Benign Prostatic Hyperplasia in Taiwan: Epidemiology, Diagnosis and Pharmacological Therapy of Lower Urinary Tract Symptoms Suggestive of BPH in Ageing Men

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a prevailing disease that affects the majority of men during the aging process. Men with progressive symptoms should receive either pharmaceutical treatment or surgical intervention. Medical therapy remains the first-line treatment in reducing lower urinary tract symptoms, preventing related complications and achieving improvement in quality of life. Both α_1-blockers and 5ARIs are effective and considered the drug-of-choice for BPH treatment. α_1-blockers are indicated for rapid symptom treatment and 5ARIs are reserved for men with prostate volume ≥ 30 mL for reducing the risk of complications and surgical intervention. Combinations of α_1-blockers and 5ARIs or α_1-blockers plus antimuscarinic agents have also proved to provide benefit for men with moderate to severe symptoms.

Key words: BPH-epidemiology, medical therapy, lower urinary tract symptoms

INTRODUCTION

Over the past decade, the treatment options for patients presenting with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) has expanded to a great extent. The development of effective pharmaceutical therapies and the introduction of minimally invasive procedures have led to the general decrease of traditional surgery (e.g. transurethral resection of the prostate (TURP), open prostatectomy) by up to 50% in some countries [1]. Recently published data shows that the prevalence of men with moderate to severe LUTS, defined clinically by an American Urological Association (AUA) Symptom Index (SI) score of >7 points, has increased from men in their 40s to those in their 80s [2]. Further, nocturia was the most prevalent of the obstructive symptoms, which occurred in 75% of men in their 60s and in as many as 83% of men in their 70s [3]. The goal of therapy for BPH is to eliminate LUTS, the hallmark of BPH, which might have a profound impact on quality of life (QoL) if left untreated. This article will review the medical treatment options available for BPH, and compare the treatment outcomes and possible complications of different therapies.

Received: June 11, 2007 Accepted: August 14, 2007
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EPIDEMIOLOGY AND NATURAL HISTORY OF BPH

It is well known that increasing age and male hormones play an important role in glandular hyperplasia and continuous enlargement of the prostate. A population-based study showed that more than 50% of men over 60 years old have histological evidence of prostate hyperplasia [4] and men aged over 80 years old have a prevalence of BPH of 80%-90% [5]. One of the largest population-based, longitudinal studies, Olmsted County study, has provided us with information about the natural history of urinary symptoms and BPH progression among men 40-79 years old [4]. During the 12-year follow-up of a randomly selected cohort of 2,115 men aged 40-79 years, an average increase in the International Prostate Symptom Score (IPSS) of 0.18 points per year was observed, ranging from 0.05 for men in their 40s to 0.44 for those in their 60s. There was also an increase in median prostate growth of 1.9% per year and a decrease in peak flow rate of 2.1% per year, which was also age-related, with men aged over 70 years showing a more rapid decline (6.2% per year) than men in their 50s (1.1% per year). The cumulative incidence of acute urinary retention (AUR) was 2.7% over 4 years, ranging from 1% for men in their 50s to 9% for men aged over 70 years. Overall, 3% of men required surgical procedures (TURP or minimal invasive surgeries) during a 6-year follow-up and this was again strongly age-related (from 0.1% for men in their 40s to 9.5% for men in their 70s) [6].

The objective measurement of BPH progression can be assessed from the increase in prostate volume, urinary flow, change in IPSS and the incidence of related urinary complications, including AUR, urinary tract infection (UTI), hematuria or bladder stones. In the 4-year Medical Therapy of Prostatic Symptoms (MTOPS) study, clinical progression of BPH was comprised of: ≥ 4 point increase in the AUA symptom score, AUI, renal insufficiency (≥ 50% rise in baseline serum creatinine and ≥ 1.5 mg/dL), recurrent UTI or urinary incontinence [7]. About 80% of BPH progression events in the MTOPS were due to increased symptom scores, followed by 12% due to AUR. Data from the placebo arms showed that men in the control group experienced 18% increase in total prostate volume and 17.4% experienced progression of disease over the 4-year duration. Another 4-year study, the Proscar Long-term Efficacy and Safety Study (PLESS), also demonstrated that the risk of AUR in the placebo arms was 7% [8]. In this double-blind, placebo-controlled study, which enrolled 3,040 men (mean age 64 years) with moderate to severe LUTS, a low peak flow rate (<15 mL/s) and an enlarged prostate, the overall incidence of BPH-related surgery was 10% over four years. In the Olmsted County study, among those men

aged 70 years or older with moderate to severe LUTS, the incidence of AUR was 34.7 per 1,000 patient-years of follow-up [4]. The risk of AUR for an average 60-year-old man has been estimated as 23% in the following 20 years.

EVALUATION AND DIAGNOSIS OF BPH

LUTS are the most prevailing complaints of men with enlarged prostates, including those symptoms associated with voiding (hesitancy, intermittency or weak urine stream) and storage (frequency, urgency, nocturia or incontinence), with the latter regarded to be the most bothersome. These symptoms become progressive in a subset of men who may require further medical or surgical treatment. The AUA Guidelines Committee recommends a urinalysis, serum prostate-specific antigen (PSA) level test and completion of a validated symptom index (AUA/IPSS symptoms index) assessment during the initial evaluation [9]. Serum PSA determination is indicated for men with life expectancy of 10 years or longer and for those whose PSA level may interfere with the treatment strategies. Further, PSA is also a useful tool for predicting the prostate size, future prostate growth, and risk of urinary retention and surgery.

Due to the progressive nature of the disease, identifying men with potentially progressive disease is important in choosing the appropriate therapy to prevent worsening of symptoms and complications that may compromise QoL. Nowadays, the two widely evaluated and obtained risk factors for BPH progression are prostate volume and PSA. Several large-scale studies have established a correlation between prostate volume and the risk of BPH progression. Anderson et al found that men with a prostate volume of > 30 mL are more likely to have moderate to severe symptoms (3.5 times), decreased flow rates (2.5 times) and AUR (3-4 times) compared to men with prostate volumes of < 30 mL [10]. The Olmsted County Study also demonstrated that the population of men with prostate volumes of more than 30 mL increased with age. Also, an enlarged prostate is correlated with increased risk of BPH-related surgery [11].

Serum PSA level also serves as a predictor for further progression of BPH. During the 4-year period of PLESS, it was found that prostate volume and PSA level predicted the risk of developing AUR [12]. Patients with higher baseline PSA levels (>1.4 ng/mL) were associated with a higher prostate annual growth rate (3.3 mL per year, compared to 0.7 mL per year in patients with PSA <1.4 ng/mL) and had a much greater risk of developing AUR (3.9% vs 0.5%). Therefore, serum PSA and prostate volume provide a simple way to aid decisions on appropriate treatment and management plans, helping to identify the patients at greater risk of BPH progression.

PHARMACOLOGICAL TREATMENTS FOR BPH

Traditionally, treating BPH has tended to focus on the short-term goals of ameliorating bothersome symptoms and improving urinary flow. Unfortunately, the progressive nature of BPH is associated with continuous enlargement of prostate tissue, worsening of symptoms, which may lead to increased risk of AUR, and a negative impact on QoL. Therefore, treatment success should be widened to achieve long-term goals. Overall, the principles of treatment for BPH are to alleviate LUTS, prevent related complications and achieve demonstrable improvement in the patient's QoL [13]. In general, patients with mild LUTS (IPSS ≤ 7) and without bothersome symptoms may be managed with observation and periodic reevaluation [14]. Currently, medical therapy is indicated for men with moderate to severe LUTS (IPSS ≥ 8) who prefer to avoid invasive treatment, patients who are not candidates for invasive procedures or those who do not consider their symptoms bothersome enough to warrant surgical intervention.

To date, there are two classes of pharmacological therapies approved for LUTS suggestive of BPH: α_1-selective adrenergic receptor antagonists (α_1-blockers) and 5α-reductase inhibitors (5-ARIs). These two classes of drugs differ in modes of action, time to achieve efficacy and adverse event profiles. The AUA guidelines on the short-term management of BPH recommend α_1-blockers for men with symptoms secondary to BPH, and 5ARIs or combination therapy for men with symptoms and measurable prostatic enlargement. Phytotherapy is also a treatment option that is used in varying degrees in different countries. However, the treatment efficacy is not clear.

Treatment outcomes of α_1-blockers

The α_1-blockers are used for treating BPH by neurally mediated relaxation of smooth muscle in the prostate and bladder neck, through the blockage of α_1-receptor-mediated sympathetic stimulation. Additional mechanisms have been postulated, such as apoptosis of prostate tissue, although they remain unclear. Currently α_1-adrenoceptor antagonists are well recognized as the commonest treatment for BPH/LUTS. A number of systemic analyses of double-blind, placebo-controlled studies have been conducted, and showed that the commonly used α_1-blockers (doxazosin, terazosin, alfuzosin, tamsulosin) are similarly effective and statistically significantly better than placebo in improving symptoms scores and urinary flow. Objectively, there was a 2-4 point decrease in AUA-SI compared to placebo [15].

The adverse events observed in patients taking α_1-blockers were significantly higher than in the placebo group, and the most common side effects were dizziness and postural hypotension [16]. The proportion of patients experiencing dizziness with doxazosin and terazosin was higher than with placebo (0-20%, corrected for placebo) and with alfuzosin or tamsulosin (0-8%, compared to placebo), which are more selective α_1-blockers. Recently both of the slow-release formulations of doxazosin and alfuzosin have shown to be similarly effective yet with lower adverse events and improved tolerability [17]. Although the same incidence of sexual adverse events was observed, tamsulosin has been demonstrated to be associated with an increased incidence of retrograde ejaculation, which was 4.5%-10% versus 0-1% for placebo [18]. However, in general, these four α_1-blockers were similarly effective and relatively safe for the treatment of BPH/LUTS.

Treatment outcomes of 5ARIs

5ARIs inhibit the conversion of testosterone to dihydrotestosterone (DHT), an important androgen mediator involved in prostate development and the transitional zone hyperplasia found in BPH, and consequently reduce the prostate volume by inducing prostatic epithelial apoptosis and atrophy. Currently two 5ARIs are prescribed for the treatment of BPH, finasteride and dutasteride. Finasteride is a selective 5AR type 2 isoenzyme inhibitor, while dutasteride is a dual inhibitor of both type 1 and 2 5AR.

The long-term safety and efficacy of finasteride has been well evaluated in PLESS. Finasteride reduced prostate volume by 18% compared with an increase of 14% in the placebo group, improved symp-

tom scores (2.6 points vs 1.0, p<0:001), increased Qmax (1.9 vs 0.2 mL/s, p<0:001), and reduced the risk of AUR by 57% and surgery by 55% [8]. In the 7-year Prostate Cancer Prevention Trial (PCPT), it was also demonstrated that finasteride treatment was associated with a lower risk of AUR (4.2% vs 6.3%), need for TURP (1.0% vs 1.9%) and number of diagnoses of BPH (5.2% vs 8.7%) compared with placebo treatment, although the subjects were men with a normal digital rectal examination (DRE) and AUA-SI [19]. In general, the reported side effects of finasteride include: decreased libido (6.4% vs 3.4% in placebo group), impotence (8.1% vs 3.7%), decreased ejaculate (3.7% vs 0.8%), <1% incidence of ejaculation disorders, rash, and breast enlargement or tenderness [20]. However, the side effects occurred mostly during the first year of treatment and decreased in incidence during subsequent years.

Similarly, a 2-year, double-blind, placebo-controlled study of dutasteride, which enrolled 4,325 men with prostate volumes of ≥ 30 mL and serum PSA values of ≥ 1.5 ng/mL, also demonstrated significant efficacy [21]. After 2 years, the dutasteride group showed reduced symptoms scores (4.5 points vs 2.3 points for placebo) and improved Qmax (2.2 mL/s compared to 0.6 mL/s with placebo), which proved that dutasteride provided similar efficacy to finasteride. Overall, several studies have shown that 5ARIs appear to be more effective among men with prostate volumes of ≥ 30-40 mL or serum PSA values of ≥ 1.4-1.5 ng/mL, which leads to the recommendation that 5ARIs should be reserved for men with larger prostates and higher serum PSA values.

Combination therapy for BPH

Due to the multifactorial cause of BPH and the distinct mechanism of α_1-blockers and 5ARIs, combinations of these two drugs are predicted to have additive effects. Recently, several large-scale, randomized, placebo-controlled studies of 5ARIs and α_1-blockers have been conducted to examine the efficacy of combination therapy for BPH. The Veterans Affairs Study, which enrolled 1,229 men over a 1-year period, examined the treatment effect of finasteride, terazosin or a combination of finasteride and terazosin versus placebo [22]. This study failed to demonstrate a significant benefit in the combination group. Similarly, the PREDICT (Prospective European Doxazosin and Combination Therapy) trial, which compared the efficacy of doxazosin and finasteride, alone or in combination, also showed no significant benefit in the combination group [23]. However, these two studies were limited by low patient number and an average prostate volume of < 40 mL, which is well known as the minimum level for therapeutic effect for finasteride. Therefore, compromised finasteride efficacy is considered to be present in these two studies.

In the 4-year MTOPS trial, 3,047 men with moderate to severe BPH symptoms were randomized into 4 arms: finasteride, doxazosin, a combination of both or placebo [8]. Both monotherapy groups showed significantly reduced risk of BPH progression of 34% with finasteride and 39% with doxazosin compared to placebo. The combination therapy of finasteride and doxazosin was effective in providing a 66% reduction in risk of BPH progression compared to placebo, which was significantly greater than that of either drug alone. By the end of the study, the results showed that combination therapy significantly reduced the risk of clinical outcomes: by 66% for BPH progression, 81% for AUR and 67% for invasive BPH therapy. The MTOPS study confirms that, for long-term treatment, patients with moderate to severe BPH may benefit from combination therapy.

Several studies examining the efficacy of dutasteride combined with α_1-blockers were also conducted. The Symptom Management After Reducing Therapy (SMART-1) study was designed to demonstrate the outcome of short-term dutasteride and tamsulosin combination therapy followed by dutasteride monotherapy in 327 men with symptomatic BPH [24]. The results showed that 77% of patients with moderate to severe symptoms treated with a combination of dutasteride and an α_1-blocker felt better or the same after the α_1-blocker was withdrawn in the sixth month. As in the MTOPS study, the combination therapy was also well tolerated. The SMART-1 study showed that α_1-blockers combined with 5ARIs are effective in controlling the symptoms of BPH for six months and the treatment effect can be maintained with dutasteride monotherapy in the majority of men with moderate to severe symptoms after the initial combination therapy.

One of the major concerns of combination therapy is the additive side-effects of both groups. A higher incidence of impotence with combination therapy compared with α_1-blocker therapy, and expected higher incidence of α_1-blocker-mediated dizziness and hypotension were observed in several studies [7,22,23]. However, the impact of combination therapy on QoL and the patients' long-term tolerability has not yet been well studied, and remains the subject of debate.

Recently a randomized study, which enrolled 879 men with moderate to severe LUTS, was conducted to examine the efficacy of tolterodine combined with tamsulosin for treatment of men with LUTS and overactive bladder [25]. The results showed that a combination of tolterodine ER plus tamsulosin for 12 weeks provided benefit for men with moderate to severe LUTS including overactive bladder, with good tolerability. This study demonstrated that a combination of α_1-blockers with antimuscarinic agents may provide therapeutic effects.

CONCLUSION

Being the most common disease among elderly men, BPH increases in its prevalence with the aging process. Evidence shows that BPH-related symptoms tend to progress in those with prostate volumes of ≥ 30 mL and serum PSA levels of ≥ 1.5 ng/mL, which can be detected by blood test and DRE in clinical practice. Pharmacological treatment of BPH is currently indicated for the initial treatment of men with moderate to severe LUTS, unless there are complications at presentation or medication fails to show efficacy. Both α_1-blockers and 5ARIs are recognized to be effective and well tolerated, with long-term open-label data to support their efficacy. Currently, α_1-blockers are the most widely used medical therapy for BPH and may provide rapid onset of symptom relief. 5ARIs reduce the risk of AUR and BPH-related surgery, and are indicated for men with enlarged prostates (≥ 30 mL). A combination of α_1-blockers and 5ARIs for men with moderate to severe symptoms may provide short- and long-term efficacy. Further, α_1-blockers plus antimuscarinic agents have also been shown to provide significant symptom relief.

In conclusion, increase in our understanding of the natural history of BPH and pharmacological therapy can help us to assess the benefits and disadvantages of treatment outcomes. The ultimate goal of BPH treatment involves not only reducing the symptoms and preventing related complications, such as AUR, but also an improvement in overall QoL and cost effectiveness.

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