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Statin therapy to improve prostate cancer outcomes: who, when and for how long?

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Mounting epidemiologic data support a role for statins in the prevention of clinically significant prostate cancer, and in improving prostate cancer-specific outcomes. These data, alongside evidence from laboratory studies demonstrating both cholesterol-mediated and non-cholesterol-mediated effects of statins on prostate cancer cells, has produced growing interest in clinical trials for statins in prostate cancer [1].

In this month's issue of European Urology, findings are presented from a double-blind window-of-opportunity trial [2] which randomized 160 statin-naïve men with prostate cancer to atorvastatin or placebo, starting at trial recruitment until radical prostatectomy (median 27 days). The authors hypothesized that statin treatment would slow prostate tumor growth, as assessed by Ki67 proliferation index and PSA level (primary endpoints), and lower histologic prostate inflammation (secondary endpoint). Overall, compliance was high (96%) and the intervention was well tolerated, with four (5%) men in the atorvastatin arm discontinuing due to minor side effects. However, in contrast to the authors' hypothesis, there was no effect of atorvastatin on prostate tumor growth (Ki67 or PSA) or inflammation, relative to placebo. In the purest sense, this was a negative trial. However, like any good study that answers one question, it raises many more. Were appropriate endpoints selected? What is the ideal timing and duration of statin treatment? Ultimately, if statins do have a role in prostate cancer – is it for all men or only some men and if only for some – how can we identify those men?

Despite growing evidence supporting an association between statins and reduced prostate cancer growth and improved outcomes, the optimal timing and duration of statin use has not yet been established. Some, though not all [3], epidemiologic data suggest that longer durations of statin use have stronger associations with prostate cancer outcomes [4], and that beginning statin therapy prior to diagnosis may further maximize the potential benefit [5]. Therefore, is it too much to expect several weeks of statins to affect tumor growth? While an 80 mg/day dose of atorvastatin, as used in this trial, can lower serum low-density lipoprotein (LDL) levels by ~50% within several weeks [6], a potential biologic effect on the prostate may take longer to manifest. Provocatively,

in a post-hoc analysis of data from the present trial, the authors reported that the effect of atorvastatin on reducing Ki67 expression was stronger with longer duration of intervention, which ranged from 4-114 days before radical prostatectomy. This finding was based on 38 men who received an intervention of at least 28 days, where there was a suggestive effect of statin use on reducing Ki67 expression, however even this post-hoc unplanned sub-analysis was not statistically significant (-14% relative to placebo, p=0.056).

In keeping with epidemiologic evidence supporting an association between statins and reduced risk of clinically significant disease, a secondary analysis of data from the current trial showed a significant effect of statin treatment on lowering PSA in high-grade (Gleason sum ≥4+3), but not low-grade tumors (-0.6 ng/ml in the atorvastatin arm vs. placebo; p=0.024). Prostate cancer has long been recognized as a heterogeneous disease, and recent efforts have identified molecular and genetically-distinct subtypes [7]. There is now growing evidence for etiologic heterogeneity across these molecular subtypes, for example, a stronger association between obesity and poor prostate cancer-specific outcomes in *TMPRSS2:ERG* fusion positive cases [8]. While molecular epidemiology studies have not yet fully explored subtype-specific statin effects, it is possible that statins could benefit some tumors but not others. A bioinformatics analysis of publically available gene expression data from almost 5,000 prostate tumors identified three subtypes (PCS1-3) [9], with PCS2 (characterized by ERG pathway activation, among other genomic features) showing increased expression of lipid and steroid synthesis pathways, perhaps suggesting increased reliance on cholesterol and thereby increased sensitivity to cholesterol targeting. Approximately half of all ~5,000

cases were PCS2. As such, if statins affected outcomes for this subtype but not others, grouping all prostate cancer cases together would underestimate the magnitude of a statin effect by 50%, potentially rendering a trial such as the current one null.

Additional laboratory studies are needed to identify potential mechanisms of sensitivity or resistance to statins. For example, the work of our group and others suggests that prostate cancer cells with a downregulated CYP27A1/27-hydroxycholesterol (27HC) signaling axis accumulate excess intracellular cholesterol [10], potentially rendering them less reliant on serum cholesterol and less sensitive to cholesterol-mediated statin effects. We also identified tumor upregulation of the LDL receptor as a potential mechanism of resistance to serum cholesterol-lowering therapy *in vivo* [11]. Upregulation of LDL receptor may enable continued tumor reliance on cholesterol by overcoming sensitivity to serum cholesterol changes. Given that statins predominantly affect *serum* cholesterol, it is possible that they will not be the best drug to target *tumor* cholesterol.

In conclusion, while the findings from this clinical trial are thought provoking, they are ultimately negative. Whether this is because statins have no effect or only affect some tumors, whether the duration of treatment was insufficient, or whether the endpoints failed to capture the effect, is unknown. Before additional trials are attempted, the next steps should be to identify tumor subtypes most sensitive to statins, in addition to identifying the optimal timing and duration of therapeutic intervention. Importantly, since men of African descent bear a disproportionate burden of prostate cancer, and given differences in molecular tumor characteristics relative to Caucasian men [12], future studies should include racially diverse cohorts wherever possible. Finally, caution is

needed given some suggestive evidence that statins may have negative effects on prostate cancer outcomes in certain subgroups of men, such as those with a body mass index >30 kg/m^2 [13], those with normal serum cholesterol or expression of certain tumor biomarkers [14]. However, these suggestions of harmful effects of statins were based on secondary analyses of non-randomized studies, and a more concerted effort using *a priori* hypotheses and careful control for potential confounding factors is required to consider negative and not just positive effects of statins.

In summary, we applaud the efforts by Dr. Murtola and colleagues. However, the negative results of the current trial coupled with well-recognized side effects (new-onset diabetes, rhabdomyolysis) highlights that caution is needed before any off-label use of these drugs is recommended. Based on the current evidence, for men with no other indication for statin use, these drugs should only be given as part of a clinical trial.

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