The effects of combination therapy with dutasteride and doxazosin clinical outcomes in men with symptomatic benign prostatic hyperplasia

Nguyen Van Trieu, Nguyen Duc Hai, Vu Dinh Trien, Nguyen Manh Hung, Luyen Trung Kien, Vu Thi Phuong Lan, Tran Duc, Nguyen Thi Thu Huong

108 Military Central Hospital

Summary

Objective: To investigate whether a combination of 0.5mg avodart plus 4mg doxazosin is more effective than 4mg doxazosin alone in treatment-naïve men with moderately to severe symptomatic benign prostatic hyperplasia (BPH) at risk of progression. *Subject and method:* This was a multi-centre, randomised, open-label, parallel-group study in 100 men with an international prostate symptom score (IPSS) ≥ 8, prostate volume ≥ 30mL and total serum PSA level of < 4ng/mL. Patients were randomised to 0.5mg avodart plus 4mg doxazosin (50 patients) or 4mg doxazosin alone (50) and followed for 6 months. The primary endpoint was symptomatic improvement from baseline to 6 months, measured by the IPSS. Secondary outcomes included BPH clinical progression, impact on quality of life (QoL), and safety. *Result:* The change in IPSS at 6 months was significantly greater for avodart plus doxazosin than doxazosin alone (-4.68 vs -0.02 points, p<0.05). With avodart plus doxazosin the risk of BPH progression was reduced by 36% (p<0.05), 18% and 12% of men in the doxazosin alone and avodart plus doxazosin groups had clinical progression, respectively, comprising symptomatic progression in most patients. Improvements in QoL (Question 8 of the IPSS) were seen in both groups but were significantly greater with avodart plus doxazosin groups compared with doxazosin alone, -1.46 vs 0.14, respectively (p<0.05). The occurrence of drug-related AEs, was greater in the combined therapy group. The most commonly reported AEs across both groups were erectile dysfunction and retrograde ejaculation, which occurred in 6% vs 0% and 6% vs 4% patients in the combined therapy and doxazosin alone groups, respectively. *Conclusion:* The combined therapy with avodart plus doxazosin resulted in rapid and sustained improvements in men with moderate to severe BPH symptoms at risk of progression with significantly greater symptom and QoL improvements and a significantly reduced risk of BPH progression compared with doxazosin alone.

Keywords: Dutasteride, doxazosin, benign prostatic hyperplasia.

1. Background

In the primary care setting, ≈ 60% of men with symptomatic benign prostatic hyperplasia (BPH) have moderate lower urinary tract symptoms (LUTS) at the time of diagnosis. An ageing population, together with the global adoption of screening and diagnostic strategies, means the prevalence of BPH and impact of LUTS is likely to escalate [3], [12].

BPH is defined by the presence of hyperplastic glands on pathological inspection of prostatic tissue. LUTS that are commonly attributed to BPH (e.g. increased urinary frequency, urgency, nocturia,

Correspondence to: Nguyen Van Trieu, Department of General Internal Medicine, 108 Military Central Hospital
Email: ngvantrieu@yahoo.com

decreased and intermittent force of stream, sensation of incomplete bladder emptying) are nonspecific and may result from a variety of other causes. However, the most important cause of LUTS is chronic bladder outlet obstruction (BOO), which may occur via two prostatic smooth muscle cells increase in number and tone to increase resistance to urinary flow in the urethra [10]. LUTS are assessed using the IPSS, with a score of 0 - 7 indicative of mild symptoms, 8 - 19 of moderate symptoms and 20 - 35 of severe symptoms.

BPH progression is characterised by an increase in LUTS over time and, in some men, serious outcomes such as acute urinary retention (AUR) and the need for surgery, most commonly transurethral resection of the prostate (TURP). Although TURP reduces LUTS in many cases, it can be associated with adverse events (AEs) including urinary incontinence and retrograde ejaculation [5], [7], [9].

The goals of BPH therapy are to decrease symptoms, improve quality of life (QoL), reduce BOO, decrease post-void residual urine volume, reverse urinary retention/renal insufficiency when present, and prevent disease progression [10].

The rationale behind combined use of an α1-blocker and a 5α-RI to control BPH-related LUTS relies on the potential synergistic effect of these two pharmaceutical agents due to their different modes of action. Doxazosin relaxes the smooth muscle tissue in the prostate and bladder neck, allowing urine to flow more freely. Avodart blocks the production of dihydrotestosterone, the metabolic driver of prostate growth. This impedes the development of symptoms related to prostatic overgrowth and, consequently, the incidence of AUR and prostate-related surgery [10].

Therefore, combined therapy with dutasteride (5ARI) and α-blocker were extensively investigated in some studies in the world such as CombAT, CONDUCT,.... [8], [11], [12]. However, in Vietnam, there is not any study relating to this treatment. Several questions remain, including: How does combined therapy compare with other approaches effective in clinical practice in Vietnam and how quickly are the benefits of combined therapy experienced after treatment initiation?

Our study was initiated to investigate whether immediate treatment in eligible men with a combination of 0.5mg avodart plus 4mg doxazosin offers faster and more profound symptom reduction than that offered by 4mg doxazosin.

2. Subject and method

2.1. Study design

Our study was a multi-centre, randomised, open-label, parallel-group study conducted between June 2018 and June 2019. Eligible patients were randomised 1 : 1 to self-administer combination of dutasteride (avodart) 0.5mg plus doxazosin 4mg once daily, or to doxazosin 4mg alone.

Patients visited the clinic after randomisation and at 12-week intervals thereafter, for up to 6 months. Patient-reported symptoms and treatment satisfaction were assessed using the IPSS, question 8 of the IPSS (IPSS-Q8; "if you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?").

Many years ago, Barry et al developed what was to become the most widely accepted and utilized validated questionnaire to measure the severity of LUTS symptoms. The International Prostate Symptom Score (IPSS) is a quantification of the severity of symptoms as it is self-reported by the patient [2]. This has become the gold standard in establishing the baseline and then follow-up score after any type (medical, natural, or surgical) of intervention for the management of BPH. Each question of the first 7 could be classified as either a "voiding" or a "storage" question.

A score of:

0 is defined as NO symptoms.

≤ 7 is defined as MILD symptoms.

≥ 8 and ≤ 19 is defined as MODERATE symptoms.

≥ 19 and ≤ 35 is defined as SEVERE symptoms.

Barry also proved in clinical trials that a minimum of a 3-point improvement on the

symptom scale was necessary for the patient to perceive the clinical improvement [2].

Question 8 on the IPSS score is the Quality of Life question or what is more aptly termed the "Bothersome Index."

This key question is "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?" A score of 0 equates to "delighted" and a score of 6 equates to "terrible."

At baseline and month 3 and month 6, patients underwent the hospital, evaluation of gynaecomastia, blood chemistry analysis, haematology, PSA tests, and urine analysis. Data on AEs were collected from the time of administration of the first study treatment dose until discontinuation.

Written informed consent was obtained from each patient before the performance of any study-specific procedures. The study protocol was approved by 108 Military Central Hospital scientific committee.

2.2. Study population

Men aged ≥ 50 years, with a confirmed clinical diagnosis of BPH and IPSS ≥ 8, prostate volume ≥ 30mL by TRUS (at screening) and total serum PSA level of < 4ng/mL were eligible for inclusion. Key exclusion criteria included: Total serum PSA level of ≥ 4ng/mL, history or evidence of prostate cancer.

2.3. Study endpoints and statistical analyses

The primary efficacy endpoint was the change in IPSS from baseline to month 3 and month 6. Secondary efficacy endpoints included: Categorical improvements in IPSS ≥ 3 points and the time to, and proportion of, patients with clinical progression of BPH (rise in total IPSS of ≥ 3 points compared with baseline, BPH-related AUR, recurrent UTI, overflow or urge incontinence). Health outcomes included change in IPSS-Q8 from baseline.

Analyses of exposure to study drug, compliance to study drug, and AEs were performed in all patients receiving medical therapy (Combined therapy with avodart plus carudxan or carudxan alone) as per protocol (treated population).

Change from baseline in IPSS and IPSS-Q8 was analysed according to last observation carried forward methodology. Mean scores were compared between treatment groups at each post-baseline visit using *t*-tests from a general linear model with effects for treatment, cluster, and baseline values at $\alpha = 0.05$.

3. Result

3.1. Patient disposition and demographics

Table 1. Baseline characteristics

Variable	Mean (SD)		
	Avodart and doxazosin (n = 50)	Doxazosin (n = 50)	p
Age, years	66.34 ± 7.99	65.68 ± 8.19	0.685
Weight, kg	61.33 (12.55)	63.24 (12.63)	0.71
Body mass index, kg/m^2	23.28 (3.53)	23.94 (3.77)	0.82
PSA level, ng/mL	2.268 ± 1.12	2.05 ± 1.16	0.335
IPSS	13.74 ± 4.33	12.62 ± 3.78	0.171
Prostate volume, mL	48.48 ± 12.61	44.52 ± 8.46	0.069
IPSS-Q8	3.34 ± 0.59	3.12 ± 0.75	0.106

In all, 200 patients were randomised into the study (recruitment period June 2018 to June 2019), 100 and 100 in the combined therapy and doxazosin alone groups, respectively. Of these, 50 (50%) and 50 (50%) completed 06 months of treatment. Baseline characteristics were similar between groups and indicative of a population with moderate to severe symptoms burden at risk of progression.

3.2. Primary efficacy endpoint

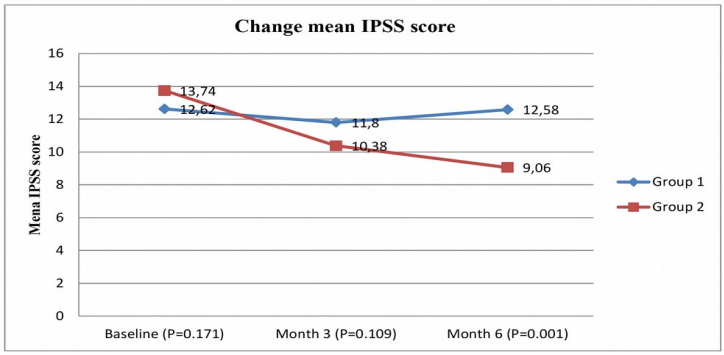

Figure 1. The mean change from baseline in IPSS at each study visit

The adjusted mean decrease in IPSS at each post-baseline visit over 6 months was significantly greater with combined therapy than with doxazosin alone one, but not significant difference observed by month 3 ($p>0.05$). At month 6, the mean change in IPSS was -4.68 with combined therapy vs -0.02 points with doxazolin alone one ($p<0.001$).

3.3. Secondary efficacy endpoints

Clinical progression

Table 2. BPH clinical progression

	Avodart and doxazosin (n = 50)	Doxazosin (n = 50)
Incidence, n (%)	5 (10)	15 (30)
Patients with BPH clinical progression component (any occurrence), n (%)		
Symptom progression	4 (8)	8 (16)
BPH-related AUR	1 (2)	6 (12)
BPH-related UTI	0 (0)	1 (2)

Categorical changes in IPSS were significantly greater at month 6 with combined therapy than with doxazosin alone one, with IPSS increased ≥ 3 points in 12% vs 30% patients, respectively ($p<0.001$). At both month 3 and month 6, BPH-related AUR was higher in doxazosin alone patients compared with combined therapy patients; 10% vs 2% and 12% vs 2%, respectively. BPH-related UTI occurred in 2% of men in the doxazosin alone therapy group but no one in combined therapy group.

Health outcomes (IPSS-Q8)

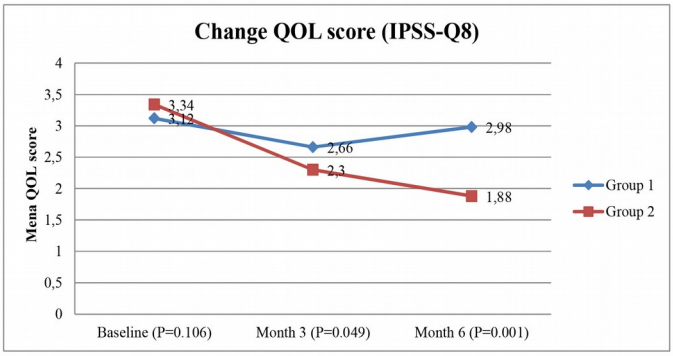

Figure 2. The mean change from baseline in IPSS-Q8 at each study visit.

The adjusted mean decrease in IPSS-Q8 at each post-baseline visit over both month 3 and month 6 were significantly greater with combined therapy than with doxazosin alone therapy, with significant differences observed by month 3 and all post-baseline assessments thereafter ($p<0.05$; Figure 2). At month 3 and month 6 the mean change in IPSS-Q8 with combined therapy and doxazosin alone therapy were -1.04 vs -0.46 points and -1.46 vs 0.14, respectively ($p<0.05$).

Safety and tolerability

Table 3. Summary of AEs occurring after randomisation (treated population)

	Avodart and doxazosin (n = 50)	Doxazosin alone (n = 50)
Patients, n (%)		
Any	10 (20)	03 (6)
Erectile dysfunction	03 (6)	0
Retrograde ejaculation	03 (6)	02 (4)
Decreased libido	1 (2)	0
Loss of libido	1 (2)	0
Orthostatic hypotension	01(2)	01 (2)
Breast tenderness	01 (02)	0
Serious AEs	0	0
Prostate cancer	0	0

AEs were monitored in all patients receiving combined therapy (50 patients) and who started treatment with doxazosin alone (50). The most commonly reported AEs across both groups were erectile dysfunction and retrograde ejaculation, which occurred in 6% vs 0% and 6% vs 4% patients in the combined therapy and doxazosin alone groups, respectively. Loss of libido occurred in 2% of men in the combined therapy group. Breast tenderness AEs occurred in 2% of men in the combined therapy group but were not considered serious. The proportion of patients with orthostatic hypotension was 2% in both groups. Prostate cancer was not seen in both group.

4. Discussion

The first randomized, placebo-controlled trials that evaluated the therapeutic effect of combined α1-blocker and 5α-RI use revealed combination treatment superiority over 5α-RI monotherapy but not over α1-blocker monotherapy. Criticism of these studies focused mainly on their relatively short duration of follow-up. Thus, MTOPS, a randomized, double-blind, placebo-controlled trial, was designed

to provide long-term data on combination treatment thanks to its 4-year follow-up period. MTOPS findings demonstrated that combination therapy with doxazosin and finasteride was superior to either α1-blocker or 5α-RI monotherapy in improving BPH-related symptoms. The MTOPS trial also showed that the risk of symptom deterioration was by far the main progression event in men with LUTS and it was significantly reduced by the combination and single-agent therapies (α1-blocker or 5α-RI) compared with placebo. The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy and finasteride but not by doxazosin [6].

Our results revealed that combined therapy resulted in greater improvement in symptoms than doxazosin alone treatment (-4.68 versus -0.04 IPSS points at month 6, $p<0.001$) (Figure 1). The changes in symptom scores between the two group in our study was more clearly compared with patient global ratings of improvement has been investigated such as the combAT and CONDUCT studies [11]. Based on this, the observed -4.68 IPSS points adjusted mean reduction in combined treatment group would be considered as moderate improvement in symptoms by patients while the change of -0.04 units seen in the doxazosin alone group would be interpreted as very mild or no LUTS improvement by patients.

Over the 6 months treatment period, combined therapy significantly reduced the risk of clinical progression by 20% compared with doxazosin alone therapy (Table 2). It is lower than the CONDUCT study (43.1% in combined therapy compared with WW-All) and the CombAT study (44.1% risk reduction seen when comparing combined therapy with tamsulosin monotherapy over a 4-year period) [8], [11]. That may explained by relatively short duration of follow-up in our study, only 6 months compared with 24 months and 48 months in the CONDUCT and the combAT studies, respectively. Clinical progression in the CombAT study was defined as deterioration in the IPSS symptom score of ≥ 4 points. However, as patients in our study and the CONDUCT study had lower symptom scores at baseline, the threshold for clinical progression was lower (≥ 3 IPSS points) [12]. Moreover, as Barry proved in clinical trials that a minimum of a 3-point improvement on the symptom scale was necessary for the patient to perceive the clinical improvement [2].

This, together with the similar risk reduction seen in our study and CONDUCT study as well over a shorter period, suggests early intervention with combined therapy could reduce the long-term risk of symptomatic progression in men with moderate-to-severe LUTS. Additionally, with need for further intervention lessened, the burden on healthcare systems and practitioners may be reduced.

The lack of a placebo control group is a potential limitation of the present study, the combAT study and the CONDUCT study as well [11], [12]. Although treatment guidelines recommend that men with moderate-to-severe LUTS usually require treatment with medical therapy, the control arm is recognised as a clinical approach for some patients at risk of progression, and was therefore chosen to enable comparison of combined group with a group that is representative of a real-life clinical approach. The health of BHP patients are always the most important. It was judged unethical to provide no treatment to patients at risk for disease progression.

The effects of combined therapy can be explained by the synergistic mechanisms of action of the component drugs [11]. Doxazosin relaxes the smooth muscle tissue in the prostate and bladder neck, allowing urine to flow more freely. Treatment provides a relatively rapid improvement of LUTS but has no effect on prostate growth. Avodart blocks the production of dihydrotestosterone, the metabolic driver of prostate growth. This impedes the development of symptoms related to prostatic overgrowth and, consequently, the incidence of AUR and prostate-related surgery.

Further investigation into the characteristics of patients who do or do not progress, together with an understanding of the pharmacological activity of different treatments, may help guide treatment decisions in future. Results from the Symptom Management after Reducing Therapy (SMART-1) study, for example, showed that the symptomatic

relief provided by dutasteride plus tamsulosin in patients with BPH at risk of disease progression was maintained in most patients when α1-blocker was removed from the combination after 24 weeks [1]. Investigating whether the combination of avodart and doxazosin is required to maintain symptomatic control in the long term, or if tapering to monotherapy with either avodart and doxazosin would be sufficient, is therefore a potential area of future research.

The safety profile the combined therapy in this study (Table 3) was similar to that reported in other studies of α-blockers and 5ARI in combination, including CombAT, CONDUCT [1], [12]. The most common drug-related AEs in either group were those affecting sexual function (Table 3). In both the CombAT and CONDUCT studies, the proportion of patients with sexual AEs was highest during the first 6 months of therapy, and diminished over the course of either treatment. The observed imbalance in the proportion of patients with serious AEs, and AEs leading to study drug discontinuation or withdrawal from the study was not unexpected. The distinct mechanisms of action of dutasteride and doxazosin may therefore account for the increased rate of AEs related to sexual dysfunction seen in the present study [4], [6]. Overall, the risks of α-blockers and 5ARI in combination with are well-characterised and manageable. As the combined therapy provides symptomatic relief and decreases the rate of progression to AUR and surgery in men with moderate LUTS, the benefit–risk profile can be considered favourable but should be carefully assessed in each patient before treatment.

5. Conclusion

In conclusion, the 6 months data from our study provide support for the effectiveness of avodart and doxazosin combined therapy in men with moderate to severe LUTS due to BPH and prostatic enlargement who are at increased risk of progression. The safety of the combined therapy in this study was consistent with the established safety profiles of α-blockers and 5ARI when prescribed individually as monotherapy and when co-administered.

References

1. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB (2003) *Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride.* Eur Urol 44: 461-466
2. Barry MJ, Williford WO, Chang Y et al (1995) *Benign prostatic hyperplasia specific health status measures in clinical research: How much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients?* J Urol 154: 1770-1774
3. Carballido J, Brenes F, Boye A, Pagliarulo A, Sessa A, Castro R (2012) *Baseline characteristics of men diagnosed with benign prostatic hyperplasia following spontaneous reporting of lower urinary tract symptoms to their general practitioner: An analysis of data from the D-IMPACT (Diagnosis IMprovement in PrimAry Care Trial) study.* Eur Urol 11: 98-99.
4. Gratzke C, Bachmann A, Descazeaud A et al (2015) *EAU Guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction.* Eur Urol. 67(6): 1099-1109.
5. Kruep EJ, Hogue SL, Eaddy MT, Chandra MD (2011) *Clinical and economic impact of early versus delayed 5-alpha reductase inhibitor therapy in men taking alpha blockers for symptomatic benign prostatic hyperplasia.* P T 36: 493-507.
6. McConnell JD, Roehrborn CG, Bautista OM et al (2003) *The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia.* N Engl J Med 349: 2387-2398.
7. Mebust WK, Holtgrewe HL, Cockett AT, Peters PC (1989) *Transurethral prostatectomy: Immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients.* J Urol 141(2): 243-247.
8. Montorsi F, Henkel T, Geboers A et al (2010) *Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe*

benign prostatic hyperplasia: 4-year data from the CombAT study. Int J Clin Pract 64: 1042-1051.

9. Rassweiler J, Teber D, Kuntz R, Hofmann R. (2006) *Complications of transurethral resection of the prostate (TURP)-incidence, management, and prevention*. Eur Urol 50: 969-980.
10. Roehrborn CG (2008) *BPH progression: Concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE.* BJU Int 101(3): 17-21.
11. Roehrborn CG, Siami P, Barkin J et al (2010) *The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study*. Eur Urol 57: 123- 131.
12. Roehrborn C, Oyarzabal Perez I, Roos E et al (2015) *Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart(®)) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results*. BJU Int 116: 450-459.