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ORIGINAL ARTICLE

Effect of Discontinuation of Tamsulosin in Korean Men with Benign Prostatic Hyperplasia Taking Tamsulosin and Dutasteride: An Open-Label, Prospective, Randomized Pilot Study

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Objective: This study was conducted to examine the effect of discontinuing tamsulosin in patients with benign prostatic hyperplasia who had been receiving combination therapy with tamsulosin and dutasteride.

Methods: The study sample consisted of 108 men with benign prostatic hyperplasia and lower urinary tract symptoms who visited our urology clinics between April 2008 and December 2010. All were assessed using the International Prostate Symptom Score (IPSS). The patients had IPSS of 8–19 and prostate volumes ≥25 mL by transrectal ultrasonography. They were put on tamsulosin and dutasteride, and the efficacy of this regimen was assessed every 12 weeks. After 48 weeks, patients were divided at random into a group continuing to take the same drug combination (group 1) and a group taking only dutasteride 0.5 mg (group 2).

Results: Sixty-nine of the original 108 patients completed the study, 36 (52%) in group 1 and 33 (48%) in group 2. The mean age of all patients was 67.96 ± 7.88 years and mean prostatic volume was 40.45 ± 12.81 mL. Mean prostate-specific antigen was 3.31 (0.4–9.9) ng/mL at the outset. The IPSS scores of the two groups at first visit, 48 and 72 weeks were, respectively, 14.69 versus 15.85 ($P = 0.322$), 12.08 versus 12.85 ($P = 0.582$) and 10.89 versus 11.06 ($P = 0.897$.) There was a statistically significant difference between the baseline and 72-week IPSS scores in both groups (group 1: $P < 0.001$, group 2: $P < 0.001$).

Conclusion: In patients with moderate IPSS, discontinuing tamsulosin after 48 weeks of combined tamsulosin and dutasteride therapy has no significant effect on outcome.

Key words dutasteride, prostatic hyperplasia, tamsulosin

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a frequent problem in ageing men, and its incidence increases with age.[1] The prevalence of BPH, based on histological evidence from autopsy studies, is >50% in men aged 51–60 and 90% by age 85.[2] Understanding BPH is becoming more important due to the increase in life expectancy.[3] α_1-Adrenoreceptor antagonists (α_1-blockers) and 5α reductase inhibitors (5ARIs) are the mainstays of therapy for lower urinary tract symptoms secondary to BPH (LUTS/BPH).[4] The aim of combination therapy is to combine the rapid symptom relief provided by the α_1-blockers with the risk reduction and prevention of BPH progression provided by the 5ARIs.[5] Useful treatment outcomes have been reported after long-term use of 5ARIs. These can prevent or retard the progression of BPH by inhibiting dihydrotestosterone (DHT) synthesis, and reduce serum levels of prostate-specific antigen (PSA).[6] Testosterone is the main circulating androgen and is converted in the prostate to DHT by the enzyme 5α-reductase.[7] DHT is the primary androgen responsible for prostatic enlargement and obstruction of the bladder outlet, thus contributing to the progressive nature of BPH.[8] A reduction of approximately 50% in PSA by 12 months is expected in men taking a 5ARI.[9] Hence, the American Urological Association Guideline on the Management of BPH recommends that 5ARIs be used to prevent progression of LUTS/BPH and to reduce the risk of urinary retention and future prostate-related surgery.[10] In a recent trial, patients with severe symptoms may benefit from longer-term combination therapy with tamsulosin and dutasteride.[11]

However, long-term continuous medical treatment without limit may reduce adherence to medication for

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socioeconomic or therapy-related reasons.[12] Nichol et al. reported that adherence in their BPH population was low, with only about 40% of patients adherent to taking any BPH medication in the form of α_1-blocker monotherapy, 5ARIs or combination therapy.[13] We conducted the present pilot study to assess the impact of discontinuing tamsulosin in patients with BPH and moderate International Prostate Symptom Score (IPSS) scores who had been on combination therapy with tamsulosin and dutasteride.

2. METHODS

2.1. Subjects

The study sample consisted of 108 men with LUTS/BPH who visited our urology clinics between April 2008 and December 2010. None had previously been given tamsulosin or dutasteride. The study was an open-label, prospective and randomized study that was conducted and approved by the Institutional Review Board of the hospital.

All the subjects were assessed using the IPSS. Patients with a baseline IPSS of 8–19 and prostate volume $\geq$25 mL by transrectal ultrasonography were selected for the study. The following subjects were excluded: (i) those with a urinary tract infection; (ii) those with diabetes mellitus or a neurological disorder; (iii) those who had undergone urinary tract surgery; (iv) those with serum PSA levels $\geq$10 ng/mL; (v) those with post-voided residual (PVR) urine >150 mL. If PVR exceeded 150 mL at any visit, the patient was restated on an α_1-blocker. If serum PSA was 4–10 ng/mL, a transrectal ultrasonography-guided prostate biopsy was performed to exclude prostate cancer.

2.2. Study design

Before enrollment in the study, patients were screened for 2 weeks to determine whether they met the inclusion criteria. Information regarding duration of illness, smoking/drinking status, and past medical history was also collected. The baseline evaluation also included a physical examination in which blood pressure and heart rate were measured, and 12-lead electrocardiography, routine hematological tests and urinalysis were performed. Thereafter, at the outset of the study (designated as baseline), all the patients were given tamsulosin 0.2 mg and dutasteride 0.5 mg/day, to be taken before sleep. The efficacy of this regimen was assessed every 12 weeks. After 48 weeks, the patients were divided into a group continuing to take the same drug combination (group 1) and a group taking only dutasteride 0.5 mg (group 2) using a random function of Open Office Calc (Open Office.org version 3.2.0, Oracle Corp., Redwood Shores, CA, USA).

2.3. Assessment

The efficacy of the combination treatment with regard to adverse effects was measured at baseline, 48 and at 72 weeks. The subjects were asked about their voiding symptoms, and at 48 and 72 weeks they were divided into the following three categories on the basis of their views of the effect of treatment: better, the same and worse. Being ''better'' and ''the same'' were taken as treatment satisfaction.

The efficacy of the combination treatment with regard to LUTS/BPH was assessed by determining patients' IPSS and by measuring PVR and maximal urine flow rate (Q_{max}). Quality of life (QoL) scores were also obtained. The safety of the combination treatment was assessed every 12 weeks by taking the patients' histories, performing physical examinations that included measuring blood pressure and heart rate, and recording adverse effects.

2.4. Statistical analysis

Comparisons of IPSS, Q_{max}, PVR and prostatic volume at the beginning and end of the study were made with Student's independent and paired *t*-test. Statistical analyses were performed with MedCalc (MedCalc version 11.2.1.0, MedCalc Software, Mariakerke, Belgium). A *P*-value of <0.05 was considered statistically significant.

3. RESULTS

In the first period (baseline to 48 weeks), 22 men (20.4%) dropped out of the study. Reasons for drop-out were: not returning for follow-up (14, 63.6%), declined to participate (5, 22.7%), discontinued combination therapy (2, 9.1%), and other reason (1, 4.6%) to undergo TURP. In the second period (48–72 weeks), another 17 (20.9%) dropped out. Reasons for drop-out were: not returning for follow-up (10, 58.8%) and declined participants (7, 41.2%). Declined participants in the second period included three patients in group 1 who continued tamsulosin again, two patients who decided to undergo TURP and two patients from group 2 who wanted to change medication due to adverse effects. In the duration of our study, three patients underwent TURP because they complained of no symptomatic improvement. Consequently, at 72 weeks, 69 men completed the study (Fig. 1).

The mean age of all patients was 67.96 $\pm$ 7.88 years and mean prostatic volume was 40.45 $\pm$ 12.81 mL. Mean serum PSA level was 3.31 (0.4–9.9) ng/mL at baseline (Table 1). Mean baseline and endpoint (72 weeks) IPSS of all subjects were 15.25 $\pm$ 4.80 and 10.97 $\pm$ 5.46 ($P < 0.001$), respectively, and QoL scores were 3.68 $\pm$ 1.17 and 2.84 $\pm$ 1.13 ($P < 0.001$), respectively. Mean baseline and endpoint Q_{max} of the total subjects were 8.14 $\pm$ 1.42 and 10.55 $\pm$ 3.11 mL/sec ($P < 0.001$), respectively, and prostatic volumes were 40.45 $\pm$ 12.81 and 26.82 $\pm$ 14.91 mL ($P < 0.001$), respectively. IPSS in the two groups at first visit, 48 and 72 weeks were 14.69 versus 15.85 ($P = 0.322$), 12.08 versus 12.85 ($P = 0.582$) and 10.89 versus 11.06 ($P = 0.897$) (Fig. 2). There was a statistically significant difference between baseline and 72-week IPSS in both groups (group 1: $P < 0.001$; group 2: $P < 0.001$). There were also significant differences in voiding and storage subscore of

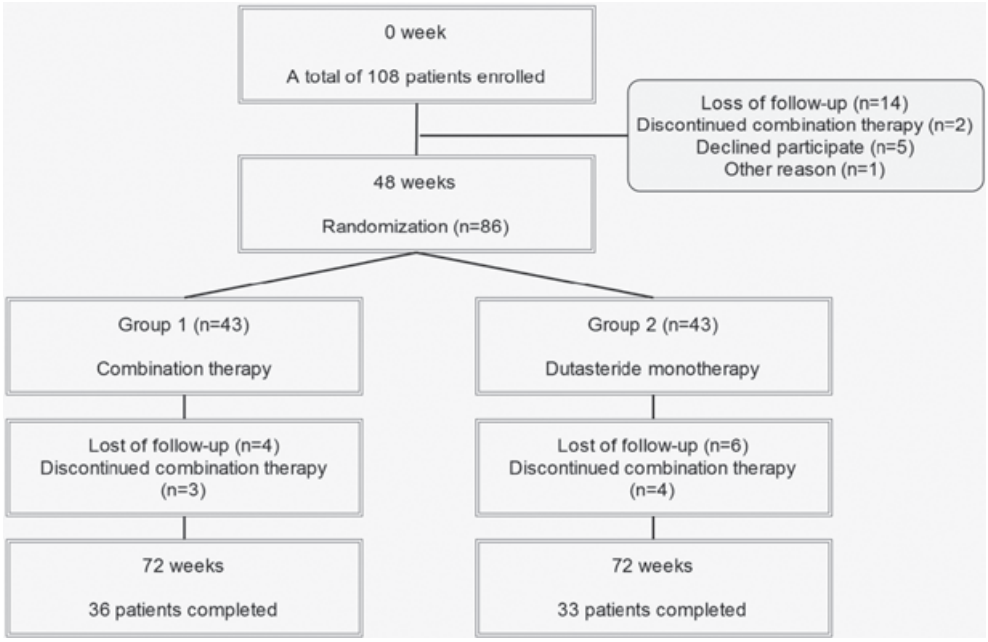

Fig. 1 Flow diagram of the study including reasons for drop-out.

TABLE 1. Baseline characteristics of the patients in the two groups

	Total	Group 1	Group 2	*P*-value
No. of patients	69	36	33	—
Mean age ± SD (year)	67.96 ± 7.88	66.92 ± 7.52	69.09 ± 8.23	0.225†
Prostate volume ± SD (mL)	40.45 ± 12.81	38.43 ± 13.01	42.65 ± 12.42	0.174†
Mean PSA (ng/mL) (range)	3.31 (0.40–9.90)	2.15 (0.40–3.97)	4.10 (0.43–9.90)	0.168†
IPSS	15.25 ± 4.80	14.69 ± 4.53	15.85 ± 5.08	0.322
Medical history				0.745‡
Hypertension (%)	25	14 (38.9)	11 (33.3)	—
Diabetes (%)	15	7 (19.4)	8 (24.2)	—

†Student's independent *t*-test. ‡Fisher's exact test. Group 1: patients who were given tamsulosin and dutasteride for 72 weeks. Group 2: patients who were given dutasteride for 24 weeks following combination therapy for 48 weeks. IPSS, international prostatic symptom score; PSA, prostate-specific antigen; SD, standard deviation.

IPSS between the two groups. Q_{max} values in the two groups at baseline, 48 and 72 weeks were 8.39 ± 1.55 versus 7.88 ± 1.22 ($P = 0.136$), 9.64 ± 2.71 versus 10.61 ± 2.67 ($P = 0.140$) and 10.44 ± 3.33 versus 10.67 ± 2.89 mL/sec ($P = 0.769$), respectively. Prostatic volumes in the two groups at baseline, 48 and 72 weeks were 38.43 ± 13.01 versus 42.65 ± 12.42 ($P = 0.174$), 30.88 ± 13.44 versus 32.72 ± 13.14 ($P = 0.135$) and 29.85 ± 14.56 versus 32.15 ± 14.27 mL ($P = 0.067$). There was a statistically significant difference between baseline and 72-week prostatic volumes in both groups (group 1: $P < 0.001$; group 2: $P < 0.001$). QoL scores in the two groups at baseline, 48 and 72 weeks were 3.92 ± 0.97 versus 3.42 ± 1.32 ($P = 0.080$), 3.42 ± 1.08 versus 2.79 ± 1.58 ($P = 0.056$) and 3.08 ± 0.10 versus 2.58 ± 1.23 ($P = 0.062$) (Table 2). In BPH progression including decreased Q_{max}, increased IPSS and increased PVR, there were no significant differences in two groups (Table 3).

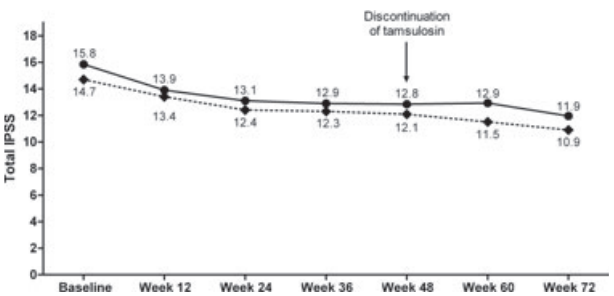

Fig. 2 Mean International Prostate Symptom Score (IPSS) for groups 1 and 2. Group 1 (-◆-): patients given tamsulosin and dutasteride for 72 weeks. Group 2 (—●—): patients given dutasteride for 24 weeks following combination therapy for 48 weeks.

Adverse effects were observed in eight men (7.4%) in the first period and in five men (5.8%) in the second period. Reduced libido was the most common adverse effect (five men in the first period; two men in the second

TABLE 2. Comparison of IPSS, QoL, Q_{max} and prostatic volume at baseline, 48 weeks and endpoint between group 1 ($n = 36$) and group 2 ($n = 33$)

		Baseline	48-week	Endpoint	*P*-value† (baseline vs endpoint)
IPSS	Group 1	14.69 ± 4.53	12.08 ± 5.94	10.86 ± 5.57	<0.001
	Group 2	15.85 ± 5.08	12.85 ± 5.94	11.06 ± 5.41	<0.001
	P-value‡	0.322	0.582	0.897	—
Storage subscore	Group 1	6.36 ± 4.15	5.83 ± 4.56	5.03 ± 3.75	0.038
	Group 2	6.24 ± 4.72	4.70 ± 3.65	5.44 ± 4.65	0.041
	P-value‡	0.912	0.260	0.687	—
Voiding subscore	Group 1	8.33 ± 4.31	6.25 ± 3.18	5.44 ± 2.54	0.001
	Group 2	9.61 ± 6.01	8.15 ± 4.72	6.03 ± 3.63	0.022
	P-value‡	0.313	0.052	0.436	—
QoL	Group 1	3.92 ± 0.97	3.42 ± 1.08	3.08 ± 0.10	<0.097
	Group 2	3.42 ± 1.32	2.79 ± 1.58	2.58 ± 1.23	0.014
	P-value‡	0.080	0.056	0.062	—
Q_{max}	Group 1	8.39 ± 1.55	9.64 ± 2.71	10.44 ± 3.33	0.002
	Group 2	7.88 ± 1.22	10.61 ± 2.67	10.67 ± 2.89	<0.001
	P-value‡	0.136	0.140	0.769	—
Prostatic volume	Group 1	38.43 ± 13.01	30.88 ± 13.44	29.85 ± 14.56	0.001
	Group 2	42.64 ± 12.42	35.72 ± 13.14	32.16 ± 14.27	<0.001
	P-value‡	0.174	0.135	0.067	—

†Student's paired *t*-test. ‡Student's independent *t*-test. Group 1: patients who were given tamsulosin and dutasteride for 72 weeks. Group 2: patients who were given dutasteride for 24 weeks following combination therapy for 48 weeks. IPSS, international prostatic symptom score; Q_{max}, maximal urine flow rate; QoL, quality of life.

TABLE 3. Comparison of BPH progression rate including Q_{max}, IPSS voiding subscore and PVR between group 1 ($n = 36$) and group 2 ($n = 33$)

	Group 1	Group 2	p-value†
Decreased Q_{max}	5	6	0.747
Increased voiding subscore	4	6	0.502
Increased PVR	3	7	0.177

†Fisher's exact test. Group 1: patients who were given tamsulosin and dutasteride for 72 weeks. Group 2: patients who were given dutasteride for 24 weeks following combination therapy for 48 weeks. IPSS, international prostatic symptom score; PVR, post-voided residual; Q_{max}, maximal urine flow rate.

period), followed by ejaculatory problem (two men each in the first and second periods), and erectile dysfunction (one man in the first period). None of the subjects dropped out of the study because of adverse effects.

4. DISCUSSION

Combining the two available types of drug in the treatment of LUTS/BPH allows patients to obtain the benefit of both, thus potentially maximizing treatment outcomes.[14] The Medical Therapy of Prostatic Symptoms (MTOPS) trial provides the most definitive data supporting the superiority of combination therapy (finasteride and doxazosin).[15] The MTOPS study found that all three treatments resulted in significant improvements in symptom scores, with combined therapy being better than either doxazosin or finasteride alone.[16] The MTOPS trial included 3047 men treated for an average of 4.5 years. Patients being treated with combination therapy experienced a similar reduction in risk of developing acute urinary retention or requiring BPH-related surgery to that of patients treated with finasteride alone.[17] The Combination of Avodart and Tamsulosin (CombAT) study was the most extensive trial evaluating the efficacy of combination therapy in patients with moderate-to-severe LUTS/BPH and enlarged prostates (more than 30 mL).[18] Combination therapy was shown to lead to greater reductions in storage subscores than dutasteride monotherapy and tamsulosin monotherapy from months 3 and 12, respectively. Recently a 4-year post hoc analysis of the CombAT data showed that combination therapy also provided significantly greater symptom improvement than either monotherapy at 4 years.[19]

Jeong et al. examined the effect of discontinuing 5ARIs on prostate volume and symptoms in BPH patients.[20] They divided the patients into two groups giving combination therapy with either finasteride 5 mg or dutasteride 0.5 mg. In their study, discontinuation of 5ARIs after combination therapy induced prostate regrowth, as well as aggravation of symptoms. Thus, they suggested that life-time use of 5ARIs should be considered for preventing BPH progression. In the Symptom Management After Reducing Therapy (SMART-1) study, Barkin et al. reported the results of combination dutasteride and tamsulosin, followed by withdrawal of the tamsulosin.[11] In their study, patients were either treated with dutasteride and tamsulosin for 36 weeks or switched to dutasteride and tamsulosin-matched placebo after 24 weeks. Eighty four percent of the subjects with moderate IPSS who were switched to dutasteride monotherapy at week 24 did so without any noticeable deterioration in their symptoms. The authors concluded that symptom improvement in response to combination therapy is maintained in the majority of patients with moderate IPSS after the α_1-blocker is withdrawn. Kobayashi et al. examined changes in voiding symptoms following discontinuation of tamsulosin monotherapy after an initial improvement in symptoms.[21] They reported that rates of successful discontinuation of tamsulosin were high throughout the

follow-up period. In their study, the inclusion criteria, similar to ours, were: (i) patients who had received tamsulosin 0.2 mg monotherapy; (ii) those who did not have severe BPH; and (iii) those who showed improvement in IPSS < 10 or QoL ≤ 3 following the tamsulosin monotherapy. Thirty-three men were enrolled in the study and 20 of them were reported to have discontinued therapy successfully after 24 weeks. The authors suggested that continuous treatment is not always needed to maintain symptom relief in patients who feel symptom improvement after initial treatment with tamsulosin. In a similar study, Yokoyama et al. examined the course of LUTS after discontinuation of successful 12 months' treatment with α_1-blockers in 75 men with LUTS/BPH.[22] They also concluded that selected patients with relatively small prostatic volumes and good flow rates after therapy can discontinue α_1-blocker treatment. These last two studies in Japan strongly suggest that continuous tamsulosin monotherapy may not be the absolute treatment of choice, especially in the actual clinical setting. In a notable paper, Issa et al. reported the result of an observational study of 1674 patients in the Ingenix Lab/Rx proprietary research database who were started on 5ARIs and α_1-blockers over a 3-year period.[23] In their study, patients' discontinued α_1-blocker treatment as early as 3 months after the start of treatment, and the dutasteride group was 64% more likely to discontinue taking the α_1-blocker than the finasteride group. They concluded that this difference could have important clinical and economic implication.

In our study, IPSS was approximately 12 and QoL was 3 at the time of tamsulosin withdrawal. Thereafter, 33 of the 43 (76.7%) subjects in group 2 completed the study. Some urologists believe that continuous treatment may not always be necessary in certain patients with LUTS/BPH. Previous studies appear to indicate that early symptom control allows for earlier discontinuation of α_1-blocker treatment in patients receiving combination therapy.[24] Based on the result of our study, patients with LUTS/BPH who are successfully treated by combination therapy may also discontinue tamsulosin. This result has important implications with regard to expense as well as with regard to the QoL of patients. Moreover, discontinuation of α_1-blocker treatment following early control of LUTS/BPH may reduce the adverse effects of α_1-blockers, such as headache, dizziness, malaise, orthostatic hypotension, syncope and ejaculatory disorder.[25] Economic benefits should also be considered in each country under different medical system. Prostate enlargement is known as a predictor of the efficacy of 5ARIs.[26] DHT reduction by dutasteride resulted ultimately in epithelial atrophy and thus in a reduction in prostate volume by 15–25% and a decrease in serum PSA by approximately 50%.[27] Thus, in determining whether isolated PSA values lie within reference ranges, serum PSA should be doubled for patients who have received dutasteride for at least 6 months.[28] In addition, discontinuation of dutasteride may be also possible in patients taken combination therapy in real clinical setting, because the etiologies of LUTS in patients with moderate IPSS and prostate volume may be multifactorial. Henceforth, challenging clinical studies on these issues will be helpful to urologists and patients in real clinical setting.

There may be a few disadvantage of combination therapy in spite of its effectiveness. None of the studies have established the period of combination therapy needed, and allowed for the adverse effects of combination therapy. This is the first prospective study of the discontinuation of tamsulosin following adequate combination therapy with tamsulosin and dutasteride. However, the present study suffers from several limitations. The first is that a placebo control group was not included. Second, the drop-out rate (36.1%) may have been higher than in previous studies. The most common cause of drop-out was follow-up loss ($n = 24$). High drop-out rate may be a result in selection bias. Small sample size in our study may be also result to the same problem. Especially, the high drop-out rate may have been responsible for the greater improvement of IPSS than seen in previous studies, since the subjects who dropped out may have experienced less improvement than the 69 subjects who completed the study. Nevertheless, our analysis may suggest that discontinuation of tamsulosin may be beneficial in clinical settings. Our study took place in conditions that clinicians encounter in their daily practice. Further randomized, double-blind, placebo-controlled studies with longer follow-up are needed to confirm our results.

5. CONCLUSION

Patients with LUTS/BPH whose symptoms improve after 48 weeks of combination therapy do not always need to continue to take tamsulosin. This result has important implications with regard to expense as well as for the QoL of patients.

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Disclosure

The authors have nothing to disclose.

REFERENCES

1. Cornu JN, Cussenot O, Haab F, Lukacs B. A widespread population study of actual medical management of lower urinary tract symptoms related to benign prostatic hyperplasia across Europe and beyond official clinical guidelines. *Eur Urol* 2010; **58**: 450–6.
2. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; **132**: 474–9.
3. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; **361**: 1359–67.
4. Donnell RF. Benign prostate hyperplasia: a review of the year's progress from bench to clinic. *Curr Opin Urol* 2011; **21**: 22–6.
5. Robert G, Descazeaud A, de la Taille A. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: who are the high-risk patients and what are the best treatment options? *Curr Opin Urol* 2011; **21**: 42–8.

6. Andriole G, Bruchovsky N, Chung LW et al. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J Urol* 2004; **172**: 1399–403.
7. Andriole GL, Humphrey P, Ray P et al. Effect of the dual 5alpha-reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol* 2004; **172**: 915–9.
8. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002; **60**: 434–41.
9. Kramer BS, Hagerty KL, Justman S et al. Use of 5alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Urol* 2009; **181**: 1642–57.
10. McVary KT, Roehrborn CG, Avins AL et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011; **185**: 1793–803.
11. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. *Eur Urol* 2003; **44**: 461–6.
12. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc* 2011; **86**: 304–14.
13. Nichol MB, Knight TK, Wu J, Barron R, Penson DF. Evaluating use patterns of and adherence to medications for benign prostatic hyperplasia. *J Urol* 2009; **181**: 2214–21; discussion 21–2.
14. Greco KA, McVary KT. The role of combination medical therapy in benign prostatic hyperplasia. *Int J Impot Res* 2008; **20**(Suppl 3): S33–43.
15. Djavan B, Handl MJ, Dianat S. Combined medical treatment using dutasteride and tamsulosin for lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Expert Opin Pharmacother* 2010; **11**: 2535–47.
16. Emberton M, Zinner N, Michel MC, Gittelman M, Chung MK, Madersbacher S. Managing the progression of lower urinary tract symptoms/benign prostatic hyperplasia: therapeutic options for the man at risk. *BJU Int* 2007; **100**: 249–53.
17. Nickel JC. Comparison of clinical trials with finasteride and dutasteride. *Rev Urol* 2004; **6**(Suppl 9): S31–9.
18. Becher E, Roehrborn CG, Siami P, Gagnier RP, Wilson TH, Montorsi F. The effects of dutasteride, tamsulosin, and the combination on storage and voiding in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the Combination of Avodart and Tamsulosin study. *Prostate Cancer Prostatic Dis* 2009; **12**: 369–74.
19. Haillot O, Fraga A, Maciukiewicz P et al. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study. *Prostate Cancer Prostatic Dis* 2011. doi: 10.1038/pcan.2011.13.
20. Jeong YB, Kwon KS, Kim SD, Kim HJ. Effect of discontinuation of 5alpha-reductase inhibitors on prostate volume and symptoms in men with BPH: a prospective study. *Urology* 2009; **73**: 802–6.
21. Kobayashi M, Tokue A, Morita T. Discontinuation of tamsulosin treatment in men with lower urinary tract symptoms: a pilot study. *Urol Int* 2006; **76**: 304–8.
22. Yokoyama T, Watanabe T, Saika T et al. Natural course of lower urinary tract symptoms following discontinuation of alpha-1-adrenergic blockers in patients with benign prostatic hyperplasia. *Int J Urol* 2007; **14**: 598–601.
23. Issa MM, Lin PJ, Eaddy MT, Shah MB, Davis EA. Comparative analysis of alpha-blocker utilization in combination with 5-alpha reductase inhibitors for enlarged prostate in a managed care setting among Medicare-aged men. *Am J Manag Care* 2008; **14**: S160–6.
24. Issa MM, Regan TS. Medical therapy for benign prostatic hyperplasia: present and future impact. *Am J Manag Care* 2007; **13**(Suppl 1): S4–9.
25. Giuliano F. Impact of medical treatments for benign prostatic hyperplasia on sexual function. *BJU Int* 2006; **97**(Suppl 2): 34–8; discussion 44–5.
26. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 1996; **48**: 398–405.
27. Roehrborn CG. The clinical benefits of dutasteride treatment for LUTS and BPH. *Rev Urol* 2004; **6**(Suppl 9): S22–30.
28. Marihart S, Harik M, Djavan B. Dutasteride: a review of current data on a novel dual inhibitor of 5alpha reductase. *Rev Urol* 2005; **7**: 203–10.