Dutasteride Treatment for Symptomatic Benign Prostatic Hyperplasia in Taiwan

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ABSTRACT

This paper reviews the evidence for medical treatment using dutasteride, a 5-alpha-reductase inhibitor (5-ARI), on clinical benign prostatic hyperplasia (BPH). Outcomes from a study using dutasteride therapy in eastern Taiwan are reported. A total of 244 men with moderate to severe lower urinary tract symptoms (IPSS ≥ 8) were enrolled prospectively. The patients' ages ranged from 48 to 95 years old (mean 72 ± 9). Inclusion criteria included International Prostate Symptom Score (IPSS) ≥ 8, maximal flow rate (Qmax) ≤12 mL/s and total prostate volume (TPV) ≥ 20 mL. The patients were treated with dutasteride 0.5 mg Q.D. alone or combined with an α -blocker, tamsulosin 0.2 mg Q.D. The IPSS, quality of life index (QoLI), TPV, Qmax, voided volume, postvoid residual (PVR) and prostate specific antigen (PSA) were measured at baseline, 6, 12 and 18 months. At 18 months after dutasteride therapy, patients' IPSS had decreased by 55%, QoLI had improved by 51%, PSA levels were reduced by 47%, Qmax had improved by 3.5 mL/s (37.6%), voided volume had increased by 23.3%, TPV was reduced by 22.4% and transition zone index (TZI) dropped by 9.5%. This study proves dutasteride is effective for treatment of symptomatic BPH.

Key words: 5-alpha-reductase inhibitor, BPH, medical treatment, lower urinary tract symptoms

INTRODUCTION

Benign prostatic hyperplasia (BPH) is highly prevalent among the elderly. It has been estimated that 50% of men over 60 years old and 80%-90% of men over 80 years old have BPH [1,2]. Although the incidence of BPH increases with age, only 10% of men with clinical BPH require intervention for lower urinary tract symptoms (LUTS). Previously, transurethral resection of the prostate (TURP) was the treatment of choice for symptomatic BPH, however pharmacological manipulation has now become the first choice of treatment for patients with BPH and moderate to severe LUTS [3]. Although medical treatment may improve LUTS in most patients with symptomatic BPH, acute urinary retention and BPH-related surgery may still become necessary during long-term medical treatment [4].

Clinical BPH

Patients with BPH might be asymptomatic and LUTS is not necessarily due to an enlarged prostate. Clinical BPH should meet at least two of the following criteria: (1) moderate to severe LUTS (IPSS ≥ 8), (2) an enlarged prostate (total prostate volume, TPV > 30 mL) and (3) a decreased maximum flow rate (Qmax<15 mL/s) [5]. Moderate to severe LUTS usually indicates greater impact on daily life. Although there is a weak correlation between LUTS and prostate size, a significant relation with uroflow and pressure flow has been found. LUTS measured by AUA-SI was found to effectively predict BPH progression to surgery. The AUA symptom score can likewise be used to quantitatively evaluate the efficacy of treatment for BPH symptoms rather than for diagnosing BPH [6]. Although an enlarged prostate might not indicate presence of bladder outlet obstruction (BOO), the mean TPV in patients with BOO is significantly higher than that in patients without BOO. The incidence of BOO in men with a TPV ≥ 40 mL was 92%, while those with a TPV of 30-40 mL had an incidence of 71.4% [7]. In addition, patients with LUTS suggestive of BPH and with a Qmax of < 10 mL/s showed greater improvement after TURP compared with those with a Qmax of > 10 mL/s. Patients without preoperative evidence of BOO also had a poor prognosis after TURP [8]. Men with a TPV of ≥ 30 mL are more likely to have moderate to severe LUTS, decreased flow rate, as well as acute urinary retention (AUR) and BPH-related surgery, compared with men with a TPV < 30 mL [9,10]. A Qmax of less than 10 mL/s is highly predictive of BOO [11], however, a Qmax of greater than 10 mL/s cannot exclude the possibility of a high pressure and high flow BOO [12]. Another predictive factor for identifying men with progressive BPH is the prostate specific antigen (PSA) test. An increasing serum PSA level is a strong predictor of prostatic volume increase and BPH progression. A PSA > 1.4 ng/mL has been associated with an increased risk of AUR, greater symptom severity and decreased Qmax, and QoL [13,14]. Finasteride, another 5-ARI, has been found significantly more effective among men with a TPV > 40 mL or a serum PSA > 1.4 ng/mL [15]. Dutasteride has also been found to reduce the risk of serious BPH complications and to improve objective disease measures in men with TPV ≥ 30 mL and a PSA ≥ 1.5 ng/mL [16].

Progression of clinical BPH may occur in patients with or without active treatment. Progression of clinical BPH is considered when a patient has acute urinary retention, renal insufficiency due to BPH, recurrent urinary tract infection (UTI) or a more than 4-point rise in baseline AUA-SI/IPSS [17]. The treatment goals for BPH have shifted from treating complications of BPH or bothersome LUTS symptoms to preventing clinical BPH progression. Among the varying therapeutic modalities for symptomatic BPH (watchful waiting, pharmaceutical therapy, minimally invasive therapies and surgery), pharmaceutical treatment provides a tolerable and effective way with a low risk of adverse events to treat or prevent progression of clinical BPH. However, because of

Received: June 23, 2007 Accepted: July 26, 2007
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the limited debulking effect of pharmaceutical therapy, it is less therapeutically effective than surgery or minimally invasive therapy.

Pharmaceutical Treatment of BPH

Currently, there are two categories of pharmaceutical therapies for BPH, alpha-adrenergic blockers (α-blockers) and 5-alpha-reductase inhibitors (5-ARI). The former can effectively reduce the smooth muscle tone in the prostate and urethra by blocking the alpha-adrenergic receptors. Among variousα-blockers, alfulzosin, doxazosin, tamsulosin and terazosin have been shown to be similarly effective for partially relieving LUTS, producing an average 4-6 point improvement on the AUA-SI [11]. However, the adverse event profile appears slightly different for the four α-blockers. Inhibiting 5-alpha-reductase catalyzes the conversion of testosterone to dihydrotestosterone in the prostate epithelia and arrests the prostate's growth while relieving symptoms of BOO. Patients treated with dutasteride, a dual 5-ARI, have shown a reduction of TPV by 25.7% and an increase of Qmax by 2.2 mL/s at 24 months [18].

The prostate is composed of glandular components and stroma. The relative proportions of epithelium and stroma are 22%-40% and 60%-78% [19]. Therefore the possible reduction of prostate volume is at most about 20%-40%. Since 5-ARI affects the prostatic glandular epithelia, its effect is greater on prostates with a higher glandular component than on prostates with a higher stromal component. 5-ARI has been found to be effective especially for patients with a prostatic weight of > 40 gm. The rate of re-treatment with alpha-blockers is higher for those with a TPV > 40 mL than those with a TPV < 40 mL [4].

The action of α-blockers on prostatic stroma is faster than that of 5-ARI on the glandular component. Clinically, the therapeutic effect of α -blockers on LUTS requires about 2 weeks, whereas it took about 12 months for 5-ARI to effect a reduction of prostatic volume [20]. Thus, rapid improvement of LUTS can be achieved using α-blockers but it takes a longer time for 5-ARI to reduce the prostate volume. However, because α-blockers cannot reduce prostatic volume and the prostate will continue to grow with time, patients treated with α-blockers alone may be at risk for increased prostate volume and resulting acute urinary retention (AUR), urinary tract infection (UTI) or may require BPH-related surgery [17].

Overall, men with smaller prostates appear to benefit from α_1-blocker therapy, while those with prostate volume > 30-40 mL benefit more from 5-ARI therapy. A combination of α-blockers and 5-ARI for treating patients with severe BPH and LUTS seems rational for achieving rapid improvement of LUTS and reduction of prostate volume in the long-term. The MTOP study has demonstrated that combination therapy with α-blockers and 5-ARI can provide a significant decrease in the incidence of BPH progression, AUR and BPH invasive therapy [17].

A single institute clinical study has shown a similar relapse rate of LUTS requiring TURP after discontinuing either medication alone, as compared with discontinuing combined treatment with α-blockers and 5-ARI after 12 months. The baseline TPV related to clinical BPH progression was evident in the patients discontinuing 5-ARI but not in the patients discontinuing α-blockers. It is interesting to find that the baseline Qmax showed no relation with BPH progression while the TPV had a strong correlation [21].

Clinical experience with dutasteride therapy for BPH in Hualien, Taiwan

This study was conducted in Tzu Chi General Hospital, Hualien, Taiwan. A total of 244 men with moderate to severe LUTS (IPSS ≥ 8) were enrolled prospectively. The patients ages ranged from 48 to 95 years old (mean 72 ± 9). Inclusion criteria consisted of IPSS ≥ 8, Qmax ≤ 12 mL/s and a TPV > 20 mL. The exclusion criteria were previous TURP, evidence of prostate cancer and neurogenic voiding dysfunction. The patients were treated with dutasteride 0.5 mg Q.D. alone or combined with an α-blocker, tamsulosin 0.2 mg Q.D. The International Prostate Symtpom Score (IPSS), quality of life index (QoLI), total prostate volume (TPV), transition zone index (TZI), maximal flow rate (Qmax), voided volume, postvoid residual (PVR) and prostate specific antigen (PSA) were measured at baseline, 6, 12 and 18 months.

The data for these BPH parameters are listed in Table 1. The changes in mean values of BPH parameters at different time intervals are shown in Fig. 1. At 18 months after dutasteride therapy, the mean IPSS decreased by 55%, QoLI improved by 51%, PSAs were reduced by 47%, Qmax improved to 3.5 mL/s (37.6%), voided volume increased by 23.3%, TPV was reduced by 22.4% and TZI was reduced by 9.5%. The PV showed no significant change throughout the study period (Fig. 1).

Pathophysiology of male LUTS

Men with LUTS may have both storage and voiding symptoms. A large multinational study revealed that 90% of men aged 50 to 80 years

Table 1. BPH Measures at Baseline and at Different Points in Time after Starting Dutasteride Therapy

		Baseline (n=244)	6 months (n= 244)	12 months (n= 130)	18 months (n= 67)
IPSS	storage	6.21 ± 3.67	4.26 ± 2.54	3.95 ± 4.85	4.13 ± 2.23
	empty	8.67 ± 6.39	3.74 ± 4.48	4.08 ± 4.85	2.79 ± 4.22
	total	14.5 ± 8.35	7.78 ± 5.65	8.03 ± 6.34	6.92 ± 5.26
QoL index		3.73 ± 1.37	2.26 ± 0.95	1.89 ± 0.97	1.86 ± 0.60
Qmax (mL/s)		10.1 ± 5.1	11.4 ± 5.5	11.2 ± 5.2	12.8 ± 6.5
Volume (mL)		178 ± 127	200 ± 129	203 ± 131	217 ± 154
PVR (mL)		71.0 ± 76	74.4 ± 72.1	72.2 ± 78.5	76.5 ± 71.2
TPV (mL)		46.2 ± 21.4	40.4 ± 18.7	39.0 ± 19.5	36.0 ± 15.8
TZI (%)		46.4 ± 14.2	44.7 ± 12.8	43.8 ± 14.3	42.1 ± 12.0
PSA (ng/mL)		3.48 ± 4.08	2.57 ± 3.20	1.91 ± 1.60	1.82 ± 1.61

QoL: quality of life; Qmax: maximum flow rate; PVR: postvoid residual; TPV: total prostate volume; TZI: transition zone index; PSA: prostate-specific antigen

suffer from potentially troublesome LUTS [22]. It has been estimated that only 25%-50% of men with histologically confirmed BPH have LUTS [2], whereas urodynamic BOO is found in only 48%-53% of men referred for investigation of their LUTS [23,24].

Overactive Bladder (OAB) comprises the same symptoms as storage LUTS and increases in prevalence with age [25]. Since most men with OAB do not experience incontinence, benign prostate obstruction (BPO) is often misdiagnosed in men with storage LUTS [26]. Male OAB symptoms may be caused by bladder dysfunctions such as detrusor overactivity (DO), detrusor underactivity (DU) or in combination with BOO. BOO may cause DO and detrusor hyperreflexia with impaired contractility (DHIC), however, previous studies have reported that only 45%-50% of men with LUTS had urodynamically confirmed DO and BOO [23,24].

Clinically, diagnoses of BPH and BOO are usually made based on a total prostate volume of more than 40 mL, a maximum flow rate of less than 10 mL/s in combination with a high LUTS symptom score, especially for the voiding symptoms [15]. Although the specificity is not high, initial treatment for BOO can be given with alpha-adrenergic antagonists to observe whether a therapeutic effect occurs before an accurate diagnosis is made [27]. However, for men with both storage and voiding symptoms, clinical diagnosis of lower urinary tract dysfunction becomes more difficult, and urodynamic pressure flow study is usually needed to accurately identify the pathophysiology and provide appropriate treatment [28].

A group of 1,407 men referred for investigation of LUTS from September 1996 to August 2006 were reviewed. All patients had both storage and voiding symptoms. Patients with overt neuropathy, clinically established BPO and previous transurethral surgery or active urinary tract infection were excluded [29].

Symptoms of bladder dysfunction included increased bladder sensation in 148 patients (10.5%), detrusor overactivity (DO) in 724 (51.5%), detrusor overactivity and impaired contractility (DHIC) in 82 (5.8%) and detrusor underactivity (DU) in 149 (10.6%). The causes of BOO included bladder neck dysfunction (BND) in 19 patients (1.4%), benign prostatic obstruction (BPO) in 413 (29.4%), urethral sphincter pseudodyssynergia in 30 (2.1%) and poor relaxation of urethral sphincter in 283 (20.1%).

Among the various lower urinary tract symptoms, frequency, slowed stream and straining were highly prevalent in all age groups. Urgency was a more common complaint in patients with bladder outlet dysfunction than in patients with bladder dysfunction. Only 61.5% of patients with DO had urgency symptoms whereas 55.2% of patients with BOO (including BND, BPO and urethral sphincter pseudodyssynergia) experienced urgency. Interestingly, 32.4% of patients with a normal bladder and urethra complained of urgency despite a lack of evidence for lower urinary tract dysfunction.

Comparison of the LUTS between 413 patients with BPO and 994 patients without BPO revealed no significant difference in the presenting storage symptoms. More than 90% of patients either with or without BPO complained of frequency and more than 80% of patients in both groups complained of slowed stream and straining to void. DO was found in 334 (80.9%) of the 413 patients with BPO but only in 388 (39.3%) of the 994 patients without BPO. By contrast, BPO was found in 334 (46.3%) of the 772 patients with DO, and in 79 (11.5%) of the 685 patients without DO.

The results showed that only 52.7% of men with both storage and voiding LUTS had bladder outlet dysfunction and only 29.4% of them had BPO. The results also indicate that men younger than 55 years old were more likely to have increased bladder sensation or poor relaxation of the urethral sphincter as a cause of LUTS. Because LUTS were not an accurate basis for diagnosing BPO, patients with LUTS should be carefully investigated to identify possible bladder or bladder outlet dysfunctions.

Increasing age was associated with increased incidence of DO and DHIC, especially when ages exceeded 76 years. In contrast, men younger than 65 had a higher incidence of increased bladder sensation. These bladder dysfunctions may relate to the trend toward increasing storage LUTS, which appear to be more closely associated with DO in elderly men and with increased bladder sensation in younger men. Symptoms of overactive bladder in men are often caused by bladder dysfunctions such as DO or DHIC, but also frequently occur in patients with bladder outlet dysfunction such as BPO, BND and poor relaxation of the urethral sphincter [30].

Constructing an algorithm of medical therapy for LUTS/BPH

An algorithm of medical therapy for LUTS/BPH was constructed based on the evidence of clinical diagnosis and therapeutic outcomes

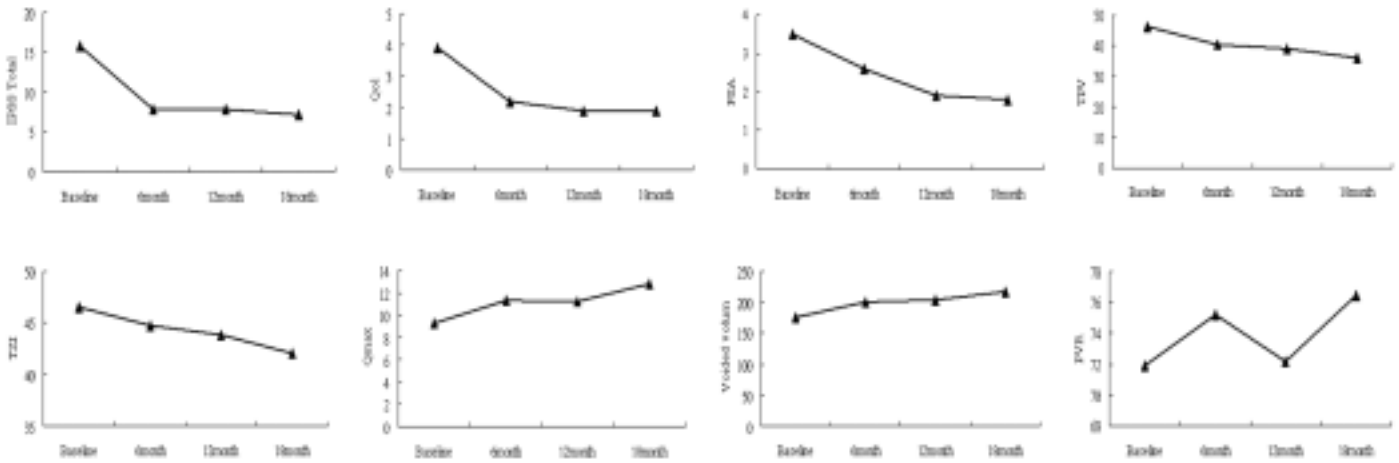

Fig. 1. Changes in BPH measures at different points in time following dutasteride therapy.

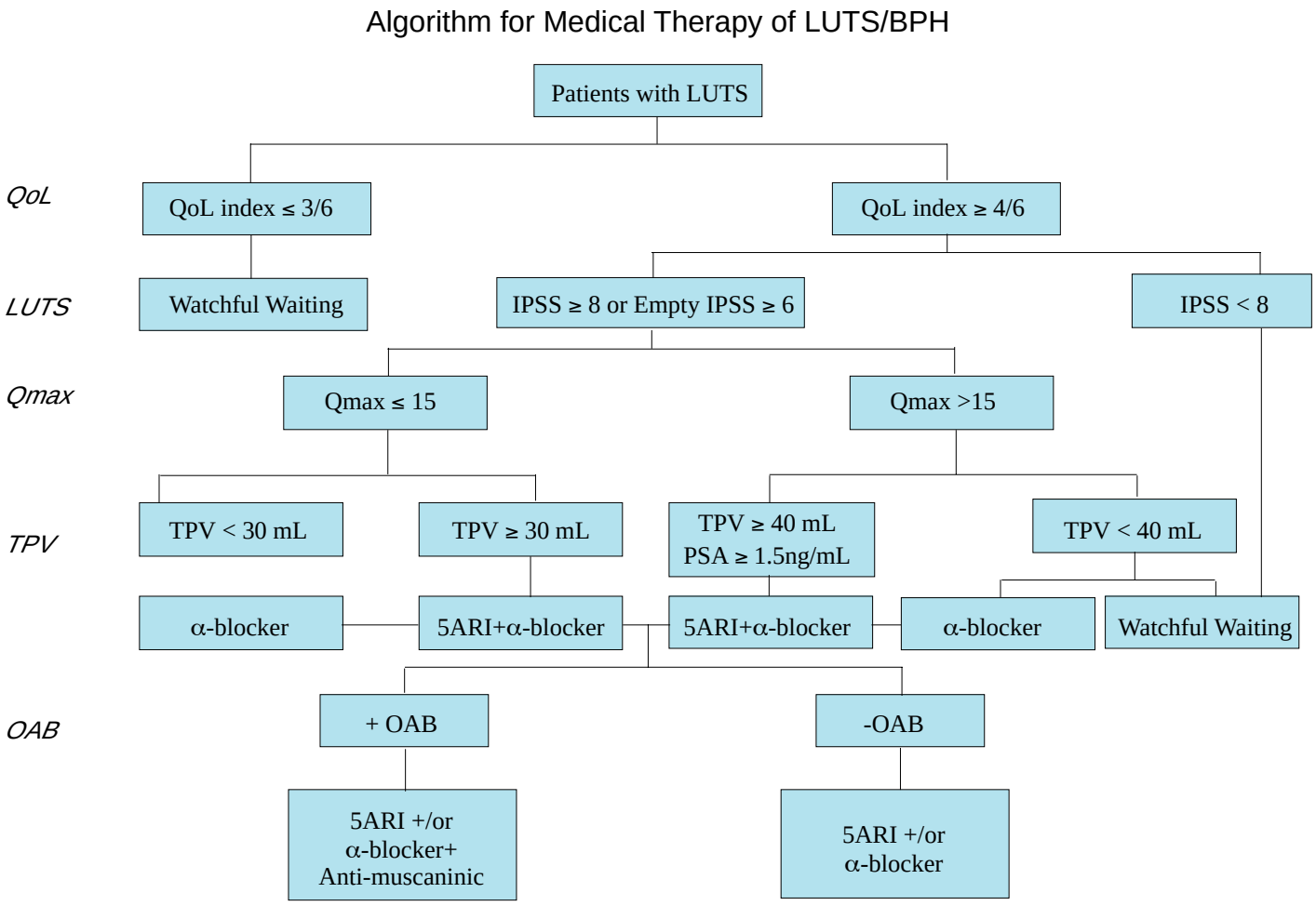

Fig. 2. Algorithm for medical therapy of lower urinary tract symptoms suggestive of BPH.

for LUTS/BPH (Fig. 2). In establishing priorities for treatment for LUTS/BPH, the QoL, LUTS, Qmax, TPV should be taken into consideration according to how much these parameters contribute to bothersomeness experienced by the patient. Patients with a lower QoL index (>3/6) and an IPSS of ≥ 8 should be treated first. According to AUA guidelines, patients with mild symptoms of BPH (AUA-SI or IPSS <8) should be managed by a strategy of watchful waiting [11]. However, if the IPSS empty score is ≥ 4, patients might also have BOO and should be treated as well. A Qmax of < 15 mL/s usually indicates BOO, but 6%-8% of patients with moderate LUTS and a Qmax >15 mL/s might have BOO if their TPV is larger than 40 mL. Since the dynamic component of the prostate contributes more to BOO in the patients with a small TPV, α-blockers can be used as first line medical therapy for patients with combined Qmax < 15 mL/s and TPV < 30 mL, or for patients with combined Qmax > 15 mL/s and TPV < 40 mL, but 5-ARI should be added to the treatment for patients with combined Qmax < 15 mL/s and TPV > 30 mL, or for patients with combined TPV ≥ 40 mL and a PSA ≥ 1.5 ng/mL. After treatment with α-blockers and/or 5-ARI, if patients are still bothered by the overactive bladder symptoms, antimuscarinic agents can be added to therapeutic regimens for relief of LUTS.

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