness occurring at the same rate in the placebo-treated patients. There were no clinically significant changes in systolic or diastolic blood pressure in the supine or standing position in the tamsulosin-treated patients.

Long-Term Efficacy Data of Tamsulosin in BPH

Long-term data on the maintenance of efficacy and safety of these agents are limited.[14,15] The reported long-term efficacy and safety of other α_1-adrenergic receptor blockers such as doxazosin and terazosin are based on an interim analysis of a small number of patients treated for 3–4 years.

European Multicenter Trials

Schulman and associates recently reported on the sustained efficacy of tamsulosin in 516 patients (from two European open-label studies that were extensions of three double-blind controlled studies) over 4 years and noted improvements in symptom scores and urine flow rates.[13] Table 1 shows the baseline characteristics of the study population. Twenty-six percent of patients had side effects considered possibly or probably drug-related, and 5% of patients discontinued treatment because of drug-related side effects (Table 2). None of the patients had significant changes in blood pressure or pulse rate.

The US Long-Term Experience

Narayan and associates recently presented the results of a 4-year extension, multicenter, open-label, phase IIIB clinical study (US527.2) to evaluate long-term efficacy, safety, and tolerability of tamsulosin for up to 6 years, the longest reported to date.[16]

Enrollees included those who had completed a previous 1-year, open-label, extension trial of tamsulosin (US93-04)10, which recruited patients from three shorter, double blind studies—US92-03A (17 weeks),[6] US92-03B (40 weeks),[7] and US93-01 (17 weeks).[5] Patients from these studies agreed to continue treatment with tamsulosin.

The primary efficacy evaluations included the change from baseline in total American Urological Association (AUA) symptom score and change in peak urine flow rate (Q_{max}), whereas the secondary efficacy evaluations included changes from baseline in AUA subset scores, Boyarsky symptom scores, the actual values and change from baseline values for average urine flow rate (a positive change measured by a uroflowmetry test reflected improvement), and an investigator's global assessment. The evaluation also included quality-of-life (QOL) index, uroflowmetry, and postvoid residual urine volumes.

The safety assessments included changes in treatment-emergent adverse events (TEAEs), digital rectal examination (DRE), physical examination, body weight, chest x-ray, vital signs, orthostatic signs, 12-lead ECG, and clinical laboratory tests (blood chemistry, prostate-specific antigen [PSA], hematology, urinalysis). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) while supine and standing were used to determine orthostatic hypotensive responses.

Of a total of 609 patients (aged 45–75 years) entering this 4-year

Table 2
Cumulative Incidence of All Reported and Drug-Related Side Effects in 516 Patients Treated With Tamsulosin for Up to 4 Years

	No. Side Effects (%)	
	All	Drug-Related
Any	390 (76)	132 (26)
α_1-adrenoceptor antagonist-associated		
Dizziness	44 (8.5)	30 (5.8)
Abnormal ejaculation	25 (4.9)	22 (4.3)
Headache	24 (4.7)	7 (1.4)
Asthenia	20 (3.9)	10 (1.9)
Rhinitis	18 (3.5)	3 (0.6)
Postural hypotension	15 (2.9)	14 (2.7)
Palpitation	14 (2.7)	7 (1.4)
Dry mouth	8 (1.6)	6 (1.2)
Syncope	5 (1.0)	0
Somnolence	4 (0.8)	2 (0.4)
Other		
Impotence	28 (5.4	15 (2.9)
Decreased libido	6 (1.2)	4 (0.8)
Urinary retention	23 (4.5)	1 (0.2)
Discontinued treatment	86 (217)	26 (5)

Adapted with permission from Schulman et al.[13]

extension trial, 159 had at least 2 years' prior exposure to tamsulosin with potential for up to 6 years of treatment; 109 patients completed all 6 years and 419 of 609 patients completed 5 years.

There was a consistent improvement in AUA symptom scores over 6 years, the mean improvement from baseline (17.4) being −8.1 to −10.9. The improvement was statistically significant each year. Improvement in symptom scores was demonstrated in 71.6%–80.7%. The mean significant ($P < .05$) improvement in Q_{max} from baseline (10.1 mL/sec) ranged from ×1.01 mL/sec to ×2.29 mL/sec. Most patients showed improvement during the first year that was sustained over 6 years.

Acute Urinary Retention

BPH is a progressive disease, and acute urinary retention (AUR) and prostate carcinoma are frequent comorbidities in the aging population with BPH. More than 1 in 10 men in their 70s will experience AUR within a 5-year period of follow-up,[17] and the risk for men in their 80s rises to nearly 1 in 3. AUR is a common indication for prostatectomy, being the presenting feature in 23%–27% of men requiring TURP. α-Blockers reduce bladder outlet resistance in BPH, which plays an important part in AUR in these men. These agents may, therefore, improve the incidence of AUR in treated patients.

AUR has been reported to occur in up to 3% of patients treated with finasteride and, as mentioned above, in up to 7% of the untreated BPH population.[18,19] It is generally considered that patients with symptomatic BPH who are on medical therapy eventually develop AUR necessitating surgery, and long-term medical therapy puts the clock back by only a few years at most. Although patients with a history of AUR were excluded from the study by Narayan and associates, all patients were at risk of developing AUR. During the entire 6-year period, AUR occurred in 11 patients (1.8%). No patient reported AUR as an adverse event during the fifth or sixth year of treatment. Only 1 patient withdrew from the study because of AUR. The low incidence of AUR in patients treated with tamsulosin for up to 6 years suggests that tamsulosin may reduce the risk of AUR in patients with BPH.

Treatment-Emergent Adverse Events With Tamsulosin

The most commonly encountered Treatment-Emergent Adverse Events (TEAEs) were infection, accidental injury, rhinitis, pain, and pharyngitis. Other adverse effects included abnormal ejaculation (8.3%), syncope (1.7%), and postural hypotension (1.3%). Compared to the short-term and 1-year extension study, the incidence of adverse events was not increased (except for accidental injury). The incidence of drug-related TEAEs declined throughout the 6-year period, and after the first 2 years of treatment, the incidence was below 5%.

There was a consistent improvement in AUA symptom scores over 6 years.

Discussion

The long-term efficacy of medical therapy in BPH is measured by the

durability of clinical response, patient satisfaction over several years, and the rate of secondary intervention (eg, surgery) for acute urinary retention. Four long-term trials of pharmacologic treatment of BPH have been published to date. Of α-blockers marketed in the United States for treating BPH for extended periods, doxazosin,[19] terazosin,[20] and tamsulosin[10] have all been demonstrated to be effective. The study by Narayan and colleagues is the longest to date, with up to 6 years' treatment of patients with tamsulosin.

The results of the long-term study by Narayan and associates demonstrate that patients with LUTS due to BPH who are treated with tamsulosin continue to have sustained relief of symptoms for up to 6 years, with excellent safety and tolerability profiles and without development of tolerance. The study confirmed the outcomes found in previous short-term clinical trials.[5–7] Adverse events (whether or not related to treatment) occurred more frequently during the first 2 years of treatment and diminished with continuation of therapy.

Patients with LUTS due to BPH who are treated with tamsulosin continue to have sustained relief of symptoms for up to 6 years, with high levels of safety and tolerability and without development of tolerance.

In addition, the rates of discontinuation due to adverse events in the study were low over the course of 4–6 years and consistent with previous experience with tamsulosin.[5-7] The overall incidence of new TEAEs has shown progressive decline over 6 years.

Tamsulosin demonstrated high tolerability and enduring safety throughout the study without development of tolerance.

In a study of comparable duration with a similar BPH population comparing finasteride with placebo,[18] the TEAE-related discontinuation rates in both arms were high (finasteride 34%; placebo 42%), suggesting a considerable impact of TEAEs.[5-7]

Summary and Conclusions

The efficacy of 0.4 mg daily of tamsulosin in patients with LUTS due to BPH is sustained for up to 6 years. Tamsulosin demonstrated high tolerability and enduring safety throughout the study without development of tolerance. Improvements in symptoms and urine flow are comparable to those in previous short-term, placebo-controlled trials and the European, 4-year, long-term, open-label extension study. New adverse events (either treatment-related or not) occurred more frequently in the first 2 years of the 6-year study and diminished as treatment continued. Treatment discontinuation due to adverse events was extremely low (15.7%, 18.7% of which was for non–drug-related factors).

Tamsulosin results in long-term improvement in patients with or without hypertension, who also have

Main Points

- α_1-Adrenergic receptor antagonists are used by 80% of physicians as the first agent to treat patients with benign prostatic hyperplasia (BPH) presenting with lower urinary tract symptoms (LUTS); 27 of 30 clinical trials have confirmed that α-blockers are effective for BPH treatment.
- Tamsulosin's α_{1A} subtype adrenergic receptor selectivity is considered to be responsible for its low cardiovascular side effects and lack of interaction with antihypertensives.
- A 4-year extension, multicenter, open-label, phase IIIB clinical study evaluated long-term efficacy, safety, and tolerability of tamsulosin for up to 6 years; the study found a consistent statistically significant improvement in AUA symptom scores over 6 years, and most patients showed improvement during the first year that was sustained over 6 years.
- The low incidence of acute urinary retention in patients treated with tamsulosin for up to 6 years suggests that tamsulosin may reduce the risk of AUR in patients with BPH.
- Response to treatment and incidence of adverse events (eg, rhinitis and abnormal ejaculation) in patients with hypertension, diabetes, or nonhypertensive cardiovascular disease did not differ significantly from that in those without.
- Abnormal ejaculation is an important side effect of tamsulosin, but it resulted in few discontinuations during treatment. It may not always be deemed important by patients, and was not linked to complaints of decreased libido, impotence, or other changes in sexual function.

similar safety profiles. Postural hypotension is extremely uncommon, as are such serious adverse events as myocardial infarction, syncope, chest pain, and prostate cancer. Long-term alterations in PSA levels are also uncommon.

The long-term efficacy and safety of tamsulosin in BPH, evident from previous shorter-term and 4-year long-term clinical trials, are proven, and this α_{1A} subtype selective adrenergic receptor blocker may be a viable long-term alternative to surgery. ■

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Editor's Summary of Meeting Presentation

Dr. Roehrborn observed that these data represent the best information regarding the long-term efficacy and safety of any of the available α-blocking agents. For both terazosin and doxazosin, limited data on no more than 100 patients are available from open-label extension trials of up to 4 years. In any open-label extension trial, particularly when patients are drawn from different prior randomized studies, there are several caveats regarding the strength of the evidence. In general, such studies suffer from a responder bias, by which only satisfied patients elect to continue, thus improving the average response of the entire cohort. This is particularly true when fewer and fewer patients are available for follow-up. The results presented are based on over 400 patients available for follow-up at 5 years out of an original cohort of 600, which is a remarkable achievement regarding compliance and retention, making this dataset the most valid information regarding the long-term efficacy and safety of α-blocking agents.

The issue of reporting of adverse events (AE) was discussed by Dr. Lepor. Often patients suffering from a given AE in the first year of the trial continue nonetheless and are counted again in subsequent years, leading to an inflation of the overall number of patients with AEs. Dr. Roehrborn noted that general policy regarding the reporting of AEs is relatively poor. He suggests reporting incidence density of AEs for predefined time periods, eg, months 1–3, 4–6, 7–12, and 12–24, which would relate the number of patients with a certain AE to the total number of patients under observation during that time period, by calculating the number of patient months of exposure. Logistically, to be able to capture AEs properly, both the onset and the resolution would have to be noted in the CRFs, such that only new-onset AEs would be reported for each time period. In addition, other factors influence AEs statistics, such as the intensity with which they are elicited by the coordinators and nurses, whether patients are asked globally

about AEs versus being given a laundry list, and the intensity of the follow-up visits. When comparing and meta-analyzing different studies, one could therefore argue that comparisons of standardized outcomes, such as symptom scores and flow rates, are more reliable than comparisons of AEs.

Lastly, the issue of dosage was brought up by Dr. Roehrborn, who mentioned that there really had never been a titration-to-response trial done with tamsulosin. According to Dr. Narayan, only 18% of patients opted to increase the dosage from 0.4 to 0.8 mg/d when given the choice in the open-label extension trial. It is clear from all randomized studies that there is a distinct increase in efficacy seen with the 0.8 mg dosage compared to the 0.4 mg dosage. However, there is also an increase in the incidence of AEs, most notably ejaculatory disturbances, which may lead to unfavorable risks versus benefit ratio as stated by Dr. Lepor. To accurately capture the incremental benefits and risks, however, a forced titration in all patients, based on the failure to achieve a predefined threshold of improvement, would be needed, as opposed to a design where the up-titration is left to the patients' discretion.