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REVIEW

A Review of Dutasteride as Monotherapy in Benign Prostatic Hyperplasia

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Abstract: Treatment of benign prostatic hyperplasia (BPH) has evolved over that last 10 years consequent to the results of several important clinical trials. Although the primary concern for patients is their symptoms, we as urologists are further concerned about the progression of disease and complications of the disease. Two classes of medications, alpha blockers and 5 alpha reductase inhibitors (5ARI), have shown excellent results for treatment of symptoms and improvement of peak urine flow. Either medication alone has benefit, however, the combination of these medications seems to have more benefit than either alone as best demonstrated by 2 major clinical trials. Though combination therapy is overall superior, evidence has shown that dutasteride as monotherapy has continually improving effects on BPH symtoms and progression of disease beyond 2 years of treatment. Given the cost and side effects of a dual treatment regimen coupled with evidence for continued symptom relief when alpha blockers are removed from combination with dutasteride, there is good evidence for use of dutasteride as long-term monotherapy. Although the evidence thus far favours dutasteride over finasteride in symptom relief and peak urine flow in BPH patients, the difference in selection criteria between finasteride and dutasteride trials creates difficulty in deciding superiority of one over the other. The evidence for dutasteride as monotherapy for BPH is reviewed herein with some comparisons to finasteride.

Keywords: prostate, benign prostatic hyperplasia, benign prostatic enlargement, neoplasm, dutasteride, finasteride

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Introduction

Lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) are highly prevalent. The majority of LUTS in aging men are likely due to BPH with a smaller contribution from a variety of other conditions (e.g. overactive bladder, stones, strictures). LUTS are traditionally divided into voiding (obstructive or emptying) and irritative (storage) symptoms. Voiding symptoms are more common, however, storage symptoms are more bothersome and have a greater impact on a patient's life.[1,2] The prevalence of BPH rises with age so that approximately 25% of men age 40 or over will suffer from LUTS.[3] For a sixty year-old man, over a lifetime, there is approximately a one in four risk of developing acute urinary retention (AUR)[4] and almost a third will require BPH-related surgery.[5]

BPH is a slowly progressing condition with an average decline in peak urine flow rate of 0.2 ml/sec/year and an average increase in prostate volume of 1–2 cc per year.[6] Larger prostates tend to suffer faster growth rates[7] and are associated with a higher chance of moderate to severe LUTS.[8] Hence, the primary aim of any treatment for BPH in the vast majority of men is to relieve bothersome obstructive and irritative symptoms that develop slowly over time.[9] Treatment is often undertaken on an elective basis for such patients. Conversely, those in whom complications of BPH occur have urgent treatment as a matter of course. A range of treatment options are available and may be tailored to the needs of every individual, taking into account their disease manifestations, success rates of treatment, possible complications and patient preference. Watchful waiting with lifestyle modifications is recommended for patients with mild symptoms, medical treatment for patients with mild-moderate symptoms, and surgery for patients who failed medical or conservative management and who have moderate-severe symptoms, and/or complications of BPH.[10,11]

Medical management has now become the favoured first line treatment and is recommended in both the EAU and AUA guidleines.[10,11] The medical treatment of LUTS suggestive of BPH is driven by two major factors: the desire to relieve bothersome symptoms and the desire to prevent disease progression.[12] Currently the three main options for medical treatment are: 5α-reductase inhibitors (5ARIs), α_1-adrenoceptor antagonists (ARBs), and their combination.[12] Anticholinergics and nutraceutical compounds, though used by some, are not considered first line. This review will focus on 5ARIs, and in particular the role of the newer agent dutasteride as monotherapy in BPH with comparisons to its cousin, finasteride. Given the correlation between prostate size and LUTS along with progression of disease, the impact of 5ARIs on prostate size builds a strong rationale for their utility in BPH management.

Androgen Metabolism and BPH Development

Prostatic epithelial cells express the androgen receptor.[13] From the beginning of embryonic differentiation to pubertal maturation and beyond, androgens are a prerequisite for the normal development and physiological control of the prostate.[14] Androgens help maintain the normal metabolic and secretory functions of the prostate. They are also implicated in the development of BPH and prostate cancer.[15] Androgens act in combination with other hormones and growth factors currently being investigated in the mechanism of BPH.[16] Androgens also interact with prostate stromal cells releasing soluble paracrine factors that are important in the growth and development of the prostate epithelium.[17] These paracrine pathways may be critical in regulating the balance between proliferation and death of prostate epithelial cells in the adult.[15]

A balanced androgen metabolism is believed to be a prerequisite for the normal androgen responsiveness of the prostate. The level of various different androgens is regulated by a complex interplay of androgen metabolising enzymes. Testosterone is the most important androgen in the process. There are reductive (e.g. 5α-reductase) and oxidative (e.g. 17β-HSOROX) enzymes involved.[18] For testosterone to be maximally active in the prostate, it must be converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase,[19,20] DHT has a much greater affinity for the androgen receptor than does testosterone which allows it to accumulate in the prostate even when circulating levels of testosterone are low.[21,22] DHT is approximately twice as potent as testosterone in studies of rats at equivalent androgen concentrations.[23]

Though serum testosterone levels decline with age, DHT concentrations remain high in the prostates of elderly men in part explaining prostate growth with age.[19]

Two 5α-reductase isoforms exist in the prostate. Finasteride inhibits only type II, whereas dutasteride inhibits type I and II with similar potency.[24] The clinical role of dual inhibition remains unclear, considering that type I has minimal expression in the prostate compared to type II.[25] Furthermore, treatment with the dual 5-ARI, dutasteride, results in a greater degree and consistency of dihydrotestosterone suppression compared with finasteride.[26] Both of these enzymes are overexpressed in BPH compared to prostate cancer where type I increases and type II decreases.[27,28] By apoptosis of prostatic cells, 5ARIs cause a reduction of prostate size by about 20%, and they reduce circulating PSA levels by approximately 50%.[27,29] From a practical point of view, due to the slow onset of action (generally greater than 6 months), 5ARIs are not suitable for intermittent treatment. Their rational use is only warranted if a multi-year treatment is intended. Their effect on the circulating PSA level needs to be considered in the use of this parameter for prostate cancer screening.

Disease Progression

The natural history of BPH involves two phases. The pathological or first phase of BPH is asymptomatic and involves a progression from microscopic to macroscopic BPH. Microscopic BPH will develop in almost all men if they live long enough while approximately half will progress to macroscopic BPH. This would suggest that additional factors not common to all men are necessary to cause microscopic to progress to macroscopic BPH.[30] The pathological phase involves development of hyperplastic changes in the transition zone of the prostate.[31] The clinical or second phase of BPH involves the progression from pathological to clinical BPH, usually manifesting as LUTS. Only about one half of patients with macroscopic BPH progress to develop clinical BPH.[30] BPH consists of mechanical (increased volume of tissue) and dynamic (smooth muscle contraction) components and it is these components that are responsible for the progression from pathological to clinical BPH.[32]

There is probably a third phase of BPH development loosely defined by BPH clinical progression. This progression may be interpreted as a deterioration of clinical variables such as LUTS, health-related quality of life and peak flow rate, increased prostate size, or unfavourable outcomes such as AUR and BPH-related surgery.[33] In support, there is evidence from longitudinal studies,[34,35] and to a lesser extent from the placebo arms of large controlled studies,[36,37] that clinical BPH is a progressive disease. Symptom worsening is by far the most frequently occurring progression event. Identifying those patients at risk of BPH progression is crucial to optimize their management.[33] The complications as a consequence of BPH progression include: urinary retention (acute or chronic); renal impairment/failure; recurrent urinary tract infections; bladder calculi; haematuria; secondary overactive bladder; incontinence (overflow or secondary to detrusor overactivity); detrusor decompensation/failure; bladder diverticulae and impaired quality of life. Lack of treatment allows overall persistent deterioration in BPH symptom severity, decline of urine flow, increase in prostate volume, risk of AUR and need for prostatic surgery over time.[38] Men who are more likely to experience disease progression have risk factors as summarised in Box 1.[38–40]

In summary, the physician can estimate the risk of progression from the patient's clinical profile based on the parameters immediately above. After predicting risk, the most appropriate treatment should be established by balancing the benefits of treatment against the possible risks and bother resulting from adverse events.[40] Such assumptions on parameters for BPH progression have recently been challenged in reviewing the large community Olmstead County study data, but further analysis from large cohorts would be needed to repute their value.[41]

Efficacy of 5 ARIs in Treating BPH

The initial benefits of 5ARIs in BPH were reported in short follow-up, early double-blind multicenter

Box 1. Risk factors for disease progression in BPH.

- Prostate volume—large baseline volume
- Age—older at higher risk
- Q_{max}—poor maximum urinary flow rate
- PSA—higher levels increasing risk
- Increased symptom severity

trials with finasteride from North America and Scandnavia.[42–44] A meta-analysis of these trials and others showed that finasteride reduced prostate symptom scores and increased peak flow rates with a greater effect in men with larger prostates (>40 ml).[45] The Proscar Long-term Efficacy and Safety Study (PLESS) subsequently showed efficacy for finasteride in reducing symptoms, prostate volume, probability of surgery and probability of urinary retention with an increase in urinary flow rate compared to placebo in patients with clinical BPH.[46] Other large population-based studies (>1000 patients) compared 5ARIs to placebo, alpha blockers or the combination of 5ARIs and alpha blockers (summarized in Table 1). As with the earlier 5ARI studies, in the combination studies 5ARIs reduced the IPSS value and increased Q_{max} in LUTS/BPH patients.[29] Symptom reduction by ARIs also varied with prostate size.

Monotherapy studies

Three multicenter randomized, double-blind, placebo-controlled trials with 0.5 mg of dutasteride as monotherapy were pooled for analysis (ARIA3001, ARIA 3002 and ARIA3003) and included over 4000 patients with a follow-up of 2 years for the initial report.[47] A subsequent 2 year open label extension allowed placebo cross-over to dutasteride treatment.[48] This pooled study is similar to the PLESS study with finasteride monotherapy to allow for some loose comparisons. The inclusion criteria were men ≥50 years of age, AUASS (American Urologic Association Symptom Score) ≥12, peak flow rate of ≤15, PSA 1.5–10, prostate volume ≥30 cm^3. In the ARIA trials serum DHT was reduced by 90% at 24 months while a separate early study with finasteride showed a serum reduction of DHT by 70%.[44] Reduction in prostate volume was 25.7% at 24 months in the ARIA study[47] compared to an 18% reduction in the PLESS study,[46] however, the PLESS study did not have an absolute prostate volume inclusion which makes comparison of the 2 studies difficult. Similar comparisons in prostate volume reduction were found in the combination studies using both of these compounds.[49,50] Otherwise, the AUASS was reduced by 13% over placebo with dutasteride, similar to PLESS and the Q_{max} increased by 2.2 ml/s, in the range or better than seen in the finasteride trials (1.6–1.9 ml/s).[46,51,52] Improvements in symptoms were noted as early as 3 months for Q_{max} and 6 months for AUASS. The ARIA study showed a 57% risk reduction of AUR and a 48% risk reduction of BPH-related surgery, nearly identical outcomes to the PLESS trial. In the subsequent 2 year open label follow-up ARIA study, the patients on dutasteride from the start continued to have improvement in BPH parameters at 4 years compared to baseline and 2 years independent of prostate volume.[48] However, those from the placebo group who crossed over to dutasteride at 2 years did not have as much improvement in BPH parameters compared to baseline, suggesting this medication has continued improvements up to 4 years. Post hoc analysis of the ARIA trials compared prostates that were 30–40 cm to those that were >40 cm showing no difference in effect on AUASI and Q_{max}.[53] By contrast, the effect on AUR was similar for smaller prostates (60% decrease compared to 55%) with the effect on preventing surgery being greater and only significant for the larger prostates (27% vs. 48%). In short, indirect comparison of the monotherapy studies involving dutasteride and finasteride suggest nearly equivalent results in treatment of BPH symptoms and progression, although some may argue dutasteride has minor advantages.

A one year randomized, double-blinded comparison of finasteride and dutasteride in men with BPH (EPICS: Enlarged Prostate International Comparator Study) found a trend for dutasteride improvement over finasteride in IPSS (International Prostate Symptom Score) that did not reach statistical significance (abstract).[54] Another non-randomized comparative trial with 240 patients, published only in abstract form, showed a small improvement in AUASI and Q_{max} for dutasteride.[55] However, dutasteride and finasteride have never been compared in long-term therapy, either as monotherapy or in combination with an alpha-blocker. These medications appear to exert continued effects beyond 1 year so comparison after only 1 year is immature.

Combination studies

The randomized, double-blind placebo-controlled trials comparing 5ARIs, alpha blockers and their combinations are summaried in Table 1. The 2 early trials evaluating terazosin (Veterans Affairs Study)[52] or doxazosin (PREDICT [Prospective European

Table 1. Large population based data to compare the effects of placebo, 5ARI, alpha blocker and combination therapy for treating BPH.

Trial and reference	Number of men and age	Inclusion	Arms	Early findings at 1 year	Later findings at 4 years
Combat[56]	n = 4844; ≥50 years age	IPSS ≥12, prostate volume ≥30 cm, PSA 1.5–10 ng/ml, and Q_{max} > 5 and ≤15 ml/s mean baseline prostate volume was 55 cc and PSA 4.0 ng/ml	3 study arms: Dutasteride (Du) vs. placebo; 2) Tamsulosin (Tam) vs. placebo 3) Combination (Tam + Du) vs. placebo	Combination Tx superior to Tam or Du alone	Combination Tx superior to Tam alone but not Du alone at reducing the relative risk of AUR or BPH-related surgery. Combination Tx superior to Tam or Du alone at improving symptoms and reducing the relative risk of BPH clinical progression
MTOPS[49]	n = 3047	AUA symptom score 8–30, Q_{max} >4 and ≤15 ml/s mean baseline prostate volume was 36.3 cc and PSA 2.4 ng/ml	4 study arms 1) placebo; 2) doxazosin (Dox; 4 to 8 mg); 3) finasteride (F; 5 mg) and 4) combination Tx (Dox + F)	Combination Tx was superior to finasteride alone but not to Dox alone	Combination Tx significantly decreased incidence of a composite end point of progression compared with Dox, F or placebo. Combination Tx significantly more effective than F or Dox for decreasing LUTS. Men with prostate volume >25 cc had a significantly greater decrease in symptoms when they received finasteride in addition to doxazosin compared with doxazosin alone
PREDICT[51]	n = 1007; 50–80 years age	IPSS ≥12, prostate volume ≥30 cm, PSA 1.5–10 ng/ml, and Q_{max} >5 and ≤15 ml/s + enlarged gland on DRE mean baseline prostate volume was 36.3 g and PSA 2.6 ng/ml	4 study arms 1) placebo (P); 2) doxazosin (Dox; 1–8 mg); 3) finasteride (F; 5 mg) and 4) combination Tx (Dox + F)	Combination Tx improved IPSS and Q_{max} compared to P and F but not against Dox alone. F alone not different from P	NA
Veterans Affairs Cooperative Studies[52]	n = 1229	AUA symptom score ≥8, Q_{max} >4 and ≤15 ml/s mean baseline prostate volume was 36.2–38. 4 cc and PSA 2.2–2.4 ng/ml	4 study arms: placebo, terazosin (Ter; 10 mg daily), finasteride (F; 5 mg daily), and combination Tx (Ter + F)	Combination Tx improved IPSS and Q_{max} compared to P and F but not against Ter alone. F alone not different from P	NA

Doxazosin and Combination Therapy] trial),[51] finasteride and their combinations were not encouraging with respect to the future of 5ARIs in BPH management. With nearly identical inclusion criteria and endpoints, both trials showed that terazosin or doxazosin had improvements over placebo or finasteride with regard to symptom scores and peak urine flow rates. Finasteride did not outperform placebo for these endpoints, nor did its combination with an alpha blocker improve on alpha blocker monotherapy. In the PREDICT trial finasteride did have a differential effect of significant improvement in obstructive symptoms with no improvement in irritative symptoms.[51] Though these trials had just over 1000 patients, they did not have the numbers or length of follow-up to assess important markers of progression such as need for surgery or risk of AUR. Recall from the monotherapy trials that the benefits of dutasteride continue up to 4 years.[48]

MTOPS study

The MTOPS (Medical Therapy of Prostatic Symptoms) study marked the first large comparative study between an alpha blocker (doxazosin) and a 5ARI (finasteride) with a long mean follow-up of 4.5 years and a primary endpoint of disease progression.[49] This was a double-blind, placebo-controlled, multi-center, clinical trial of 3047 men randomized to 4 study arms 1) placebo; 2) doxazosin [4 to 8 mg]; 3) finasteride [5 mg] and 4) combination of both doxazosin and finasteride. Disease progression, defined as an increase in AUASS of 4, AUR, renal insufficiency, recurrent UTIs and urinary incontinence, was prevented equally by doxazosin and finasteride with an even greater effect when the 2 medications were combined. From the standpoint of 5ARI monotherapy, incidence of AUR and need for BPH-related surgery were only prevented by finasteride in long-term follow-up regardless of doxazosin treatment status,[49] supporting the results of the PLESS and ARIA studies.[46,47] Unlike the Veterans Affairs and PREDICT studies, finasteride alone did improve overall AUASS and peak urine flow compared to placebo at 4 years and even more so when combined with doxazosin.[49] This finding coincides with the long-term open label ARIA dutasteride study described above showing a cumulative symptom benefit of treatment up to 4 years.[48]

CombAT study

Due to the encouraging results of the MTOPs trial with combination therapy for BPH, further studies examining the type I and II 5ARI dutasteride were pursued, in this case with the selective alpha 1a blocker tamsulosin. The CombAT study (Combination of Avodart™ [dutasteride] and tamsulosin) was a multicentre (35), double-blind, parallel-group randomized control trial with 4844 men.[56] Its main limitation was the lack of a placebo arm. The aims of this study were to investigate whether combination therapy was more effective than either monotherapy in reducing the relative risk for AUR, BPH-related surgery, and BPH clinical progression over 4 years in men at increased risk of progression. The inclusion criteria for this study selected for men at higher risk of progression than the MTOPs study with an I-PSS of ≥12, a prostate volume of ≥30 cm^3, and a PSA of 1.5–10 ng/ml, with other criteria being similar to MTOPS (age ≥50 yr, clinical diagnosis of BPH, Q_{max} >5 and ≤15 ml/s with voided volume of ≥125 ml). The mean prostate size was 55.0 cc and 36.3 cc and the mean PSA was 2.4 ng/ml and 4.0 ng/ml for the participants in the CombAT and MTOPS studies, respectively, reflecting the greater percentage of higher risk patients in the CombAT study.

The combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg daily) or each alone were tested with a 2 year primary end point of change in I-PSS from baseline[50] and 4 year primary endpoints of time to first AUR or BPH-related surgery.[56] Secondary end points included BPH clinical progression, symptoms, Q_{max}, prostate volume, safety, and tolerability. Unlike the MTOPS trial, the CombAT trial closely followed the temporal changes in endpoints over 4 years. As such, the initial 2 year report showed that the dutasteride influence on combination therapy was evident by 9 months continuing out to 2 years as demonstrated by the combination arm having greater effects on I-PSS, Q_{max} and quality of life measures than either monotherapy arm.[50,57] As well, dutasteride alone started to outperform tamsulosin for I-PSS and Q_{max} endpoints at 2 years,[50] with a continued cumulative effect out to 48 months in the follow-up report.[56] In fact, at 48 months there was no significant difference in Q_{max} between dutasteride and combination therapy. By comparison, in the MTOPS study doxazosin had

more impact on the AUASS and a trend for lower Q_{max} than finasteride at 4 years.[49] Furthermore, a lower symptom score was not found at 1 year in the combination arm of the MTOPS study compared to doxazosin. In the 4 year follow-up CombAT data, combination therapy was significantly superior to tamsulosin monotherapy, but not dutasteride monotherapy in reducing the relative risk of AUR or BPH-related surgery,[56] mirroring the results of the MTOPS trial.[49] Likewise, combination therapy was significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression,[56] as defined previously in the MTOPS trial.[49] In conclusion, the CombAT study supports the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement. Additional evidence suggests that dutasteride monotherapy is better than alpha blocker monotherapy in the long-term.

In a post hoc analysis of the combAT trial 2 year data, the effect of individual baseline parameters for each arm of the study were determined for the study endpoints.[58] With respect to the main endpoint, prostate symptom score, a greater impact of dutasteride over tamsulosin was observed in those with an I-PSS >16, prostate volume >49 cc, PSA >3.5 ng/ml and I-PSS QoL score ≥4, suggesting these are rough criteria for those who may benefit from monotherapy. As for Q_{max} outcomes, combination therapy only outperformed dutasteride in those with PSA and prostate volumes above the 75 percentile. Clearly, those with larger prostates and higher PSAs have greater benefit with dutasteride coinciding with the size reduction impact of this drug.

Discontinuation of alpha blockers in combination tharapy

The results of the MTOPS and CombAT trials both suggest combination therapy is better than 5ARI monotherapy at the 4 year mark. The higher incidence of adverse effects, the increased cost of combination therapy and the need for prolonged therapy argue for a reductionist medical approach to this condition. One recent small study investigated the discontinuation of 5ARIs in patients on combination therapy and found prostate regrowth and worsening of symptoms after 1 year of cessation, emphasizing the importance of 5ARIs in prolonged therapy.[59] In an opposing design, the SMART trial (Symptom Management After Reducing Therapy) observed the affect of removing the alpha blocker (tamsulosin) after 6 months of combined therapy with dutasteride.[57] With I-PSS as the primary outcome, the investigators found that 77% of patients had symptoms that were the same or better after only 3 months of alpha blocker removal. In reference to the CombAT study, the effects of dutasteride continue past 2 years suggesting that removal of the alpha blocker at later time points may be even less noticeable.

Other Potential Benefits of ARIs

In BPH, 5ARIs can reduce symptomatic hematuria and also blood loss during transurethral prostate surgery, possibly due to their effects on prostatic vascularisation.[60] More recently, as part of the Prostate Cancer Prevention Trial (PCPT) involving over 18,000 men, it was concluded that finasteride delays the appearance of prostate cancer whilst reducing the risk of urinary problems.[61] However, there was an increased risk of high grade prostate cancer (Gleason score 7 or greater) leading to the discontinuation of this study. Thus the benefits need to be weighed against the sexual side effects and the potential increased risk of high-grade prostate carcinoma.[62] Further recent analysis of PCPT has highlighted the finding that finasteride therapy significantly reduced the risk of prostate cancer by 24.8% ($P < 0.001$) compared with placebo.[63] Further analyses of the data from the PCPT together with other clinical findings strongly suggest that the increase in high-grade tumours in the finasteride arm is an artefact.[63] The impact of this new analysis is yet to be realised and may lead to finsateride becoming more favored in the treatment of BPH and potentially to prevent prostate cancer. The Reduction by Dutasteride of prostate cancer Events (REDUCE) trial although not fully reported has been presented demonstrating similar results to the PCPT trial in reducing prostate cancer.[64]

Side Effects of Dutasteride

The tolerability of 5ARIs in most studies has been excellent with the most relevant adverse effects being related to sexual function. These include reduced libido, erectile dysfunction, and, less frequently,

abnormal ejaculation.[29,65] Specifically for the dutasteride monotherapy arm in the CombAT study,[50] the side effects were: erectile dysfunction (6.0%); retrograde ejaculation (0.6%); altered (decreased) libido (2.8%); ejaculation failure (0.5%); semen volume decreased (0.3%); loss of libido (1.3%); breast enlargement (1.8%); nipple pain (0.6%); breast tenderness (1.0%) and dizziness (0.7%). Only 4% of patients in the dutasteride arm withdrew from the study as a consequence of a drug-related adverse event with an additional 8% withdrawing for other reasons. By comparison, in the MTOPS trial 24% of patients discontinued finasteride and though the exact number was not specified, they stated that "most often, treatment was discontinued because of adverse effects."[49]

Summary and Conclusions

An argument can be put forth for 5ARI monotherapy in the long-term management of BPH in selected individuals. The most common medical treatment for BPH is an alpha-blocker, as the majority of patients treated have a prostate volume of less than 40 cc. For those with larger prostates and other risk factors for progression, combination therapy or a 5ARI alone is more appropriate. Early advantages for alpha blockers are evident, but beyond 2 years it is clear that dutasteride is superior as demonstrated in the CombAT trial. Such findings were not demonstrated with finasteride in the MTOPS trial, however, the patient cohort had small prostates and lower PSAs, both parameters that impact the influence of 5ARIs. The equal effect of dutasteride versus combination therapy on Q_{max} and the event rates of AUR and BPH-related surgery is also compelling evidence for monotherapy. These outcomes coupled with evidence that early removal of alpha blockers, but not 5ARIs from combination therapy is associated with continued symptom management, further supports monotherapy. Cost effectiveness is always an issue, especially considering the prevalence of BPH. Factoring in the reduced side effect profile with monotherapy compared to combination therapy is also important. Given that alpha blockers are effective in the initial stages of combination therapy it seems appropriate to initiate patients on both medications and in particular those with a higher risk of progression (i.e. prostates >30 cc, PSA > 1.5).

Several questions remain: 1) for those on combination therapy, in whom should you discontinue an alpha blocker; 2) when is the best time to discontinue it; and 3) should dutasteride be used over finasteride? To answer question 1, discontinuing an alpha blocker in anyone on combined therapy is a reasonable option with evidence that the majority have no worsening of symptoms. Moreover, the onset of drug efficacy for alpha blockers is so rapid that if symptoms surface after removal, restarting the drug should have full effects within days—which is not true for 5ARIs. In reference to question 2, there is evidence that removal of an alpha blocker as early as 6 months after combination therapy allows for continued symptom relief in more than three quarters of patients. However, it is not until approximately 2 years after dutasteride therapy that it outperforms tamsulosin in all endpoints. Perhaps the 1–2 year range would be less noticeable for discontinuation of an alpha blocker. The last question is the most challenging as there are no long-term direct comparisons between finasteride and dutasteride. The CombAT trial data certainly favours dutasteride since it shows advantages over an alpha blocker in all endpoints at 2 years while in the MTOPS trial finasteride had less efficacy for improving symptoms than an alpha blocker at 4 years. However, the odds were already weighing in favour of dutasteride before initiating the CombAT trial since the participants had larger prostates and higher PSAs, both know to affect the efficacy of 5ARIs. In summary, there is evidence that duatasteride can be used in monotherapy for BPH and low grade evidence that it outperforms finasteride.

Disclosures

Dr. Fleshner is a member of the global advisory board for Glaxo Smith Kline, a global and local investigator for the REDEEM trial and is also a local investigator for the REDUCE trial.

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors confirm that they have permission to reproduce any copyrighted material.

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