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Short Communication

Comparison of the response to treatment between Asian and Caucasian men with benign prostatic hyperplasia: Long-term results from the combination of dutasteride and tamsulosin study

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Abbreviations & Acronyms
5AR = 5α-reductase
5ARI = 5α-reductase inhibitor
AE = adverse events
AUR = acute urinary retention
BII = BPH impact index
BMI = body mass index
BPH = benign prostatic hyperplasia
CombAT = Combination of Avodart and Tamsulosin
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
PSA = prostate-specific antigen
PV = prostate volume
Q_{max} = maximum urinary flow rate
QoL = quality of life
SAE = serious adverse events

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Abstract: The Combination of Avodart and Tamsulosin study was a 4-year, randomized, double-blind study of the efficacy and safety of dutasteride and tamsulosin, alone or in combination, in men with moderate-to-severe benign prostatic hyperplasia. In this post-hoc investigation, we analyzed primary and secondary end-points from the Combination of Avodart and Tamsulosin study in Asian ($n = 325$) and Caucasian men ($n = 4259$). The incidence of acute urinary retention or benign prostatic hyperplasia-related surgery did not differ significantly between treatment groups in the Asian subpopulation. In Caucasian men, the incidence of acute urinary retention/benign prostatic hyperplasia-related surgery was significantly lower in the combination therapy group compared with the tamsulosin monotherapy group ($P < 0.001$), but not compared with dutasteride monotherapy. Combination therapy significantly increased the time to benign prostatic hyperplasia clinical progression and resulted in improved International Prostate Symptom Score, maximum urinary flow rate, quality of life, and reduced prostate volume in Asian and Caucasian men who received combination therapy compared with tamsulosin monotherapy. Combination therapy also significantly improved ($P < 0.05$) time to benign prostatic hyperplasia clinical progression, International Prostate Symptom Score, maximum urinary flow rate and quality of life versus dutasteride in the Caucasian subpopulation. The adverse-event profile was comparable between subpopulations. In conclusion, Asian and Caucasian men respond similarly to these treatments, despite apparent racial differences in 5α-reductase activity.

Key words: Asian, benign prostatic hyperplasia, Caucasian, dutasteride, tamsulosin.

Introduction

The CombAT trial investigated the efficacy and safety of dutasteride and tamsulosin, alone or in combination, on symptoms and clinical outcomes in men with moderate-to-severe BPH and an enlarged prostate (PV ≥30 cm^3).[1] At 4 years, LUTS and overall clinical progression improved significantly with dutasteride/tamsulosin combination therapy compared with either monotherapy.[2]

Participants in CombAT were predominantly Caucasian.[1] Generally, results from the overall population can be extrapolated to smaller racial subgroups. However, compared with Caucasian men, studies have found decreased activity of 5AR[3,4] and variability in the gene encoding the 5AR type 2 enzyme in Asian men.[5,6] Moderate-to-severe LUTS are more prevalent in Asian men than in men in most Western countries.[7] Furthermore, men of Asian ethnicity living in Asia and the Far East have lower PV and PSA levels than Western and Caucasian men, and differences in the relationship between PV and PSA have been reported in populations from China, Taiwan, Korea and Japan.[8–10] Specifically, per volume unit of prostate gland, there might be a greater release of PSA compared with Caucasian men.[11]

A post-hoc analysis of the CombAT study at 2 years showed that dutasteride/tamsulosin combination therapy significantly improved symptoms, Q_{max} and QoL, reduced PV, and improved treatment satisfaction compared with tamsulosin monotherapy in Asian men.[12,13] Here, we report 4-year results from the CombAT study for Asian and Caucasian subpopulations.

Methods

Participants and study design

The design and outcomes of the CombAT study have been reported.[1,13] Briefly, CombAT is a multinational, multicenter, double-blind, parallel-group study. Eligible patients were randomized in a 1:1:1 ratio to 4 years of once-daily treatment with dutasteride 0.5 mg and tamsulosin 0.4 mg, alone or in combination.[1] All participants provided written informed consent and the study was approved by the relevant ethics committee or institutional review board for each study site.

The 4-year primary end-point was time to first event of AUR or BPH-related prostatic surgery. The secondary end-points included time to BPH clinical progression, and IPSS, Q_{max}, PV and IPSS question 8.[13] Clinical progression was defined as symptom deterioration (≥4 unit increase in IPSS), recurrent urinary tract infection or urosepsis, or BPH-related AUR, incontinence or renal insufficiency.

Statistical analysis

Ethnicity, recorded for each participant in the study, formed the basis of this post-hoc comparison. The intent-to-treat population included all participants randomized to study treatment. Statistical analyses compared combination therapy versus each monotherapy group within the Asian and Caucasian subgroups. Missing values were accounted for using last observation carried forward, and significance was defined by a two-sided *P*-value of $P < 0.05$.

The time to and incidence of AUR or BPH-related surgery were compared between groups using the log–rank and Mantel–Haenszel tests, respectively. BPH clinical progression was analyzed similarly. Additional treatment group comparisons were carried out using *t*-tests from a general linear model for IPSS, Q_{max}, PV, IPSS question 8 (BPH-related health status) and the BII. The incidence of AE was compared between treatment groups using Fisher's exact test.

Results

Participants disposition and demographics

The CombAT population ($n = 4844$) was predominantly Caucasian ($n = 4259$), with a sizeable Asian population ($n = 325$). A total of 239 (74%) Asian and 2803 (66%) Caucasian men completed the Month 48 visit.

Asian men came from Korea (36%), the Philippines (23%), Taiwan (22%) and Thailand (7%), as well as Canada (5%), South Africa (<1%), the UK (<1%) and the USA (6%). Baseline characteristics of the subpopulations by treatment group are provided in Table 1.

Primary outcomes

In the Asian subpopulation, differences in the incidence of AUR or BPH-related surgery were not statistically significant for combination therapy versus either monotherapy. The incidence of AUR or BPH-related surgery in the Caucasian subpopulation was significantly lower with combination therapy compared with tamsulosin monotherapy ($P < 0.001$), but there was no significant difference for combination versus dutasteride (Fig. 1).

Secondary outcomes

The incidence of BPH clinical progression was significantly lower in the combination group compared with the tamsulosin group in both the Asian and Caucasian subpopulations ($P < 0.05$; Table 2). The incidence of BPH clinical progression was also significantly lower in the combination group compared with the dutasteride group in the Caucasian subpopulation.

Within the Asian subpopulation, men who received combination therapy had significantly greater improvements in IPSS, Q_{max} and QoL (IPSS question 8 and BII score), and greater reductions in PV compared with those who received tamsulosin monotherapy (Table 2). Differences between the combination therapy and dutasteride monotherapy were not statistically significant. Caucasian men who received combination therapy experienced significantly greater improvements in IPSS, Q_{max} and QoL compared with either monotherapy. The reduction in PV was significantly greater for Caucasian men who received combination therapy compared with tamsulosin but not dutasteride monotherapy.

Safety and tolerability

In both subpopulations, a similar proportion of patients in each treatment group experienced AE and SAE (Table 3). The proportion of participants in either subpopulation experiencing drug-related AE was significantly higher in the combination group compared with the monotherapy groups ($P < 0.05$).

Discussion

This is the first analysis to offer a comparison of combination treatment with a 5ARI plus an α-blocker with either monotherapy in a sizeable Asian population. At 4 years, compared with tamsulosin monotherapy, combination therapy extended the time to BPH clinical progression and

Table 1 Patient demographics and baseline characteristics

Asian subpopulation				
Parameter (mean ± SD, except where stated)	Asian subpopulation	Asian population by treatment group		
	Total (*n* = 325)	Combination† (*n* = 107)	Dutasteride (*n* = 106)	Tamsulosin (*n* = 112)
Age (years)	66.7 ± 7.09	66.6 ± 7.64	66.0 ± 6.20	67.5 ± 7.33
BMI	23.9 ± 3.39	24.4 ± 3.43	23.6 ± 3.49	23.9 ± 3.21
PV (cm^3)	48.2 ± 18.76	47.7 ± 18.71	48.8 ± 16.91	48.1 ± 20.53
Total serum PSA (ng/mL)	4.1 ± 2.13	4.0 ± 2.12	4.3 ± 2.15	4.0 ± 2.12
Previous α-blocker use, *n* (%)	244 (75%)	79 (74%)	85 (80%)	80 (71%)
Previous 5ARI use, *n* (%)	43 (14%)	17 (17%)	11 (11%)	15 (14%)
IPSS	17.8 ± 6.76	17.7 ± 7.21	17.8 ± 6.60	17.8 ± 6.53
IPSS question 8 (BPH-related health status)	3.8 ± 1.53	3.7 ± 1.61	3.9 ± 1.51	3.9 ± 1.45
BII	6.2 ± 3.15	6.2 ± 3.34	6.0 ± 2.97	6.4 ± 3.15
Q_{max} (mL/s)	10.5 ± 4.05	11.2 ± 4.15	9.8 ± 3.88	10.6 ± 4.05
Caucasian subpopulation				
Parameter (mean ± SD, except where stated)	Caucasian subpopulation	Caucasian population by treatment group		
	Total (*n* = 4259)	Combination† (*n* = 1421)	Dutasteride (*n* = 1433)	Tamsulosin (*n* = 1405)
Age (years)	66.1 ± 6.98	66.1 ± 7.00	66.1 ± 7.02	66.2 ± 6.93
BMI	27.6 ± 3.95	27.6 ± 3.95	27.6 ± 3.91	27.6 ± 3.99
PV (cm^3)	55.7 ± 23.87	55.6 ± 23.94	55.0 ± 23.12	56.5 ± 24.54
Total serum PSA (ng/mL)	4.0 ± 2.07	4.0 ± 2.05	3.9 ± 2.07	4.1 ± 2.09
Previous α-blocker use, *n* (%)	2105 (49%)	697 (49%)	704 (49%)	704 (50%)
Previous 5ARI use, *n* (%)	464 (11%)	144 (10%)	172 (12%)	148 (11%)
IPSS	16.3 ± 6.05	16.4 ± 6.19	16.2 ± 5.93	16.3 ± 6.03
IPSS question 8 (BPH-related health status)	3.6 ± 1.24	3.6 ± 1.24	3.6 ± 1.24	3.6 ± 1.24
BII	5.2 ± 3.01	5.2 ± 3.00	5.2 ± 2.98	5.2 ± 3.05
Q_{max} (mL/s)	10.7 ± 3.58	10.9 ± 3.56	10.7 ± 3.53	10.7 ± 3.64

†Dutasteride/tamsulosin combination.

Table 2 Efficacy outcomes at 48 months

	Asian subpopulation			Caucasian subpopulation		
	Combination (*n* = 107)	Dutasteride (*n* = 106)	Tamsulosin (*n* = 112)	Combination (*n* = 1421)	Dutasteride (*n* = 1433)	Tamsulosin (*n* = 1405)
AUR or BPH-related surgery, *n* (%)	7 (6.5%)	2 (1.9%)	12 (10.7%)	58 (4.1%)	79 (5.5%)	169 (12.0%)†
BPH clinical progression, *n* (%)	20 (18.7%)	19 (17.9%)	37 (33.0%)†	172 (12.1%)	254 (17.7%)†	286 (20.4%)†
Change in IPSS	–6.4 (0.67)	–4.9 (0.68)	–2.3 (0.66)†	–6.4 (0.17)	–5.5 (0.17)†	–4.1 (0.17)†
Change in Q_{max}, mL/s	1.9 (0.48)	1.6 (0.50)	0.3 (0.46)†	2.5 (0.13)	2.1 (0.13)†	0.8 (0.13)†
Percent change in PV, %	–29.9 (2.09)	–30.2 (2.18)	0.7 (2.94)†	–27.2 (0.70)	–28.0 (0.69)	4.0 (1.00)†
Change in IPSS question 8	–1.8 (0.14)	–1.5 (0.14)	–1.0 (0.13)†	–1.5 (0.04)	–1.3 (0.04)†	–1.1 (0.04)†
Change in BII	–2.6 (0.28)	–2.1 (0.29)	–0.9 (0.28)†	–2.2 (0.07)	–1.8 (0.07)†	–1.3 (0.07)†

†$P < 0.05$ versus combination. Values are adjusted (least squares) mean changes from baseline (standard error), except where indicated.

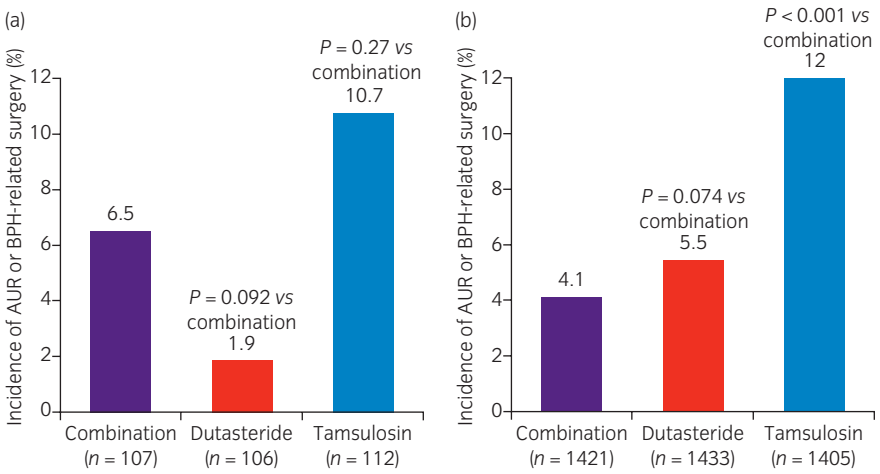

Fig. 1 Incidence of AUR or BPH-related surgery (%) in Asian and Caucasian populations at 48 months.

Table 3 Incidence of adverse events

	Asian subpopulation			Caucasian subpopulation		
	Combination (*n* = 107)	Dutasteride (*n* = 106)	Tamsulosin (*n* = 112)	Combination (*n* = 1421)	Dutasteride (*n* = 1433)	Tamsulosin (*n* = 1405)
Any AE	95 (89%)	87 (82%)	98 (88%)	1019 (72%)	1027 (72%)	994 (71%)
Any SAE	25 (23%)	30 (28%)	28 (25%)	262 (18%)	288 (20%)	299 (21%)
Any drug-related AE	34 (32%)	12 (11%)†	20 (18%)†	399 (28%)	305 (21%)†	255 (18%)†
Any drug-related AE leading to study withdrawal	5 (5%)	2 (2%)	3 (3%)	84 (6%)	57 (4%)†	50 (4%)†
Drug-related AE occurring in ≥1% of any treatment group						
Erectile dysfunction	8 (7%)	5 (5%)	5 (4%)	123 (9%)	97 (7%)	73 (5%)
Decreased libido	7 (7%)	2 (2%)	1 (<1%)	52 (4%)	42 (3%)	28 (2%)
Dizziness	4 (4%)	2 (2%)	1 (<1%)	24 (2%)	11 (<1%)	24 (2%)
Decreased semen volume	1 (<1%)	1 (<1%)	4 (4%)	32 (2%)	5 (<1%)	10 (<1%)
Retrograde ejaculation	4 (4%)	0 (0%)	1 (<1%)	63 (4%)	10 (<1%)	17 (1%)
Breast tenderness	2 (2%)	0 (0%)	0 (0%)	18 (1%)	16 (1%)	6 (<1%)
Ejaculation failure	2 (2%)	0 (0%)	0 (0%)	41 (3%)	10 (<1%)	14 (<1%)
Libido loss	2 (2%)	0 (0%)	0 (0%)	26 (2%)	20 (1%)	14 (<1%)
Gynecomastia	1 (<1%)	0 (0%)	0 (0%)	25 (2%)	34 (2%)	14 (<1%)
Nipple pain	0 (0%)	0 (0%)	0 (0%)	20 (1%)	14 (<1%)	5 (<1%)
Other AE						
Prostate cancer	2 (2%)	4 (4%)	4 (4%)	32 (2%)	35 (2%)	57 (4%)

Data presented as *n* (%). $P < 0.05$. †Combination versus dutasteride and versus tamsulosin monotherapy.

resulted in significantly greater reductions in PV and improvements in IPSS, Q_{max} and QoL. However, differences between combination therapy and dutasteride monotherapy within the Asian subpopulation were not statistically significant. These results show that the benefits of combination therapy observed at 2 years in Asian men[12] were maintained to 4 years.

The overall CombAT population was predominantly Caucasian (4259/4844 participants); therefore, it is not surprising that results from the Caucasian subpopulation mirror those of the overall CombAT population.[2] In the present study, and in the overall results, combination therapy: (i) extended the time to AUR or BPH-related surgery versus tamsulosin; (ii) extended the time to BPH clinical progression versus either monotherapy; (iii) improved IPSS, Q_{max} and QoL versus either monotherapy; and (iv) reduced PV versus tamsulosin monotherapy.

Combination therapy was well tolerated in the Asian subpopulation and the safety profile was similar to that observed in the Caucasian subpopulation, although the dose of tamsulosin used in the present study was higher than that commonly prescribed for Asian men in clinical practice.

Although the incidence of drug-related AE was higher in the combination therapy groups ($P < 0.05$ for combination *vs* either monotherapy in Asian and Caucasian subpopulation), withdrawal rates because of drug-related AE were low (2–6%).

Asian and Caucasian men showed a similar response to combination therapy compared with tamsulosin monotherapy based on improvements in the secondary end-points; however, in contrast to Caucasian men, there were no significant differences between combination therapy and dutasteride monotherapy in the Asian population. For changes in IPSS, Q_{max}, IPSS question 8 and BII, we see a similar trend between dutasteride and combination therapy in Asian and Caucasian subpopulations, although we do not see a difference between treatment groups within the Asian population for the overall less commonly observed outcomes of AUR and BPH clinical progression. This observation suggests that the difference in results between the Asian and Caucasian men is most likely due to the small sample size and therefore the reduced power to detect statistically significantly differences between treatment groups with the Asian subgroup; however, this finding could also represent a difference in the response of Asian and Caucasian men to combination therapy compared with dutasteride monotherapy.

In conclusion, in Asian men with moderate-to-severe LUTS, treatment with dutasteride/tamsulosin combination therapy compared with tamsulosin monotherapy provided significantly superior and sustained reduction in PV and improvement in IPSS, Q_{max} and QoL, and also resulted in a longer time to BPH clinical progression. These results are comparable to those of the Caucasian subpopulation, suggesting that Asian and Caucasian men respond similarly to these modes of treatment, despite apparent racial differences in 5AR activity.

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Conflict of interest

Byung-Ha Chung and Seung Hwan Lee declare no conflict of interest. Claus G Roehrborn is a paid consultant for GlaxoSmithKline. Paul F Siami is an advisor, speaker and research investigator for GlaxoSmithKline and Pfizer; a speaker and research investigator for Endo Pharmaceuticals; and an investigator for Merck, Allergan, Johnson & Johnson, TAP, Ferring and Nymox. Kim Major-Walker and Timothy H Wilson are employees of GlaxoSmithKline and hold GlaxoSmithKline equity ownership/stock. Francesco Montorsi is a paid speaker for GlaxoSmithKline.

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