Consequences of Switching 5α-Reductase Inhibitors on Prostate Specific Antigen Velocity

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Abbreviations and Acronyms

5AR = 5α-reductase
5ARI = 5AR inhibitor
BPH = benign prostatic hyperplasia
CaP = prostate cancer
DHT = dihydrotestosterone
EDW = Enterprise Data Warehouse
LUTS = lower urinary tract symptoms
PSA = prostate specific antigen
PSA_1 = PSA measurement 1
PSA_2 = PSA measurement 2
PSA_3 = PSA measurement 3
PSA_4 = PSA measurement 4
PSAV = PSA velocity

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Purpose: The 5α-reductase inhibitors improve urinary symptoms related to benign prostatic hyperplasia, deter benign prostatic hyperplasia progression and provide prostate cancer chemoprevention. Currently there are a number of 5α-reductase inhibitor formularies, including Proscar®, generic finasteride and dutasteride. While all formularies decrease serum prostate specific antigen (a proxy for prostate volume), they may not accomplish this to the same degree, which may have dramatic effects on prostate specific antigen kinetics in men changing 5α-reductase inhibitor formularies. We examined prostate specific antigen velocity after changes in 5α-reductase inhibitor formularies.

Materials and Methods: We identified patients treated with 2 or more 5α-reductase inhibitor formularies who had sufficient prostate specific antigen values to calculate prostate specific antigen velocity during each 5α-reductase inhibitor treatment. Patient data were grouped depending on the formularies received. Statistical analysis was done to compare prostate specific antigen velocity at various time points while on different 5α-reductase inhibitors.

Results: Eight men changed from dutasteride to generic finasteride (group 1), 21 changed from dutasteride to Proscar (group 2), 49 changed from Proscar to dutasteride (group 3) and 77 changed from Proscar to generic finasteride (group 4). We noted a significant increase in prostate specific antigen velocity in groups 1 and 2 ($p < 0.05$), and 4 ($p < 0.005$). The increase was greater than 0.35 ng/ml per year, the common cutoff for prostate biopsy recommendations, in more than a third of patients.

Conclusions: Results confirm that changing 5α-reductase inhibitors drugs can be associated with a clinically significant change in prostate specific antigen velocity. These prostate specific antigen velocity changes could place patients at risk for unnecessary prostate biopsy. Additional prospective studies are warranted.

Key Words: prostate; prostate-specific antigen; finasteride; dutasteride; drugs, generic

Dihydrotestosterone, formed from testosterone by 2 5AR isoenzymes (types 1 and 2), is critical for prostate gland development, growth and maintenance.[1–3] DHT is also associated with BPH and CaP.[4,5] The 5ARIs finasteride (Proscar) and dutasteride (Avodart®) are currently used for benign prostatic pathology. Finasteride is selective for the type 2 isoenzyme and dutasteride inhibits types 1 and 2.[6]

LUTS secondary to BPH are common in aging men. With time progressive LUTS can significantly impair patient quality of life, and lead to urinary retention and BPH related surgery.[7] The Medical Therapy of Prostatic Symptoms trial and the

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Combination of Avodart® and Tamsulosin in Combination study showed that combination therapy with a 5ARI and an α-adrenergic antagonist decreases the BPH progression rate and improves LUTS.[8,9] It was recently noted that 5ARI is also useful for CaP chemoprevention.[10,11]

Proscar and Avodart are the available 5ARI brand name medications currently approved in men with an enlarged prostate. However, generic substitutes are the most rapidly growing prescriptions in the United States.[12,13] Generics are thought to have the same efficacy as brand medications but their regulatory approval is less stringent and may be associated with unrecognized physiological or biochemical changes. For example, while generics must contain the same active medication(s) as their branded counterparts, inactive ingredients such as preservatives or binders may be substituted.[14,15] The efficacy of 5ARI generic formularies was recently brought into question. For example, recent analysis of a relatively small population of patients with BPH revealed differences in outcomes between generic and branded finasteride.[16]

DHT production is inhibited by 5ARIs, which directly impacts prostate growth, size and decrease in PSA, a proxy for prostate volume.[17] Based on formulary and different affinities for the 5AR isoenzyme subtypes different 5ARIs may be associated with different PSA decreases. Any differences in the ability to decrease serum PSA could have meaningful consequences on PSA kinetics, which is particularly relevant in an era when PSA and PSAV continue to be used as CaP screening tools.[18] However, to our knowledge the extent to which different 5ARI formularies influence PSA has yet to be determined. Thus, we evaluated whether switching between different 5ARI formularies is associated with PSAV alterations.

METHODS

Northwestern EDW, a large institutional review board approved database, contains clinical information on patients treated at Northwestern Memorial Hospital and Faculty Foundation between January 2002 and August 2009. This database was used to identify patients with BPH who were treated with 2 or more 5ARI formularies. Baseline information was obtained on all patients, including the American Urological Association symptom index and quality of life scores. The start and stop dates of all BPH medications were also recorded, including 5ARIs, α-adrenergic antagonists, anticholinergics and phosphodiesterase inhibitors. All men were on α-adrenergic antagonists. We recorded 5ARIs as Proscar, generic finasteride and Avodart. Proscar prescriptions in the database before June 19, 2006 were classified as Proscar or finasteride since Proscar was still under patent and generic finasteride was not available. After this date they were classified separately as generic finasteride or Proscar.

Included patients were categorized into group 1—men started on dutasteride and changed to generic finasteride, group 2—men started on dutasteride and changed to Proscar, group 3—men started on Proscar and changed to dutasteride and group 4—men started on Proscar and changed to finasteride. Since this study was retrospective, telephone contact was made with a representative sample of 20% of the included population to verify that current prescriptions in hand matched data recorded in EDW.

Additional inclusion requirements were 2 or more serum PSA values (PSA_1 to PSA_4) recorded during each drug treatment (fig. 1). All included men were also treated with a 5ARI for at least 90 days before the first included PSA value (fig. 1). We excluded patients who were given only 1 5ARI formulary, underwent urological surgery during the treatment period, were diagnosed with CaP or had an insufficient number of PSA values to calculate PSAV.

PSAV was calculated by linear regression analysis, as previously described.[19] Three PSAV values were determined per patient, including 1) PSAVa—during the initial 5ARI treatment formulary, 2) PSAVb—during the change from the first to the second 5ARI and 3) PSAVc—during

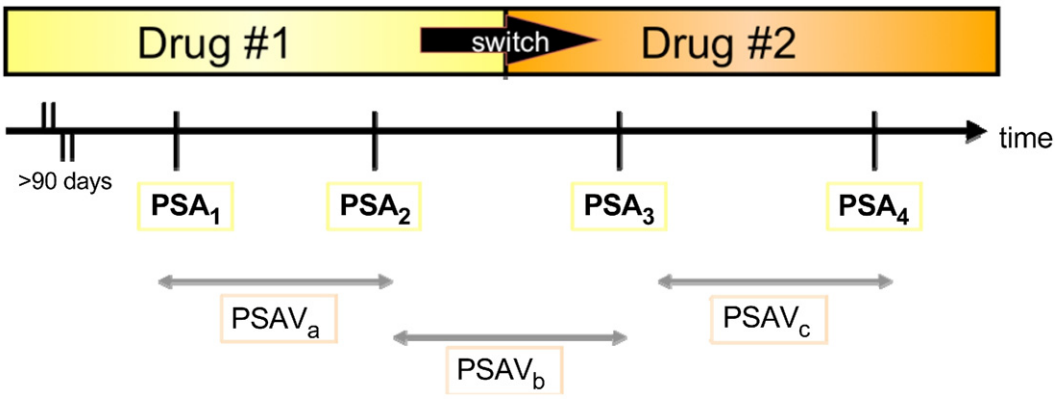

Figure 1. Monitoring PSA and PSAV during different 5ARI formularies. Patients were maintained on 5ARI (*Drug #1*) for at least 90 days. All had enough serum PSA values (PSA_1 and PSA_2) to calculate PSAVa. Patients were changed to another 5ARI (*Drug #2*) and all subsequently had enough serum PSA values (PSA_3 and PSA_4) to calculate PSAVc. PSAVb was calculated during switch period from drugs 1 to 2.