Effect of Finasteride and/or Terazosin on Serum PSA: Results of VA Cooperative Study #359

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BACKGROUND. Medical management of benign prostatic hyperplasia (BPH) giving rise to lower urinary tract symptomatology (LUTS) has emerged as the mainstay for first-line therapy. Prostate-specific antigen (PSA) is the most important method of detecting prostate carcinoma. The effect of finasteride on PSA has been widely reported. Little data exist with respect to alpha-adrenergic blocking therapy in men treated for BPH. In the present investigation we set out to evaluate the effect of these two forms of therapy.
METHODS. Patients enrolled in the VA Cooperative Study #359 trial were evaluated. This study evaluated men with moderate LUTS owing to BPH in four treatment groups: placebo (P), finasteride (F), terazosin (T), and combination of finasteride plus terazosin (C). Men were recruited at 31 VA medical centers and had a baseline in 52-week PSA determination at the respective sites.
RESULTS. There was no significant difference in baseline PSA between four groups (mean range, 2.0–2.9 ng/ml). Statistically significant reduction in PSA levels was observed at 52 weeks in the F and C arms ($P < 0.001$), whereas significant increases were observed in the T and P arms ($P < 0.01$). Additionally, there was no significant difference in PSA response between the T and P arms. Thirty percent of men in the C or F arms had more than 40–60% reduction of PSA. In contrast, the majority of men on T or P had less than 40% change in PSA. Only 35% of men on F or C had the expected 40–60% reduction in PSA level.
CONCLUSIONS. These data demonstrate no clinically significant effect of T on PSA level. The heterogeneity of PSA response to F may make monitoring patients for the development of prostate cancer problematic. *Prostate 39:234–239, 1999.*

KEY WORDS: **PSA; BPH; finasteride; terazosin**

INTRODUCTION

Prostate carcinoma is the most common malignancy among men in the United States and the second most common cause of cancer deaths [1]. A third of men older than 50 will have incidental carcinoma found at autopsy; however, the lifetime risk of clinically detected prostate cancer is approximately 9.5% [2]. The significance of prostate cancer has generated increased interest in early detection with digital rectal examinations, transrectal ultrasound, and serum prostate-specific antigen (PSA). PSA has been demonstrated to detect clinically important cancer and, in conjunction with other studies, has been shown to be the best predictor of carcinoma [3–8].

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Benign prostatic hyperplasia (BPH), with resulting symptomatic bladder outlet obstruction and prostate cancer, is prevalent in the same age range. The symptoms of BPH vary from obstructive and irritative voiding symptoms to urinary retention, azotemia, urinary tract infections, and hematuria [9]. Traditionally, surgery is the treatment most commonly offered to men with BPH, the goal being symptomatic relief. Recently, pharmacological approaches have become increasingly employed for the management of BPH [10–12].

5-alpha reductase inhibitors, such as finasteride, are one of the two major classes of medications for the treatment of BPH. Finasteride decreases prostatic dihydrotestosterone concentrations, resulting in cellular atrophy and apoptosis with consequent decrease in size of the prostate [13]. The utility of finasteride in BPH has been well-documented in several studies which reported a significant decrease in the symptoms of BPH [14–17]. The clinical significance of finasteride's effects on symptom scores is controversial. It is widely accepted that finasteride also causes a significant reduction in serum PSA levels of approximately 50% [18–20]. Clinicians routinely use the "multiply by 2" rule for PSA levels following initiation of finasteride therapy in order to establish a new baseline level. This adjustment of PSA level is valid only if the overwhelming majority of men experience a 50% reduction in PSA levels.

In 1976, Caine et al. [21] reported the successful treatment of BPH with alpha-1 adrenergic antagonists. Since then, several investigations have documented the significant therapeutic benefit in men with BPH [22–24]. Terazosin, a long-acting alpha-1 blocker, has been approved for the treatment of symptomatic BPH.

To date, the effect of terazosin on PSA has not been well-documented. Milam et al. [25] and Jones et al. [26] in preliminary studies noted that terazosin does not significantly affect serum PSA levels. However, Brown et al. [27] reported a decrease in PSA after 2 months of terazosin.

Due to the widespread use of finasteride and terazosin for BPH and the desire to monitor these patients for prostatic carcinoma, the effects of these drugs on serum PSA demands investigation. VA Cooperative Study #359, a 52-week double-blind, placebo-controlled, randomized clinical trial, offered a unique setting in which to study the effects of terazosin and finasteride on serum PSA levels.

MATERIALS AND METHODS

Details of the trial and the major findings have been previously published [10]. The protocol for VA Cooperative Study #359 was approved by the Cooperative Studies Evaluation Committee and the Human Rights Committee of the Cooperative Studies Program Coordinating Center, Department of Veterans Affairs (Perry Point, MD); all the men gave informed consent.

Recruitment, Eligibility, and Exclusion

Men aged 45–80 years with symptomatic BPH were interviewed and screened by study coordinators in outpatient clinics at participating Veterans Affairs Medical Centers. To be eligible for the study, participants needed to fulfill the requirements of a mean peak urinary-flow of no more than 15 ml per sec and no less than 4 ml per sec, with a minimal voided volume of 125 ml, a mean residual volume after voiding of less than 300 ml, and a mean American Urological Association (AUA) BPH symptom score of at least 8.

Men were excluded if they had taken an alpha-adrenergic-agonist drug, a cholinergic agonist or antagonist, a topical beta-adrenergic antagonist for glaucoma, or any antihypertensive except a diuretic or an angiotensin-converting-enzyme inhibitor within 2 weeks before the lead-in period. Willing participants were also excluded if they had taken an androgen, estrogen, or drug causing androgen inhibition within the preceding 3 months. Causes for exclusion also included a history of prostate cancer, pelvic irradiation, surgery for BPH or bladder-neck obstruction, active urinary tract infection, urethral stricture, recurrent urinary tract infections, cystoscopy or biopsy of the prostate within the previous 2 weeks, prior pelvic surgery that could interfere with normal bladder function, clinically important renal or hepatic impairment, and a serum concentration of PSA above 10 ng per ml.

The subjects were then randomly assigned by a central computer in equal proportions to receive terazosin titrated to 10 mg/day and finasteride placebo (the terazosin group), finasteride at 5 mg/day and terazosin placebo (the finasteride group), both terazosin and finasteride (the combination group), and terazosin placebo and finasteride placebo (the placebo group) for 1 year.

Follow-Up of Patients

The subjects were reevaluated after 2, 4, 8, 13, 19, 26, 32, 39, 45, and 52 weeks. Blood samples were obtained at 4, 26, and 52 weeks for hematologic analysis and studies of blood chemistry. Serum concentrations of PSA were measured at baseline and 52 weeks. PSA levels were determined by the laboratory services of each individual center. There was no uniform assay or central processing of the samples.

Statistical Analysis

Statistical analysis of the group mean changes between baseline and 52 weeks was performed by use of pooled *t*-tests.

TABLE I. Baseline Characteristics of 1,229 Men With Benign Prostatic Hyperplasia According to Treatment Groups*

Characteristic	Combination	Finasteride	Terazosin	Placebo
Age (years)	65 ± 7	65 ± 7	65 ± 7	65 ± 7
Prostatic volume (cm^3)	37.2 ± 1.1	36.3 ± 1.0	37.5 ± 1.1	38.4 ± 1.3
White race (%)	80	79	81	79
Serum PSA (ng/ml)	2.4 + 2.0	2.3 + 1.9	2.2 + 2.1	2.3 + 1.9

*Plus-or-minus values are means ± standard deviation.

RESULTS

Of the 1,689 men screened, 1,229 (73%) met the criteria for entry into the study and were enrolled from December 1992–March 1994. The follow-up was completed by March 1995. Of the 2,339 men who entered the study, 222 were not receiving the study medications at the end of 52 weeks. The mean degree of compliance with the study medication as determined by pill counts ranged from 94–98% in each group.

As previously reported [10], the mean changes from baseline in American Urological Association symptom scores in the placebo, finasteride, terazosin, and combination-therapy groups at 1 year were decreases of 2.6, 3.2, 6.1, and 6.2 points, respectively ($P < 0.001$ for comparisons of both terazosin and combination therapy with finasteride and with placebo). The mean changes at 1 year in peak urinary-flow rates were increases of 1.4, 1.6, 2.7, and 3.2 ml per sec, respectively ($P < 0.001$ for the same comparisons). Finasteride was no more effective on either measure than placebo. Terazosin provided effective therapy, whereas finasteride did not, and the combination was no more effective than terazosin alone.

The baseline serum concentration of PSA was not significantly different between the four groups, suggesting that for this as well as all significant BPH-related parameters, the randomization was successful (Table I). Additionally, the race stratification was not significantly different between the four groups (Table II).

A significant reduction in PSA at 52 weeks was observed in the F and C arms ($P < 0.001$), with mean PSA levels falling from 2.26 to 1.22 ng/ml and 2.38 to 1.36 ng/ml, respectively. Thirty percent of men in the F and C arms had more than 40–60% reduction of PSA. Only 34% of men on F or C had the expected 40–60% reduction in PSA level.

Significant increases in PSA levels at 52 weeks were seen in the T and P arms ($P < 0.01$), with mean levels rising from 2.18 to 2.49 ng/ml and 2.34 to 2.60 ng/ml, respectively (Table III). The majority of men on T or P had less than a 40% change in PSA from baseline levels.

The absolute value change in PSA for the F and C arms are shown in Table IV. Fifty percent of men in the F and C arms had an absolute value decrease of at least 0.75 ng/ml, and almost 30% of the men in the same treatment groups displayed decreases of at least 1.5 ng/ml. Conversely, only 10% of men in the T and P arms had a 0.75 ng/ml decrease in serum PSA value, and less than 5% had a 1.5 ng/ml decrease. Twenty-three percent of the placebo group displayed an increase in 0.75 ng/ml over the course of the study, while 19% of the terazosin arm had a similar increase. Less than 4% of the combination and finasteride patients showed the same increases. The serum PSA response to terazosin was not significantly different from placebo.

DISCUSSION

VA Cooperative Study #359 was the first to assess the effect of terazosin, alone or in combination with finasteride, on serum PSA in men with symptomatic BPH. Terazosin treatment significantly improved the symptoms of BPH, including increasing peak flow rate and decreasing AUA symptom score. Finasteride did not significantly alter these parameters and was no more effective than placebo. Furthermore, the combination of finasteride and terazosin was no more effective than terazosin alone [10]. The widespread use of finasteride and terazosin for BPH in a population also possibly harboring prostate carcinoma demands that we understand how to monitor these patients with PSA, the best tumor marker.

Nine hundred and ninety patients completed the study, divided equally among the terazosin, finasteride, combination, or placebo groups. There were no statistically significant differences in baseline PSA. The proportion of African-American men in our study approached that of the U.S. population. Eighty-two percent of the men completed the 52-week study in their designated treatment groups, and compliance approached 100%.

The effects of terazosin and placebo on group mean serum PSA levels were similar, with significant in-

TABLE II. Race Stratification for 1,229 Men According to Treatment Group

Race	Frequency (column percentage)				
	Combination	Finasteride	Terazosin	Placebo	Total
American Indian	0 (0.00)	3 (0.97)	1 (0.33)	2 (0.66)	6
Asian/Pacific Islander	3 (0.97)	5 (1.61)	1 (0.33)	6 (1.97)	15
Black, not Hispanic	32 (10.36)	28 (9.03)	34 (11.15)	27 (8.85)	121
Black, Hispanic	5 (1.62)	5 (1.61)	2 (0.66)	1 (0.33)	13
White, not Hispanic	248 (80.26)	246 (79.35)	246 (80.66)	240 (78.69)	980
White, Hispanic	21 (6.80)	23 (7.42)	21 (6.89)	29 (9.51)	94
Total	309	310	305	305	1,229

TABLE III. Percent Change From Baseline PSA for Each Treatment Group*

PSA change	Combination percent	Finasteride percent	Terazosin percent	Placebo percent
>60% increase	3.7	3.5	14.2	14.4
40–59% increase	2.6	1.9	8.0	9.1
20–39% increase	2.6	1.2	18.6	17.4
0–19% increase	7.3	8.1	25.5	32.2
1–19% decrease	5.5	6.2	13.8	9.9
20–39% decrease	16.8	16.2	13.1	9.5
40–60% decrease	30.3	34.0	4.7	4.6
>60% decrease	31.4	29.0	2.2	3.0

*Numbers in columns represent percentage of patients within treatment group. Significant reductions were seen in the finasteride and combination arms ($P < 0.001$), and significant increases seen in the terazosin and placebo arms ($P < 0.01$).

TABLE IV. Absolute Value Change From Baseline PSA for Each Treatment Group*

Absolute value change	Combination	Finasteride	Terazosin	Placebo
Increase, 2.0 ng/ml	2.4	1.7	4.8	6.3
Increase, 1.5 ng/ml	2.8	2.1	8.4	7.9
Increase, 1.0 ng/ml	2.8	2.9	13.1	16.2
Increase, 0.75 ng/ml	4	3.5	19.1	22.9
Increase, 0.5 ng/ml	4.8	5.9	31.9	33.2
Increase, 0.5 ng/ml	66.1	64.3	15.9	13.4
Increase, 0.75 ng/ml	48.8	47.7	10.4	10.3
Increase, 1.0 ng/ml	38.7	39.9	7.2	7.9
Increase, 1.5 ng/ml	26.2	27.7	2.8	5.9
Increase, 2.0 ng/ml	18.5	18.9	2	3.6

*Numbers in columns represent percentage of patients within treatment group.

creases in PSA level seen at the 52-week visit. Since PSA levels were measured at baseline and 52 weeks posttreatment in all subjects, the 1-year PSA velocity in the control group was evaluable. Several investigations postulated that annual increases in PSA of 0.75 ng/ml or greater than 20% over baseline were indicative of men who would develop prostatic carcinoma [28,29]. However, Porter et al. [30] reported on a series of men with a 1-year interval between PSA determinations. No PSA velocity parameter (including median PSA velocity, median percent PSA increase per year, 0.75 mg/ml per year, or an increase of 20%) was useful in stratification of those men with or without prostatic carcinoma as evidenced by ultrasound-guided biospy. In our present cohort of patients, approximately 20% of the placebo and terazosin arms

TABLE V. Percent Change From Baseline PSA If PSA in Combination and Finasteride Groups is Multiplied by 2

PSA change	Combination percent	Finasteride percent	Terazosin percent	Placebo percent
>60% increase	24.1	22.0	14.2	14.4
40–59% increase	5.8	7.3	8.0	9.1
20–39% increase	10.6	10.8	18.6	17.4
0–19% increase	15.7	18.2	25.5	32.2
1–19% decrease	12.8	12.7	13.8	9.9
20–39% decrease	15.7	15.4	13.1	9.5
40–60% decrease	8.4	9.7	4.7	4.6
>60% decrease	6.9	3.9	2.2	3.0

displayed an increase in 0.75 ng/ml over the 1-year study. Less than 4% of the combination and finasteride patients showed the same increase. Thus, we cannot draw conclusions about the possibility of prostatic carcinoma in our subset of patients who displayed increases in serum PSA greater than 0.75 ng/ml or greater than a 20% increase.

The majority of PSA levels in patients of the terazosin and placebo arms were within 40% of baseline (71.0% and 68.0%, respectively). In fact, the profiles of PSA change between the placebo and terazosin groups were virtually identical. This finding confirms previous reports that terazosin does not significantly affect serum PSA concentration, and that monitoring these patients for prostatic carcinoma is not confounded by concomitant terazosin usage. The observation that approximately 14% of men in the placebo and terazosin-alone cohort had a 60% or greater increase in PSA may certainly be an indication of occult malignancy not surprising in this population; obviously, without biopsies this cannot be confirmed.

Approximately 30% of the men in the finasteride and combination arms had a greater than 60% reduction in their serum PSA. Overall, 66% of the men in the finasteride and combination arms did not fall within the 40–60% reduction in PSA which has been previously documented, thus violating the "multiply-by-2" rule. To confirm these findings, we multiplied serum PSA by 2 in the combination and finasteride cohort (Table V). The PSA values after the proposed corrective adjustments were not similar to those in the placebo or terazosin groups, once again revealing the complex response of PSA to finasteride.

It is unclear why in our study such a heterogeneity of response to finasteride was seen. One could argue that the samples were not centrally processed but instead were analyzed by individual centers across the country, and thus were subject to analytic variation. However, Jacobsen et al. [31] in 1993 reported on a large study investigating the effect of different assays in different laboratories. Other multiple studies showed that analytical variation has a coefficient of variation of only approximately 3–12% for most PSA assay systems available [32,33]. They found that analytic variation owing to assay variation contributes negligibly to differences in PSA measurements. Brawer et al. [34,35] showed similar results in multiple trials. These reports provide reassurance that serum PSA levels from different centers are generally consistent and can reliably be compared. The randomized design of this study precludes the possibility of systematic laboratory bias likely contributing to the heterogeneity of the effect of finasteride on PSA. Furthermore, we feel that multicenter processing is not a liability in our study but offers an advantage by casting a "real-world" light on the issue of PSA levels. Clinicians across the country do not centrally process their PSA levels on routine screening.

Additionally, several studies investigated the potential effect of biologic variation, the physiological fluctuation of serum PSA that occurs within a given patient, and how this may affect serial PSA values [36,39]. Nixon et al. [40] reported that the median critical difference assuring statistically significant differences between two measurements is 20.5%, owing to considerable biologic variation. When observing the PSA changes in the finasteride and combination groups in the present investigation, the majority of patients displayed changes greater than those attributable to biologic variation. Thus, biologic variation in itself is an unlikely explanation for the large proportion of patients in the finasteride arm who fell outside the expected 40–60% reduction in serum PSA.

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