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Review

The use of 5-alpha reductase inhibitors in the treatment of benign prostatic hyperplasia

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Abstract Benign prostatic hyperplasia (BPH) is characterized by an enlarged prostate, lower urinary tract symptoms (LUTS), and a decreased urinary flow rate. Common in older men, BPH is a progressive disease that can eventually lead to complications including acute urinary retention (AUR) and the need for BPH-related surgery. Both normal and abnormal prostate growth is driven by the androgen dihydrotestosterone (DHT), which is formed from testosterone under the influence of 5-alpha reductase. Thus, 5-alpha reductase inhibitors (5-ARIs) effectively reduce the serum and intraprostatic concentration of DHT, causing an involution of prostate tissue. Two 5-ARIs are currently available for the treatment of BPH—finasteride and dutasteride. Both have been demonstrated to decrease prostate volume, improve LUTS and urinary flow rates, which ultimately reduces the risk of AUR and BPH-related surgery. Therefore, either alone or in combination with other BPH medications, 5-ARIs are a mainstay of BPH management.

1. Introduction

Benign prostatic hyperplasia (BPH) is a common problem among men aged over 50 years and its prevalence increases with age [1,2]. Characterized by lower urinary tract symptoms (LUTS), enlarged prostate size, and decreased urinary flow rate, the progressive nature of BPH can be quantified by increases in LUTS severity according to the International Prostate Symptom Score (IPSS), deterioration in peak urinary flow rate (Q_{max}), episodes of acute urinary retention (AUR), or the need for BPH-related surgery [3].

Prostate volume appears to be the greatest risk factor associated with BPH progression, as men with prostate volumes of 30 mL or greater have a 3–4 times higher likelihood of moderate-to-severe LUTS as defined by the IPSS, 2–3 times higher incidence of reduced Q_{max}, and 3–4 times higher likelihood to experience AUR when compared to men with prostate volumes less than 30 mL [4]. Increasing

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prostate volume is also associated with the need for BPH-related surgery [5]. Serum prostate-specific antigen (PSA), as a biomarker for prostate volume, appears to predict BPH progression. In patients with a PSA of 1.4 ng/mL or higher, the annual rate of prostate growth was seen as high as 3.3 g, and was associated with an increased risk of AUR, worse LUTS, and decreases in Q_{max} [6,7]. Observing the BPH progression rates in men who were treated in the placebo arm of the Medical Therapy of Prostatic Symptoms (MTOPS) trial, a number of baseline predictors for an increased risk of BPH progression were identified—prostate volume $\geq$30 g, PSA $>$1.5 ng/mL, Q_{max} $<$10 mL/s, post-void residual urine $>$38 mL, and age $\geq$62 years [8].

Over the last 20 years, the treatment of BPH has transitioned from surgery to medical management with the advent of selective alpha-adrenergic blockers and 5-alpha reductase inhibitors (5-ARI) [9–11]. While alpha-adrenergic blockers treat LUTS associated with BPH, 5-ARI treat the obstructive component of the disease by reducing prostate volume. The purpose of this review is to examine the mechanism of action of 5-ARIs, their efficacy and safety, and their role in the management of BPH.

2. Mechanism of action of 5-ARIs

Normal prostate development as well as BPH progression occurs under the influence of dihydrotestosterone (DHT), which is a derivative of testosterone with a higher affinity for the androgen receptor [12]. The conversion of testosterone to DHT occurs by the enzyme 5-alpha reductase; therefore, DHT production can be inhibited by 5-ARIs. Although both commercially available 5-ARIs are 4-azasteroids that behave as selective, irreversible inhibitors of 5-alpha reductase, dutasteride inhibits both isoenzymes of 5-alpha reductase (types 1 and 2), while finasteride only inhibits 5-alpha reductase type 2 [13,14]. Furthermore, studies have demonstrated that dutasteride is a 45 times more potent inhibitor of 5-alpha reductase type 1 and a 2.5 times more potent inhibitor of 5-alpha reductase type 2, when compared to finasteride [15,16].

3. Biologic efficacy of 5-ARIs

As discussed above, 5-ARIs act to reduce the serum and intraprostatic DHT concentration, thereby causing involution of the prostatic epithelium and slowing the progression of BPH [17]. The efficacy of both finasteride and dutasteride in reducing DHT has been demonstrated in a number of studies. In a direct comparison of dutasteride (0.5 mg/day) to finasteride (5 mg/day), the mean serum DHT levels after 24 weeks of treatment were found to be suppressed by 95% *vs*. 71%, respectively [18]. The effect of 5-ARIs becomes more pronounced within the prostatic tissue, as finasteride was found to reduce intraprostatic DHT levels by 80% (1 mg daily) and 91% (5 mg daily) over the course of 8 weeks compared to placebo [19]. In a separate study, dutasteride (0.5 mg daily) was found to reduce intraprostatic DHT levels by 94% over the course of 12 weeks compared to placebo [20].

While the direct effects of 5-ARI lead to a dramatic reduction in serum DHT levels, other laboratory values are also affected by 5-ARI use. Serum testosterone elevations are known to occur with both finasteride and dutasteride use, but values will typically remain within the normal laboratory range [18]. Additionally, given the intended effect of 5-ARI causing the involution of prostatic epithelial tissue, which is the main source of intraprostatic as well as serum PSA, the inhibition of DHT by 5-ARI indirectly results in a decrease in PSA. For example, the use of finasteride for 12 months duration has been found to lower serum PSA by approximately 50% [21].

4. Clinical efficacy of 5-ARIs

4.1. Monotherapy

A number of studies have examined finasteride and dutasteride use as monotherapy for BPH. In one of the longer studies of finasteride therapy, 36 months of treatment was found to reduce prostate volume by 27% compared to baseline, improve Q_{max} by 2.3 mL/s, and improve IPSS by 3.6 points [22]. In order to clarify which patients benefited most from finasteride treatment, a meta-analysis of the six early trials of finasteride—pooling 2601 men—was performed. Boyle et al. [23] found that men with larger baseline prostate volumes benefited most from finasteride use: IPSS improved by 1.8 *vs*. 2.8 points in those with prostate volume $<$20 g *vs*. $>$60 g, and Q_{max} improved 0.9 mL/s *vs*. 1.8 mL/s, respectively. They concluded that finasteride was most effective in men with larger prostates ($>$40 g). As a result, the Proscar Long-Term Efficacy and Safety Study (PLESS)—a multicenter, randomized, double-blind, placebo controlled trial—enrolled 3040 men with symptomatic LUTS (based on IPSS and Q_{max}) with a mean 55 g prostate volume among participants. Over a 4-year study period, finasteride reduced prostate volume by 18% versus an increase of 14% in the placebo group. Additionally, the finasteride group had improvements in IPSS (2.6 *vs*. 1.0 points in the placebo arm) and Q_{max} (1.9 mL/s *vs*. 0.2 mL/s in the placebo arm). Most importantly, the finasteride group had a significantly reduced risk of AUR (57%) and BPH-related surgery (55%) as compared to the placebo group [24].

The clinical efficacy of dutasteride has been examined in multiple 2-year, double-blind, placebo controlled studies [25]. Including 4325 men with prostate volumes $>$30 g, dutasteride treatment significantly improved IPSS (4.5 points *vs*. 2.3 points for placebo) and Q_{max} (2 mL/s *vs*. 0.6 mL/s for placebo). Similar to PLESS, the dutasteride was associated with a significant risk reduction of AUR (57%) and BPH-related surgery (48%). A proportion of these men (n = 1188) were enrolled in an open-label 2-year continuation phase of therapy (4-year total of dutasteride therapy), with a very low rate of AUR and BPH-related surgery (2.4% and 2.6%, respectively) [26]. In comparison, the placebo group of PLESS had a 4-year cumulative risk of 7% for AUR and 10% for BPH-related surgery [24].

Although the primary outcome measure was related to prostate cancer rather than BPH, the Prostate Cancer Prevention Trial (PCPT) provides insight into the clinical efficacy of finasteride. In a 7-year study of men with a clinically normal prostate examination who were randomized to finasteride or placebo, the PCPT confirmed that

finasteride reduces the number of BPH diagnoses (5.2% *vs*. 8.7% for placebo), reduces the risk of AUR (4.2% *vs*. 6.3% for placebo), reduces the need for BPH-related surgery (1.0% *vs*. 1.9% for placebo) [27]. Similarly, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial demonstrated a significantly lower risk of AUR in men that were randomized to dutasteride during a 4 year period (1.6% *vs*. 6.7% for placebo) [28].

4.2. Combination therapy

As alpha-adrenergic blockers (alpha blockers) and 5-ARI have different mechanisms of action in the treatment of BPH, the combination of these two types of medications are thought to be synergistic [29]. Alpha blockers have been demonstrated to improve LUTS related to BPH and have a faster onset of symptom relief compared to 5-ARI; however, alpha blockers have not been shown to reduce the long-term risk of AUR or need for BPH-related surgery [30]. In fact, the longer term reductions in risk of AUR and need for BPH-related surgery were unique to 5-ARIs in the MTOPS trial, which randomized over 3400 men to the alpha blocker doxazosin or finasteride or both for a mean follow-up of 4.5 years. More importantly, in the MTOPS study, the risk of overall clinical progression (defined as IPSS increase of $\geq$4 points, AUR, incontinence, renal insufficiency, or recurrent urinary tract infections) was reduced by 66% with combination therapy as compared to 39% with doxazosin alone and 34% with finasteride alone [8].

Similarly, the Combination of Avodart and Tamsulosin (CombAT) trial examined the effect of dutasteride and the alpha blocker tamsulosin in combination and alone on the risk of AUR or need for BPH-related surgery. With 4844 men randomized and 3195 followed through the study duration of 4 years, combination therapy was found to significantly reduce the risk of AUR or BPH-related surgery by 66% compared to tamsulosin alone and by 20% compared to dutasteride alone. Additionally, combination therapy was associated with a significant reduction in IPSS when compared to either medication alone (6.3 points *vs*. 3.8 points for tamsulosin and 5.3 points for dutasteride) [31].

Not all trials have demonstrated superiority of combination therapy for BPH treatment. Neither the Veterans Affairs (VA) trial nor the Prospective European Doxazosin and Combination Therapy (PREDICT) study did not demonstrate a benefit for combination therapy over alpha blockers alone. The VA trial compared the alpha blocker terazosin and finasteride, as well as combination therapy, in a group of 1229 men with BPH. Lepor et al. [32] found no significant improvements for combination therapy over terazosin alone in IPSS or Q_{max} after 1 year of treatment. Similarly, the PREDICT study compared the alpha blocker doxazosin and finasteride, as well as combination therapy, in a group of 1100 men with BPH. No significant improvements in IPSS or Q_{max} were seen with finasteride over placebo after 1 year of treatment; and the combination of finasteride and doxazosin did not significantly improve these parameters over doxazosin alone [33]. The lack of benefit with combination therapy in both of these trials are attributed to the study design minimizing the effect of finasteride. By including men with smaller prostate volumes, examining the treatment effects are a relatively short duration of treatment, and excluding more clinically meaningful endpoints (e.g. risk of AUR or need for BPH-related surgery), the known benefits of finasteride in BPH treatment were nullified.

5. Tolerability of 5-ARIs

Finasteride was demonstrated to be well tolerated in PLESS, with the number of withdrawals from treatment due to side effects similar in the finasteride and placebo groups (11.5% *vs*. 10.9%). The side effects more frequently encountered in the finasteride group as compared to placebo were decreased libido, impotence, decreased ejaculate volume, ejaculation disorders, breast enlargement, breast tenderness, and general rash [24]. Similar tolerability profiles were found in PCPT, with sexual side effects and gynecomastia more common with finasteride treatment compared to placebo [27]. In the studies of dutasteride, the drug-related adverse event rate was similar between dutasteride and placebo (19% *vs*. 14%). The same proportion of men withdrew from the dutasteride and placebo groups due to side effects (8.9% in both groups) [25]. With dutasteride use for 4 years, the rate of newly reported sexual side effects generally decreased with time; however, gynecomastia had a relatively constant rate of incidence (1.3% in year 1 and 2, 1.8% in year 3, and 0.7% in year 4) [26]. In the MTOPS and CombAT trials, combination therapy with 5-ARIs and alpha blockers appear to be well tolerated with a similar side effect profile to the individual monotherapies used in combination [8,31].

6. Clinical guidelines for 5-ARIs

Given the numerous studies demonstrating the clinical efficacy of 5-ARIs in the treatment of BPH, both the European Association of Urology (EAU) and the American Urologic Association (AUA) include 5-ARIs prominently in their guidelines for management of BPH. The EAU gives a grade A recommendation for the use of 5-ARIs for patients with moderate to severe LUTS and enlarged prostates ($>$40 g) and a grade A recommendation for the use of 5-ARIs in combination with alpha blockers for men likely to develop disease progression (e.g., larger prostate volume, reduced Q_{max}) [34]. Similarly, the AUA guidelines for management of BPH discuss 5-ARIs as an option for combination therapy with alpha blockers in men with demonstrable prostatic enlargement, noting the prevention of BPH progression noted with 5-ARI use (e.g., risk of AUR and need for BPH-related surgery). Additionally, the AUA guidelines specifically recommend against the use of 5-ARIs in men without prostatic enlargement [35].

Given the results of the PCPT and the REDUCE trial, clinicians must keep in mind the associations between 5-ARI use and prostate cancer. In the PCPT, patients randomized to finasteride had a roughly 25% lower incidence of prostate cancer as compared to placebo, but an increased proportion of prostate cancer diagnoses were high grade (37% *vs*. 22%) [27]. Similarly in the REDUCE trial, the prostate cancer incidence was 23% lower for men randomized to dutasteride, but the incidence of the highest grades of prostate

cancer (e.g., Gleason score 8—10) was greater than placebo (0.9% *vs.* 0.6%, $p = 0.15$) [28]. Many subsequent studies have demonstrated that the higher rate of high grade prostate cancer found with 5-ARI treatment was a result of selective inhibition of low grade cancers and decreased prostate volume resulting in improved biopsy yield [36,37]. However, the Food and Drug Administration has added a black box warning to 5-ARIs concerning the increased risk of developing high grade prostate cancer.

7. Conclusion

The natural history of BPH is that of a progressive disease that can lead to AUR or the need for BPH-related surgery in some men. The prevention of BPH progression as well as the LUTS related to BPH are important elements to successful BPH management. Among the available BPH medications, only 5-ARIs have been shown to decrease prostate volume, thus reducing the risk of AUR and BPH-related surgery as compared to placebo. For men with enlarged prostates, the use of 5-ARI alone or in combination with alpha blockers is a mainstay of BPH treatment, and is reinforced by both the EAU and AUA guidelines for management.

Conflicts of interest

The authors declare no conflicts of interest.

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