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Dutasteride with As-Needed Tamsulosin in Men at Risk of Benign Prostatic Hypertrophy Progression

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ABSTRACT

Purpose: The primary aim of this study was to investigate whether initial therapy with dutasteride followed by dutasteride with as-needed tamsulosin can prevent symptom progression in patients at a high risk of clinical progression of benign prostatic hyperplasia (BPH).

Patients and Methods: This study was an open-label, single-site pilot study of 63 patients. Patients were men > 50 years of age, with a clinical diagnosis of BPH based on medical history, symptom scores, and medical exams. Each patient was prescribed 0.5 mg once daily of dutasteride for 1 year, at which time 0.4 mg once daily of tamsulosin was added. After 3 months of combination therapy, subjects were counseled to taper or discontinue tamsulosin and to restart only on an as-needed basis. Patients returned to the clinic at 6, 9, and 12 months when they were evaluated and drug compliance was measured.

Results: Adding tamsulosin to dutasteride resulted in a 41% improvement in IPSS and a 62% improvement in Qmax after 3 and 6 months, respectively, which were maintained regardless of subsequent tamsulosin use.

Conclusion: The partial or total withdrawal of tamsulosin after 1 year of 5-ARI, followed by combination therapy for 3 months, resulted in little or no deterioration of LUTS in men with BPH in the final 12 months of the study.

	Dutasteride after 1 year (n = 63)	Dutasteride + tamsulosin	As-needed tamsulosin		
	Baseline	3 months	6 months	9 months	12 months
IPSS	19.80	11.76	11.30	12.07	11.31
Qmax	9.75	n/a	15.84	n/a	20.43

KEYWORDS: Dutasteride; Tamsulosin; Benign prostatic hyperplasia
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original study

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INTRODUCTION

There is little doubt about the existence of benign prostatic hyperplasia (BPH) in men in the United States. Prevalence is at 40% in men 60 years of age and 90% for men 80 years or older [1]. Symptomatic BPH left untreated can progress to a worsening of symptoms, obstruction, acute urinary retention, infection, and the need for surgery [2]. Lower urinary tract symptoms (LUTS) typically arise from the prostate or bladder. Symptoms are classified into obstructive or irritative, and they can be rated on a scale, such as the International Prostate Symptom Score (IPSS). Currently, there are 2 drug classes with different mechanisms of action, which are the mainstay of the medical management of BPH. One class is the alpha-antagonist (α-blocker) and the second are the 5-alpha-reductase inhibitors (5-ARI). Efficacy with either agent as monotherapy has been demonstrated in other trials [3,4]. The use of these 2 classes in combination therapy to control LUTS due to BPH has been established in a number of studies [1,5].

Barkin et al. have demonstrated that BPH symptom relief can be maintained after withdrawal of the alpha-blocker tamsulosin from sustained combination therapy of dutasteride and tamsulosin. However, it has not been shown whether patients with BPH, who are at high risk for symptom progression and who achieve optimal improvement of symptoms on combination therapy followed by withdrawal of the alpha-blocker, will maintain the degree of improvement relative to the continuous coadministration of the 2 agents.

The objective of this study is to look at men with BPH who are at a high risk for symptom progression and who achieve optimal improvement of symptoms on combination therapy followed by withdrawal of the alpha-blocker. Will returning the alpha-blocker on an as-needed basis for symptom control maintain the degree of improvement relative to the continuous coadministration of the 2 agents?

This study in men with moderate to severe symptomatic BPH investigated the efficacy and safety of treatment with dutasteride (0.5 mg) once daily for 1 year and tamsulosin (0.4 mg), administered once daily for 3 months. Subjects were then counseled to begin flexible dosing of tamsulosin, if possible, taking it only on an as-needed basis, depending on the severity of symptoms and the clinical outcome.

METHODS

Study Design

This single-site, open-label study included 63 men > 50 years of age, with clinical diagnoses of BPH. Baseline assessments prior to beginning the study included eligibility criteria, medical history, physical exams (including digital rectal examination [DRE]), concomitant medication, hematology, serum chemistry, serum PSA, prostate volume by transrectal ultrasound (TRUS), maximum urine flow (Qmax), post-void residue (PVR), urinalysis, adverse events, BPH symptoms (IPSS), AUR (surgery/resource utilization), BPH impact index (BII), and evidence of urinary tract infection (UTI). Those subjects meeting all inclusion and exclusion criteria began combination therapy with 0.5 mg once daily of dutasteride and 0.4 mg once daily of tamsulosin for the first 3 months. Subjects then returned to the clinic every 3 months, for the next 9 months, for symptom assessment, dutasteride continuance counseling, and placement on flexible tamsulosin dosing on an as-needed basis according to symptom decline or improvement.

At the 3-month study visit, concomitant medications, adverse events, and vital signs were recorded. Subjects were questioned for evidence of UTI, AUR, hematuria, and hematospermia, and asked to complete the BII, PPSM, and IPSS. Any unused study medication was collected and counted, and a new 3-month supply was dispensed. Subjects were counseled to:

1. continue dutasteride on a daily basis,
2. discontinue, taper, or restart their tamsulosin as symptoms might dictate, and
3. return to the clinic in 3 months.

At the 6-month study visit, the same assessments from the previous visit were again made, with the addition of PVR and urine flowmetry. A new supply of study medications was dispensed, subjects were counseled to discontinue, taper, or restart their tamsulosin as symptoms might dictate, and return to the clinic in 3 months. Subjects were counseled to:

1. continue dutasteride on a daily basis,
2. discontinue, taper, or restart their tamsulosin as symptoms might dictate, and
3. return to clinic in 3 months.

At a 9-month study visit, concomitant medications, adverse events, and vital signs were recorded. Subjects were questioned for evidence of UTI, AUR, hematuria, and hematospermia, and asked to complete the BII, PPSM, and IPSS. Any unused study

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medication was collected and counted, and a new 3-month supply was dispensed. Subjects were counseled to:

1. continue dutasteride on a daily basis,
2. discontinue, taper, or restart their tamsulosin as symptoms might dictate, and
3. return to the clinic in 3 months.

Subjects returned to the clinic at 12 months. Unused study medications were collected and counted. Subjects were evaluated as before, which included hematology, chemistry, total serum PSA, PVR, and flowmetry. Subjects were thanked and discharged from study participation.

LUTS were assessed at screening, baseline, and every 3 months using the self-administered IPSS questionnaire, including the BPH-related health status evaluation (question 8). PSA, hematology, and serum chemistries were performed at baseline, 6-month, and 12-month visits. Quality of life (QoL) was assessed using the PPSM and BII every 3 months. Qmax and PVR measurements were made at the initial screening, baseline, 6-month visit, and 12-month visit. TRUS was performed at the initial screening. Evidence for UTI, hematuria, and hematospermia was assessed every 3 months.

Study Population

Men > 50 years of age with a clinical diagnosis of BPH by medical history and physical exam, including digital rectal examination, were enrolled in the study. Other entry criteria were IPSS > 12, prostate volume > 30 cc (TRUS), total serum PSA > 1.5 ng/ml, Qmax > 5 and < 15 ml/second, minimum voided volume > 125 ml (based on 2 voids), and the ability to give informed consent and comply with the protocol for 1 year. Exclusion criteria were total serum PSA > 10 ng/ml, history or evidence of prostate cancer, previous prostate surgery, cystoscopic examination or catheterization within 7 days prior to screening, AUR within 3 months prior to screening, post-void residual volume > 250 ml, a history of breast cancer, any history or current use of drugs that would enhance or diminish the action of the study drugs or the occurrence of side effects (including anabolic steroids), the use of phytotherapy for BPH, renal insufficiency, malignancy other than basal-cell carcinoma, hypersensitivity to any study component, or participation in another study concurrently.

Study Endpoints

The primary endpoints were to determine the proportion of subjects who were able to discontinue tamsulosin without deterioration of symptoms and the average amount of tamsulosin saved by those able to reduce or discontinue its usage. Effectiveness was assessed using IPSS and Qmax, while quality of life was measured by BII and PPSM. Safety was measured by UTI and AUR incidence and resource utilization. Pharmacoeconomic impact was calculated via direct tablet count.

Table 1. Baseline characteristics.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11t1

Baseline parameters	Value*
Age (years)	66.63
IPSS	19.8
PSA (nag/mL)	4.73
Prostate volume	57.65 cc
Qmax	9.75 ml/sec
PVR volume	82.33 ml

*Unless otherwise noted, values are means.

Statistical Considerations

This was an open-label, single-arm observational study. All subjects were included in the intent-to-treat population. The population was analyzed in 4 dynamic cohorts based on tamsulosin usage after 3 months of combination therapy.

1. No change in dose as initiated at baseline.
2. Increased or restarted tamsulosin after tapering or discontinuing.
3. Reduced tamsulosin dosage.
4. Discontinued tamsulosin completely.

The percent change in tamsulosin usage was based on the actual amount used based on pill count. For IPSS, Qmax, and QoL assessments, the values and change from month 0 were compared at month 3, month 6, month 9, and month 12.

RESULTS

Subject Demographics and Disposition

Sixty-three subjects were enrolled in the study and entered into the combination therapy phase. Fifty-four subjects completed the study, 6 subjects discontinued due to adverse events, 2 subjects withdrew consent, and 1 subject was lost to follow-up (Tables 1 and 2). The mean age was 66 and the majority of

Table 2. Baseline characteristics by final cohort.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11t2

Baseline characteristics of tamsulosin usage cohorts (12 month visit)				
Parameter	No change	Increased or restarted	reduced dose	Discontinued
N	6	17	14	17
Age				
IPSS	22 (16-26)	22 (14-35)	19 (12-30	18 (12-30)
Qmax	10.2 (7.3-13.7)	10 (5.7-14.8)	10.5 (6.1-14.8)	10.4 (5.4-18.4)
PSA	6.5 (3.2-9.7)	4.4 (1.7-12.4)	4.9 (1.5-10.9)	4.2 (1.3-10.1)
Prostate volume	61.7 (42.5-80.2)	62.6 (32.1-127.9)	57.6 (32.7-85.4)	51.2 (30-107.6)
PVR	80.5 (10-237)	94.9 (52-218)	67.7 (5-176)	82.5 (22-200)

the patients were Caucasian. Mean baseline values for IPSS and Qmax for all subjects were 19.80 and 9.75 ml/sec, respectively.

Effectiveness Endpoints

The mean total IPSS values after 3, 6, 9, and 12 months are represented in Table 3. All subjects had symptom improvement with the addition of tamsulosin; however, the symptoms appeared to be somewhat stable in all groups at 6 months, 9 months, and 12 months, regardless of tamsulosin usage (Figures 1 and 2). There was no clinically significant difference in the mean change from month 3 between groups at 12 months.

The 3-month combination of dutasteride therapy resulted in at least a 3-point improvement in IPSS scores, suggesting a meaningful improvement (Figures 1 and 2). After flexible dosing was initiated, the initial benefit was maintained across all groups, regardless of tamsulosin dosing.

Changes from baseline for Qmax and BII stratified by cohort are represented in Figures 3 and 4, respectively. As with IPSS, Qmax improvement achieved following tamsulosin dosing was maintained in all groups through 12 months. Similarly, BII changes were also maintained through month 12.

Cohorts were further stratified into 2 groups to see if prostate volume had any correlation with tamsulosin usage: subjects with PV 30 to 50 mL and subjects with PV > 50 mL. Median prostate size across all subjects was 48.8 mL. Due to the small size of this study, tamsulosin usage cohorts were combined into 2 groups: subjects who were able to reduce or discontinue

Figure 1. Mean IPSS score by tamsulosin use.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11f1

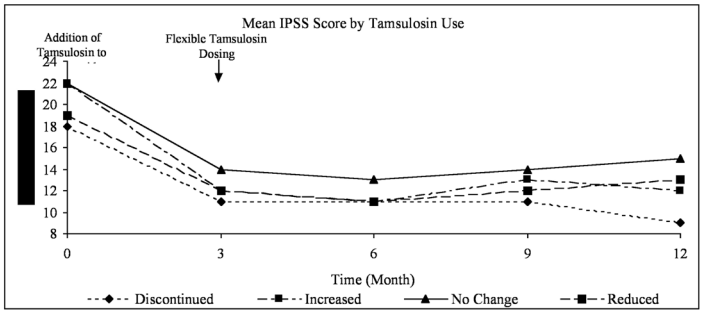


Figure 2. Mean IPSS change from baseline by tamsulosin use.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.10f5

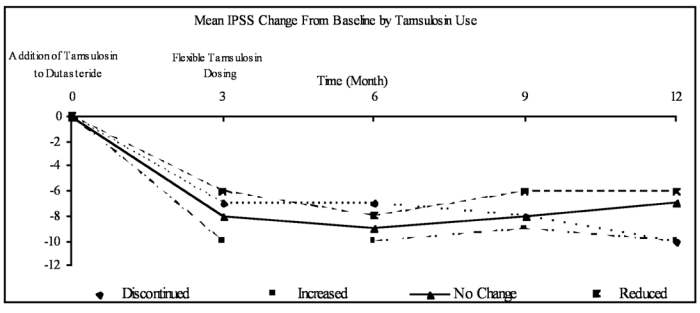


Figure 3. Qmax changes from baseline by tamsulosin use.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11f3

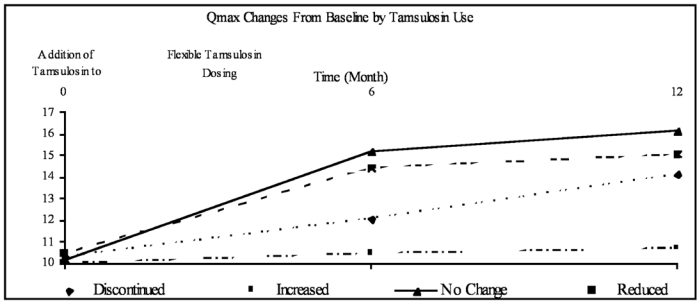
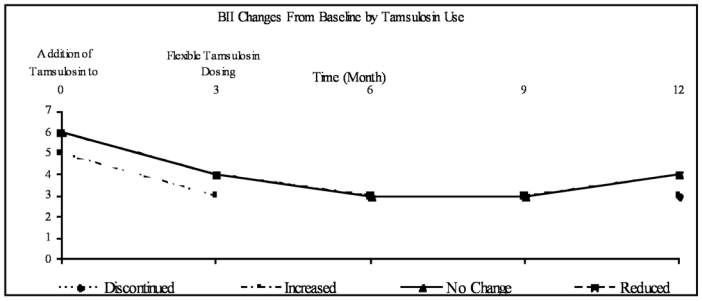


Figure 4. BII changes from baseline by tamsulosin use.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11f4



tamsulosin usage, and subjects who either had no change or increased tamsulosin usage, respectively (Table 5).

The Patient Perception of Study Medication (PPSM) questionnaire was evaluated case by case. While these patients reported outcomes that were inconsistent across all measures in all cohorts, it appears to the investigator that trends were consistent with the objective measures also employed in this study.

Safety Profile and Tolerability

Tolerability has been well established in previous studies, in both monotherapy and combination regimens. Adverse events emergent in this study are reported in Table 4. Of 149 total adverse events reported, only 27 were designated as possibly or probably study-drug related: 8 had altered ejaculation, 4 had vertigo, 3 had fatigue, 2 had nasal congestion, 2 had gynecomastia, 2 had erectile dysfunction, 2 had decreased libido, 1 had urgency incontinence, 1 had headache, 1 had rash, and 1 had postural hypotension. Two subjects were discontinued from study participation while the remainder completed the study. No subjects experienced AUR that required utilization of resources, such as catheterization or surgery.

Six subjects experienced 11 serious adverse events but none were study related. There was 1 death, but the remaining subjects completed the study.

DISCUSSION

Men with BPH often present with a wide constellation of LUTS that respond well to pharmacotherapy. Long-range studies have demonstrated that both dutasteride and tamsulosin can

Table 3. Changes in mean values for IPSS and Qmax, for all subjects.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11t3

	Baseline	3 months	6 months	9 months	12 months
IPSS	19.8	11.76	11.3	12.07	11.31
Qmax	9.75	n/a	15.84	n/a	20.43

Table 4. Adverse events by body system.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11t4

Number of patients with at least 1 adverse event, by body system		
Body system	Total	Drug related
Body as a whole	7	3
Cardiovascular system	18	1
Digestive system	9	1
Endocrine system	6	2
Hemic and lymphatic system	0	0
Metabolic and nutritional disorders	2	0
Musculoskeletal system	18	0
Nervous system	19	4
Respiratory system	31	1
Skin and appendages	15	2
Urogenital system	24	13

Table 5. Number of patients in each cohort, further divided by prostate volume.
http://dx.doi.org/10.3834/uij.1944-5784.2012.02.11t5

	PV = 30-50 mL	PV > 50 mL
Reduced/discontinued tamsulosin	18	13
No change/increased tamsulosin	10	13

initiate rapid improvement and maintain that level of relief for an extended period. We also know that combination therapy provides enhanced symptom relief when compared to monotherapy. Unfortunately, the number of study-drug related adverse events increase with combination therapy, as demonstrated in the combination of Avodart and tamsulosin (CombAT) trial.

Remarkably, all subjects maintained similar improvement from baseline at 1 year, regardless of whether the subject:

1. made no change in tamsulosin usage as initiated at baseline,
2. restarted tamsulosin after tapering or discontinuing tamsulosin,
3. reduced tamsulosin usage, or
4. discontinued tamsulosin completely.

These data suggest that:

1. in patients whose symptoms are not adequately controlled on a 5-ARI alone, the addition of tamsulosin shows an additional benefit in symptom improvement, and
2. after maximal improvement has been seen in combination therapy, individualization of the tamsulosin dose based upon the patient's clinical status dosing might be possible (coadministration with dutasteride and tamsulosin or monotherapy with dutasteride).

Furthermore, analysis of tamsulosin usage by prostate volume revealed that patients with smaller prostates (30 to 50 mL) were more likely to reduce or discontinue tamsulosin usage, whereas patients with larger prostates (> 50 mL) had similar outcomes across all cohorts.

We also observed that those subjects who started with the highest IPSS scores at baseline, and who had derived the greatest benefit from adding tamsulosin, tended to stay on combination therapy or added tamsulosin after discontinuing at 3 months. This may have resulted from reluctance to discontinue symptom relief or the perception of symptoms returning after discontinuing combination therapy. Those subjects who were on dutasteride monotherapy at 1 year seemed to trend toward further improvement, but the sample size was insufficient to produce confirmatory results. No subjects experienced AUR or required utilization of resources for safety issues, underscoring the safety of all of the self-selected regimens.

CONCLUSION

This study, while small in size, suggests that symptom relief in subjects with BPH may be maintained or improved with dutasteride monotherapy following symptom optimization with dutasteride and tamsulosin combination therapy for 3 months. The limitations to this trial are it's size and observational design. Prostate volume may be a key clinical parameter to the use of intermittent combination of tamsulosin and dutasteride. A larger prospective, statistically adequate, double blind placebo-controlled study will be needed to corroborate our results.

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