The Effects of Dutasteride, Tamsulosin and Combination Therapy on Lower Urinary Tract Symptoms in Men With Benign Prostatic Hyperplasia and Prostatic Enlargement: 2-Year Results From the CombAT Study

Claus G. Roehrborn,*,† Paul Siami,‡ Jack Barkin,† Ronaldo Damião,† Kim Major-Walker,† Betsy Morrill† and Francesco Montorsi§ on behalf of the CombAT Study Group

From the Department of Urology, University of Texas Southwestern Medical Center (CGR), Dallas, Texas, Welborn Clinic (PS), Evansville, Indiana, Department of Urology, University of Toronto (JB), Toronto, Ontario, Canada, Serviço de Urologia, Hospital Universitário Pedro Ernesto-Universidade do Estado do Rio de Janeiro (RD), Rio de Janeiro, Brazil, Research and Development, GlaxoSmithKline (KMW, BM), Research Triangle Park, North Carolina, and Department of Urology, Universita Vita Salute San Raffaele (FM), Milan, Italy

Purpose: We investigated whether combination therapy with dutasteride and tamsulosin is more effective than either monotherapy alone for improving symptoms and long-term outcomes in men with moderate to severe lower urinary tract symptoms and prostatic enlargement (30 cc or greater). We report preplanned 2-year analyses.

Materials and Methods: The CombAT study is an ongoing, multicenter, randomized, double-blind, parallel group study. Men 50 years or older with a clinical diagnosis of benign prostatic hyperplasia, International Prostate Symptom Score 12 points or greater, prostate volume 30 cc or greater, total serum prostate specific antigen 1.5 ng/ml or greater to 10 ng/ml or less and peak urinary flow greater than 5 to 15 ml per second or less with a minimum voided volume of 125 ml or greater were randomized to 0.5 mg dutasteride, 0.4 mg tamsulosin or the combination once daily for 4 years. Symptoms were assessed every 3 months and peak urinary flow was assessed every 6 months. The primary end point at 2 years was the change in International Prostate Symptom Score from baseline.

Results: Combination therapy resulted in significantly greater improvements in symptoms vs dutasteride from month 3 and tamsulosin from month 9, and in benign prostatic hyperplasia related health status from months 3 and 12, respectively. There was a significantly greater improvement from baseline in peak urinary flow for combination therapy vs dutasteride and tamsulosin monotherapies from month 6. There was a significant increase in drug related adverse events with combination therapy vs monotherapies, although most did not result in the cessation of therapy.

Conclusions: In men with moderate to severe lower urinary tract symptoms and prostate enlargement (30 cc or greater) combination therapy provides a significantly greater degree of benefit than tamsulosin or dutasteride monotherapy.

Key Words: prostate; prostatic hyperplasia; drug therapy, combination; tamsulosin; dutasteride

Although a combination of a 5-ARI and an α-blocker for LUTS in men with BPH was investigated in 2 early 1-year, placebo controlled studies,[1,2] the long-term potential of combination therapy remained undefined until the availability of data from the MTOPS study.[3] The principle finding was that combination therapy significantly decreased the 4-year incidence of a composite end point of progression compared with doxazosin, finasteride or placebo. Combination therapy was also significantly more effective than finasteride or doxazosin alone for decreasing LUTS at 4 years, although at 1 year combination therapy was superior to finasteride monotherapy but not to doxazosin monotherapy.

Although the MTOPS study contributed substantially to our understanding of the role of combination therapy for symptomatic BPH, outstanding issues remain. 1) Only a subset of men entering the study were at heightened risk for progression due to a prostate volume of 30 cc or greater and/or PSA 1.5 ng/ml or greater. Therefore, prospective analysis of the potential benefit of combination therapy in these men has not been performed. 2) Use of a composite end point in MTOPS and the restricted availability of symptom data at 1 and 4 years provided limited insight into the onset of benefit for combination therapy over monotherapies. 3) The MTOPS study used type 2 selective 5-ARI finasteride. Treatment with the dual 5-ARI dutasteride results in a greater degree and consistency of dihydrotestosterone suppression compared with finasteride.[4] To our knowledge an assessment of the combination of dutasteride and an α-blocker vs monotherapies on short-term and long-term BPH outcomes has not been performed to date.

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* Correspondence: Department of Urology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Moss Clinical Science Building (J) 8 142, Dallas, Texas 75390-9110 (telephone: 001-214-648-2941; FAX: 001-214-648-0365; e-mail: claus.roehrborn@utsouthwestern.edu).
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For another article on a related topic see page 770.

The aim of the ongoing CombAT study is to investigate whether combination therapy with dutasteride and the α-blocker tamsulosin is more effective than either monotherapy alone for improving the symptoms and long-term clinical outcomes of AUR and BPH related prostatic surgery in men with moderate to severe symptoms of BPH and a prostate volume of 30 cc or greater. We report the results of analyses of the 2-year primary and secondary end points of LUTS, Qmax and prostate volume, and further analyses of efficacy data as well as safety and tolerability outcomes.

MATERIALS AND METHODS

Study Design

The CombAT study is a multicenter (446 investigators in 35 countries), randomized, double-blind, parallel group study, of which the design was previously reported.[5] Following screening eligible subjects were entered into a single-blind, placebo run-in period, during which they received tamsulosin and dutasteride placebos for 4 weeks. All subjects were then randomized in a 1:1:1 ratio to receive 0.5 mg dutasteride once daily and 0.4 mg tamsulosin once daily, 0.5 mg dutasteride and tamsulosin matched placebo or 0.4 mg tamsulosin and dutasteride matched placebo orally for 4 years. A double placebo group was not included because the 2 monotherapies have demonstrated efficacy in placebo controlled studies. Therefore, it was considered unethical to treat this patient group with placebo for 4 years.

LUTS were assessed at screening, baseline and every 3 months using the self-administered I-PSS questionnaire, including BPH related health status evaluation (question 8). Qmax measurements were made at screening, baseline and every 6 months. TRUS was performed at screening and annually to calculate total prostate volume obtained by formula. Transition zone volume was determined in a subset of patients at centers where there was expertise with this measurement.

Adverse events were recorded at every 3-month visit. TRUS guided prostate biopsies for prostate cancer could be performed during the study at investigator discretion. Prostate cancer diagnoses were recorded as part of the study protocol. Investigator blinding to treatment was maintained by an independent, unblinded reviewer who doubled the PSA value in subjects receiving dutasteride or combination therapy with the value randomly stated as the doubled value, or 0.1 units higher or lower.

Study Population

Men 50 years or older with a clinical diagnosis of BPH by medical history and physical examination, including digital rectal examination, were eligible for inclusion. Other principle inclusion criteria were an I-PSS of 12 points or greater, prostate volume 30 cc or greater on TRUS, total serum PSA 1.5 ng/ml or greater and Qmax more than 5 to 15 ml per second or less with a minimum voided volume of 125 ml or greater. Principal exclusion criteria were total serum PSA greater than 10.0 ng/ml, a history or evidence of prostate cancer, previous prostatic surgery or a history of AUR within 3 months before study entry.

Study End Points

For the planned analysis at 2 years the primary end point was the change in I-PSS from baseline. The first primary end point was for the combination vs dutasteride and the second end point was for the combination vs tamsulosin. Secondary end points were then analyzed in a predefined hierarchy to avoid multiplicity issues (see Appendix). We report certain outcome variables, including I-PSS (question 8), Qmax and prostate volume. The time to event/proportion of subjects with AUR and BPH related prostatic surgery is a 4-year study end point.

Statistical Analyses

The primary population of subjects that was statistically analyzed was the intent to treat population, which consisted of all subjects randomized to double-blind study treatment. The last observation carried forward approach was used. Superiority for the combination vs dutasteride and tamsulosin was based on a 2-sided $p \leq 0.01$ in favor of the combination arm with $\alpha = 0.01$ selected to ensure a statistically powerful finding that the result was highly inconsistent with the null hypothesis of no treatment effect. The change in baseline I-PSS was also compared at each post-baseline assessment for combination therapy vs each monotherapy using a general linear model with adjustments for treatment, investigative site cluster and baseline I-PSS at $\alpha = 0.01$. Superiority of combination vs dutasteride and tamsulosin for all secondary end point tests was based on a 2-sided p value in favor of the combination arm. Post-hoc analyses of changes in I-PSS and Qmax for dutasteride vs tamsulosin at month 24 were also performed outside of the primary and secondary end point hierarchy.

RESULTS

Subject Demographics and Disposition

Of the 4,844 men randomized to treatment (intent to treat population) 3,822 (79%) completed the month 24 visit with comparable rates of discontinuation in the 3 treatment groups (fig. 1). Table 1 lists patient demographics and baseline characteristics. They were comparable in the 3 treatment groups.

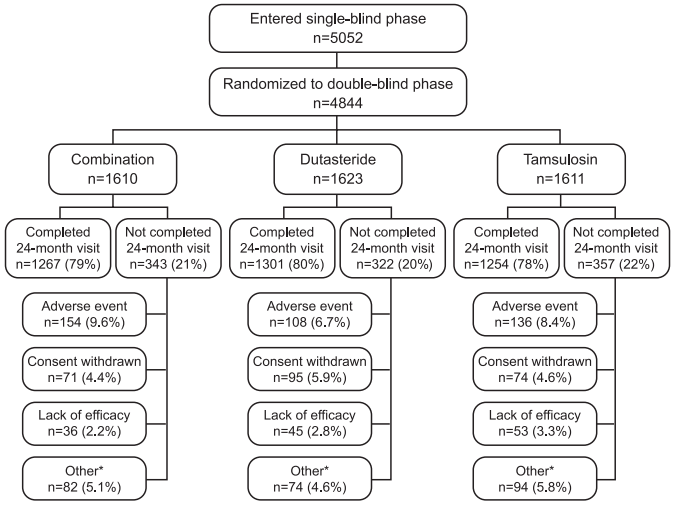

FIG. 1. Subject disposition. Asterisk indicates lost to followup, protocol violation and other causes of discontinuation.

TABLE 1. *Baseline demographics and patient characteristics*

	Combination	Dutasteride	Tamsulosin	All Pts
No. pts	1,610	1,623	1,611	4,844
Mean ± SD age	66.0 ± 7.05	66.0 ± 6.99	66.2 ± 7.00	66.1 ± 7.01
No. white ethnicity (%)	1,421 (88)	1,433 (88)	1,405 (87)	4,259 (88)
Mean ± SD total I-PSS score (points)	16.6 ± 6.35	16.4 ± 6.03	16.4 ± 6.10	16.4 ± 6.16
Mean ± SD yrs since first LUTS	5.4 ± 5.07	5.3 ± 4.69	5.4 ± 4.76	5.4 ± 4.84
Prostate vol (cc):				
Mean ± SD total	54.7 ± 23.51	54.6 ± 23.02	55.8 ± 24.18	55.0 ± 23.58
Median total	48.9	48.4	49.6	48.9
Mean ± SD transition zone*	27.7 ± 20.20	30.3 ± 21.02	30.5 ± 24.47	29.5 ± 21.97
Mean ± SD serum PSA (ng/ml)	4.0 ± 2.05	3.9 ± 2.06	4.0 ± 2.08	4.0 ± 2.08
Mean ± SD Qmax (ml/sec)	10.9 ± 3.62	10.6 ± 3.57	10.7 ± 3.66	10.7 ± 3.62
Mean ± SD post-void residual vol (ml)	68.1 ± 66.01	67.4 ± 63.49	67.7 ± 65.14	67.7 ± 64.87
No. sexually active (%)	1,176 (73)	1,189 (73)	1,164 (72)	3,529 (73)
No. previous α-blocker use (%)	805 (50)	820 (51)	819 (51)	2,444 (50)
No. previous 5-ARI use (%)	171 (11)	188 (12)	172 (11)	531 (11)

* In a subset of 656 men.

Primary End Points

From screening to baseline mean I-PSS decreased from 19.3, 19.1 and 18.9 to 16.6, 16.4 and 16.4 points in the combination, dutasteride and tamsulosin groups, respectively. At month 24 mean ± SE decreases in I-PSS from baseline were 6.2 ± 0.15 points for combination therapy vs 4.9 ± 0.15 and 4.3 ± 0.15 points for dutasteride and tamsulosin, respectively (fig. 2). The decrease for combination therapy was significantly greater vs that of either monotherapy (each comparison p <0.001). These changes in score resulted in a mean I-PSS at month 24 of 10.1 ± 0.16, 11.4 ± 0.16 and 11.9 ± 0.17 in the combination, dutasteride and tamsulosin groups, respectively. The adjusted mean difference between combination therapy and tamsulosin at month 24 was −1.8 points and between combination therapy and dutasteride it was −1.3 points. A significantly greater decrease from baseline in symptom score was observed for combination therapy vs dutasteride from month 3 and for combination therapy vs tamsulosin from month 9. The significance level in the analysis for dutasteride vs tamsulosin at month 24 was p = 0.0113. Changes in BPH related health status score from baseline at month 24 were −1.4, −1.1 and −1.1 points in the combination, dutasteride and tamsulosin groups, respectively. The decrease for combination therapy was significantly greater vs that of either monotherapy (each comparison p <0.001).

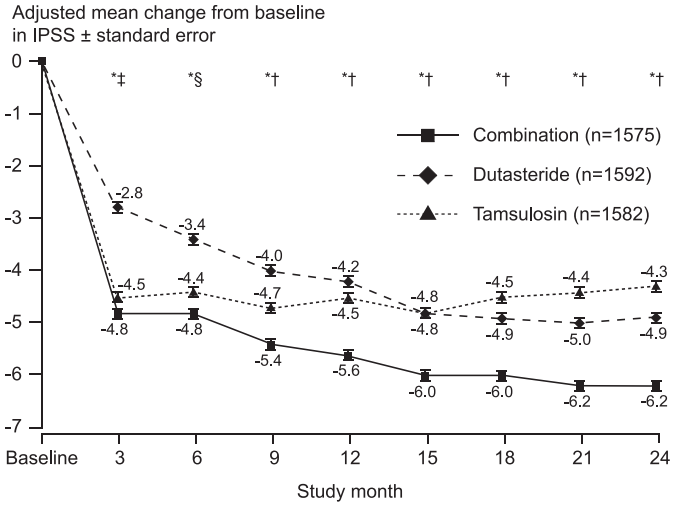

FIG. 2. Mean ± SE adjusted change in I-PSS from baseline by visit and treatment group. Asterisk indicates combination vs dutasteride p <0.001. Dagger indicates combination vs tamsulosin p <0.001. Double dagger indicates combination vs tamsulosin p = 0.18. Curly indicates combination vs tamsulosin p = 0.032.

Secondary End Points

I-PSS responders (25% or greater, 2-point or greater and 3-point or greater improvement). The proportion of men classified as I-PSS responders at month 24 by each criterion in the combination group was significantly greater than the proportion in the dutasteride or tamsulosin groups (each p <0.001, fig. 3).

Qmax and Qmax responders (30% or greater and 3 ml per second or greater improvement). At month 24 increases in Qmax from baseline were 2.4 ± 0.12 ml per second for combination therapy vs 1.9 ± 0.12 and 0.9 ± 0.12 ml per second for dutasteride and tamsulosin, respectively (fig. 4). The decrease for combination therapy was significantly greater vs that of either monotherapy (each comparison p ≤0.003). These changes in the flow rate resulted in values at month 24 of 13.3 ± 0.14, 12.7 ± 0.14 and 11.7 ± 0.12 ml per second in the combination, dutasteride and tamsulosin groups, respectively. The adjusted mean difference between

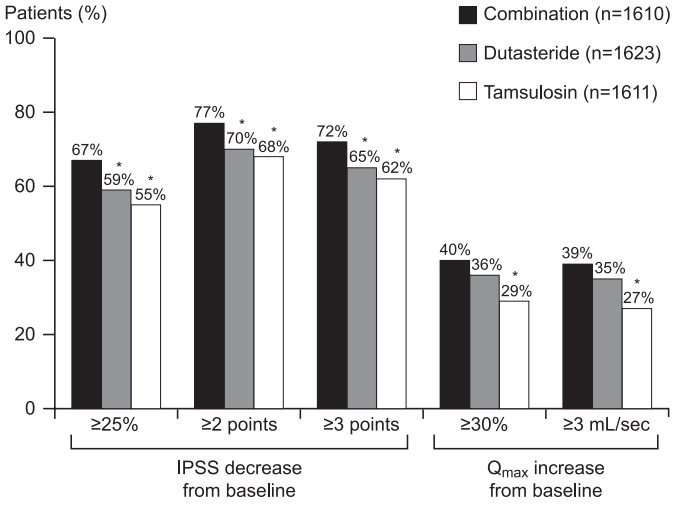

FIG. 3. Proportion of patients classified as I-PSS and Qmax responders at month 24 by treatment group. Asterisk indicates p <0.001 vs combination.

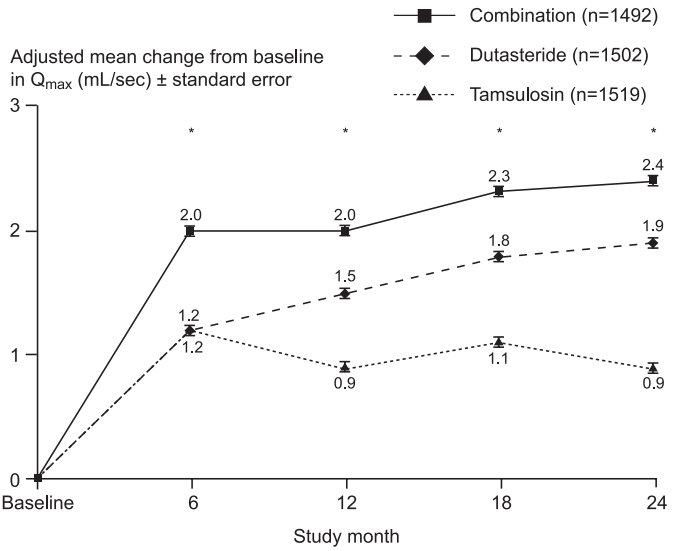

FIG. 4. Mean ± SE adjusted change in Qmax from baseline by visit and treatment group. Asterisk indicates combination vs dutasteride and tamsulosin p ≤0.006.

combination therapy and tamsulosin at month 24 was 1.5 ml per second and between combination therapy and dutasteride it was 0.5 ml per second. A significantly greater improvement from baseline in Qmax was observed for combination therapy vs dutasteride and tamsulosin from months 6 to 24 (each p ≤0.006). The significance level in the analysis for dutasteride vs tamsulosin at month 24 was p <0.0001.

The proportions of men at month 24 classified as Qmax responders were significantly greater in the combination group than in the tamsulosin group (each p <0.001, fig. 3). Although the proportion of men with a 30% or greater Qmax response was greater in the combination than in the dutasteride group (p = 0.043), this did not attain the prespecified level of significance. Thus, interpretation of the significance level for the proportion of men with a 3 ml per second or greater improvement was not performed.

Total and transition zone prostate volume. At month 24 the adjusted mean percent change in total prostate volume from baseline was −26.9% ± 0.62% in the combination group, −28.0% ± 0.61% in the dutasteride group and 0.0% ± 0.84% in the tamsulosin group (combination vs tamsulosin p <0.001 and combination vs dutasteride p not significant). At month 24 the adjusted mean percent change in transition zone volume from baseline was −23.4% ± 5.63% in the combination group, −22.8% ± 5.86% in the dutasteride group and 8.8% ± 8.22% in the tamsulosin group (combination vs tamsulosin p <0.001 and combination vs dutasteride p not significant).

Safety and Tolerability

Table 2 lists adverse event data, as reported by the investigators. Although the total number of drug related adverse events was significantly greater in the combination group compared with that in either monotherapy group, only 5% or less of the men in each treatment group, including the combination group, withdrew from the study as a result of these events. Drug related adverse events that were numerically more common in the combination group than in either monotherapy group were erectile dysfunction, retrograde ejaculation, altered (decreased) libido, ejaculation failure, semen volume decreased, loss of libido and nipple pain. Prostate cancer was reported in 58 men, including 21 in the combination group, 11 in the dutasteride group and 26 in the tamsulosin group. No cases of floppy iris syndrome[6] or breast neoplasms were reported. Serum PSA decreased by a median of 56.0% and 55.0% from baseline in the combination and dutasteride groups, respectively, and it increased in the tamsulosin group by 12.1%.

DISCUSSION

In men with moderate to severe LUTS and an enlarged prostate treatment with combination therapy provided a significantly greater degree of symptom and Qmax improvement, and improvement in BPH related health status compared with that of either monotherapy alone. Combination therapy resulted in a greater improvement in symptom score than either monotherapy at all assessments with this margin statistically significant from month 3 vs dutasteride and from month 9 vs tamsulosin. To our knowledge the CombAT study is the first to

TABLE 2. *Adverse events*

	% Combination	% Dutasteride	% Tamsulosin
No. pts	1,610	1,623	1,611
Any adverse event*	65	64	63
Any serious adverse event*	12	12	13
Any drug related adverse event†	24	18	16
Any serious drug related adverse event	Less than 1	Less than 1	Less than 1
Any adverse event leading to study withdrawal*	10	8	9
Any drug related adverse event leading to study withdrawal	5	3	3
Drug related adverse events in 1% or greater of any treatment group:			
Erectile dysfunction	7.4	6.0	3.8
Retrograde ejaculation	4.2	0.6	1.1
Altered (decreased) libido	3.4	2.8	1.7
Ejaculation failure	2.4	0.5	0.8
Semen volume decreased	1.8	0.3	0.8
Loss of libido	1.7	1.3	0.9
Dizziness	1.6	0.7	1.7
Breast enlargement	1.4	1.8	0.8
Nipple pain	1.2	0.6	0.3
Breast tenderness	1.0	1.0	0.3

* Combination vs dutasteride and tamsulosin p not significant.
† Combination vs dutasteride and tamsulosin p <0.001.

demonstrate a benefit for combination therapy over the 2 monotherapies in the first 12 months of therapy.

During the time of the current analysis the margin of symptom benefit for combination therapy over dutasteride monotherapy was maintained. The margin of benefit for combination therapy vs tamsulosin increased from month 15, reflecting continued improvement in the combination arm coupled with a decreasing benefit of tamsulosin monotherapy. Treatment with dutasteride resulted in a pattern of increasing symptom improvement with time, which was maintained during long-term treatment, as in previous studies.[7] Overall combination therapy provided a greater degree of symptom improvement with short-term and long-term use compared with that of either monotherapy.

Although there was a higher rate of adverse events in the combination group than in either monotherapy group, rates of withdrawal due to drug related adverse events were low in all groups and a higher proportion of men withdrew from the study in the monotherapy groups vs the combination group due to a lack of efficacy. Overall the profile of events for combination therapy was consistent with that reported for the 2 monotherapies. Tamsulosin and dutasteride have an effect on ejaculatory function, although probably through different mechanisms.[8,9] This probably accounts for the more than additive rate of ejaculatory dysfunction. However, these events did not lead to a substantial discontinuation rate in this population of elderly men. The number of men with prostate cancer reported as an adverse event was not substantial enough for robust analysis. However, the difference between the combined dutasteride groups and the tamsulosin monotherapy group was similar to that reported in the dutasteride phase IIIa program.[10] The ongoing REDUCE (Reduction by Dutasteride of Prostate Cancer Events) study has been initiated to determine the effect of dutasteride on the risk of biopsy detectable prostate cancer.[11]

In contrast with the CombAT study, in which combination therapy was superior to the 2 monotherapies by 1 year, in the MTOPS study the symptom score in the combination group was significantly lower than in the 5-ARI group but not in the α-blocker group after a year of therapy.[3] This difference in outcomes likely reflects the overall risk of progression in the MTOPS vs the CombAT population. In the MTOPS study mean baseline prostate volume was 36.3 cc and PSA was 2.4 ng/ml, each substantially lower than 55.0 cc and 4.0 ng/ml, respectively, in the CombAT population. Indeed, in the MTOPS study median prostate volume was 31 cc and, therefore, 50% of men were without prostate enlargement. In an analysis of the MTOPS database combination therapy had a significantly greater benefit on symptoms and Qmax vs α-blocker monotherapy at year 4 in men with a baseline prostate volume of 25 cc or greater but not in those with a baseline prostate volume of less than 25 cc.[12] Taken together the results of the CombAT 2-year analysis and the 4-year MTOPS data support the observation that in men with prostate enlargement (30 cc or greater) and moderate to severe LUTS significant further symptomatic benefit is achieved by combination therapy over either monotherapy alone.

A limitation of the CombAT study is the absence of a double placebo arm. As a result of knowing that all treatment allocations were to an active agent, the theoretical potential exists for an exaggerated symptom response. However, while the I-PSS improvement in the dutasteride arm of the CombAT study was greater than that in a similar population in placebo controlled studies (4.9 vs 4.5 points),[7] the difference was marginal. Any difference attributable to this effect would have applied to all study arms.

CONCLUSIONS

Combination therapy provided a significantly greater degree of benefit than tamsulosin or dutasteride monotherapy in terms of symptoms, urinary flow and BPH related health status in men with moderate to severe LUTS and prostatic enlargement (30 cc or greater). Data from the remaining 2 years of the CombAT study will provide further information on the pattern of symptoms and long-term outcomes (AUR and the need for BPH related surgery) associated with combination therapy vs tamsulosin and dutasteride monotherapies.

ACKNOWLEDGMENTS

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APPENDIX

CombAT study secondary end point hierarchy

Comparison of combination vs dutasteride	Comparison of combination vs tamsulosin
The proportion of men with an improvement from baseline in the I-PSS of 25% or greater, 2 points or greater and 3 points or greater (I-PSS responders)	The proportion of men with an improvement from baseline in the I-PSS of 25% or greater, 2 points or greater and 3 points or greater (I-PSS responders)
Change in Qmax from baseline	Percent change from baseline in total prostate volume (additionally, transition zone volume in a subset of patients)
The proportion of men with improvement from baseline in Qmax of 30% or greater and 3 ml per second or greater (Qmax responders)	Change in Qmax from baseline
Change in BPH Impact Index score from baseline	The proportion of men with improvement from baseline in Qmax of 30% or greater and 3 ml per second or greater (Qmax responders)
Change in score of the quality of life question of the I-PSS questionnaire	Change in BPH Impact Index score from baseline
Score for each patient perception of study medication question	Change in score of the quality of life question from the I-PSS questionnaire
Percent change from baseline in total prostate volume (additionally, transition zone volume in a subset of patients)	Score for each patient perception of study medication question

Abbreviations and Acronyms

5-ARI	=	5α-reductase inhibitor
AUR	=	acute urinary retention
BPH	=	benign prostatic hyperplasia
CombAT	=	Combination of Avodart and Tamsulosin
I-PSS	=	International Prostate Symptom Score
LUTS	=	lower urinary tract symptoms
MTOPS	=	Medical Therapy of Prostatic Symptoms
PSA	=	prostate specific antigen
Qmax	=	peak urinary flow
TRUS	=	transrectal ultrasound

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EDITORIAL COMMENT

The use of combination therapy using an α-blocker and a 5-ARI has gained increased acceptance in the medical community. In fact, more than 50% of dutasteride prescriptions written by primary care physicians or urologists are written in combination with an α-blocker. The data from CombAT conclusively demonstrate symptomatic improvement superiority with the combination of dutasteride and tamsulosin vs monotherapy. Finally, dutasteride monotherapy was superior to tamsulosin with respect to symptoms at 18 months.

One must be wary of over interpreting the data. CombAT represents only a subset of men with LUTS. Men with a prostate of less than 30 ml or PSA less than 1.5 ng/ml were excluded from study. Median prostate size in this study was between 54% and 57% larger than in MTOPS, a unique population (reference 3 in article). Are the data presented being driven by the large prostates in the study population? One would suspect a different effect of dutasteride at various categorical cutoffs of prostate size, ie 40, 50 and greater than 50 ml. In addition, more than 50% of randomized patients had been on an α-blocker previously. Were there different responses and/or prostate size at baseline between drug naïve men vs those exposed to an α-blocker? It would be of interest to ascertain whether α-blocker failure was more likely in men with a larger prostate, ie greater than 40 and 50 ml.

Nevertheless, CombAT is an important contribution to our evolving understanding of the management of LUTS. 1) Combination therapy will be a mainstay with continuing research into optimal components, ie α-blocker, anticholinergic, phosphodiestarase-5 or 5-ARI.[1] 2) The 5-ARIs and specifically in this study dutasteride are widely accepted as the backbone of therapy because of their unparalleled affect on disease management and they are also highly effective for relieving symptoms in select patients. 3) The α-blockers probably do not work as effectively in large prostates as they do in smaller prostates. What remains indisputable is that prostate size and symptom type, ie storage vs voiding at baseline, will drive therapeutic choices and optimize outcomes.

Steven A. Kaplan
Department of Urology
Institute for Bladder and Prostate Health
Weill Cornell Medical College
Cornell University
New York, New York

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