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

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Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor
AUC = area under the curve
NPV = negative predictive value
PPV = positive predictive value
PSA = prostate specific antigen
REDUCE = REduction by DUtasteride of prostate Cancer Events
ROC = receiver operating characteristic

Submitted for publication May 11, 2010.
Supported by GlaxoSmithKline.
The REDUCE study was supported by GlaxoSmithKline.
Clinical Trial Registration NCT00056407 (www.clinicaltrials.gov).

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† Financial interest and/or other relationship with Aeterna Zentaris, Amgen, Cambridge Endo, EMD Serono, Envisioneering Medical, Ferring Pharmaceuticals, GenProbe, GlaxoSmithKline, Myriad Genetics, Nema Steba, Onconome, Veridex and Viking Medical.

Purpose: We assessed whether dutasteride enhances the usefulness of total prostate specific antigen for diagnosing clinically significant prostate cancer.
Materials and Methods: The 4-year REDUCE study evaluated the efficacy and safety of 0.5 mg dutasteride daily for prostate cancer risk reduction in men with a prostate specific antigen of 2.5 to 10.0 ng/ml and a negative prostate biopsy. Specificity, sensitivity, and positive and negative predictive values of prostate specific antigen for the diagnosis of prostate cancer were assessed.
Results: Final prostate specific antigen before biopsy and change from month 6 to final prostate specific antigen performed better for the diagnosis of Gleason score 7–10 tumors in men who received dutasteride vs placebo as assessed by the area under the ROC curves (0.700 vs 0.650, p = 0.0491; and 0.699 vs 0.593, p = 0.0001, respectively). Increases in prostate specific antigen were associated with a higher likelihood of biopsy detectable, Gleason score 7–10 and clinically significant (modified Epstein criteria) prostate cancer. Percentage decreases in prostate specific antigen from baseline to month 6 in the dutasteride arm did not predict prostate cancer overall or Gleason score 7–10 cancer.
Conclusions: In men with a previously negative prostate biopsy, prostate specific antigen performed better during the 4-year study as a marker of prostate cancer in men who received dutasteride vs placebo. The degree of prostate specific antigen increase after 6 months was a better indicator of clinically significant cancer in the dutasteride arm than in the placebo arm. Conversely, the initial decrease in prostate specific antigen in men taking dutasteride did not predict the likelihood of prostate cancer.

Key Words: prostatic neoplasms, dutasteride, prostate-specific antigen, sensitivity and specificity

0022-5347/11/1851-0126/0
THE JOURNAL OF UROLOGY®

Vol. 185, 126-131, January 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2010.09.011

‡ Financial interest and/or other relationship with Accuray-Device Study, BD Diagnostics, Bioniche, Bostwick Laboratories, Capstone, CRITICAL, DermFISH, EDAP, GlaxoSmithKline, Globe Immune, GTx, Novartis, Prourocare, Sanofi-Aventis, Spectrum Pharmaceuticals and UroFISH.

§ Financial interest and/or other relationship with GlaxoSmithKline and Sanofi.

‖ Financial interest and/or other relationship with GlaxoSmithKline, Ferring, Watson, AstraZeneca, Sanofi-Aventis, VIVUS, Cougar Biotechnology, *Reviews in Urology* and the France Foundation, GE Healthcare, EDAP, Photocure, Dendreon, Antigenics and the Prostate Conditions Education Council.

¶ Financial interest and/or other relationship with GlaxoSmithKline, GP Pharm, and Merck Sharp and Dohme (MSD).

** Financial interest and/or other relationship with Bayer-Schering, GlaxoSmithKline, Pierre Fabre Medicament and Recordati.

†† Financial interest and/or other relationship with GlaxoSmithKline, Ferring Pharmaceuticals and AstraZeneca.

‡‡ Financial interest and/or other relationship with GlaxoSmithKline, Orion Pharma and Ferring Pharmaceuticals.

§§ Financial interest and/or other relationship with GlaxoSmithKline and Pfizer.

‖‖ Financial interest and/or other relationship with GlaxoSmithKline.

Serum PSA remains the most widely validated marker of prostate cancer risk.[1] Widespread implementation of PSA screening has led to the diagnosis of many low volume, low grade cancers that are less likely to cause harm had they not been diagnosed.[2] The primary observation of the REDUCE study was that treatment with the dual 5ARI dutasteride resulted in a 23% relative risk reduction in biopsy detectable prostate cancer in men with an increased PSA (2.5 ng/ml or greater) and negative prostate biopsy before study entry.[3] In the REDUCE study PSA driven unscheduled (for-cause) biopsies were uncommon, allowing for an unbiased assessment of the usefulness of serum PSA measurements for the diagnosis of prostate cancer. Dutasteride may enhance the usefulness of PSA for the diagnosis of clinically significant prostate cancer by suppressing PSA synthesis from benign prostate tissue and cancer in which growth is controlled by dutasteride, allowing subsequent PSA changes to better reflect the biology of dutasteride resistant cancer. Conversely, it has been argued that 5ARIs may mask the diagnosis of prostate cancer by suppressing PSA synthesis.[4] These analyses from the REDUCE study were designed to address both hypotheses.

MATERIALS AND METHODS

Study Population

The design of the REDUCE study has been reported.[5] Eligible men were 50 to 75 years old with a serum PSA of 2.5 to 10 ng/ml if 50 to 60 years old, or 3 to 10 ng/ml if older than 60 years, and a single, negative prostate biopsy (6 to 12 cores) within 6 months before enrollment (independent of the study).

Study Design

The REDUCE study was a 4-year, multicenter, double-blind, placebo controlled study.[5] Eligible subjects were randomized to 0.5 mg dutasteride daily or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc.) was assessed every 6 months, with doubled PSA values ($\pm$0.1 ng/ml in half of the subjects) reported to investigators for men receiving dutasteride.[5] Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent 10-core transrectal ultrasound guided biopsy at 2 and 4 years (protocol dependent biopsies), and unscheduled biopsies were performed if clinically indicated (protocol independent biopsies). For-cause biopsies obtained during months 19 to 24 and 43 to 48 replaced those scheduled for years 2 and 4, and were included in the definition of protocol dependent biopsies.

Statistical Analyses

Analyses were conducted of men who had undergone at least 1 biopsy (biopsied population). To compare various PSA constructs to predict prostate cancer, AUC values from ROC curves were calculated for baseline PSA, final PSA and change in PSA from month 6 to final PSA (by treatment group). Final PSA was defined as the last PSA value recorded before prostate cancer diagnosis and for men without prostate cancer it was the last PSA value before the final cancer assessment biopsy. PSA measurements made on the same date as the biopsy (or up to 42 days afterward) were excluded from analysis. Actual PSA values for dutasteride and placebo were used in this analysis.

The value of PSA and PSA dynamics during the first 2 years were examined. However, 68.6% (4,044 of 5,899) of month 24 PSA measurements were done on the day or after the date of biopsy and, thus, were excluded from study. Month 6 PSA was defined as the nadir for the purposes of these analyses. Differences between AUC values were examined using the z-test. Sensitivity, specificity, PPV and NPV for prostate cancer detection were analyzed by treatment group, by threshold values for final PSA and by absolute change in PSA from month 6 to final PSA.

RESULTS

Study Population and Baseline Characteristics

Demographics of the biopsied population in this study are similar to those of the overall REDUCE study population.[3] Of 8,122 men in the efficacy population 3,305 (81.6%) in the dutasteride group and 3,424 (84.1%) in the placebo group underwent at least 1 prostate biopsy during the study ($p = 0.004$). For the biopsied population prostate cancer was detected in 659 men (19.9%) in the dutasteride group and 858 (25.1%) in the placebo group ($p < 0.0001$). Gleason 7–10 cancer was detected in 220 men (6.7%) in the dutasteride group and 233 (6.8%) in the placebo group ($p = 0.81$). Most prostate cancer was diagnosed from protocol dependent biopsies, with 41