Re: Effect of Dutasteride on the Risk of Prostate Cancer

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Expert’s summary:
In this 4-yr, multicenter, randomized, double-blind, placebo-controlled study (REDUCE), the authors compared dutasteride 0.5 mg daily to determine the risk reduction of biopsy-detectable prostate cancer (PCa). Eligible men were 50–75 yr old, had a PSA between 2.5 and 10 ng/ml, and had one negative prostate biopsy (6–12 cores) within 6 mo before inclusion. Subjects underwent a 10-core transrectal biopsy at 2 yr and 4 yr. Dutasteride resulted in an absolute risk reduction of 5.1% and a 23% relative risk reduction with no increased risk for high-grade tumors. Men on dutasteride had a 77% risk reduction for acute urinary retention and a 73% risk reduction for benign prostatic hyperplasia (BPH)-related surgery but had higher rates for erectile dysfunction (3.3%), decreased libido (1.7%), and loss of libido (0.6%) and compared to placebo.

Expert’s comments:
For a variety of reasons, PCa is the ideal target for chemoprevention/risk reduction. The pivotal role of dihydrotestosterone (DHT) for prostate cancer development renders 5α-reductase inhibition a rational approach in this respect. Although the overall risk reduction (23%) was similar to results from the Prostate Cancer Prevention Trial (PCPT; 25%), there are a number of differences between these two important trials [1]: (1) Dutasteride inhibits both 5α-reductase isoenzymes (types 1 and 2), and type 1 expression is increased during PCa development [2]; (2) REDUCE recruited men at increased risk for PCa (PSA 2.5–10.0 ng/ml), and all men had a negative biopsy at baseline; (3) REDUCE showed no increased risk for high-grade cancers; (4) REDUCE had a shorter study period (4 yr); and (5) REDUCE was international versus PCPT, which was in the United States only.

The REDUCE data are important, new, and of clinical relevance. One major criticism of REDUCE and PCPT is the fact that an impact on disease progression or PCa mortality is not proven. Given the fact that the majority of avoided cancers had Gleason scores <7, it is unlikely that this approach has an effect on disease progression or even on mortality [3]. However, even if more aggressive cancers (Gleason score ≥7) were only marginally affected by dutasteride, a 25% risk reduction of predominantly low-grade cancers means a 25% reduction of the psychological burden of a cancer diagnosis. Virtually all men with a PCa diagnosis in this age group, including those with lower Gleason scores, receive active treatment (usually radical prostatectomy or some form of radiotherapy) with substantial treatment-related morbidity. Therefore, in my mind, a 25% risk reduction is a clinically relevant end point [4].

Should we adopt this approach and offer dutasteride to all men aged 50–70 yr? Clearly, the answer is no, as elegantly pointed out by Clarke at the 2010 European Association of Urology meeting [5]: The costs involved, the induced morbidity (sexual side effects) on a population-based scale, and the lack of effect on PCa mortality prohibits this approach. Yet, in a well-defined, high-risk population (as recruited for REDUCE: PSA 2.5–10 ng/ml), this possibility needs to be carefully discussed. The positive effects of dutasteride on various BPH parameters (eg, need for surgery, acute urinary retention) are additional arguments because this cohort is also at an increased risk for BPH disease progression (mean prostate volume in the REDUCE population was 46 ml). The downside is sexual side effects that usually appear in the first months of the treatment and decrease with prolonged use of dutasteride.

PCPT and REDUCE, with more than 26 000 men included for placebo-controlled trials, provide level 1 evidence that 5α-reductase inhibitors are capable of reducing the risk of PCa by about 25%. Although this approach is not justified on a population-based scale, it seems appropriate to carefully discuss PCa risk reduction with men at increased risk, including those with a positive family history.

Conflicts of interest: The author is a member of the European GlaxoSmithKline (GSK) advisory board and has received lecture fees from GSK.

References

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