

5-ARI use in active surveillance: Different paradigm than primary prevention but caution still needed

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The role of 5-alpha-reductase inhibitors (5-ARIs) in prostate disease continues to be complex. For now, using 5-ARIs broadly for primary prevention of prostate cancer appears inappropriate and this is underscored by the U.S. Food and Drug Administration and Health Canada warnings on finasteride and dutasteride labels of possible association with high-grade prostate cancer.

However, the role of 5-ARIs in patients already diagnosed with prostate cancer remains an open question. Chiang and colleagues explore 5-ARIs in the setting of active surveillance.¹ Other studies have explored prostate-specific antigen (PSA) kinetics around 5-ARIs, but this study is novel in examining the PSA doubling time (PSADT) after the initial decline in PSA induced by 5-ARIs. The authors observed that PSADT accelerated after the PSA nadir compared to the pre-5-ARI PSADT (25.2 vs. 55.8 months); they hypothesized this acceleration reflected true growth of the prostate cancer without confounding of surrounding BPH.

This finding is at first glance counterintuitive, as the authors acknowledge. Evidence suggests 5-ARIs have a suppressive effect on prostate cancer, particularly low-grade prostate cancer. The Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) study, which randomized men on active surveillance to either dutasteride or placebo for 3 years, showed a 38% reduction in the risk of progression driven mostly by a reduction in the rate of progression due to volume of cancer.² There is also evidence 5-ARIs have a suppressive effect in more advanced prostate cancers. Schroder and colleagues randomized men with biochemical recurrence after surgery or radiotherapy to either dutasteride or placebo.³ Time to PSA doubling was significantly reduced in the dutasteride arm by 66%. In the radiotherapy subgroup, a situation that

more approximates the active surveillance setting, where the prostate is still in situ, the time to PSA doubling was more pronounced (relative risk reduction = 74%). Further still, Scholz and colleagues retrospectively examined 60 patients treated with intermittent androgen deprivation therapy (ADT) and finasteride and compared them to 41 patients treated with intermittent ADT alone. Finasteride use was associated with a doubling in time off ADT (31 vs. 15 months).⁴

The authors' findings could simply be a product of small sample size ($n = 29$); however, the findings may not be as counterintuitive as the evidence cited above would suggest. It is possible the natural history of men on active surveillance is for PSADT to accelerate over time regardless of 5-ARI use. Surveillance series have reported PSADT, often at the time of reclassification, but not change in PSADT over long-term follow-up. The time to nadir was not reported in the current study. However, a secondary analysis of the REDUCE trial observed that at 6 months only 13% of patients reached PSA nadir and at 1 year only 30%. It was not until 4 years that 100% of patients reached their nadir. Thus, it is likely the current study may just be comparing early active surveillance PSADT with PSADT years later in the active surveillance journey. We could gain some insight into this PSADT acceleration if the authors reported PSADT in the non-5-ARI group calculated at 2 intervals similar to the 5-ARI group.

It is worrisome that long-term use (i.e., >5 years) of 5-ARIs in patients on active surveillance is poorly characterized. It is possible the PSADT acceleration observed in this study reflects biology and thus represents an acquired resistance to 5-ARI suppression. The long-term implications of this are not yet known. This could lead to earlier resistance to other forms of androgen suppression.

Physicians and patients are understandably trepidatious about using 5-ARIs in primary prevention, as it involves treating healthy men. However, treating men already diagnosed with prostate cancer is a very different paradigm and one we should continue to explore. Studies, like the one presented, are a helpful step in understanding the role of

5-ARIs. Whether the authors' observations reflect biology requires exploring other datasets or pooling datasets to accrue enough men on 5-ARIs with computable pre- and post-nadir PSADT and correlating these with reclassification events and survival outcomes. Until then, the long-term safety of 5-ARI use in men with prostate cancer remains unknown, but the answer is rapidly needed.

Competing interests: Dr. Hamilton declares no competing financial or personal interests.

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