Uroxatral Measures Favorably

In BPH, prostatic hyperplasia increases urethral resistance, resulting in compensatory changes in bladder function. Obstruction-induced changes in detrusor function, compounded by age-related changes in the functioning of the bladder lead to urinary frequency, urgency, and nocturia, the most bothersome BPH-related complaints. In this study, Uroxatral was measured against alternative treatments.

Pharmacologic Treatments for BPH
Prescribed pharmacologic agents include 5 alpha-reductase inhibitors (5ARIs) and alpha-adrenergic blockers. While many men use over-the-counter phytotherapeutic agents, these are not monitored by the FDA and are not recommended under the current AUA guidelines for treatment. Currently, no combination approaches are FDA approved.

- Treatment options for BPH include watchful waiting, medical therapy, and various surgical procedures1
- Alpha-adrenergic blocker therapy is appropriate for patients with signs and symptoms of BPH1-5[1]
- The 5ARIs are appropriate and effective treatments for symptomatic BPH in men with enlarged prostates to improve symptoms, reduce acute urinary retention (AUR), and reduce the risk of need for BPH-related surgery. The ARIs are HYTRIN® (terazosin hydrochloride), CARDURA® (doxazosin mesylate), FLOMAX® (tamsulosin hydrochloride), Uroxatral® (alfuzosin HCl extended-release tablets), PROSCAR® (finasteride) and AVODART™ (dutasteride)

5-ARIs for the Treatment of BPH

5-ARIs (5-Alpha-Reductase Inhibitors):
Pharmacologic Profile
The 5-ARI finasteride has a favorable physiologic profile.

- Finasteride is a 5-ARI that inhibits Type II 5-alpha-reductase
- Finasteride dosed at 5 mg/day for up to 4 years suppressed DHT by 70%. Median circulating serum T rose in conjunction with DHT suppression, ranging from 10% to 20% (within the normal range)
- Administration of finasteride 5 mg once daily was associated with a decrease of prostate volume by 17.9% in a 4-year study
- Treatment with finasteride reduces serum PSA downward by 50%; Free to total PSA ratio (F/T ratio) remains unchanged
- The serum half-life of finasteride is about 8 hours and dosing is 5 mg once dail

Clinical Efficacy and Adverse Effects of 5ARIs Are Comparable

The 5-ARI finasteride has a favorable physiologic profile.

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[1] AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003): chapter 1: diagnosis and treatment recommendations. *J Urol.* 2003;170:530-547.

- All sexual side effects only slightly higher in Finasteride as compared to Dutasteride, including erectile dysfunction, decreased libido and ejaculatory disorder.
- AUR risk reduction comparable in both Finasteride and Dutasteride
- Finasteride reduced surgery risk by 55%[2]

Alpha-Blockers for the Treatment of BPH

AUA Guidelines

Alpha-blocker therapy is based on the hypothesis that clinical BPH is partly caused by alpha-adrenergic-mediated contraction of prostatic smooth muscle, resulting in bladder outlet obstruction.

Dosing of Alpha-Blockers for BPH

Alfuzosin and tamsulosin are not indicated for hypertension, while the older alpha-blockers doxazosin and terazosin are. Alfuzosin and tamsulosin do not require dose titration to minimize hypertensive effects.

- On titration: note that unlike other agents, Uroxatral® (alfuzosin HCl extended-release tablets [10 mg]) does not need titration, while some patients on tamsulosin require the higher dose of 0.8 mg1-4
- Each of these agents has a long enough half-life to permit once-daily administration1-4

Side Effect Profiles Differentiate Alpha-Blockers

All alpha-blockers are effective in BPH treatment.
They can be differentiated by their side effect profile regarding CV side effects and sexual side effects.
Uroxatral had low incidence of both vasodilatory effects and ejaculatory dysfunction.

Terazosin: Adverse Events Occurring Significantly More Often Than With Placebo

Adverse events that happened significantly more often with terazosin than with placebo in BPH patients were asthenia, postural hypotension, dizziness, somnolence, nasal congestion, and impotence.[3]

Tamsulosin vs Placebo: BPH Symptoms

In two US, multicenter, placebo-controlled, double-blind studies of 13 weeks' duration, 1,487 men with BPH were randomized to treatment with placebo, tamsulosin 0.4

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[2] 1. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of Finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med.* 1998;338:557-563.
See dosage and administration on each:

[3] HYTRIN® (terazosin hydrochloride) Prescribing Information. North Chicago, IL: Abbott Laboratories; 2001

mg/d, or tamsulosin 0.8 mg/d after receiving tamsulosin 0.4 mg/d for 1 week. In both studies, total AUA symptom scores in men taking tamsulosin 0.4 and 0.8 mg decreased significantly from placebo.

- Two separate studies of tamsulosin at 0.4 mg and 0.8 mg examined mean change in symptom scores
- Note that there is no significant differences between 0.4 mg and 0.8 mg in symptom improvement or peak flow rate
- Patients treated with tamsulosin showed a rapid decrease in symptoms beginning after 1 week of treatment that was sustained throughout the 13 weeks of the trial. Compared with those given placebo, patients treated with either dose of tamsulosin showed a significantly greater improvement ($P<.05$) in AUA Symptom Index scores at week 13
- There were no significant differences in improvement observed between the 0.4-mg and 0.8-mg doses of tamsulosin[4]

Tamsulosin Adverse Effects: Abnormal Ejaculation and Rhinitis

Key adverse events with tamsulosin are the vasodilatory responses like headache and dizziness, and other issues like rhinitis. Of key importance is the high incidence of abnormal ejaculation—up to 18% in patients taking the 0.8 mg dose tamsulosin.

- Shown here are adverse events that are related to the vasodilitory response of patients administered tamsulosin 0.4 mg or 0.8 mg at higher rates than in the placebo group during the two 13-week, placebo-controlled US trials (N=1,487 men)
- Notable is the dose-dependent high incidence of rhinitis and ejaculatory dysfunction (EjD), described as "Abnormal ejaculation," which includes ejaculation failure, ejaculation disorder, retrograde ejaculation, and ejaculation decrease
- Dizziness was reported by 14.9% (75/502) of patients in the 0.4-mg group, 17.1% (84/492) in the 0.8-mg group, and 10.1% (50/493) in the placebo group

Alfuzosin

Alfuzosin was introduced in Europe in 1987, at 2.5 mg tid, moving to a bid formulation in 1994, and is now available in a once-daily formulation. It has a huge database of human subject experience—3.7 million patient years. In June 2003, the 10-mg qd formulation (UROXATRAL) was approved by the FDA in the United States.

- Alfuzosin was the first alpha-adrenergic blocker to be marketed exclusively for the treatment of symptomatic BPH. It was marketed throughout Europe as an immediate-release 2.5-mg tid formulation in 1987, as a slow-release 5-mg bid

[4] FLOMAX® (tamsulosin hydrochloride) Prescribing Information. Ridgefield, Conn: Boehringer Ingelheim Pharmaceuticals, Inc.; 2000.

formulation in 1994, and recently as a new extended-release 10-mg once-daily formulation
- As of May 2000, alfuzosin was approved in 87 countries throughout Europe, Asia, and Latin America and was being marketed in 60 countries
- The US Food and Drug Administration approved UROXATRAL (alfuzosin 10 mg qd) on June 12, 2003, for the treatment of signs and symptoms of BPH. Other formulations of alfuzosin will ***not*** be available in the United States

Uroxatral ®

This slide shows the time course and main phases of the in-vitro dissolution of UROXATRAL. The Geomatrix® delivery system for UROXATRAL means the single capsule breaks down and diffuses evenly over time and is unaffected by gastric pH (as modified by antacids, proton pump inhibitors, etc.), but is affected by altered motility, such as in diarrhea.

- The Geomatrix® delivery system of UROXATRAL contains three distinct layers. The white inner core is the hydrophilic active matrix core with alfuzosin hydrochloride. The upper and lower layers are the swellable and erodible layers that control hydration and swelling of the core, slowing down dissolution and making it linear1,2
- This combination of layers, each with different rates of swelling, gelling, and erosion, is what accounts for the rate of drug release. When the tablet is first swallowed, the drug concentration is high but the surface area is small. As time goes by and the core swells, the surface area expands to compensate for the decrease in drug concentration
- **Swelling phase**: The tablet first swells, increasing the gastric residence time to about 6 hours. Erosion and diffusion occur, allowing for absorption of 30% of alfuzosin. As aqueous fluid progressively penetrates the matrix surface, the drug is released through the process of diffusion. Simultaneously, the non-erodible barrier swells at a predetermined rate, which increases the volume of the tablet
- **Constant diffusing:** The swelling is completed. During the next 6 hours in the small intestine, the tablet continues to erode, providing constant dissolution and releasing an additional 40% of the drug. Dissolution is independent of the medium pH
- **Final dissolution:** Finally, in the colon, the tablet disintegrates over an additional 8 hours, and dissolution is complete, liberating the remaining 30% of alfuzosin. In this final part of the dissolution process, the erodible barrier dissolves so that the tip can finally reach the large surface of the active white layer and a constant dissolution rate of drug is maintained
- Because of these qualities of the Geomatrix® delivery system, the UROXATRAL tablet should not be crushed or broken[5]

Uroxatral Works Fast: Improves Flow Rate At First Dose

6 SkyePharma. Oral GEOMATRIX® animation. Available at: http://www.skyepharma.com/oral_xatral.html.

In this study the effect of the first dose of Uroxatral on peak flow rate 8hrs post dose was measured. As you can see there was a significant improvement in peak flow rate over placebo in both analyses. The first dose of Uroxatral is effective.[6]

Uroxatral Improves Symptoms: Total IPSS Score and Subscores
Three double-blind, randomized, placebo-controlled studies with similar protocols were conducted in the United States and Europe. Each study consisted of a 1-month placebo run-in phase, followed by a 3-month, double-blind, randomized, placebo-controlled treatment phase, followed by an open-label extension for up to 24 months.
Data for 955 patients with BPH who participated in these trials and were randomized to once-daily alfuzosin 10 mg (n=473) or placebo (n=482) were pooled to assess the safety and efficacy of this new, extended-release formulation.

Primary efficacy parameters included improvements from baseline to the end of the study (day 84) in IPSS total score, obstructive and irritative subscores, and peak flow rate.
Alfuzosin 10 mg once daily produced significantly greater improvement than placebo in the IPSS total score at endpoint: the percentage of patients with an improvement of at least 3 points in the IPSS was significantly greater in the alfuzosin group (75.7%) than in the placebo group (61.5%, $P<.001$; data not shown).
There was also significant improvement in both irritative and obstructive subscores in patients receiving alfuzosin 10 mg once daily compared with placebo ($P=.0004$ and $P=.0009$, respectively).

Uroxatral Improves Symptoms for All Prostate Volumes
The improvement in IPSS total scores seen in alfuzosin-treated patients was not influenced by prostate size at baseline.
As shown here, the mean change from baseline in IPSS in alfuzosin-treated patients was similar in all prostate volume subgroups.

Combination Therapy in the Management of BPH

In a study of 3047 patient over 4.5 years, the risk of AUR, urinary incontinence and renal insufficiency was significantly reduced by Doxasozin (39%) and Finasteride (34%).

Long-term combination therapy of Doxasozin and Finasteride was better in reducing benign prostatic hyperplasia than either drug alone.[7]

Combination Therapy Conclusions

- BPH is a highly prevalent disease with significant morbidity related to:

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[6] Marks L, Bernabe C, Gittelman M, et al. First dose efficacy of alfuzosin once daily in men with symptomatic benign prostatic hyperplasia. *Urology.* 2003;62:888-893

[7] McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387-2398

    - Decreased quality of life
    - Decreased sexual function
- The ease of dosing for alfuzosin makes it the first line of treatment for BPH
- Alfuzosin is a selective alpha-blocker with efficacy comparable to other alpha blockers and a lower incidence of adverse events

Overall Conclusions

- BPH is a highly prevalent disease with significant morbidity related to:
    - Decreased quality of life
    - Decreased sexual function
- The ease of dosing for alfuzosin makes it the first line of treatment for BPH
- Alfuzosin is a selective alpha-blocker with efficacy comparable to other alpha blockers and a lower incidence of adverse events