Re: Dutasteride in Localised Prostate Cancer Management: The REDEEM Randomised, Double-Blind, Placebo-Controlled Trial

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Background: We aimed to investigate the safety and efficacy of dutasteride, a 5α-reductase inhibitor, on prostate cancer progression in men with low-risk disease who chose to be followed up with active surveillance. Methods: In our 3 year, randomised, double-blind, placebo-controlled study, undertaken at 65 academic medical centres or outpatient clinics in North America, we enrolled men aged 48–82 years who had low-volume, Gleason score 5–6 prostate cancer and had chosen to be followed up with active surveillance. We randomly allocated participants in a one-to-one ratio, stratified by site and in block sizes of four, to receive once-daily dutasteride 0·5 mg or matching placebo. Participants were followed up for 3 years, with 12-core prostate biopsy samples obtained after 18 months and 3 years. The primary endpoint was time to prostate cancer progression, defined as the number of days between the start of study treatment and the earlier of either pathological progression (in patients with ≥1 biopsy assessment after baseline) or therapeutic progression (start of medical therapy). This trial is registered with ClinicalTrials.gov, number NCT00363311. Findings: Between Aug 10, 2006, and March 26, 2007, we randomly allocated 302 participants, of whom 289 (96%) had at least one biopsy procedure after baseline and were included in the primary analysis. By 3 years, 54 (38%) of 144 men in the dutasteride group and 70 (48%) of 145 controls had prostate cancer progression (pathological or therapeutic; hazard ratio 0·62, 95% CI 0·43–0·89; p=0·009). Incidence of adverse events was much the same between treatment groups. 35 (24%) men in the dutasteride group and 23 (15%) controls had sexual adverse events or breast enlargement or tenderness. Eight (5%) men in the dutasteride group and seven (5%) controls had cardiovascular adverse events, but there were no prostate cancer-related deaths or instances of metastatic disease. Interpretation: Dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer.

Editorial Comment: This is a 3-year, placebo controlled, randomized trial evaluating the efficacy of dutasteride in delaying progression of disease in men who are on active surveillance. If you only read the abstract, you might agree with the following quote from *The New York Times*: "This study potentially affects 100,000 patients or more annually . . . For those of us who deal with this disease, this is potentially a big deal."[1] Unfortunately like many other articles on 5α-reductase inhibitors (5ARIs), you have to put on your Sherlock Holmes hat if you want to find the truth. At 18 months although there was a modest reduction in pathological progression in patients taking dutasteride (23% versus 35%), by 3 years this difference disappeared. The primary end point included not only a reduction in pathological progression, but also progression to treatment. Although the investigators and patients were blinded to treatment (dutasteride vs placebo), they were provided with actual prostate specific antigen (PSA) concentrations that were not corrected for the effect of the drug. Thus, anyone in his right mind with prostate cancer who saw his PSA fall 50% would be unlikely to seek out treatment. The authors defend this strategy because they believe that it reflects the "real

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world approach to the management of patients." What world do they live in—one without shared decision making and attorneys? Are they really suggesting that physicians should fool themselves or lie to their patients?

I thought everyone knew that the PSA levels should always be corrected for the effect of the drug in patients taking 5ARIs. However, someone I respect recently told me that if he has a patient with a negative biopsy who is worried about his rising PSA, he will start a 5ARI. Before you follow that advice there are several things you should consider. The authors neglected to inform the reader that based on findings from the 2 largest active surveillance programs in North America, PSA kinetics do not reliably predict adverse pathology and should not be used to replace surveillance biopsies for monitoring men on active surveillance.[2–4] So if a patient is worried, he should first be informed of this fact. Second, despite what you have been told, 5ARIs do not improve the detection of high grade disease because they shrink the prostate or improve the performance of PSA. This has been conclusively disproved by the Food and Drug Administration. Finally, the Food and Drug Administration has also shown that 5ARIs increase the risk of the development of high grade disease.[5–7] That is a fact, not an artifact. Think of how you would feel if a patient you placed on a 5ARI developed Gleason 8 to 10 disease while on active surveillance. Even if this were not a concern, it is a costly strategy to use daily dutasteride potentially for many years strictly as an antidote to anxiety.

What should we conclude? Just like the use of 5ARIs for prevention, if one uses them to delay treatment in men on active surveillance, they only work if you lie to the patient about what his PSA really is. In the editorial that accompanied this article Parker concluded that dutasteride cannot be recommended as an adjunct to active surveillance.[8]

Patrick C. Walsh, M.D.

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Re: Effect of Treatment With 5-α Reductase Inhibitors on Progression in Monitored Men with Favourable-Risk Prostate Cancer

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Objective: To determine whether 5-α reductase inhibitor (5-ARI) use delays cancer reclassification in an active surveillance (AS) cohort. Patients and Methods: We performed a retrospective study of 587 men enrolled in an AS programme, who had no history of 5-ARI use. Chi-squared and t-tests were used to compare characteristics of 5-ARI users and non-users. Univariable and multivariable proportional hazards models, treating 5-ARI use as a time-dependent covariate, were used to evaluate the influence of 5-ARIs on the risk of a subsequent biopsy no longer meeting criteria for continued AS (i.e.