Preliminary Evaluation of the Effect of Dutasteride on PCA3 in Post-DRE Urine Sediments: A Randomized, Open-Label, Parallel-Group Pilot Study

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BACKGROUND. Dutasteride is commonly used in patients that are also at risk for prostate cancer (PCa). Therefore, the influence of dutasteride on PCa markers has to be studied. To date, only the effect of dutasteride on serum prostate-specific antigen (PSA) has been studied. This was the first study to investigate the effect of dutasteride on the new PCa marker PCA3, longitudinally and in a dose dependent manner.
METHODS. From April 25, 2005 to October 31, 2006, 16 subjects with benign prostatic hyperplasia (BPH) and 9 subjects with clinically localized PCa were enrolled at the urological outpatient clinics of one university hospital and one community hospital. Eight subjects with BPH and five with PCa received 0.5 mg dutasteride once daily for 3 months, eight with BPH and four with PCa received 3.5 mg. No subjects were withdrawn because of adverse effects.
RESULTS. In all four groups both 0.5 and 3.5 mg dutasteride had a variable effect on the PCA3 score. In contrast, its other effects were consistent as it rapidly reduced serum DHT by $\geq$90%, over time increased serum T by 20–30%, over time halved serum PSA and decreased prostate volume by 10–16%.
CONCLUSIONS. In this exploratory/pilot study the effect of dutasteride on the PCA3 score was variable. This should be taken into account while using PCA3 in diagnostics. As this study was exploratory, the influence of androgen-deprivation therapy on the PCA3 score should be analyzed further. *Prostate 69: 1624–1634, 2009.* © 2009 Wiley-Liss, Inc.

KEY WORDS: **dutasteride; prostate cancer antigen 3; prostatic neoplasms; pilot projects; urine**

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men. The estimated number of new cases in Europe in the year 2006 was 345,900, accounting for about 20% of all newly diagnosed cancers in European men. The estimated number of PCa deaths was 87,400, accounting for about 9% of all cancer deaths in European men [1].

Dutasteride is a dual 5α-reductase inhibitor (5ARI) used in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH), either as monotherapy [2], or in combination with an α-blocker [3]. Dutasteride exerts its effect on prostate tissue by binding both the type 1 and type 2 isoenzymes of 5α-reductase (5AR) to inhibit the conversion of the androgen testosterone (T) to the more potent androgen dihydrotestosterone (DHT). In different daily doses,

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dutasteride has shown to provide near-maximal suppression of serum and more importantly intra-prostatic DHT levels in both men with BPH and men with PCa [4–6].

Pooled data from phase III studies in BPH showed that dutasteride significantly reduced PCa, reported as an adverse event, in men with BPH [7]. This led up to the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial that tests the hypothesis that treatment with dutasteride decreases the incidence and progression of PCa by the suppression of prostatic DHT [8]. At the same time, the REduction by Dutasteride of clinical progression Events in Expectant Management (REDEEM) trial evaluates the potential for dutasteride to delay disease progression in men with biopsy-proven, low-risk, localized PCa that are candidates for expectant management [9].

Prostate cancer gene 3 (PCA3) is a new PCa marker. It is a prostate-specific, non-coding mRNA that is highly overexpressed in PCa tissue compared with benign prostate tissue [10,11]. Its value as a diagnostic marker by means of the PCA3 score identifying PCa cells in urine or urinary sediments after digital rectal examination (DRE) has been shown in several large multicenter studies [12–15]. In vitro data have shown that, similar to the expression of prostate-specific antigen (PSA), the expression of PCA3 is androgen sensitive [16,17].

Pending the results of the two abovementioned large trials [8,9], there may be an increasing role for dutasteride in PCa risk reduction and even the early treatment of PCa in the near future. Follow up with PCa markers during dutasteride treatment will be crucial, but to date only the effect of dutasteride on serum PSA has been studied [18]. To our knowledge, there has been no report of the effect of dutasteride on PCA3. Filling this void, this exploratory randomized, open-label, parallel-group pilot study is the first study to investigate the effect of dutasteride on the PCA3 score, longitudinally and in a dose dependent manner, in both men with BPH and men with clinically localized PCa.

MATERIALS AND METHODS

Study Design and Population

This was a randomized, open-label, parallel-group pilot study, to assess the effect on the PCA3 score, longitudinally and in a dose dependent manner, of 0.5 or 3.5 mg dutasteride administered orally once daily, for 3 months in men with BPH and men with biopsy-proven, clinically localized PCa.

In the urological outpatient clinics of one university and one community hospital, the charts of both men with BPH and men with clinically localized PCa who had underwent a prostate biopsy within the last 6 months were reviewed for inclusion in this study (MPMQvG and HV). Possibly eligible subjects were contacted and invited for a first screening visit. On the second visit, that is, the baseline visit, all eligible subjects were enrolled and randomized by a random draw of an unmarked, sealed envelope containing the dose (MPMQvG and HV).

The Institutional Review Boards had approved the study and it was conducted in accordance with ''good clinical practice'' and all applicable regulatory requirements. Beforehand, all subjects had received study information and they had signed their written informed consent. All samples and data were collected prospectively.

BPH Groups Inclusion Criteria

Men aged 50 or over, with a clinical diagnosis of BPH by medical history and physical examination including DRE, were considered eligible for inclusion. Other principle inclusion criteria for the BPH groups were an international prostate symptom score $\geq$12 points at screening, a prostate volume $\geq$30 ml measured by transrectal ultrasound (TRUS), a total serum PSA of 2.5–10 ng/ml at screening (extremes included), a Q_{max} $\geq$5 ml/sec at screening, a post-void residual volume $\leq$250 ml (measured by suprapubic ultrasound) at screening, and the exclusion of PCa by a negative prostate biopsy as a result of local management within 6 months prior to screening.

PCa Groups Inclusion Criteria

Men aged 50 or over, with biopsy-proven, clinically localized PCa (defined as at least 5% of one biopsy core and at least 1 mm of cancer), eligible and scheduled for radical prostatectomy, were considered eligible for inclusion.

BPH and PCa Groups Exclusion Criteria

Principle exclusion criteria for both the BPH and the PCa groups were the inability to void spontaneously (e.g., the dependence on transurethral or suprapubic catheter for micturation), a history of PCa (prior to the current diagnosis for the PCa groups), previous prostatic surgery, a history of acute urinary retention within 3 months prior to screening and the use of any investigational or marketed 5ARI, anabolic steroids or any drug with anti-androgenic properties within 12 months prior to screening.

Subjects

Both the subjects with BPH and the subjects with PCa were randomly assigned to take either 0.5 or

3.5 mg, that is, seven 0.5 mg capsules, dutasteride orally once daily. The study thus comprised four groups of subjects:

- subjects with BPH assigned to take 0.5 mg dutasteride once daily,
- subjects with BPH assigned to take 3.5 mg dutasteride once daily,
- subjects with PCa assigned to take 0.5 mg dutasteride once daily,
- subjects with PCa assigned to take 3.5 mg dutasteride once daily.

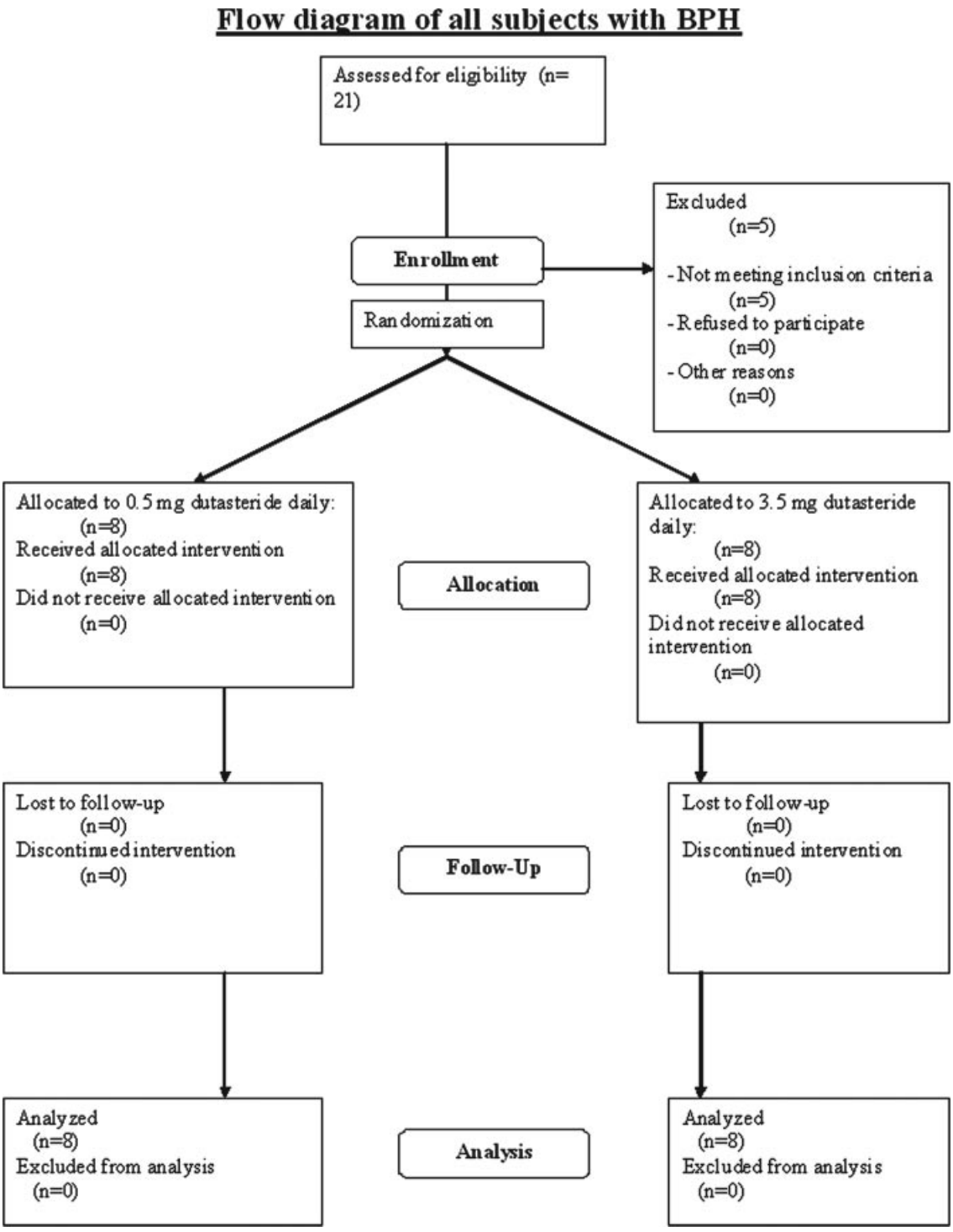

Fig. 1. Flow diagram of all subjects with benign prostatic hyperplasia (BPH).

The aim was to enroll 10 subjects in each group, adding up to a total of 40. This number was chosen under the assumption of obtaining sufficient data to do a proper pharmacodynamic analysis on, while avoiding a lengthy inclusion period. As this was an exploratory/pilot study to establish the values for parameters needed for an appropriate power calculation, there were no data to base a power calculation or sample size on.

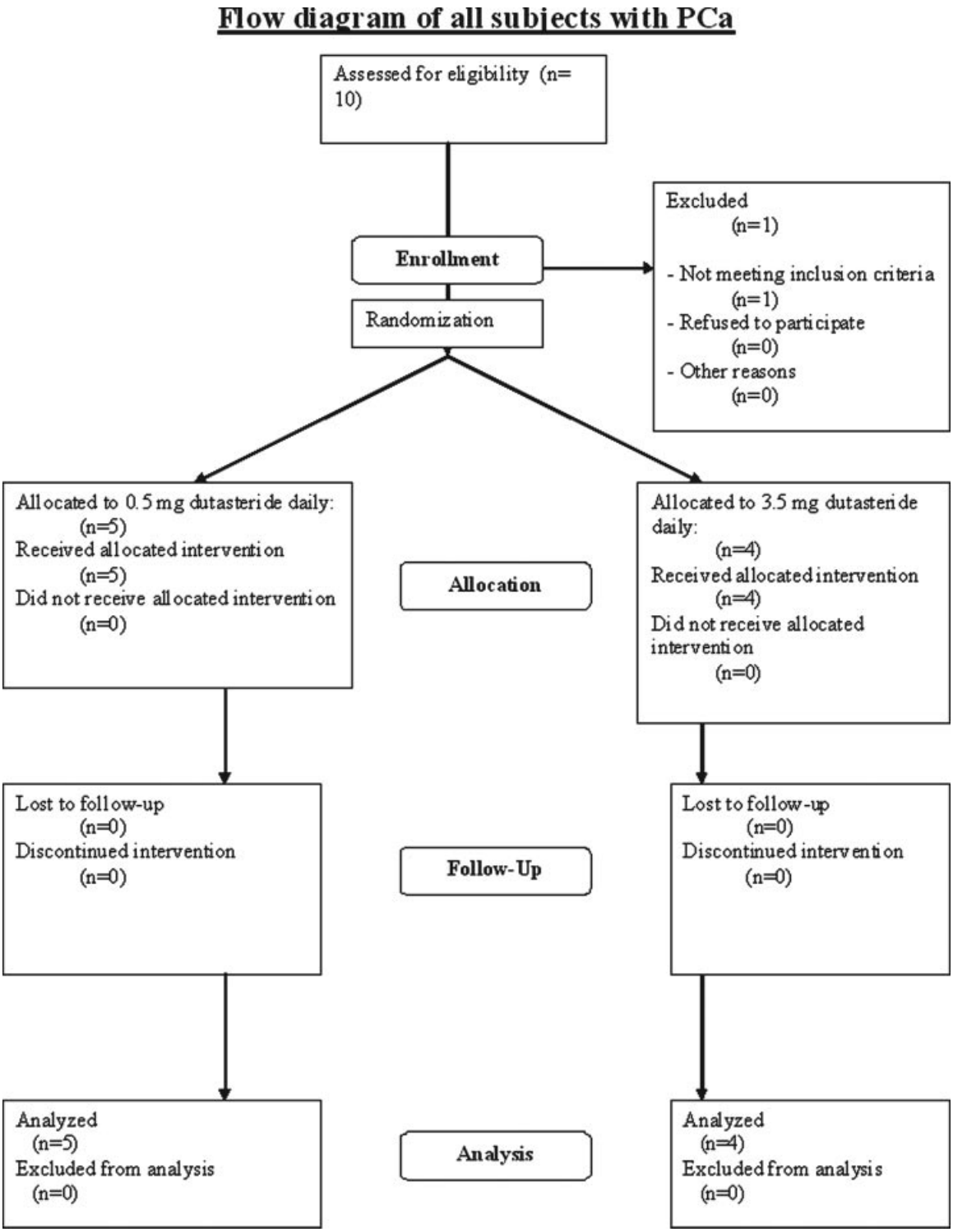

Fig. 2. Flow diagram of all subjects with prostate cancer (PCa).

The relative change from baseline was assessed for all subjects separately and for all groups, thus all subjects served as their own controls. Therefore, a (placebo) control group was not used. The choice for an open-label study was based on the assumption that this would not effect the changes in the PCA3 score, as this is an objective parameter.

Measurements

All subjects returned to the outpatient clinic after 1, 2, and 3 month(s) post-baseline and 4 months thereafter for a final safety follow-up visit. The total treatment phase comprised the first three months. All subjects underwent TRUS to measure total prostate volume at baseline and at the end of the treatment phase. Blood samples for circulating levels of serum T, DHT, and PSA were collected from all subjects at every visit except at screening and at the safety follow-up visit. Directly afterwards a DRE was performed after which the subjects were asked to void. The first voided urine was collected in a coded container with 4 ml 0.5 M EDTA. The samples from the community hospital were immediately cooled to 4°C and were mailed in batches with cold packs to the laboratory in the university hospital. These samples were processed within 48 hr after acquisition to guarantee good sample quality. The samples taken at the university hospital were processed within 1 hr. Upon centrifugation at 4°C and 700*g* for 10 min, urinary sediments were obtained. These urinary sediments were washed twice with ice-cold PBS (at 4°C and 700*g* for 10 min), snap-frozen in liquid nitrogen, and stored at −70°C. The urinary sediments were spiked with 20 μg of *E. coli* tRNA as a carrier (Roche Diagnostics, Almere, The Netherlands) and total RNA was extracted from these urinary sediments, using TRIzol Reagent (Invitrogen, Breda, The Netherlands). Eight microliters of extracted RNA was dissolved in 2.6 ml of detergent-based stabilization buffer, which lyses the cells and stabilizes the RNA [19]. The PCA3 and PSA mRNA transcripts were amplified and quantified as previously described [19]. As this was a pilot study, the calculated number of PCA3 or PSA mRNA transcripts was included for analysis even if it exceeded the assays calibrator range.

The PCA3 score was then calculated by dividing the number of PCA3 mRNA transcripts by the number of PSA mRNA transcripts detected in a given sample and multiplying the result by 1,000, thereby using the number of PSA mRNA transcripts to correct for the number of prostate cells present.

Statistical Analysis

The results of an intention-to-treat analysis are presented.

TABLE I. Baseline Clinical Features BPH Groups

	Randomized to 0.5 mg dutasteride				Randomized to 3.5 mg dutasteride				
Clinical feature	Mean ± SD	Median (range)	No. of subjects	%	Mean ± SD	Median (range)	No. of subjects	%	Difference
Age (year)	63.4 ± 6.2		8	100	62.9 ± 2.0		8	100	$P = 0.83$[b]
PCA3 score	24 ± 22	18 (1–62)	8	100	22 ± 13	21.5 (5–44)	8	100	$P = 0.75$[c]
Total prostate volume (ml)[a]	78.5 ± 25.3		8	100	61.4 ± 24.7		8	100	$P = 0.19$[b]
Serum DHT value (ng/ml)	1.78 ± 0.85		7	87.5	1.75 ± 0.95		8	100	$P = 0.95$[b]
Serum T value (ng/ml)	18.18 ± 6.87		8	100	16.33 ± 4.36		8	100	$P = 0.53$[b]
Serum PSA value (ng/ml)	6.76 ± 2.06		8	100	6.55 ± 2.93		8	100	$P = 0.88$[b]

BPH, benign prostatic hyperplasia; PCA3, prostate cancer gene 3; DHT, dihydrotestosterone; T, testosterone; PSA, prostate-specific antigen.
[a]Measured by transrectal ultrasound.
[b]Using two-sided *t*-test.
[c]Using two-sided Wilcoxon rank sum test.

TABLE II. Baseline Clinical Features PCa Groups, Prostate Biopsy and Radical Prostatectomy Pathology

	Randomized to 0.5 mg dutasteride				Randomized to 3.5 mg dutasteride				
Clinical feature	Mean ± SD	Median (range)	No. of subjects	%	Mean ± SD	Median (range)	No. of subjects	%	Difference
Age (year)	56.1 ± 4.7		5	100	58.8 ± 2.8		4	100	$P = 0.33$[b]
PCA3 score	77 ± 52	61 (19–132)	5	100	31 ± 36	17 (6–85)	4	100	$P = 0.11$[c]
Total prostate volume (ml)[a]	32.1 ± 16.2		5	100	38.8 ± 18.8		4	100	$P = 0.58$[b]
Serum DHT value (ng/ml)	1.60 ± 0.58		5	100	1.58 ± 0.62		4	100	$P = 0.95$[b]
Serum T value (ng/ml)	17.44 ± 6.03		5	100	13.00 ± 2.45		4	100	$P = 0.21$[b]
Serum PSA value (ng/ml)	7.26 ± 2.12		5	100	10.80 ± 6.38		4	100	$P = 0.28$[b]
PCa clinical stage									
cT1c			4	80			3	75	
cT2			1	20			1	25	
Prostate biopsy pathology									
Gleason score									
4			1	20					
6			3	60			4	100	
7			1	20					
Radical prostatectomy pathology									
Gleason score									
5			1	20					
6			1	20					
7			2	40			3	75	
8							1	25	
Biopsy Gleason score vs. radical prostatectomy PCa Gleason score									
Identical			2	40					
Upgrading			1	20			4	100	
Downgrading			1	20					
PCa pathological stage									
pT2			5	100			4	100	

PCa, prostate cancer; PCA3, prostate cancer gene 3; DHT, dihydrotestosterone; T, testosterone; PSA, prostate-specific antigen.
[a]Measured by transrectal ultrasound.
[b]Using two-sided *t*-test.
[c]Using two-sided Wilcoxon rank sum test.

The method of handling missing values was the observed-cases approach, that is, missing values at post-baseline assessments were not imputed and were regarded as missing. Change from baseline for each man was computed as post-baseline value minus baseline value, relative change from baseline as change from baseline divided by baseline value.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 15.0.1 for Microsoft Windows.

Study Registry

This study was registered at *ClinicalTrials.gov* (study identifier: NCT00375765).

RESULTS

Population

From April 25, 2005 to October 31, 2006, a total of 31 subjects were assessed for eligibility, that is, 21 subjects with BPH and 10 subjects with PCa. Six of these subjects (five with BPH and one with PCa) did not meet the inclusion criteria and were therefore excluded. Thus 25 subjects (16 with BPH and nine with PCa) were enrolled and randomized to treatment. No subjects were lost to follow-up, discontinued treatment because of adverse effects or other reasons, or had to be excluded from analysis. Therefore, all 25 enrolled subjects could be analyzed. Details are shown in Figure 1 for subjects with BPH and in Figure 2 for subjects with PCa.

The study thus comprised four groups of subjects:

- eight subjects with BPH who had received 0.5 mg dutasteride once daily,
- eight subjects with BPH who had received 3.5 mg dutasteride once daily,
- five subjects with PCa who had received 0.5 mg dutasteride once daily,
- four subjects with PCa who had received 3.5 mg dutasteride once daily.

Three subjects with BPH were screened and two were enrolled in the community hospital, the rest of the subjects were screened and enrolled in the university hospital.

Baseline Features

Table I shows the baseline clinical features of the two BPH groups. Table II shows the baseline clinical features of the two PCa groups and the prostate biopsy and radical prostatectomy pathology.

PCA3 Score

Figure 3 and Table III show the mean relative change from baseline PCA3 score per group after 1, 2, and 3 months of dutasteride treatment.

Table IV shows the PCA3 scores per subject and the mean relative change from baseline PCA3 score after 1, 2, and 3 months of dutasteride treatment.

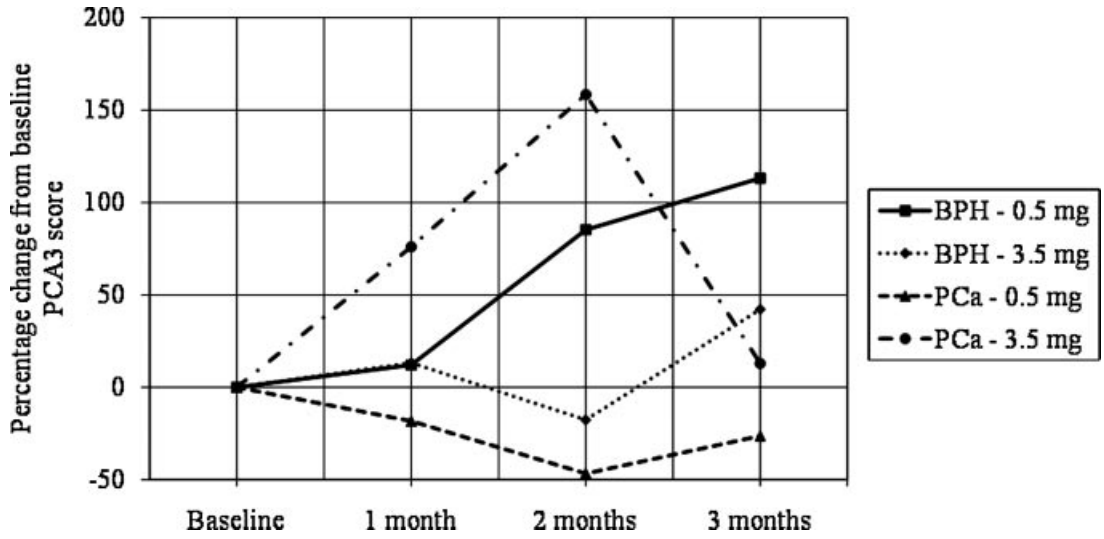

Fig. 3. Mean relative change from baseline PCA3 score per group after 1, 2, and 3 months of dutasteride treatment. Abbreviations: BPH—0.5 mg, group of subjects with benign prostatic hyperplasia (BPH) who received 0.5 mg dutasteride; BPH—3.5 mg, group of subjects with benign prostatic hyperplasia who received 3.5 mg dutasteride; PCa—0.5 mg, group of subjects with prostate cancer who received 0.5 mg dutasteride; PCa—3.5 mg, group of subjects with prostate cancer who received 3.5 mg dutasteride.

TABLE III. Mean Relative Change From Baseline PCA3 Score and Serum DHT, T, and PSA Per Group After 1, 2, and 3 Months of Dutasteride Treatment

Group	Dutasteride dose (mg)	Mean relative change from baseline PCA3 score (SD)			Mean relative change from baseline serum DHT (SD)			Mean relative change from baseline serum T (SD)			Mean relative change from baseline serum PSA (SD)		
		After 1 month	After 2 months	After 3 months	After 1 month	After 2 months	After 3 months	After 1 month	After 2 months	After 3 months	After 1 month	After 2 months	After 3 months
BPH	0.5	12 (86)	85 (186)	113 (249)	−93 (5)	−93 (5)	−94 (4)	13 (25)	13 (15)	20 (17)	−20 (21)	−38 (22)	−42 (24)
BPH	3.5	13 (80)	−18 (77)	42 (129)	−90 (9)	−95 (2)	−96 (3)	16 (21)	26 (23)	22 (23)	−28 (18)	−43 (16)	−54 (18)
PCa	0.5	−18 (69)	−47 (21)	−26 (14)	−84 (21)	−94 (4)	−89 (7)	6 (25)	12 (17)	21 (38)	−45 (12)	−59 (7)	−61 (10)
PCa	3.5	76 (126)	158 (284)	13 (75)	−94 (4)	−96 (1)	−96 (2)	40 (36)	38 (16)	29 (15)	−31 (38)	−60 (13)	−45 (20)

BPH, benign prostatic hyperplasia; DHT, dihydrotestosterone; PCa, prostate cancer; PCA3, prostate cancer gene 3; PSA, prostate-specific antigen; T, testosterone.

Serum DHT, T, and PSA

Figure 4 and Table III show the mean relative change from baseline serum DHT, T, and PSA per group after 1, 2, and 3 months of dutasteride treatment.

Prostate Volume

The mean ± SD relative change from baseline prostate volume was −11 ± 8% for the subjects with BPH who received 0.5 mg dutasteride, −16 ± 8% for the subjects with BPH who received 3.5 mg dutasteride, −15 ± 11% for the subjects with PCa who received 0.5 mg dutasteride and −10 ± 9% for the subjects with PCa who received 3.5 mg dutasteride.

Adverse Events

In general, adverse events were mild to moderate and resolved spontaneously. No serious adverse events were reported. Drug-related adverse events were mostly sexually related. None of the subjects withdrew from the study as a result of these adverse events.

DISCUSSION

This was the first study to date to investigate the effect of dutasteride on the PCA3 score longitudinally and in a dose dependent manner. In general, in all four groups both 0.5 and 3.5 mg dutasteride once daily:

- had a variable effect on the PCA3 score,
- rapidly reduced serum DHT by ≥90%,
- over time increased serum T by 20–30%,
- over time halved serum PSA,
- decreased prostate volume by 10–16%.

The effect of dutasteride on the PCA3 score was not clearly time dependent, but the effect of dutasteride on serum DHT, T, and PSA was.

Overall, no striking differences were found between the subjects with BPH who received 0.5 mg dutasteride and those who received 3.5 mg, nor between the subjects with PCa who received 0.5 mg dutasteride and those who received 3.5 mg. Because of the small number of subjects, no statistical analysis were performed on the results.

Dutasteride had the expected effect on serum DHT, T, and PSA, and on prostate volume. This effect was consistently seen across all four groups (Fig. 4). In contrast, the effect of dutasteride on the PCA3 score was variable between groups (Fig. 3), between subjects within one group and also in several subjects over time (Table IV).

Several interesting observations can be made when scrutinizing the results of this study. The mean relative

TABLE IV. PCA3 Scores Per Subject at Baseline and After 1, 2, and 3 Months of Dutasteride Treatment

			PCA3 score (relative change from baseline)			
Subject number	Group	Dutasteride dose (mg)	Baseline	After 1 month	After 2 months	After 3 months
5	BPH	0.5	1	3 (+200%)	6 (+500%)	6 (+500%)
6			6	5 (−17%)	7 (+17%)	7 (+17%)
8			12	18 (+50%)	20 (+67%)	74 (+517%)
11			15	6 (−60%)	12 (−20%)	6 (−60%)
12			21	17 (−19%)	16 (−24%)	33 (+57%)
19			22	13 (−41%)	4 (−82%)	5 (−77%)
21			52	25 (−52%)	69 (+33%)	17 (−67%)
53			62	84 (+35%)	181 (+192%)	74 (+19%)
1	BPH	3.5	9	2 (−78%)	2 (−78%)	0 (−100%)
7			19	14 (−26%)	20 (+5%)	23 (+21%)
10			5	6 (+20%)	12 (+140%)	10 (+100%)
13			18	44 (+144%)	17 (−6%)	70 (+289%)
14			24	45 (+88%)	14 (−42%)	41 (+71%)
24			44	16 (−64%)	12 (−73%)	21 (−52%)
27			24	26 (+8%)	7 (−71%)	16 (−33%)
51			35	—[a]	19 (−46%)	31 (−11%)
9	PCa	0.5	131	102 (−22%)	112 (−15%)	112 (−15%)
16			19	23 (+21%)	12 (−37%)	12 (−37%)
17			61	108 (+77%)	25 (−59%)	44 (−28%)
23			42	7 (−83%)	16 (−62%)	24 (−43%)
28			132	21 (−84%)	52 (−61%)	120 (−9%)
3	PCa	3.5	15	33 (+120%)	17 (+13%)	4 (−73%)
4			85	79 (−7%)	76 (−11%)	157 (+85%)
15			19	11 (−42%)	28 (+47%)	14 (−26%)
18			6	20 (+233%)	41 (+583%)	10 (+67%)

BPH, benign prostatic hyperplasia; PCa, prostate cancer; PCA3, prostate cancer gene 3.
[a]Value missing.

change from baseline PCA3 score per group shows variability over time. This is caused by the extreme values for one or two of the subjects in the group and the small number of subjects per group. Partin et al. [20] have reported preliminary data indicating that the PCA3 score in an individual subject is quite stable over time. In this study, however, the PCA3 score did not appear to be stable in several subjects using dutasteride. In this context it is important to consider the absolute values for the PCA3 score in addition to the relative change from baseline (Table IV).

In particular, subjects 8 and 53 (with BPH who received 0.5 mg dutasteride), and subjects 13 and 14 (with BPH who received 3.5 mg dutasteride) showed large variations in PCA3 score, including repeated values above the internationally proposed cut-off of 35 [12–14]. Importantly, none of these subjects with BPH have been diagnosed with PCa during the years of follow-up. The same is true for subject 21 (with BPH who received 0.5 mg dutasteride).

In comparison, the variations in PCA3 score in the subjects with PCa were less prominent, especially when considering the absolute values for the PCA3 score and not just the relative change from baseline.

To calculate the PCA3 score, the number of PCA3 mRNA transcripts is divided by the number of PSA mRNA transcripts, thereby correcting for the number of prostate cells present in the urine sample. Both the number of PCA3 and PSA mRNA transcripts in this fraction are the sum of the number of transcripts from shed PCa cells and the number of transcripts from shed benign prostate cells. PCA3 expression in PCa cells is 66-fold increased compared to PCA3 expression in benign prostate cells boosting the numerator of the fraction, while PSA expression in both cell types is similar, stabilizing the denominator [21]. This results in an elevated PCA3 score in subjects with PCa. Therefore, the effect of dutasteride on the expression of PCA3 in PCa cells is pivotal in its effect on the PCA3 score, whereas the effect on the other three parameters in the fraction is of minor importance.

It could be expected that the mechanism of androgen regulation and thus the effect of dutasteride (and other hormonal treatment) thereon,

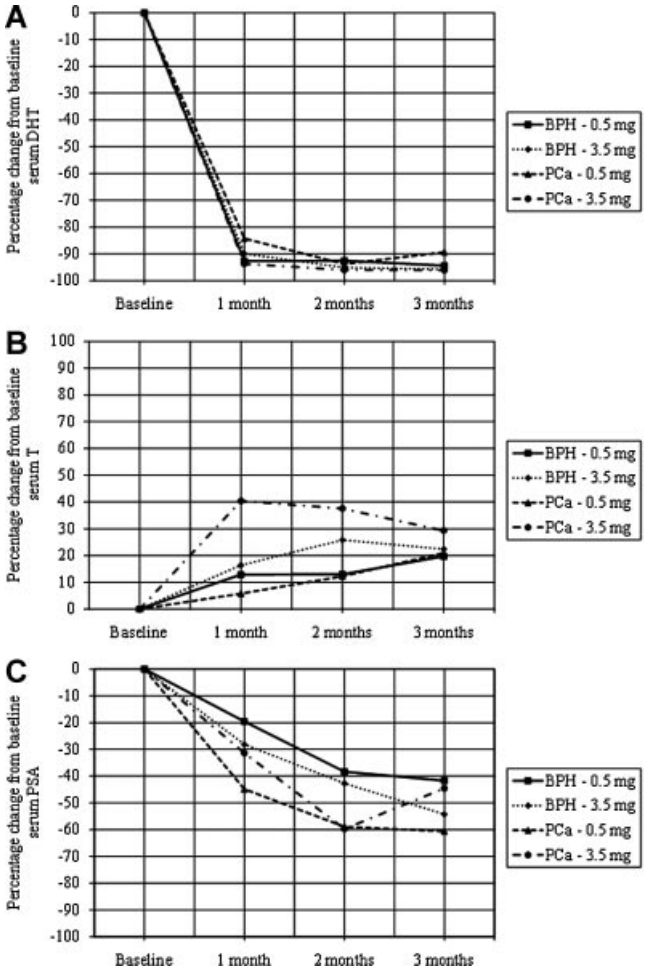

Fig. 4. Mean relative change from: (**A**) baseline serum dihydrotestosterone (DHT), (**B**) testosterone (T), and (**C**) prostate-specific antigen (PSA) per group after 1, 2, and 3 months of dutasteride treatment. Abbreviations: BPH—0.5 mg, group of subjects with benign prostatic hyperplasia (BPH) who received 0.5 mg dutasteride; BPH—3.5 mg, group of subjects with benign prostatic hyperplasia who received 3.5 mg dutasteride; PCa—0.5 mg, group of subjects with prostate cancer who received 0.5 mg dutasteride; PCa—3.5 mg, group of subjects with prostate cancer who received 3.5 mg dutasteride.

differs considerably between PCa cells and benign prostate cells. In addition, it is very likely that this mechanism also differs between PCa cells of different malignant potential, that is, with different inherent tendencies towards androgen independence. The effect of dutasteride on a patient's PCA3 score can be an early indication of the effect of androgen-deprivation therapy on PCa. Therefore, the influence of androgen-deprivation therapy on the PCA3 score should be analyzed further.

The most important limitation of this pilot study was the small number of subjects. Moreover, due to the strict inclusion and exclusion criteria its recruitment rate proved very slow. After $2\frac{1}{2}$ years the study was ended after randomization of 26 of the initially planned 40 subjects. However, it has to be noted that this study was strictly exploratory.

CONCLUSIONS

In this exploratory/pilot study the effect of dutasteride on the PCA3 score was variable. This should be taken into account while using PCA3 in diagnostics. As this study was exploratory, the influence of androgen-deprivation therapy on the PCA3 score should be analyzed further.

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