Therapeutic Effectiveness of Dutasteride in Clinical Benign Prostatic Hyperplasia in Taiwanese Men

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ABSTRACT

Objective: To evaluate the efficacy and safety of dutasteride in treatment of clinical benign prostatic hyperplasia (BPH) in Taiwanese men. **Materials and Methods:** This study was designed as a single-arm, open-label trial. The clinical BPH confirmed patients received dutasteride 0.5 mg daily. Patients were evaluated at baseline screening and at a minimum of 2 required visits. Evaluated parameters included the international prostate symptom score, quality of life index, total prostatic volume, transition zone index, maximum flow rate, voided volume, postvoid residual volume (PVR) and prostate specific antigen value. **Results:** A total of 173 men entered this study, of which 102 were treated for more than 12 months. Changes in evaluated parameters and quality of life index between baseline, 6 months and 12 months were all statistically significant except for PVR. The total prostatic volume decreased by 13.4% at 6 months and by 22.1% at 12 months compared with baseline. **Conclusion:** Dutasteride is safe and effective for patients with BPH. A 12 month course of dutasteride can reduce the volume of an enlarged prostate and relieve lower urinary tract symptoms.

Key words: BPH, 5-alpha-reductase inhibitor, lower urinary tract symptom

INTRODUCTION

Medical treatment with an α-1 adrenergic blocking agent or a 5-α-reductase inhibitor (5-ARI) has become the first choice in management of benign prostatic hyperplasia (BPH). Treatment with α-1 blockers such as terazosin, tamsulosin, doxazosin or alfulzosin has been found to result in rapid improvement in the maximum flow rate (Qmax) and quality of life (QoL) index [1,2]. Treatment with a 5-ARI such as finasteride or dutasteride has been found to reduce total prostatic volume (TPV) and surgical risk in long-term follow-up [3-6]. Combination therapy with both α-1 blockers and 5-ARI has a better long-term therapeutic outcome compared with treatment using a single medication or a placebo [5]. A good therapeutic result was maintained following the discontinuation of doxazosin after 6 months in 70% of BPH patients treated with dutasteride and doxazosin [6]. It has been suggested that a TPV of more than 40 mL might be associated with a higher risk of clinical progression of BPH, acute urinary retention (AUR), and the need for BPH-related surgical intervention [7]. Combined therapy has been suggested for patients with large BPH (≥ 30 or 40 mL) and lower urinary tract symptoms (LUTS) whereas alpha-1 blockers alone were suggested for those with a small BPH (< 30 mL) [8].

In the medical treatment of clinical BPH, 5-ARI has been proven to reduce the prostatic volume as well as improve the LUTS symptom score and QoL index [3,4,8]. Dutasteride is a type 1 and type 2 dual 5-ARI which has been demonstrated to have long-term clinical effects in the reduction of BPH progression and BPH-related complications [6, 8].

The prostate is smaller in Asians than Caucasians. Previous studies also demonstrated that a TPV of more than 40 mL can be used to predict that 90% of patients with LUTS have bladder outlet obstruction [9]. However, a transitional zone index (TZI) of more than 0.5 is more important in the diagnosis of bladder outlet obstruction than TPV and is a good predictor for response to medical therapy [10]. Although 5-ARI has been shown to effectively reduce the prostate volume in the west, this therapeutic outcome might not be achieved in Asian countries.

The aims of this study were as follows: (1) to investigate the parameters (TPV, TZI) correlated with clinical improvement and to establish if there is any predictive value of these parameters in the response to dutasteride, (2) to evaluate the efficacy and safety of dutasteride in treatment of clinical BPH in Taiwanese patients.

MATERIALS AND METHODS

This study was the first year report for the Taiwanese Dutasteride Survey in the Hualien district. A total of at least 100 evaluable patients completed the 12 month treatment at Buddhist Tzu Chi General Hospital, Hualien. It was estimated that a total of 1,000 patients would be enrolled in Taiwan in 2007 through 2008.

Patients must meet all the following criteria to be eligible to enter the trial: (1) age 45 years or above; (2) have clinical BPH, defined as having two of the following: TPV ≥ 20 mL, Qmax ≤ 12 mL/s and moderate LUTS with an international prostate symptom score (IPSS) ≥ 8 points; (3) prostate specific antigen (PSA) value ≤ 4 ng/mL, or > 4 ng/mL and no malignancy on biopsy; (4) no active urinary tract infection; (5) no AUR; (6) no neurogenic bladder or detrusor underactivity. The exclusion criteria included: (1) TPV less than 20 mL; (2) history of prostatic cancer, (3) chronic stroke, Parkinson's disease or other severe neurological disease with poor ambulation and detrusor underactivity; (4) severe cardiopulmonary disease and inability to receive regular follow-up; (5) confirmed diagnosis of uncontrolled acute urinary tract infection; (6) abnormal liver or renal function, (7) any contraindication to digital rectal examination or transrectal sonography of the prostate

Received: January 1, 2007 Accepted: February 15, 2007
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This study was designed as a single-arm, open-label trial. Patients with confirmed clinical BPH received dutasteride 0.5 mg daily. Patients were evaluated at baseline screening and at at a minimum of 2 required visits. Evaluated parameters included IPSS, QoL index, TPV, TZI, Qmax, voided volume, PVR and PSA value. The IPSS was further classified into storage IPSS (including symptoms of frequency, urgency, nocturia) and emptying IPSS (including symptoms of hesitancy, intermittency, residual urine sensation and straining to void). The IPSS and QoL index were adapted from the recommendations of the International Continence Society [11].

The primary end-point was to evaluate the efficacy of dutasteride treatment by evaluating the net changes in the IPSS and QoL index in patients from baseline to 12 months after the first day of treatment. The secondary end-points were to evaluate the efficacy of dutasteride treatment by evaluating the net changes in TPV, TZI, Qmax, voided volume, PVR and PSA from baseline to 12 months after the start of treatment.

Any clinical BPH progression was also recorded during the study period. Clinical BPH progression was defined as the presence of one of the following during the study period: (1) increase in IPSS > 4 points compared to baseline value, (2) decrease in Qmax >2 mL/s, (3) acute urinary tract or genital tract infection, (4) PVR increased by 150 ml compared with baseline value, (5) AUR, (6) abnormal renal function defined as an elevated creatinine value of > 1.5 mg% or increase of 50% of the baseline value, (7) hydronephrosis or (8) urinary incontinence .

The data at baseline and 6 and 12 months after the first day of treatment were expressed as mean ± SD. Statistical analysis was performed by paired t-test for changes within groups and by Student's t-test for comparison between groups. A p value of less than 0.05 was considered significant.

Table 1. The Parameters at Baseline, 6 Months and 12 Months after Dutasteride Treatment

		Baseline (n=173)	6 Months (n=173)	12 Months (n=102)	P value
IPSS	empty	10.5 ± 6.0	3.9 ± 4.2	4.1 ± 4.4	0.000
	storage	7.1 ± 3.8	4.4 ± 2.8	4.0 ± 2.9	0.000*
	Total	17.6 ± 6.7	8.3 ± 5.3	8.1 ± 5.1	0.000#
QoL Index		4.3 ± 0.95	2.4 ± 0.94	1.9 ± 0.86	0.000
					0.006*
					0.000#
TPV (mL)		47.1 ± 20.8	40.8 ± 19.5	36.7 ± 19.5	0.000
					0.000*#
TZI (%)		46.7 ± 14.2	44.7 ± 12.8	44.4 ± 14.3	0.013
					0.792*
					0.019#
Qmax (mL/s)		9.4 ± 4.7	10.9 ± 5.4	10.8 ± 5.4	0.000
					0.142*
					0.001#
Voided volume (mL)		161 ± 121	179 ± 126	189 ± 130	0.042
					0.834*
					0.001#
PVR (mL)		74.7 ± 83.4	68.9 ± 66.5	65.2 ± 79.2	0.362
					0.336*
					0.377#
PSA (ng/mL)		3.27 ± 3.57	2.45 ± 3.203	1.92 ± 1.52	0.000
					0.336*
					0.000#

*: P value between 6 months and 12 months; #: between baseline and 12 months

RESULTS

A total of 173 men entered the study. Their ages ranged from 48 to 95 years with a mean of 72 years. All patients were treated with dutasteride 0.5 mg daily for more than 6 months, and 102 patients were treated for more than 12 months. Seventy-two of these 102 patients received combination therapy with an alpha-blocker (terazosin 2 mg or tamsulosin 0.2 mg) daily, while the other 30 received monotherapy with dutasteride.

The TPV at baseline was 20 to 40 mL in 82 patients, 41 to 60 mL in 45 patients, 61 to 80 mL in 36 patients and more than 81 mL in 10 patients. The mean ages of these 4 groups of patients were not significantly different. All 72 patients receiving combination therapy had a TPV of more than 40 mL at baseline.

The evaluated parameters at baseline, 6 months and 12 months are listed in Table 1. At 6 months, there were significant

Table 2. The Parameters at Baseline and 12 Months after Dutasteride Treatment in Patients with TPV ≤ 40 mL and TPV > 40 mL

		TPV > 40 mL		TPV ≤ 40 mL		P value
		Baseline	12 months	Baseline	12 months	
IPSS	empty	10.3 ± 6.1	4.0 ± 4.3	10.6 ± 6.0	4.0 ± 4.4	0.000* #
	storage	7.9 ± 3.7	4.7 ± 2.8	6.1 ± 3.7	3.7 ± 2.9	0.000* #
	total	18.1 ± 5.7	8.6 ± 4.1	16.3 ± 5.3	8.1 ± 5.1	0.000* #
QoL Index		4.4 ± 0.87	1.9 ± 0.83	4.3 ± 0.99	1.9 ± 0.89	0.000* #
TPV (mL)		62.1 ± 17.6	55.2 ± 12.4	30.5 ± 6.1	26.7 ± 7.4	0.000* #
TZI (%)		52.7 ± 13.3	52.6 ± 10.7	40.2 ± 12.1	40.0 ± 14.3	N.S.
Qmax (mL/s)		9.4 ± 4.8	10.9 ± 5.2	9.4 ± 4.6	10.8 ± 5.5	N.S.
Voided volume (mL)		144 ± 111	182 ± 122	179 ± 130	197 ± 137	N.S.
PVR (mL)		81.4 ± 95.1	63.9 ± 79.2	67.2 ± 67.4	66.5 ± 79.4	N.S.
PSA (ng/mL)		4.26 ± 3.68	2.49 ± 1.44	2.18 ± 3.13	1.62 ± 1.48	N.S.

*: P value in patient group of TPV > 40 mL; #: in patient group of TPV ≤ 40 mL between baseline and 12 months

changes in all parameters except for PVR. The emptying IPSS, QoL index and TPV were significantly improved from 6 months to 12 months, however, the other parameters showed no significant improvement at 12 months. The TPV decreased by 13.4% at 6 months and by 22.1% at 12 months compared with baseline. However, the change in TZI was not correlated with the change in TPV at 6 months (-4.1%) or 12 months (-4.9%).

Table 2 shows a comparison between patients with TPV ≤ 40 mL and TPV > 40 mL. The improvements in IPSS, TPV and QoL index were significant at 12 months after dutasteride therapy. However, the changes in Qmax and voided volume were not significant. TPV decreased by 11.1% in the patients with TPV >40 mL whereas it decreased by 15.7% in those with TPV ≤ 40 mL.

The adverse events in the patients treated with dutasteride were mild. Only 3 patients (1.7%) complained of erectile dysfunction, 5 (2.9%) had somatic complaints such as dizziness and general weakness, and 5 (2.9%) had epigastralgia and abdominal discomfort. There was no clinical BPH progression in this first year survey.

DISCUSSION

The results of this preliminary study indicate that dutasteride is safe and effective in treating patients with clinical BPH. After a 12 month treatment course, the prostate volume decreased by 22%, and LUTS and the QoL index all significantly improved. The therapeutic effectiveness for Taiwanese men is similar to that reported for western BPH patients.

Dutasteride is a 5-alpha-reductase inhibitor which inhibits both type 1 and type 2 5-alpha-reductase. 5-alpha-reductase catalyzes conversion of testosterone to dihydrotestosterone. Inhibition of 5-alpha-reductase can arrest prostatic growth and relieve prostatic obstruction. Previous investigations have shown that long-term use of a 5-alpa-reductase inhibitor can effectively treat BPH, especially in patients with a prostatic weight > 40 gm, and it is effective in treating prostatic hematuria [3-5,7,8]. Finasteride and dutasteride are appropriate and effective treatments for patients with LUTS associated with demonstrable prostate enlargement [12].

Although 5-ARI is effective in reduction of TPV and partially relieves LUTS, the therapeutic effects occur more slowly than in alpha-blocker therapy. In patients with severe LUTS and a large TPV, initial combination therapy with an alpha-blocker and a 5-alpha-reductase inhibitor is necessary to rapidly relieve LUTS and induce progressive shrinkage of prostatic volume [12]. In the long-term medical therapy for BPH, however, alpha-blockers cannot alleviate the slow increase of TPV, which results in a higher risk of AUR and higher rate of surgery. By contrast, 5-ARI reduces the risk of subsequent AUR and the need for BPH-related surgery [5,8]. Therefore, 5-ARI may be used optionally to prevent progression of BPH in patients with an enlarged prostate but without bothersome LUTS [12].

CONCLUSION

The results of this study have demonstrated that dutasteride is effective for patients with BPH. In patients proven to have an enlarged prostate and LUTS, a 12-month treatment course of dutasteride can reduce the prostate volume and relieve LUTS.

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