Drug Trial Report

Tamsulosin : Auroselective Alpha Receptor Blocker for treatment of Benign Prostatic Hyperplasia

Apul Goel[1]

Tamsulosin clearly offers advantages over other a1-adrenoceptor antagonists in terms of the need for a single daily dose only, and its low potential for hypotensive effects or interference with concomitant antihypertensive therapy. Dosage titration at the start of treatment is not necessary for the tamsulosin. Tamsulosin has a rapid onset of action and is effective in patients with moderate as well as severe symptoms. In combination with dutasteride, tamsulosin provides significantly greater benefit in men with moderate-to-severe LUTS associated with BPH.

[*J Indian Med Assoc* 2019; **117(11):** 41-4]

Key words **: Benign Prostatic Hyperplasia, Bladder Outlet Obstruction, Benign Prostatic Enlargement**

Benign prostatic hyperplasia (BPH) is a common problem faced by aging menthat negatively impacts quality of life. BPH is histologically characterized as an increase in the total number of stromal and glandular epithelial cells within the transition zone of the prostate gland. This hyperplasia causes the non-malignant, overgrowth of the prostate gland[1].

With advancing age, the force of urinary stream decreases. One important reason for this decline in force of the urinary stream is Bladder Outlet Obstruction (BOO) arising directly from Benign Prostatic Enlargement (BPE). This leads to Lower Urinary Tract Symptoms (LUTS), impaired bladder emptying (post-void residual urine), and predisposes to urinary tract infection. Fig 1 depicts the clinical manifestation of the BPH[1].

BPH is the fourth most prevalent disease in men aged >50 years. About 60% of men aged >50 years have histologic evidence of BPH. The prevalence progressively increases in men aged ≥70 years to 80%[2].

The pathogenesis of BPH is not yet fully understood. Several mechanisms are proposed to be involved in the development and progression of BPH. Although aging represents the central mechanism, recent novel findings also highlighted the key role of metabolic syndrome, systemic and local hormonal and vascular alterations, as well as prostatic inflammation that stimulates cellular proliferationasthe important mechanism involved in the development and progression of the BPH (Fig 2). An unknown stimulus would initiate inflammation that would create a pro-inflammatory environment within the prostate. BPH patients with Metabolic Syndrome have higher prostate growth rate and larger prostate volume[3].

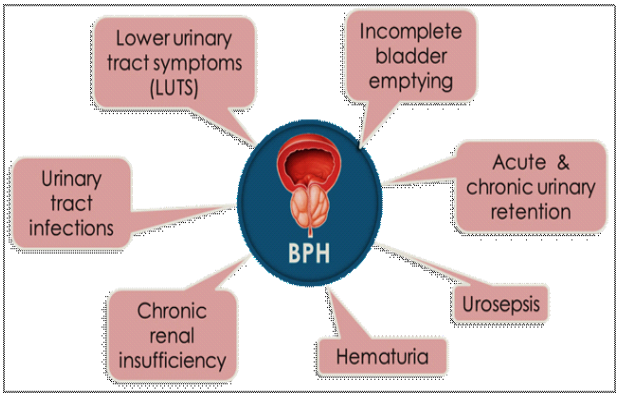

Fig 1 — Clinical manifestation of the BPH

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Management of BPH :

Target indications for treating BPH include reversing existing signs and symptoms of the disease or preventing the progression of the disease (Table 1)[1].

Management of BPH involves a cascade from watchful waiting, self-management, medical therapy, and surgical therapy (Fig 3).

Current therapeutic strategies for the treatment of LUST/BPH include alpha-blockers, 5-α reductase inhibitors, phosphodiesterase-5 (PDE-5) inhibitors, and anticholinergics. Among these therapeutic options, alpha-1 blockers are the first line of treatment for BPH. Tamsulosin, doxazosin, terazosin, alfuzosin and silodosinare the long-acting alpha-1 blockers approved for the treatment of BPH[1].

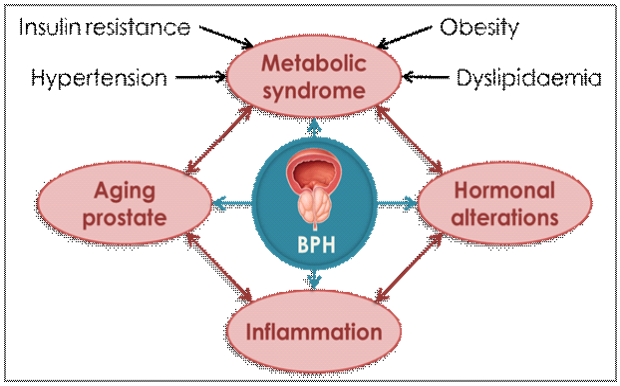

Fig 2 — Aetiology of BPH

Table 1 — *Rationale for treatment of BPH*

- To improveLUTS
- Eliminating hematuria secondary to BPH
- Improving bladder emptying
- Reversing acute urinary retention
- Preventing LUTS progression
- Preventing the development of acute urinary retention

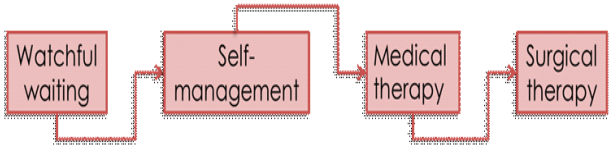

Fig 3 — Cascade of BPH management

Tamsulosin for Treatment of BPH :

Pharmacodynamic properties and mechanism of action of tamsulosin —

Functional studies showed that a1 adrenoceptor subtype predominates in the prostate gland, prostatic capsule, prostatic urethra, and trigone. These receptors mediatebladder neck/prostatic muscle contraction. On the contrary, relaxation of the prostate smooth muscle improves urine flow and causes improvement in symptoms of LUTS in men with BPH (Fig 4). Tamsulosin is third-generation uro-selective a1A adrenergic receptor blocker indicated for the treatment of LUTS associated with BPH (LUTS/BPH)[4,5].

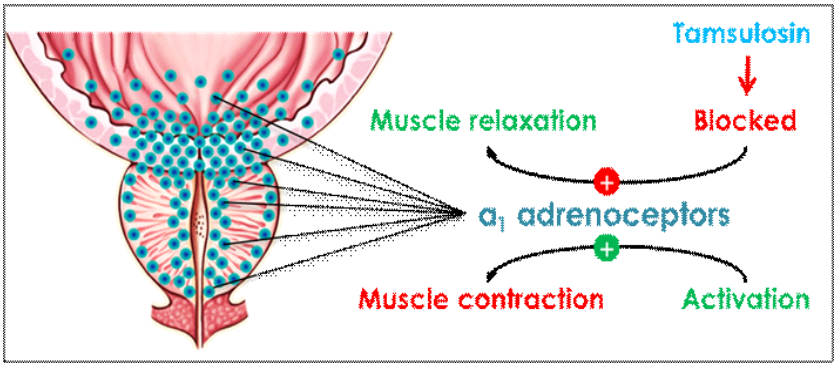

Fig 4 — Mechanism of action of Tamsulosin

Tamsulosin is generally well tolerated. Tamsulosin is associated with a lower potential for cardiovascular adverse effects[5].

Dosage of tamsulosin in BPH —

The starting dosage of tamsulosin for BPH management is 0.4 mg once daily orally with food. The dosage can be increased to 0.8 mg once daily in patients who fail to respond to the 0.4 mg dose after 2-4 weeks of administration[4].

Dosage adjustments are not required on the basis of age or mild to moderate hepatic impairment/renal dysfunction[5].

Tamsulosin in combination with dutasteride for treatment of BPH —

Dutasteride is a 5α- reductase inhibitor. Treatment with 5-α reductase inhibitors suppresses the dihydrotestosterone (DHT) levels, which lead to the induced apoptosis of prostatic cells that reduces prostate volume. Dutasteride reduces serum DHT levels by 95%, leading to a reduction of approximately 94-97% of DHT levels in the prostate. The rationale behind the combined use of tamsulosin with dutasteride to control BPH-related LUTS relies on the potential synergistic effect due to their different modes of action[6]. Treatment with tamsulosin and dutasteride combination provides significantly greater benefit in men with moderate-to-severe LUTSassociated with BPH and prostatic enlargement (usually greater than 40-ml)[7].

Clinical Efficacy and Safety of Tamsulosin for Management of BPH :

Efficacy and Safety of Tamsulosin in Patients with LUTS Associated with BPH —

Objectives :

To evaluate the efficacy and safety of two once-daily doses (either 0.4 mg or 0.8 mg) of tamsulosin in patients with benign prostatic hyperplasia.

Methods :

This was a phase III, randomized, parallel-design, double-blind trial. A total of 756 patients with BPH were randomized to receive either tamsulosin (0.4 and 0.8 mg/day) or placebo. Primary efficacy parameters were improvement in the total American Urological Association symptom index (AUA-SI) score and peak urinary flow (Q_{max}).

Results :

- Statistically significant improvements in efficacy parameters were seen in tamsulosin-treated group compared with placebo-treated patients (Fig 5). They-axis showschange in AUA-SI score.
- The0.4-mg/day dose demonstrated a rapid onset of action (4 to 8 hours) based on Qmax after the first dose of double-blind medication.
- Excellent tolerance at 1-week after the initial 0.4-mg/day dose and continued

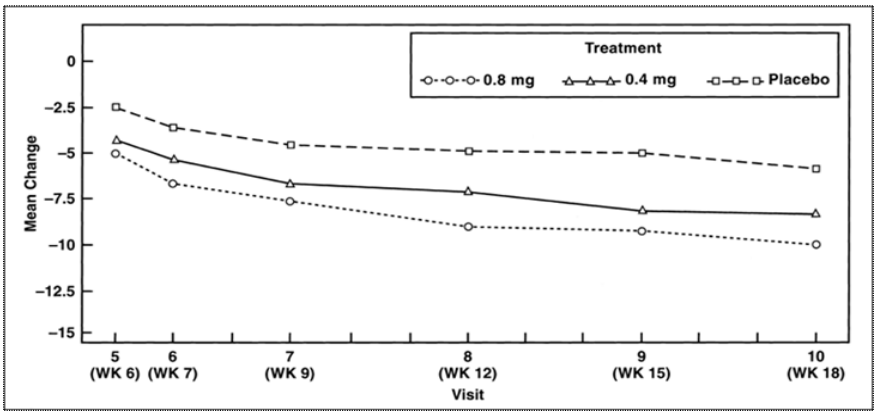

Fig 5 — Mean change from baseline in total AUA-SI score

tolerance during the additional 12 weeks of 0.4- and 0.8-mg/day dosing.

Conclusion :

Tamsulosin was effective and well-tolerated in men with BPH at both the 0.4 and 0.8 mg/day dose levels, without the blood-pressure-lowering effects[8].

Better Efficacy of Tamsulosin versus Terazosin in the Treatment of BPH —

Objectives :

To evaluate the efficacy and tolerability of tamsulosin versus terazosin in men with signs and symptoms of BPH.

Methods :

This was 11-week, randomized, open-label, multi-center, parallel-design study. A total of 1993 patients with BPH and moderate-to-severe LUTS were randomized to receive tamsulosin (0.4 mg/day) or terazosin (5 mg/day).

Results :

- Following the 4-days of treatment, the tamsulosin group demonstrated a clinically and statistically significant difference in total AUA-SI score in favor of tamsulosin.
- After 4-days of treatment, the adjusted mean changes in AUA-SI scores were –5.1 and –3.8 (P<0.001) for tamsulosin and terazosin treated patients, respectively (Fig 6).
- Secondary efficacy endpoint score comparisons also were statistically significant in favour of tamsulosin.
- Dizziness and somnolence were reported significantly more often (each, P<0.001) in the terazosin group than in the tamsulosin group. Tamsulosin was associated with fewer discontinuations due to adverse events.

Conclusions :

After 4-days of treatment with tamsulosin, reduction in BPH symptom severity was significantly greater than treatment with terazosin. This indicates a more rapid onset of clinical action of tamsulosin. Tamsulosin was well tolerated, with fewer adverse events associated with reduced blood pressure[9].

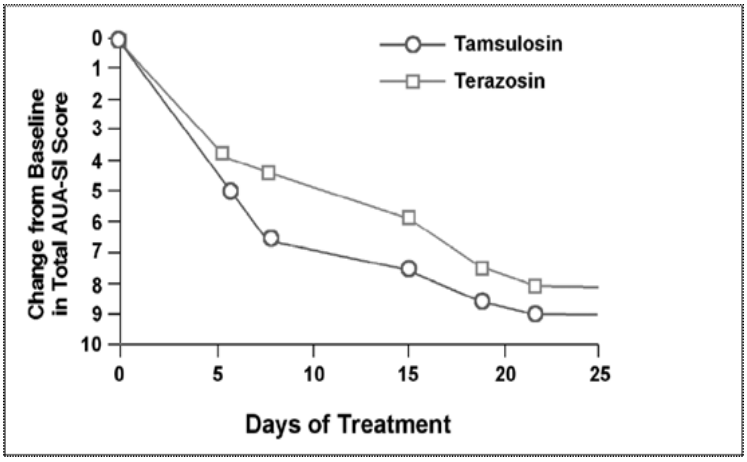

Fig 6 — Change from baseline in total AUA-SI score

Comparable Efficacy and Advantages of Tamsulosin over Alfuzosin —

Objectives :

To compare the efficacy and tolerability of the alpha-1-subtype selective drug tamsulosin with the non-subtype-selective agent alfuzosin in the treatment of patients with LUTS associated with BPH.

Methods :

This was a randomized, parallel-design, double-blind, randomized, parallel-design, double-blind phase III trial. A total of 256 patients with BPH and LUTS suggestive of BOO (symptomatic BPH) received tamsulosin 0.4 mg once daily or alfuzosin 2.5 mg three times daily for 12 weeks.

Results :

- Tamsulosin and alfuzosin produced comparable improvements in Qmax and total Boyarsky symptom score (Fig 7).
- Both treatments were well tolerated.
- Tamsulosin had no statistically significant effect on blood pressure,while alfuzosin induced a significant reduction in both standing and supine blood pressure, compared with baseline (P < 0.05).

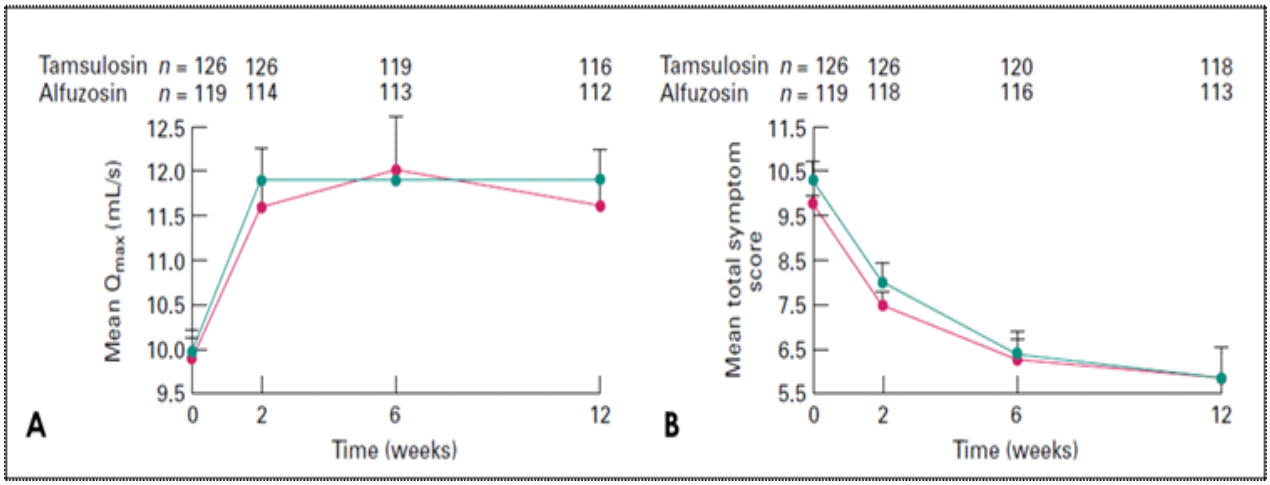

Fig 7 — (A) Mean maximum urinary flow rate. (B) Mean total Boyarsky symptom score (Green: Tamsulosin; Red: Alfuzosin)

Conclusion :

Tamsulosin, in contrast to other currently available alpha 1-adrenoceptor antagonists, can be administered without dose titration. Another advantage compared with alfuzosin is the once-daily dosing regimen of tamsulosin[10].

Tamsulosin in Combination with Dutasteride for Treatment of BPH: Combat study —

Objective :

To evaluate efficacy of combination therapy with tamsulosin and dutasteride in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression over 4 years in men at increased risk of progression.

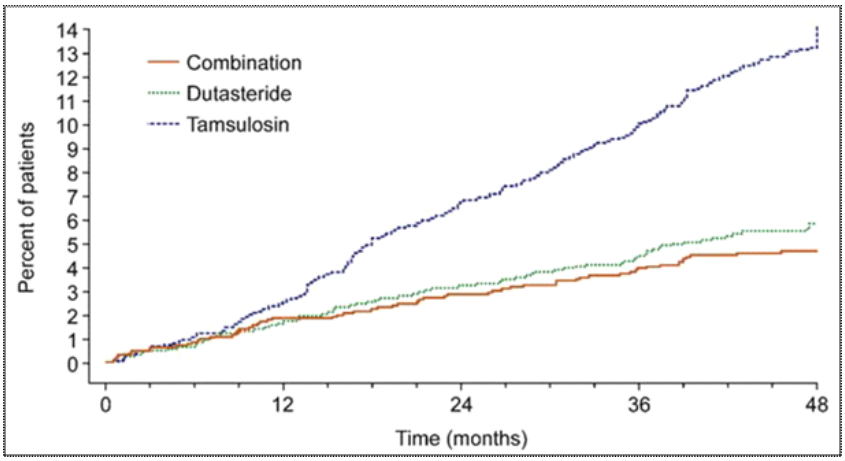

Fig 8 — Kaplan-Meier estimates of time to the first episode of acute urinary retention or benign prostatic hyperplasia-related prostatic surgery

Methods :

This was a 4-year, multicenter, randomized, double-blind, and parallel-group study. A total of 4844 men with a clinical diagnosis of BPH, International Prostate Symptom Score ≥12, prostate volume ≥30 cm^3, prostate-specific antigen 1.5-10 ng/ml, and maximum urinary flow rate (Q_{max}) >5 and =15 ml/s with minimum voided volume ≥125 ml.

Results :

- Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery.
- Combination therapy was also significantly reduced the relative risk of BPH clinical progression.
- Combination therapy provided significantly greater symptom benefit at 4 years.
- Safety and tolerability of combination therapy was consistent with previous experience with dutasteride and tamsulosin monotherapies.

Conclusions :

This study supported the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement[7].

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