calculated using the Wilcoxon rank sum test.

RESULTS: Median PSA, PSA velocity, and PSADV are shown for the placebo and dutasteride treatment cohorts at 24 months in Table 1. Median PSA velocity in both the placebo and treatment groups were positive independent of a prostate cancer diagnosis. Results of PSADV stratified by treatment and biopsy results are seen in the boxplots in Figure 1. There was a significantly more robust reduction in PSADV in those without cancer on biopsy compared to those with prostate cancer in the treatment arm (P = 0.0019).

CONCLUSIONS: The magnitude of change in PSADV after dutasteride therapy may be an additional diagnostic adjunct to aid in the identification of those at lower risk for prostate cancer on repeat biopsy. This measurement may reduce unnecessary prostate biopsies and the increasingly prevalent associated risks of the procedure.

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Key Words: Prostate cancer diagnosis; PSA; Prostate cancer; 5-alpha reductase inhibitor

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ABSTRACT

AIM: Prostate specific antigen (PSA) is a widely utilized screening marker for prostate cancer. Its performance in detecting prostate cancer is enhanced with the 5α-reductase inhibitor (5αRI) dutasteride. We evaluated if PSA density velocity (PSADV) further improved the ability to predict prostate cancer risk on repeat biopsy utilizing the REDUCE trial data in order to avoid unnecessary biopsies.

MATERIALS AND METHODS: The REDUCE study randomized 8,231 men aged 50 to 75 years with a PSA between 2.5 and 10 ng/mL and a previously benign prostate biopsy. Prostate volume, PSA and biopsy results at 24 months were available for 1,074 subjects. PSADV, defined as the change in PSA density divided by the number of days between PSA measurements (ng/mL/cc/day), was calculated and compared between the placebo and treatment groups and further stratified by prostate biopsy results. Statistical significance was calculated using the Wilcoxon rank sum test.

RESULTS: Median PSA, PSA velocity, and PSADV are shown for the placebo and dutasteride treatment cohorts at 24 months in Table 1. Median PSA velocity in both the placebo and treatment groups were positive independent of a prostate cancer diagnosis. Results of PSADV stratified by treatment and biopsy results are seen in the boxplots in Figure 1. There was a significantly more robust reduction in PSADV in those without cancer on biopsy compared to those with prostate cancer in the treatment arm (P = 0.0019).

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INTRODUCTION

Prostate cancer (CaP) is the most prevalent malignancy among American men. The American Cancer Society estimates a total of 2.8 million men in the United States have CaP with 241,740 new cases diagnosed in 2012[1]. This increase in CaP detection is undoubtedly a result of prostate specific antigen (PSA) screening as well as modifications to traditional transrectal ultrasonography (TRUS) guided prostate biopsies.
TRUS guided prostate biopsies remain the mainstay of histologic diagnosis of CaP. A recent review of the SEER database revealed that of T1 prostate cancers, 94% are diagnosed by TRUS biopsy compared to only 6% by transurethral resection[14]. However, a majority of prostate biopsies fail to detect malignancy and are a source of patient discomfort, morbidity, and anxiety. Complications are not uncommon with a reported complication rate including minor complications as high as 63%[17]. In addition, prostate biopsy confers a 2.65-fold higher risk of hospital admission compared to a control population based on multivariable analysis of the SEER database[18]. This observation is likely related to the increasing prevalence of fluoroquinolone resistance within the population undergoing TRUS prostate biopsy, which is reportedly as high as 22% based on pre-biopsy rectal swab cultures[19].

PSA screening remains a sensitive but nonspecific predictor of benign versus malignant disease. In fact, there is significant physiologic variation in serial measurements of PSA creating difficulty in interpreting the results of this screening test[16-17]. Considerable efforts to improve the performance of PSA as a screening tool have been made.

Previous reports have suggested that treatment with 5α-reductase inhibitors (5αRIs) may improve the diagnostic yield of available screening tools for CaP[10-14]. In order to combine considerations of prostate volume and PSA kinetics in conjunction with 5αRI therapy, we evaluated if PSA density velocity (PSADV) further improved the ability to predict prostate cancer risk on repeat biopsy. We utilized the REDUCE trial data in order to evaluate this concept. To our knowledge, this is the only study comparing the combination of PSA kinetics with consideration of prostate volume between those on a 5αRI versus placebo.

MATERIALS AND METHODS

The study design of the REDUCE trial has been previously described in depth[13]. The trial was a 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study investigating the chemoprevention effects of the non-selective 5αRI dutasteride. A total of 8,231 men aged 50 to 75 years underwent randomization to a 0.5mg daily dose of dutasteride or placebo. Men between 50 and 60 years of age were eligible if their baseline PSA value was 3.0 to 10.0 ng per milliliter, while those men over the age of 60 years were included if the PSA value was 2.5 to 10.0 ng per milliliter, while those men over the age of 60 years were included if the PSA value was 3.0 to 10.0 ng per milliliter. All participants had undergone a 6-12 core TRUS prostate biopsy within 6 months of enrollment without evidence of prostate cancer (pathology was centrally reviewed and confirmed). Men were excluded from participation if they had previously been biopsied more than once; had known prostate cancer of any grade, high-grade intraepithelial neoplasia, atypical small acinar proliferation, or had a prostate volume greater than 80 mL. In addition, men with severe lower urinary tract symptoms defined as an International Prostate Symptom Score (IPSS) of 25 or higher, or 20 or higher with concomitant alpha-blocker therapy were also excluded from the study.

Study protocol called for assessments every 6 months with PSA and IPSS measurements. PSA levels in patients taking dutasteride were adjusted by a factor of two. Prostate biopsies were performed at 2 and subsequently 4 years or if clinically indicated as judged by the study physician (protocol-independent).

Of the 8,231 men originally randomized, prostate volume, PSA and biopsy results at 24 months were available for 1,074 subjects (after excluding measurements on or up to 42 days after biopsy, or after prostate cancer diagnosis or final biopsy) PSADV, defined as the change in PSA density divided by the number of days between PSA measurements (ng/ml/cc/day), was calculated and compared between the placebo and treatment groups and further stratified by prostate biopsy results. Statistical significance was calculated using the Wilcoxon rank sum test performed at the significance level of 0.05.

RESULTS

Data were analyzed from the 1,074 patients with available PSA values, prostate volumes and biopsy results at the 2-year interval of the study. A total of 532 patients in the placebo group were compared to 542 patients in the dutasteride treatment arm. Because the aim of this subset analysis of the REDUCE trial was to investigate the discriminatory ability of PSADV (compared to other PSA parameters) to predict biopsy-detected CaP, the placebo and treatment groups were then stratified into those with a negative or positive TRUS biopsy. Within the placebo cohort, 95 patients received a diagnosis of CaP while 437 patients remained without evidence of malignancy. The dutasteride cohort was comprised of 58 patients with biopsy-proven prostate cancer and 484 patients without CaP at 2 years.

Median baseline PSA was similar in the placebo and dutasteride groups irrespective of a CaP diagnosis and were 5.8 (placebo with CaP), 5.6 (placebo without CaP), 5.2 (dutasteride with cancer) and 5.5 (dutasteride without CaP) ng/mL. Median PSA at 24 months in the placebo group increased to 6.6 and 5.7 ng/mL for those with and without cancer respectively, which correlated to median PSAVs (ng/mL per day × 10²) of 15.8 and 5.2. As expected, the median PSA at 24 months in those on dutasteride decreased to 3.0 (dutasteride with cancer) and 2.2 (dutasteride without cancer) ng/mL. The calculated median PSAVs for these two cohorts were -34.9 and -37.9 ng/mL per day × 10² in patients with and without CaP on 2-year TRUS biopsy respectively P = 0.03.

In order to account for the dual effect of 5αRI on PSA and prostate volume, we calculated the PSADV (ng/mL/cc per day × 10²) at 24 months for each group. The median PSADV was positive (> 0) only in the group of patients on placebo who were diagnosed with CaP and was 15.9. The remainder of the groups had a negative (< 0) median PSADV, with values of -4.8 (placebo without cancer), -46.3 (dutasteride with cancer) and -73.2 (dutasteride without cancer). The results of PSA, PSAV, and PSADV among the subgroups are summarized in Table 1. Using the Wilcoxon rank sum test, there was a significant difference in PSADV between those patients taking dutasteride with CaP at 2 years and those without CaP (median of 46.3 vs -73.2, P = 0.0019). Results of PSADV stratified by treatment and biopsy results are seen in the boxplots in Figure 1.

Figure 2 depicts ROC curves for PSADV.

DISCUSSION

Prostate cancer remains a very commonly encountered clinical entity for primary care physicians and urologists alike. We have seen an increased detection of CaP as a result of early screening efforts in the PSA era. However, PSA is a non-specific marker for prostate cancer and may be increased for a variety of reasons, most notably due to CaP or BPH[10]. This inevitably creates the difficult diagnostic quandary engendering considerable patient anxiety and physician uncertainty.

Contemporary extended prostate biopsy schemes have significantly improved the cancer detection rates compared to the historical sextant
Table 1 PSA parameters at Entry and 24 months including PSADV.

| Endpoint (ng/mL) | Visit | Placebo w Pca | Placebo w/o Pca | Dutasteride w/ Pca | Dutasteride w/o Pca | P value |
|----------------|-------|---------------|----------------|-------------------|--------------------|---------|
| PSA | Entry | 5.8 | 5.6 | 5.2 | 5.5 | <0.001 |
| | 24 months | 6.6 | 5.7 | 6 | 2.2 | <0.001 |
| PSADV (ng/mL/day × 10^6) | 24 months | 15.8 | 5.2 | -34.9 | -37.9 | 0.03 |
| PSADV (ng/mL/ce/day × 10^6) | 24 months | 15.9 | -4.8 | -46.3 | -73.2 | 0.002 |

Figure 1 PSA DV with Confidence Intervals at 24 months in Patients with and without CaP on and not on Dutasteride.

biopsy scheme[24]. The unifying theme of extended biopsies is one of maximizing cores taken from the lateral peripheral zone, the most common site of CaP. Extended, saturation, and transperineal biopsy templates have been studied and CaP detection rates range from 29-43%[18-20]. Regardless of the approach to biopsy, there remains a majority of patients at risk for CaP with a negative biopsy.

Knowing the limitations of PSA as a screening test for the detection of prostate cancer, many have investigated refinements in PSA including corrections for volume (PSAD), molecular forms (F/T PSA), and kinetics (PSAV) to improve the predictive value of CaP detection of TRUS biopsy. In a study of 1,708 men referred for prostate biopsy, Elliott et al. determined that PSAD had a significantly higher area under the curve (AUC) than PSA for detecting all CaP (0.737 vs 0.633, P < 0.001) as well as for detecting high grade (0.766 vs 0.673, P < 0.001) and high volume (0.843 vs 0.755, P < 0.001) disease[21]. Similarly, in a large study of 1,051 men with a PSA between 4 to 10 ng/mL undergoing TRUS biopsy, the AUC for percent free PSA (0.745) was higher than transition zone PSAD (0.691), PSAD (0.618), and total PSA (0.603)[21].

5-alpha reductase (5aR) is the enzyme expressed in prostate tissue responsible for the conversion of testosterone to dihydrotestosterone (DHT) (the more potent ligand for androgen receptors within the prostate) and exists in two isoforms, type 1 and type 2. Research has shown that 5aR levels are disproportionately expressed in patients with prostate cancer, with increased levels detected in men with localized high grade CaP. 5aR levels are higher in benign tissue adjacent to foci of prostate cancer[22]. Given the shortcomings of PSA as a predictor of CaP on prostate biopsy coupled with the incongruous expression of 5aR in prostate glands harboring cancer, others have investigated the ability of 5aRI therapy to differentially alter PSA in a manner to improve its ability to predict the presence of cancer on subsequent prostate biopsy.

Two large randomized, double-blind, placebo-controlled trials, the Prostate Cancer Prevention Trial (PCPT) and the REDUCE trial have reported on the role of 5aRI therapy for chemoprevention of CaP[24,25]. Both trials showed a significant reduction in overall prostate detection risk, but concerns regarding an increased proportion of high grade CaP have rendered 5aRI therapy controversial for chemoprevention. However, on subset analyses of both trials, PSA demonstrated improved sensitivity in overall prostate cancer detection as well as high grade CaP compared to those treated with placebo[26-28].

In the present study, the REDUCE trial data was utilized in order to evaluate a novel PSA parameter, PSADV, as a test to further discriminate between those patients with an elevated PSA due to CaP versus BPH. We found that in those patients treated with 0.5mg of dutasteride daily over a 2-year period, those with an ultimate diagnosis of prostate cancer demonstrated a significantly less pronounced decrease in PSADV compared to those without CaP. In this subset analysis, the PSADV was statistically different in the treatment arm subjects depending on the presence of prostate cancer diagnosis date, as well as those occurring on or after the last cancer assessment biopsy in year 1-2. PSA measurement on the date of a biopsy (or within 42 days after) have been deleted.

Figure 2 ROC Curve for CaP using PSADV as Diagnostic Marker.

Note: Analysis excludes measurement occurring on or after the prostate cancer diagnosis date, as well as those occurring on or after the last cancer assessment biopsy in year 1-2. PSA measurement on the date of a biopsy (or within 42 days after) have been deleted.

Figure 2 ROC Curve for CaP using PSADV as Diagnostic Marker.

CONCLUSION

We postulate that PSADV may be an invaluable diagnostic adjunct to help urologists decide which patients will benefit from repeat biopsy.
versus those that are more appropriately managed without biopsy. PSADV therefore may reduce not only unnecessary prostate biopsies but also may assist in identifying higher grade clinical significant prostate cancer.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1. Siegel R, Desantis C, Virgo K et al. Cancer treatment and survivorship statistics, 2012. CA: a cancer journal for clinicians 2012; 62: 220-241.
2. Meeks JJ, Maschino AC, Mcvary KT, Sandhu JS. Clinically significant prostate cancer is rarely missed by ablative procedures of the prostate in men with prostate specific antigen less than 4ng/ml. J Urol 2013; 189: 111-115.
3. Rodriguez LV, and Terris MK. Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. J Urol 1998; 160: 2115-2120.
4. Loeb S, Carter HB, Berndt SI et al. Complications after prostate biopsy: data from SEER-Medicare. J Urol 2011; 186: 1830.
5. Liss MA, Chang A, Santos R et al. Prevalence and significance of fluoroquinolone resistant Escherichia coli in patients undergoing transrectal ultrasound guided prostate needle biopsy. J Urol 2011; 185: 1283.
6. Roehrborn CG, Pickens GJ, Carmody T. Variability of repeated serum prostate-specific antigen (PSA) measurements with less than 90 days in a well-defined population. Urology 1996; 47: 59-66.
7. Brawer MK, Daum P, Petteway JC, Wener MH. Assay variability in serum prostate-specific antigen determination. Prostate 1995; 27: 1-6.
8. Kaplan SA, Ghafar MA, Volpe MA et al. PSA response to finasteride challenge in men with a serum PSA greater than 4ng/ml and previous negative prostate biopsy: Preliminary study. Urology 2002; 60: 464-468.
9. Handel LN, Agarwal S, Schif F, Kelty PJ, Cohen SI. Can effect of finasteride on prostate-specific antigen be used to decrease repeat prostate biopsy? Urology 2006; 64.
10. Thompson IM, Chi C, Ankerst DP et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 2006; 98: 1128-1133.
11. Andriole GL, Bostwick D, Brawley OW et al. The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: Results from the REDUCE study. J Urol 2011; 185: 126-131.
12. Andriole GL, Guess HA, Epstein JI et al. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: Results of a randomized double-blind, placebo-controlled clinical trial. Urology 1998; 52: 195-202.
13. Roehrborn CG, Andriole GL, Wilson TH et al. Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostate in the combination of Avodart and tamulosin trial. Eur Urol 2011; 59: 244-249.
14. Kaplan SA, Lee RK, Chung DE et al. Prostate biopsy in response to a change in nadir prostate specific antigen of 0.4 ng/ml after treatment with 5α-reductase inhibitors markedly enhances the detection rate of prostate cancer. J Urol 2012; 188: 757-761.
15. Andriole G, Bostwick D, Brawley OW et al. Chemoprevention of prostate cancer in men at high risk: rationale and design of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. J Urol 2004; 172: 1314-1317.
16. Stamey TA, Yang N, Hay AR et al. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987; 317: 909.
17. Hong YM, Lai FC, Chon CC et al. Impact of prior biopsy scheme on pathologic features of cancers detected on repeat biopsies. Urol Oncol 2004; 22: 7.
18. Babaian RJ, Toi A, Kamoi K et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. J Urol 2000; 163: 152.
19. Stewart CS, Leibovich BC, Weaver AL et al. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. J Urol 2001; 166: 86.
20. Igel TC, Knight MK, Young PR et al. Systematic transperineal ultrasound guided template biopsy of the prostate in patients at high risk. J Urol 2001; 165: 1575.
21. Elliott CS, Shinghal R, Presti JC. The performance of prostate specific antigen, prostate specific antigen density and transition zone density in the era of extended biopsy schemes. J Urol 2008; 179: 1756.
22. Djaovan B, Zlotta A, Remzi M et al. Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. J Urol 2000; 163: 1144.
23. Thomas LN, Douglas RC, Lazier CB et al. Levels of 5α-reductase type 1 and type 2 are increased in localized high grade compared to low grade prostate cancer. J Urol 2008; 179: 147.
24. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003; 349: 215-224.
25. Andriole GL, Bostwick DG, Brawley OW et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010; 362: 1192-1202.
26. Andriole GL, Bostwick DG, Brawley OW et al. The Effect of Dutasteride on the Usefulness of Prostate Specific Antigen for the Diagnosis of High Grade and Clinically Relevant Prostate Cancer in Men With a Previous Negative Biopsy: Results From the REDUCE Study. Journal of Urology 2011; 185: 126-131.

Peer reviewers: Steve Keir, Associate Professor – Surgery, Director of Translational Research, The Preston Robert Tisch Brain Tumor Center, Duke University, Durham, North Carolina, USA; Elizabeth Ferreir Martinez, Professor, São Leopoldo Mandic Institute and Research Center, Department of Pathology and Cell Biology, José Rocha Junqueira Street, 13 – Campinas, São Paulo, Brazil; Sachin C. Sarode, Associate Professor, Dept of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College and Hospital, Sant Tukaram nagar, Pimpri, Pune 411018, India.