Alpha-1 Adrenergic Antagonist and 5-Alpha Reductase Inhibitor for the Treatment of Male Lower Urinary Tract Symptoms/Benign Prostate Hyperplasia

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INTRODUCTION

Lower urinary tract symptoms (LUTS) include urinary frequency, hesitancy, weakening stream, urgency and nocturia. They are common in older men and are frequently associated with benign prostate hyperplasia (BPH), benign prostate enlargement, benign prostate obstruction or bladder outlet obstruction [1-5]. In addition to excretion, pressure on the urethra and subsequent obstruction of urinary flow by an enlarged prostate gland, LUTS may also result from an increased concentration of prostate smooth muscle and from bladder dysfunction [6-9]. The pathophysiology of BPH comprises a dynamic component related to prostate smooth muscle tension and a static component related to prostate size [10]. Thus, there are different potential therapeutic targets. Prostatic obstruction can be hit either by using α-blockers or 5α-reductase inhibitors (5-ARIs), irritative bladder symptoms can be treated by antimuscarinic agents and partially by α-blockers and, finally, α-blockers may also have an impact at the spinal cord level. This was the rationale for the medical therapy of prostatic symptoms.

In the 1990s, most physicians preferred α-blocker monotherapy over combination treatment of α-blockers and 5-ARIs. In contrast, the long-term trial results of the Medical Therapy of Prostatic Symptoms (MTOPS) study reported that during a follow-up period of up to 4.5 years the progression of BPH, aggravated BPH symptoms and BPH-related surgery were more significantly decreased in the combination treatment group, using both doxazosin and finasteride, than in the monotherapy group, using either doxazosin or finasteride [11]. Having reviewed the evidence, should we recommend a combination of α-blockers and 5-ARIs as standard therapy for BPH?

ARE ALL α-BLOCKERS CREATED EQUAL?

The recognition by Lepor and associates in the 1980s that prostatic smooth muscle tension is mediated by the α_1-adrenoreceptors led to the development of α-blockers as a treatment for LUTS. This dynamic component of prostatic obstruction accounts for approximately 40% of outflow obstruction due to BPH [12]. There are 4 α-blockers that are FDA-approved to treat LUTS: doxazosin, terazosin, tamsulosin and alfuzosin. It is imperative when comparing different α_1-blockers to recognize that both efficacy and tolerability are dose dependent, and observed differences in both efficacy and toxicity may simply be due to different levels of α_1-blocker being achieved and not inherent advantages or disadvantages of the specific drug. It is therefore important to compare both efficacy and tolerability at various doses. 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) [13].

Terazosin was the first selective long-acting α_1-blocker investigated for the treatment of BPH that showed statistically significant changes in LUTS were also clinically significant [14]. The dose titration beginning at 1 mg should be performed for first-time older users to avoid the first-dose effect. Terazosin doses of 2 mg, 5 mg or 10 mg were administrated once daily, and only 4% and 7 of the participants randomized to placebo and terazosin, respectively, withdrew from the 3-month study because of an adverse event. Doxazosin was the second α_1-blocker approved by the FDA for the treatment of symptomatic BPH. The potential advantage of doxazosin was its longer half-life tolerability. The first-dose effect should also be avoided. On the basis of its comparable efficacy and tolerability to terazosin, doxazosin's longer half-life does not seem to confirm any clinical advantage. Both terazosin and doxazosin exhibit lowering of blood pressure only in those men who are hypertensive at baseline [15,16].

Tamsulosin was the third α_1-blocker to be approved by the FDA for the treatment of BPH. Tamsulosin was brought on to the market as the first subtype-selective α_1-antagonist for the treatment of BPH. Tamsulosin's α_1-subtype selectivity is supported by binding studies showing that tamsulosin is approximately 10 times more selective for the α_{1a} subtype than for the α_{1b} subtype [17,18]. There is no demonstrable selectivity by tamsulosin for the α_{1a} versus α_{1d} subtypes. The modest receptor selectivity of tamsulosin, however, is not sufficient to result in a clinically meaningful advantage. The primary reason tamsulosin was prescribed over terazosin and doxazosin was not greater efficacy or better tolerability but simply the lack of dose titration. The prescribing community placed a greater value on eliminating the dose response at the expense of increasing the incidence of ejaculatory dysfunction. Recent studies have demonstrated that tamsulosin causes anejaculation and not retrograde ejaculation [19].

Alfuzosin SR is the fourth α_1-selective blocker approved by the FDA for the treatment of BPH. The ability to eliminate dose titration is most likely due to its slow release formulation. Alfuzosin SR 10 mg achieved a clinically significant improvement in LUTS without dose

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titration. Many consider alfuzosin SR 10 mg to be the superior α1-blocker currently available for treating BPH because it achieves clinically significant improvement in LUTS without the requirement for dose titration. In addition to alfuzosin SR, doxazosin SR is another slow release formulation. Both slow release formulation α_1-blockers have minimal adverse effects such as dizziness, asthenia and ejaculatory dysfunction relative to the other available α-blockers.

5 ALPHA-REDUCTASE INHIBITOR

Finasteride, a 5-α-reductase inhibitor, was the first hormonal agent critically evaluated for the treatment of BPH. Serum testosterone is minimally increased in response to finasteride, thereby eliminating the consequences of castrate levels of testosterone achieved by gonadotropin-releasing hormone analogues and the estrogenic effects associated with antiandrogens, such as gynecomastia and breast tenderness, which result from marked upregulation of testosterone and its aromatization to estrogens [20]. The overall treatment-related benefit of finasteride, 5 mg, relative to placebo was a 16.3% reduction in symptom score and 14.6% increase in peak flow rate. The treatment-related reduction in prostate size was 16.9%. The long-term efficacy of finasteride has been shown to exhibit a 57% reduction in risk of episodes of acute urinary retention (AUR) and a 55% reduction in risk of progression to surgical intervention, relative to placebo [21]. In men with very large prostates (58-150 mL), finasteride reduced the risk of AUR by 74% [22].

Dutasteride is a new dual 5-ARI for the treatment of BPH. In 2-year placebo-controlled clinical trials, the drug has been demonstrated to reduce prostate volume by approximately 26%, improve symptoms, improve urinary flow, reduce the incidence of AUR and decrease the likelihood of BPH-related surgery [23,24]. Dutasteride inhibits the 5α-reductase isoenzymes (Type 1 and Type 2) that mediate the synthesis of dihydrotestosterone (DHT), which is the primary androgen responsible for hyperplastic growth in BPH [24]. Finasteride differs from dutasteride in that it inhibits only Type 2 5α-reductase isoenzyme at therapeutic doses [21]. The dual inhibition of dutasteride leads to near-complete suppression of serum DHT (>90%), whereas the inhibition of Type 2 5α-reductase by finasteride reduces serum DHT by approximately 70% [23]. Theoretically, the greater suppression of DHT arising from dual 5α-reductase inhibition could result in greater efficacy than is observed with selective Type 2 inhibition, which could allow escape of DHT from Type 1-mediated synthesis. In a 12-month study, dutasteride was compared with finasteride and produced numerically, but not statistically significantly, greater improvements in urinary flow rate and symptom scores after 1 year of treatment.

SHOULD COMBINATION THERAPY BE STANDARD FOR BPH?

The MTOPS study enrolled 3,047 men, which provided 81% power to detect a 33% reduction in the incidence of disease progression in an active-therapy group, allowing for a 5% loss to follow-up per year [11]. Clinical disease progression was defined as the occurrence of any of the following: a ≥ 4-point increase from baseline in the AUA symptom score, AUR, urinary tract infection, urosepsis, incontinence, or an increase in serum creatinine level to ≥ 1.5 mg/dL or to a value ≥50% above baseline. After the first year, there was little difference between the doxazosin and combination groups but, over the following 3 years, combination therapy was significantly better than any other therapy at preventing progression. The number of patients who needed to be treated to prevent one instance of overall clinical progression was 8.4 for the combination group, 13.7 for the doxazosin group and 15.0 for the finasteride group. In a preplanned subgroup analysis of patients with larger prostates, the number who needed to be treated was halved in the combination group. When individual progression events were looked at, an interesting observation could be made regarding the cumulative incidence of AUR. Combination therapy reduced the relative risk of developing retention by 81%. Finasteride delayed the time to AUR, and reduced the rate and relative risk of retention, whereas doxazosin only delayed its onset. The risk of invasive therapy was reduced by 64% in the finasteride group and by 67% in the combination group. Doxazosin alone did not reduce the cumulative risk. The number of patients who needed to be treated to prevent one patient from undergoing invasive therapy was 25.9 for the combination group, 60.1 for the doxazosin group and 29.0 for the finasteride group. Again, the number needing to be treated was initially halved among patients with larger glands. Serum prostate-specific antigen (PSA) was an accurate marker for prostate size.

Before jumping to a conclusion about the use of combination therapy for BPH, one other piece of evidence should be mentioned. The Symptom Management After Reducing Therapy (SMART-1) trial examined the combination of dutasteride and tamsulosin followed by withdrawal of tamsulosin in symptomatic men [25]. This trial enrolled a smaller group of patients and was not placebo-controlled. Patients were randomized to dutasteride and tamsulosin for 36 weeks, or to both for 24 weeks followed by dutasteride plus placebo for a further 12 weeks. Consistent with earlier trials, the combination produced a rapid improvement in symptoms. After tamsulosin withdrawal, the condition of patients with mild or moderate symptoms did not deteriorate but the condition of patients with severe symptoms did.

Should we recommend a combination of an α-blocker and 5-α-reductase inhibitor as standard therapy for BPH? On the basis of a single large placebo-controlled trial, the answer has to be yes but, practically, it should not be recommended for every case. Candidates for combination treatment are patients with severe symptoms and a larger prostate, for whom withdrawal of the α-blocker at 6 months is not an option. Serum PSA can be used as a surrogate marker for prostate size. A combination is significantly more effective than either agent alone at reducing the relative risk of disease progression, which was a more frequent event in the MTOPS trial than the development of AUR or the requirement for invasive therapy.

In conclusion, the MTOPS study gives some rational and convincing results in favor of the use of a combination treatment for BPH. The exact place of combination therapy in the medical treatment of BPH remains to be precisely determined but, nowadays, the conception of BPH as a disease is changing. BPH can no longer be considered as a simple disease: it is a chronic, complex disease that may need more than one single agent in order for it to be cured.

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