Factors in Predicting Failure With Medical Therapy for BPH

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Perhaps more than other common disorders, the management of benign prostatic hyperplasia (BPH) has been subject to the "treatment du jour" approach. Although pharmacotherapy has largely replaced surgery in the treatment of BPH, recommendations for optimal therapy seem to change every time a new study is published. α-Blockers, 5α-reductase inhibitors, and combination therapy with the 2 have all proved highly effective, in both trials and clinical practice. Nevertheless, medical therapy does not work for everyone, and identification of baseline factors that can help predict failure with a particular therapy is needed. Currently, the evidence supports the use of single-agent α-blocker therapy for patients with low prostate volumes at baseline, and combination therapy for patients with larger prostates. Symptom severity at baseline also seems predictive of success or failure.

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Benign prostatic hyperplasia (BPH), the nonmalignant enlargement of the prostate secondary to increased cellular growth, commonly afflicts elderly men. The incidence of BPH is increasing along with an increasing average life expectancy. Treatment of BPH has undergone continual change over the past 15 years with the number of transurethral resections of the prostate (TURPs) declining coincident with the number of prescriptions written for α-blockers and 5α-reductase inhibitors increasing.[1]

The "treatment du jour" is based on the latest study published, US Food and Drug Administration (FDA) approvals, and Medicare reimbursement. For example, in the early 1990s, symptomatic improvement was the gold standard and α-blockade was deemed to be best suited to achieve optimal results. Moreover, based on the Veterans Affairs Cooperative Study, combination therapy was thought to be unnecessary, expensive, and of no advantage at 1 year.[2] Then, with the publication of the Proscar Long-term Efficacy and Safety Study (PLESS), 5α-reductase inhibitors came back into vogue[3] and the dialogue on BPH was modified—no longer were we simply treating symptoms; slowing the progression of disease became the new modus operandi. Attempts to optimize and predict which patients were at greatest risk for progression of disease became the focus of investigators, and the use of prostate-specific antigen (PSA) as a proxy for prostate size was popularized. Most recently, the results of the Medical Therapy of Prostatic Symptoms (MTOPS) study have again changed the landscape of medical therapy for BPH,[4] suggesting that combination therapy with an α-blocker and a 5α-reductase inhibitor is the best way both to alleviate symptoms and to prevent progression of disease. So where are we now? More importantly, are there factors that can help predict failure with medical therapy?

Failure of medical therapy can be assessed in various ways. These include cessation of current treatment in favor of 1) other medications (eg, changing from a 5α-reductase inhibitor to an α-blocker), 2) minimally invasive therapy such as microwave therapy or transurethral needle ablation, 3) surgical intervention such as TURP or photoselective vaporization of the prostate, or 4) watchful waiting. Ultimately, patients will convert to another therapy if they perceive a lack of benefit or improvement of their lower urinary tract symptoms (LUTS), intolerable side effects, or progression of disease, such as urinary retention or intractable urinary tract infection (UTI).

Are All Medications Created Equal?

The recognition by Lepor and associates[5] in the 1980s that prostatic smooth muscle tension is mediated by the α_1-adrenoceptors led to the development of α-blockade as a treatment for LUTS. This dynamic component of prostatic obstruction accounts for approximately 40% of outflow obstruction due to BPH.[6] There are currently 4 α-blockers that are FDA-approved to treat LUTS: doxazosin, terazosin, tamsulosin, and alfuzosin. The American Urological Association (AUA) Practice Guidelines committee believes that all 4 are equally effective, causing on average a 4 to 6 point improvement in AUA symptom score (which most patients perceive as a meaningful change).[7] In addition, the improvement in maximal urinary flow rate is similar among all 4 agents.

5α-reductase inhibitors such as finasteride and dutasteride inhibit the enzymatic conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase. DHT levels decrease with therapy, although not to castrate levels. As the primary hormonal stimulus for prostate growth is removed, the prostate shrinks and the static component of LUTS is diminished. Unlike α-blockers, whose effects are felt within days, treatment with 5α-reductase inhibitors takes longer before symptomatic improvement is noted.[1] Patients experience on average a 3-point improvement in AUA symptom score, although the greatest improvement is seen in patients with larger prostates (> 40 g).

5α-reductase inhibitors were the first therapy shown to alter the natural history of BPH. In the landmark PLESS study, more than 3000 men were followed for 4 years. Finasteride therapy reduced the risk of BPH-related surgery by 55% compared to placebo, and also reduced the risk of acute urinary retention by 57%.[3]

Dutasteride is a new drug that inhibits both type 1 and type 2 5α-reductase isoenzymes. DHT is 90% suppressed by dutasteride versus 70% by finasteride. Despite a theoretical benefit to additional DHT suppression, similar effects on symptom scores and flow rates and similar side effects are seen when compared to finasteride. Thus far, no published head-to-head trials directly compare the 2 drugs.[7,8]

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The data suggest that clinical efficacy among agents within a given class is similar. Are there differences when the 2 classes of agents are combined? The initial experience with combining α-blocker and 5α-reductase therapy was not promising. In a Veterans Affairs Cooperative Group study, 1 year of combination therapy was no more effective than monotherapy in improving symptoms or flow rates, and substantially increased the cost of treatment.[2]

The recently published MTOPS study has changed our thinking regarding combination therapy.[4] More than 3000 men were randomized to receive either placebo, doxazosin (an α-blocker), finasteride (a 5α-reductase inhibitor), or both. The principal outcome followed was clinical progression, defined as either an increase of at least 4 points in AUA symptom score, or urinary retention, incontinence, renal insufficiency, or recurrent UTI. Other dependent variables included maximal urinary flow rate, serum PSA levels, and incidence of invasive therapy. After a median 4.5 years of follow-up, the median reduction in AUA symptom score was 4 for placebo, 6 for doxazosin, 5 for finasteride, and 7 for combination therapy. All differences were statistically significant.

Clinical progression, as measured by increasing AUA symptom score, occurred in 4.5 per 100 patients per year in the placebo group. Doxazosin and finasteride reduced the risk of progression by 39% and 34%, respectively; although significantly different from placebo, the difference between the 2 agents was not. Combination therapy caused a 66% risk reduction of clinical progression compared to placebo, and this was significantly different from the other 3 arms. Secondary analysis showed that prostate volumes greater than 40 cc and serum PSA levels > 4.0 ng/mL predicted a better response to combination therapy. Looking specifically at acute urinary retention, the risk reductions for doxazosin, finasteride, and combination therapy were 31%, 67%, and 79%, respectively. Finasteride and combination therapy also reduced the risk of invasive procedures by 64% and 67%, respectively, but there was no significant effect with doxazosin compared to placebo.

Much can be gleaned from the MTOPS data. First, combination therapy is the most effective treatment to effect symptomatic improvement and to slow disease progression. Although this conclusion is different from previous trials of combination therapy, the data are actually consistent. Similar to the Veterans Affairs Cooperative Group study, at 1 year's follow-up in the MTOPS trial, there was no difference in symptoms between finasteride and placebo or between combination therapy and doxazosin alone. However, at 4 years' follow-up, we see the effect of finasteride compared to placebo, and the overall benefit of combination therapy. Second, an α-blocker alone can reduce clinical progression, as defined by symptom deterioration. Although it delayed the time to acute urinary retention, doxazosin did not significantly decrease its cumulative incidence as compared to placebo, nor did it have any effect on the incidence of surgical procedures. Third, with a clinical progression rate of 4.5 per 100 patients per year in the placebo group, we can accurately counsel patients with LUTS that over 5 years their risk of progression is approximately 20% without treatment. Finally, although doxazosin and finasteride are the best-tested agents in combination therapy and despite a lack of any head-to-head trials comparing different agents used in combination, the AUA practice guidelines committee believes that all α-blockers and 5α-reductase inhibitors should be equally effective in combination.[7]

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Side Effect Profile

Adverse side effects commonly reported with different α-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction, most commonly occurring in about 5% to 9% of patients.[6] Consequently, clinical observation of uroselectivity—the degree to which a given agent acts on prostate and bladder tissues with desired benefits on LUTS while producing minimal adverse effects—remains one of the primary considerations when choosing an α-blocker for the management of LUTS associated with BPH.[6] The efficacy of currently available antagonists, pooled from a number of trials, as well as selected side effects, are listed in Table 1.[9-14]

With the presence of α-adrenergic receptors throughout the vascular bed, it is not surprising that the primary adverse events related to the pharmaceutical blockade of those receptors would be cardiovascular.[15] Uroselectivity is a desirable feature of an α-blocker.[16] It was expected that agents with increased α_{1A}-receptor specificity would result in improved uroselectivity. The rationale for increasing subtype specificity was the potential to decrease the incidence of adverse cardiovascular events that are potentially associated with the

Table 1
Comparison of Current α_1-Adrenoceptor (α1AR) Antagonists

α1AR-antagonist (No. studies)	Discontinuation (%)	Dizziness (%)	Hypotension (%)	Ejaculation dysfunction (%)
Alfuzosin OD	8-11	2.1-7.4	0.7-3.4	0.0-0.6
Placebo	4-6	1.3-2.9	0.0-3.4	0.0-1.3
Doxazosin	11-22	17-24	2.5-8.0	0.0
Placebo	4-23	4-6	0.0-0.0	0.0
Tamsulosin	7-13	3-11	0.0-0.0	1.0-26.0
Placebo	9-11	0-5	0.5-1.0	0.0-1.0
Terazosin	16-38	3-26	2-9	0.0-1.4
Placebo	16-46	3-7	0.5-1	0.0-1.0

OD, once daily.

inhibition of the α_{1B} receptor. However, this has not been the case, as described in the previous section. Thus, pharmacologic selectivity does not translate into clinical uroselectivity.

The antihypertensive activity of doxazosin was compared with that of the diuretic chlorthalidone in the prevention of major cardiovascular events in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[17] The trial was halted after an interim analysis revealed that patients treated with doxazosin had a 25% increase in the secondary endpoint of combined cardiovascular disease, primarily driven by a 2-fold increase in episodes of congestive heart failure (CHF). Although this trial indicates that patients with cardiovascular disease at risk for CHF should receive a diuretic, it does not preclude that patients with or without cardiovascular disease and LUTS associated with BPH should be treated with an α-blocker.

Lower urinary tract symptoms are associated with significant impairment in sexual activity, satisfaction with sexual relationships, and quality of life. It is therefore not surprising that a significant number of sexually active men with LUTS/BPH consult physicians for erectile dysfunction (ED) and other genitourinary difficulties. Although sexual activity normally diminishes with age, impaired sexual performance remains an undesirable side effect of BPH, and treatment often produces significant clinical improvement and symptom reduction. Clinical evaluations have now confirmed previous studies in preclinical models showing that blockade of α-adrenergic activity can improve sexual function. In one study, patients with ED treated with intracavernosal alprostadil injection showed a significant improvement in sexual function when they also received an oral α_1-adrenoceptor blocker ($P < .01$).[18]

In the setting of treatment for LUTS/BPH, Höfner and colleagues[19] demonstrated through a sexual function score determined from a lifestyle questionnaire that treatment with tamsulosin actually improves sexual function, compared with placebo. This finding is supported by the results of a validated BPH-specific health-related quality-of-life questionnaire administered to patients treated with alfuzosin. Treatment with this agent was associated with significant improvements in perceived sexuality at 12 months ($P < .0001$).[20]

As described above, abnormal ejaculation is a class effect of treatment with α_1-adrenoceptor blockers, though rarely serious enough to prompt patients to withdraw from treatment (the risk of ejaculation disorders due to α-blocker therapy for BPH is much lower than that from surgical intervention for BPH). However, an increased incidence of this side effect has been reported with tamsulosin.[21]

DHT provides the major growth stimulus in the prostate as a result of its 4- to 5-fold higher affinity for the prostatic androgen receptor compared to testosterone. The effect of decreasing levels of testosterone, the precursor of DHT, by chemical castration with luteinizing hormone–releasing hormone agonists like nafarelin acetate has been investigated. However, decreased serum testosterone is associated with intolerable sexual side effects, particularly ED and decreased libido, as well as gynecomastia and hot flushes secondary to abnormal testosterone:estradiol ratios. With this in mind, selective 5α-reductase inhibitors were developed and investigated for improving LUTS without the sexual side effects associated with reduced testosterone levels.

Factors That Predict Progression of Disease

The MTOPS trial was the first placebo-controlled study to assess the effect of medical therapy on the risk of overall clinical progression of BPH.[4] MTOPS demonstrated that the risk of clinical progression of BPH was significantly reduced by the α-blocker doxazosin (39% risk reduction) and by the 5α-reductase inhibitor finasteride (34% risk reduction) relative to placebo. Moreover, combination therapy with finasteride plus doxazosin led to a

significantly greater reduction in risk of BPH progression relative to placebo (66% risk reduction) compared to that for either drug alone.

The AUA guidelines on management of BPH recommend the combination of an α-blocker and a 5α-reductase inhibitor (specifically, doxazosin and finasteride) as an appropriate medical therapy option in patients with bothersome LUTS (AUA symptom score ≥ 8) associated with "demonstrable prostatic enlargement," generally interpreted in clinical practice as meaning a baseline total prostate volume (TPV) ≥ 40 mL.

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A recent analysis of data suggests that baseline prostate volume may predict progression of disease. In men with a baseline prostate volume ≥ 25 mL, treatment with combination therapy led to a greater reduction in risk of clinical progression of BPH compared to that for either doxazosin alone or finasteride alone. The data were too variable (due to low number of patients and BPH progression events) to allow determination of the relationship between baseline prostate volume and the effect of treatment on relative risk of BPH progression in men with a baseline prostate volume < 25 mL.[22]

The findings from this MTOPS data analysis provide valuable information for physicians and patients with LUTS concerning the selection of an optimal medical therapy for the management of clinical progression of BPH. In the minority (31%) of randomized patients who had very small prostates (baseline TPV < 25 mL), the risk of clinical BPH progression with the combination of doxazosin and finasteride was not significantly different from that for either drug alone, with a greater relative risk (RR) for combination therapy versus doxazosin alone (RR: 0.74; 95% confidence interval, 0.36, 1.51) than for combination therapy versus finasteride alone (RR: 0.54; 95% confidence interval, 0.27, 1.09). These data indicate that optimal management of BPH progression events in men with a baseline TPV < 25 mL can be achieved with α-blocker therapy alone. In the majority (69%) of randomized patients who had a baseline TPV ≥ 25 mL, treatment with the combination of doxazosin and finasteride led to a significant reduction (average RR reduction of approximately 50%) in the risk of BPH progression compared to either drug alone, indicating that the combination of doxazosin and finasteride is the best medical therapy in these patients.[22]

How Many Men Stop Medical Therapy for BPH?

There are few studies that describe the failure rate with medical therapy. Ultimately, there are a number of reasons patients fail medical therapy. In our own published series, 30% of patients stopped their medications at 2 years.[23] In a more recent series, 77.1% of men remained on medical therapy at 54 months.[24] Predictive factors were more severe symptoms and a larger prostate volume at baseline. In an open-label long-term study of the safety and efficacy of terazosin in 494 men with BPH, 56.9% were still taking terazosin at 42 months.[25] Similarly, in 450 men prescribed doxazosin and followed long-term, the continuation rate was 58.4% at 48 months.[26]

Main Points

- The treatment of benign prostatic hyperplasia (BPH) has changed greatly over the past 15 years, from surgical intervention to pharmacological management. However, rather than a gold standard, BPH has been subject to a "treatment du jour" approach (eg, α-blockers, 5α-reductase inhibitors, combination therapy), with optimal medical therapy changing with the latest published study.
- According to current thinking, combination therapy with an α-blocker and a 5α-reductase inhibitor is the most effective treatment to effect symptomatic improvement and to slow disease progression.
- Recent data analysis suggests that optimal management of BPH progression in men with very small prostates at baseline can be achieved with α-blocker therapy alone, whereas combination therapy is more effective in patients with larger prostates.
- In addition to baseline prostate volume, symptom severity at baseline can be a predictive factor.
- Ultimately, patients will change to another therapy if they perceive a lack of benefit or improvement of their lower urinary tract symptoms, intolerable side effects, or progression of disease. Factors that can predict failure with medical therapy have been elusive, but analysis of data from several large clinical trials offers a number of clues.

Clearly, the use of medical therapy for BPH is on the increase. Medical therapy has obvious and well-documented efficacy in treating LUTS as well as altering progression of disease. Nevertheless, medical therapy does not work for everyone. Inherent to the use of medications is that some patients will not respond, some will have adverse events, and some will progress. Identification of baseline factors that can help predict failure with medical therapy continues to evolve. Larger prostates, as determined by increased volume and elevated PSA, as well as higher baseline symptoms seem to predict failure. Until clear, reproducible, and well-defined predictors of treatment failure become available, most men will continue to be prescribed a pill for BPH. ■

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