Prostate Disease:
A Primary Care Perspective

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Many important prostate cancer studies in areas of prevention, screening and treatment have recently been reported and add greatly to our understanding of the disease. Many of these involve 5α-reductase inhibitors (5-ARIs) that have long been used in the medical therapy of benign prostatic hyperplasia (BPH).

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The development of BPH is an androgen dependent process mediated by the enzymatic conversion of testosterone to dihydrotestosterone (DHT) by 5 α-reductase (5-AR).[1] Two known isozymes of 5-AR exist-type 1 and type 2. Currently finasteride, a competitive type 2 5-ARI (most commonly found in prostate) and dutasteride, a dual inhibitor of both type 1 and type 2 5-AR, are the standard agents used for androgen suppression and cytoreduction in BPH treatment. By additionally inhibiting the type 1 5-AR isozymes, found in the skin and liver, dutasteride has a greater impact on inhibiting serum DHT levels.[2] Type 1 is also more commonly found in prostate cancer tissue rather than BPH raising the possibility of chemoprevention and treatment strategies with dutasteride.

Data from the Medical Therapy of Prostatic Symptoms (MTOPS)[3] study reveals that combination therapy with doxazosin and finasteride is significantly more effective than either monotherapy or placebo for BPH. After four years of follow-up, there was a 66% reduction in the risk of clinical BPH progression, 81% reduction in the risk of acute urinary retention and 67% reduction in the need for BPH-related surgery compared with placebo. The therapeutic benefit of combination therapy was more pronounced in patients with larger prostates, including volumes ranging from 25 ml to 40 ml and > 40 ml.[3]

Similarly, data from the combination of Avodart® and Tamsulosin (CombAt) study, where the patients were at higher risk of clinical progression given larger mean prostate volume and higher mean PSA showed that combination therapy with dutasteride and tamsulosin resulted in significantly greater improvements in International Prostate Symptom Score (IPSS) and flow rates than either monotherapy at two years.[4]

Prostate cancer is the most common non-cutaneous cancer in men and conventional treatment options are associated with high morbidity and loss of quality of life. The negative

effects of treatment, elderly onset and high prevalence make prostate cancer a well-suited candidate for prevention strategies. Recent data from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) failed to yield any prevention of prostate cancer in subjects taking either supplement alone or in combination after an average of five years.[5] The focus on chemoprevention has thus shifted to 5-ARIs in light of data from the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. The PCPT revealed a 24.8% reduction in biopsy detected prostate cancer prevalence after a seven year period in the group receiving daily finasteride (18.4% prevalence) compared to placebo (24.4% prevalence).[6]

Similarly, the results from the REDUCE trial, which recruited men at higher risk for prostate cancer than the PCPT, showed that there was a 23% risk reduction in biopsy detected prostate cancer over four years for the daily dutasteride group compared with placebo.[7]

Furthermore, in the important subgroup of high-risk patients with family history, the risk reduction was 32%. Both 5-ARIs were well tolerated and also had a beneficial effect on lower urinary tract symptoms. The REDUCE trial did not show any increase in high-risk cancer unlike the artifactual result seen in the PCPT.

Two recent, randomized trials have looked at the effect of prostate cancer screening on mortality. The Prostate, Lung, Colon and Ovary (PLCO) trial found no difference in prostate cancer mortality at seven to 10 years of follow-up between the screened and non-screened group.[8] These results may be skewed because of the substantial screening in the control group, leaving an effective window of screening of only 33% (85% screened in the screening group and 52% screened in the control group).

The European Randomized Study of Screening for Prostate Cancer (ERSPC) did demonstrate a 20% relative reduction in prostate cancer mortality in the screened group at nine years.[9] However, data from the ERSPC revealed that 1,410 men would need to be screened and 48 men treated for prevention of one prostate cancer death over 10 years.

Given this data, it is clear that early detection of prostate cancer should be performed in a shared decision-making process with patients and a discussion regarding pros and cons should be undertaken before PSA testing occurs, as it is not possible to conclude that screening is associated with more benefit than harm at this time.[10] Furthermore, given the lack of benefit seen with screening and early diagnosis and the significant risk of overtreatment and resultant morbidity/mortality, preventative strategies with 5-ARIs seem especially appealing in light of the REDUCE trial results.

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