Current Urology Reports (2019) 20: 40
https://doi.org/10.1007/s11934-019-0899-z

BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

BPH: Why Do Patients Fail Medical Therapy?

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Published online: 6 June 2019

Abstract
Purpose of Review In this article, we review why patients may fail medical therapy for benign prostatic hyperplasia (BPH) and by doing so, gain a better understanding of the disease process and how to optimize the care of these patients.
Recent Findings A growing body of literature has attempted to better characterize the various mechanisms by which patients develop BPH as well as identify predictors of disease progression and treatment failure.
Summary BPH is a heterogenous disease process. A more personalized approach to treatment, including patient selection for medical or surgical management, would allow us to optimize patient care.

Keywords Benign prostatic hyperplasia · Medical therapy · Alpha-blockers · 5alpha-reductase inhibitors · Predictors of treatment failure · Clinical trial results

Introduction

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) affect about 20% of 40-year-old males and almost 50% of men in their 80s [1, 2]. The management of LUTS secondary to BPH has changed significantly over the last several decades. Since the 1990s, medical management with an α-blocker (AB) and/or a 5α-reductase inhibitor (5ARI) has been first-line treatment. However, a significant proportion of men go on to need surgical intervention either because of medication failure or disease progression. The purpose of this review is to better understand why patients fail medical therapy and in doing so to help optimize the management of these patients.

This article is part of the Topical Collection on *Benign Prostatic Hyperplasia*

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A Historical Perspective

ABs were identified as a potential therapy for BPH in 1976 when Caine et al. showed that activation of α-receptors caused prostatic smooth muscle contraction and that by administering ABs, this contraction could be inhibited [3]. Lepor et al. further classified the α-receptors in the prostate and in 1992 published the results of a randomized placebo-controlled trial of the AB terazosin for the treatment of BPH [4, 5]. They found that terazosin led to significant improvements in peak urine flow rates (Q_{max}) and Boyarsky symptom scores. These results led to the FDA approval of ABs for the management of BPH in 1992.

The role of androgens in prostate growth was demonstrated in the 1940s, when studies showed that injecting testosterone into rats increased their prostate size [6]. Then, in the 1970s, researchers identified several families in the Dominican Republic that had genotypically male children with ambiguous genitalia who were raised as females until puberty, at which time they became phenotypically male, although their prostates remained small and dysplastic [6, 7]. After administering radioactive testosterone to these patients, researchers found a low conversion of testosterone to dihydrotestosterone (DHT) and that compared with unaffected patients, these patients had high urinary levels of 5α-reductase metabolites. These results showed that a 5α-reductase defect impaired the conversion of testosterone to DHT and that DHT was

important in the development of male external genitalia and the prostate [7, 8]. In 1992, finasteride became FDA approved for the treatment of BPH after Gomerly et al. published results of a randomized controlled trial demonstrating the safety and efficacy of 1 year of finasteride therapy [9].

Trials Demonstrating the Effects and Side Effects of Medical Therapy

ABs are the most commonly used medical therapy for treating LUTS. They have been shown to prevent symptom progression, are generally well tolerated, and reduce the cost of medical therapy. As stated above, terazosin (Hytrin) was the first AB approved for the treatment of BPH. Subsequently, doxazosin (Cardura) was approved. Both terazosin and doxazosin need to be dose titrated. Tamsulosin (Flomax) was the first selective AB to be approved. Tamsulosin 0.4 mg and 0.8 mg both lead to improvements in Q_{max} and symptom score, with some evidence suggesting that 0.8 mg is more efficacious but causes more adverse events [10]. The primary advantage of tamsulosin is that it does not require dose titration. The fourth AB to be approved was alfuzosin (Uroxatral), which like tamsulosin does not require dose titration. Lastly, silodosin (Rapoflo) was approved for the treatment of BPH. All ABs are thought to be of comparable efficacy and no conclusive differences have been established [11]. However, side effect profiles are variable (Table 1) [12–16].

Currently, there are two 5ARIs, finasteride and dutasteride, that can be prescribed for patients with BPH. 5α-reductase has two isoforms, type 1 and type 2. Finasteride only inhibits type 2 whereas dutasteride inhibits both type 1 and type 2. Dutasteride also has a longer half-life (4 weeks vs 8 h). The only randomized controlled trial to compare finasteride and dutasteride reported similar efficacies and rates of adverse events at 1 year [17]. However, a propensity-matched cohort study with a longer follow-up duration found that patients on dutasteride were less likely to undergo surgery for BPH at 5 years' follow-up [18]. One retrospective analysis found that patients on dutasteride were more likely than those on finasteride to experience breast tenderness/enlargement, erectile dysfunction, ejaculatory dysfunction, and decreased libido [19]. However, these results have not been confirmed.

More recent studies have focused on mental health complications associated with ABs and 5ARIs. A population-based cohort study of more than 93,000 Canadian men, who used either finasteride or dutasteride for an average of 1.57 years, found that these men had an increased risk of self-harm within the first 18 months of initiating therapy, although there was no increased suicide risk. They were also at an increased risk of depression that was most pronounced within the first 18 months [20•]. A cross-sectional survey of 4035 Polish men also found a 1.5-fold increased risk of depression among men on a 5ARI [21]. Furthermore, Irwig assessed depressive symptoms in former-finasteride users with persistent sexual side effects and found that compared with controls, these patients had a significantly higher incidence of depressive symptoms and suicidal ideation [22]. A propensity score–matched analysis of patients on five different BPH medications, including tamsulosin and finasteride, and patients who were not on medical therapy, found that patients on tamsulosin had an increased incidence of dementia compared with patients who were not on medical therapy, who were on finasteride, or on one of the other ABs [23]. However, a similar propensity score–matched analysis of Korean men found that there was no difference in the incidence of dementia among patients being treated with tamsulosin [24].

Other treatments for LUTS include phosphodiesterase type 5 (PDE-5) inhibitors and anticholinergics/β3 agonists. In multiple studies, PDE-5 inhibitors have been shown to improve IPSS scores without affecting Q_{max} or post-void residual urine volumes [25–27]. A metanalysis of four randomized controlled trials that examined the effects of tadalafil on LUTS found that both patients with and without ED experienced improvements in IPSS scores [28]. All studies that have evaluated PDE-5 inhibitors have short follow up and have not

Table 1 Adverse events of the ABs compared with placebo

Drug	Asthenia	Rhinitis	Dizziness	Headache	Syncope	Hypotension	Postural hypotension	Libido	EjD	ED
Placebo	1.1–7	0.2, 5	4.6–7.4	0.9–18	0–4	1.5	0.5–1.5	1–1.9	0–1.5	1.8–5
Terazosin	14	7	26	6	1		8	3	0.3	6
Doxazosin	10.5**	N/R	15.6**	N/R	1	5.1**	5.8**	3.6	0.4	5.8
Tamsulosin										
0.4	5	12*	10	20	N/R	N/R	N/R	N/R	6**†	N/R
0.8	5	15**	11*	18	N/R	N/R	N/R	N/R	18**†	N/R
Alfuzosin	2.1		6	3.3	0.7	N/R	1.2	N/R	0.4	2
Silodosin		2.1	3.2	2.4	N/R	N/R	2.6	N/R	28.1	N/R

*$p < 0.05$ compared ** $p < 0.01$ compared with placebo. † $p < 0.05$ tamsulosin 0.4 mg vs 0.8 mg. *N/R*, not reported

analyzed disease progression. Therefore, although tadalafil is FDA approved for the treatment of LUTS, it is difficult to draw any conclusions about its long-term efficacy [29]. The role of anticholinergics in the management of BPH and LUTS has also been examined. Detrusor overactivity and associated over active bladder have been identified in 45–50% of men with BPH. Treatment with anticholinergic monotherapy has had variable results. In a large randomized trial, patients who were treated with tolterodine and tamsulosin or tamsulosin alone had significant improvements in IPSS score compared with placebo, while those treated with tolterodine monotherapy did not [30].

Since ABs and 5ARIs alone and/or in combination are the first-line treatment of LUTS, the remainder of this review will focus on these two treatments [11, 29].

Trials Demonstrating Effects of Combination Therapy

After the approval of ABs and 5ARIs for the treatment of BPH, several pivotal trials were published evaluating their combined use. The Medical Therapy of Prostatic Symptoms (MTOPS) trial randomized over 3000 men to receive therapy with either placebo, an AB (doxazosin), a 5ARI (finasteride), or combination therapy. The primary outcome was clinical progression, which was defined as a 4-point or greater increase in AUA symptom score, urinary retention, incontinence, renal insufficiency, or recurrent UTI. The study found that at 4 years' follow-up, compared with placebo, treatment with an AB and 5ARI significantly reduced the rate of clinical progression by 39% and 34%, respectively. Combination therapy reduced the rate of disease progression by 66%, which was a significantly greater reduction than either medication alone [31]. MTOPS also helped delineate which patients would benefit the most from combination therapy. For patients with prostate volumes (PV) of < 25 mL, the risk of progression with combination therapy was not significantly less than either drug alone but was associated with more side effects. Therefore, these patients are likely to benefit the most from monotherapy with an AB [32].

The Combination of Avodart and Tamsulosin (CombAT) study also attempted to determine if combination therapy was better than treatment with either a 5ARI or AB alone. The primary end point was time to first episode of urinary retention or BPH-related prostatic surgery. Combination therapy decreased the risk of urinary retention or BPH surgery by 66% compared with an AB and by 20% compared with a 5ARI. Similar to MTOPS, a 5ARI and combination therapy, as opposed to just an AB, benefited men with a PV > 40 mL or a PSA ≥ 1.5 ng/mL [33].

The studies above demonstrated that medical management is an effective strategy for treating BPH. However, some patients will fail medical therapy for one of three reasons: not being adherent, not responding to treatment, or disease progression.

Persistence with Medical Therapy

Rates of patient persistence with medical therapy for BPH vary in the literature from 30 to 40% [34–36]. In a population-based cohort study, Cindolo et al. found that of 1.4 million men treated with 5ARIs or ABs, either alone or in combination, only 29% continued with medical therapy at 1 year. Medication adherence was poorest among men on combination therapy, only 9% of whom continued with therapy at 1 year [36]. Persistence with medical therapy is hampered by the side effects of treatment. In several studies, the most common reason for discontinuing therapy was medication side effects [31, 34].

Patients Who Do Not Respond to Medical Therapy

Although ABs and 5ARIs can improve symptoms and prevent disease progression, at least 25–30% of patients have no response and 7% of patients progress despite therapy. The patients who do not respond are either resistant to therapy or have a symptom etiology that is not being treated by the prescribed medications.

There are several mechanisms of resistance to current therapies. For example, response to ABs depends on the density of α-receptors in the prostate and the adenoma [37]. In addition, the mRNA expression of α-receptor subtypes can predict the response to prescribed AB therapy [38]. Similarly, response to 5ARIs depends on the expression of 5α-reductase. Up to 30% of patients do not express 5α-reductase type 2 in their radical prostatectomy specimen and therefore would not respond to 5ARIs [39]. Epigenetic modifications may account for why some men do not express 5α-reductase. Bechis et al. found that methylation of the 5α-reductase gene promoter is associated with a lack of 5α-reductase type 2 protein expression [40, 41]. Age and BMI are associated with methylation, which would explain why obesity and age are associated with an increased likelihood of failing 5ARI therapy [40]. In addition, Kang et al. found that polymorphisms in two 5α-reductase genes, SRD5A1 and SR5A2, are associated with post-5ARI treatment change in prostate volumes and IPSS scores [42].

Another explanation for treatment failure or progression is that prostatic growth is the result of multiple factors some of which are not being targeted by current treatments. More specifically, several studies have shown that BPH tissue has a high volume of inflammatory infiltrate, which is composed primarily of T cells as well as B lymphocytes and

macrophages [43, 44]. The cytokines released from these cells may lead to BPH by increasing growth factor production and angiogenesis similar to a wound healing response [43]. In addition, cytokine release has been implicated as a driving factor in epithelial and stromal cell proliferation [45]. Clinically, higher levels of prostatic inflammation have been associated with larger prostates and higher IPSS scores [44]. The risk of acute urinary retention is also greater in men with prostatic inflammation than those without [46].

Several studies have found that prostate growth and LUTS symptoms can be improved by decreasing inflammation. The most extensively studied treatment is BXL 628 (elocalcitol), a vitamin D3 analog that reduces prostate size in animal and human models in part by reducing IL-8 section [47•]. Cyclooxygenase isoform 2 (COX-2) inhibitors have also been evaluated as a potential therapeutic target to improve BPH. A metanalysis of three studies evaluating the effects of COX-2 inhibitors on LUTS found that patients had significant improvements in urinary flow rates compared with both placebo and current BPH therapies [48].

Predictors of BPH Progression and Treatment Success

Since not all patients respond to medications and some progress despite treatment, current care practices would improve if physicians could identify patients likely to fail medical management as these patients may benefit from early surgical intervention. Baseline patient characteristics that have correlated with disease progression include age, obesity, prostate size, higher PSA values, and presence of prostatic inflammation [49–52]. Voiding parameters that have been strongly associated with both the development of urinary retention and disease progression include higher post-void residual volumes and a lower Q_{max} [50, 53]. More recent data suggest that depression may also be associated with LUTS progression [54].

Prostatic inflammation has been identified not only as an important factor in BPH development but also as a predictor of BPH progression. Sub-analyses of the MTOPS population found that patients with a greater concentration of inflammatory markers in their prostate biopsy specimens were significantly more likely to experience urinary retention, worsening of their symptoms, or incontinence [55, 56]. Chronic inflammation was also associated with an increased risk of disease progression and developing urinary retention on sub-analysis of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial population [57•].

Predictors of disease progression while on medical therapy are similar to the predictors of overall disease progression. Higher IPSS scores and larger prostates correlate with failure of medical therapy [58, 59]. Sonographic findings, such as intra-prostatic protrusion (IPP), also predict medical treatment failure and need for surgical intervention [60, 61•, 62•]. Other sonographic findings that may predict progression or failure of medical therapy are bladder wall thickness and estimated bladder weight [63].

Conclusion

Since the 1990s, medical management with an AB or 5ARI has been the first-line treatment for men with BPH. However, a significant proportion of men will eventually need surgery either because of medication non-compliance, medication failure, or disease progression.

In this review, we have explored mechanisms of resistance to current therapies, including decreased expression of α-receptors and 5α-reductase, which may be related to acquired epigenetic modifications. We also identified other causes of BPH and potential therapies. In addition, we reviewed predictors of disease progression. Understanding why patients fail medical therapy is paramount to the more effective treatment of patients and to the identification of novel therapies.

Compliance with Ethical Standards

Conflict of Interest Zeynep G. Gul and Steven A. Kaplan each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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