

PROGRESSION OF LOWER URINARY TRACT SYMPTOMS AFTER DISCONTINUATION OF ONE MEDICATION FROM TWO-YEAR COMBINED ALPHA-BLOCKER AND 5-ALPHA-REDUCTASE INHIBITOR THERAPY FOR BENIGN PROSTATIC HYPERPLASIA IN MEN

Hypothesis / aims of study

Benign prostatic hyperplasia (BPH) is highly prevalent in men. Combined alpha-blocker and 5-alpha-reductase inhibitor (5ARI) (combination therapy) has been proven effective in reducing lower urinary tract symptoms (LUTS) and decreasing total prostatic volume (TPV). However, there has been no data showing how long should a man take combination therapy for LUTS. Whether the LUTS will relapse or transurethral resection of the prostate (TURP) becomes necessary after discontinuing one or both medications? Can men with LUTS discontinue one medication from combination therapy after a period of therapeutic duration without compromising LUTS and maintaining therapeutic effect? This study was designed to investigate the above questions in a cohort of patients with BPH and LUTS who have been treated with combination therapy for 2 years.

Study design, materials and methods

A total of 200 men aged more than 45 years, with TPV ≥ 30 ml, maximum flow rate (Qmax) < 15 ml/s, International Prostatic Symptom Score (IPSS) ≥ 8 , and quality of life (QoL) index ≥ 4 were prospectively enrolled in this open, unblinded, randomized comparative study. All patients received combination therapy with 5-ARI (dutasteride 5mg QD) and alpha-blocker (doxazosin 4mg QD) for their LUTS/BPH for 2 years. Then they were randomly assigned to the 5-ARI discontinue group (DC-5ARI) or alpha-blocker discontinue group (DC-alpha-blocker). Each group remained taking one single drug (monotherapy) and followed up for 12 months more. The primary end-point was progression of LUTS from discontinuation baseline to 12 months. The definitions of LUTS progression were: IPSS increase ≥ 4 , Qmax decrease ≥ 2 ml/s, TPV increase $\geq 20\%$, postvoid residual (PVR) increase $\geq 50\%$ compared to baseline values, and the occurrence of acute urinary retention (AUR) and the need for TURP. Secondary end-points were the net change of the following parameters from discontinuation baseline to 12 months: (1) IPSS-total, IPSS-empty, IPSS-storage, (2) QoL index, (3) TPV, (4) transition zone index (TZI), (5) Qmax, (6) voided volume, (7) PVR, (8) prostatic specific antigen (PSA) values. When patients had intolerable LUTS progression they were advised to resume combination therapy or surgical intervention including TURP. The rate of LUTS progression and all parameters at baseline of discontinuation and 12 months were compared between two groups.

Results

Among the patients, 87 were assigned to DC-5ARI group (mean age 76.3 ± 8.2 years) and 113 were DC-alpha-blocker group (mean age 74.3 ± 8.7 years). The prostate and uroflow parameters were similar between two groups either at baseline or 2 years after combination therapy. The changes of parameters from baseline of discontinuation to 12 months were similar in both groups, but the TPV and PSA showed greater increase in DC-5ARI group than DC-alpha-blocker group at 12 months. Resumed combination therapy was necessary in 30 (35.5%) patients of DC-5ARI group and in 35 (31%) of DC-alpha-blocker group ($p=0.875$). The mean duration from discontinued to resumed medication was 5 ± 4.4 months in DC-alpha-blocker group and 7.8 ± 3.8 months in DC-5ARI group ($P<0.05$). By the end of study, the progression rates of IPSS, Qmax, PVR were similar in both groups and were significantly higher in patients who continued to DC medication than those who resumed combination therapy. (Table 1) The TPV progression was significantly higher in DC-5ARI group (34/87, 38%) than DC-alpha-blocker group (9/113, 8%) ($p<0.01$). Occurrence of AUR or TURP was noted in 14 (16%) of DC-5ARI group and in 8 (7%) of DC-alpha-blocker group. ($p<0.05$)

Interpretation of results

Combination therapy for 2 years is effective in improving LUTS in men with LUTS/BPH. After 2-year combination therapy, discontinuation of either one medication induced progression of LUTS or uroflow parameters in most of patients. Increased TPV and greater risk of the occurrence of AUR or needing TURP were noted in patients who discontinued 5ARI. However, resuming combination therapy in either group greatly improved LUTS and uroflow parameters after discontinuing one medication from the combination therapy.

Concluding message

Combination 5ARI and alpha-blocker therapy for men with BPH and bothersome LUTS is effective. Discontinuing one medication from combination therapy for 2 years resulted in high LUTS progression rate and the need for surgical intervention in DC-5ARI or DC-alpha-blocker group. Resuming medication could reverse the progression of LUTS.

Table 2. Progression of BPH/LUTS after discontinuing (DC) one drug after combination therapy (Tx) for 2 years

Progression	DC 5-ARI (n=87)		DC alpha-blocker (n=113)	
	Continued DC (n=57)	Resume Tx (n=30)	Continued DC (n=78)	Resume Tx (n=35)
IPSS-Total increased ≥ 4	10 (17.5%)	12 (40%)	10 (12%)	19(54%)

Qmax reduced \geq 2ml/s	45(79%)	21(70%)	51(65%)	24(68%)
PVR increased \geq 50%	12 (21%)	8(26.7%)	21(26%)	12(34%)
TPV increased \geq 20%	23 (40%)	11(36.6%)	7(8.9%)	2(5.7%)
AUR, TURP, Or AUR + TURP	11 (19%)	3 (10%)	5(6%)	3(8%)
Any one of the above items	49 (86%)	27(90%)	68(87%)	32(90%)

DC 5-ARI N=87, no progression n=11, progression n=76

DC alaph-blocker N=113, no progression n=13, progression n=100

<i>Specify source of funding or grant</i>	Nil
<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	HUMAN
<i>Was this study approved by an ethics committee?</i>	Yes
<i>Specify Name of Ethics Committee</i>	Research Ethics Committee of Buddhist Tzu Chi General Hospital
<i>Was the Declaration of Helsinki followed?</i>	Yes
<i>Was informed consent obtained from the patients?</i>	Yes