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Response to "Comments on sirolimus use and risk of cutaneous squamous cell carcinoma (SCC) in solid organ transplant recipients" (SOTRs)

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To the Editor: We thank the authors of the commentary on sirolimus use and risk of cutaneous squamous cell carcinoma (SCC) in solid organ transplant recipients (SOTRs) for raising some important concerns, namely: (1) lack of information on dose, (2) lack of information on other drugs associated with SCC risk (aside from azathioprine), and (3) lack of information on tumor invasiveness and possible incomplete case capture.

We did not include dose as a variable in our models because there was very little variability in dosing regimens in our SOTR cohort. The mean daily dose of sirolimus was between 1.0 and 1.5 mg/d for the majority of our exposed cohort (n = 512, 88.6%), with n = 45 (7.9%) dispensed less than 1 mg/d; and n = 21 (3.6%) dispensed more than 1.5 mg/d. Given this lack of variability, we did not have the ability to draw meaningful conclusions about dose in our analyses.

We agree with the authors that various immunosuppressive regimens and certain drugs used in the immunocompromised population, such as voriconazole, can impact SCC risk. The immunosuppressive regimens initiated in a mixed transplant cohort are often dictated by transplant type. To control for immunosuppressive regimens at a macro level, we accounted for transplant type in our models. In addition, we performed a literature search to examine salient drugs that could impact SCC risk among SOTRs, and azathioprine emerged as the strongest predictor, independent of transplant type. Recently published work in a mixed SOTR cohort has validated azathioprine as the agent most strongly associated with SCC risk, independent of transplant type.[1] We agree and have recently shown that agents, such as voriconazole, are associated with increased SCC risk.[2] However, voriconazole is almost exclusively used among lung transplant recipients, and given that we controlled for transplant type, is unlikely to be a true confounder in our analysis.

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Finally, we agree with the authors that nonbiopsy-proven SCCs treated presumptively with destructive modalities would not have been captured in our outcomes. Presumptive treatment of skin cancers without a definitive biopsy specimen is not within the standard of care for transplant recipients, many of whom die from SCC. For treatment of nonbiopsy-proven SCCs to have confounded the association, it would have to be differentially associated with sirolimus exposure. There is no reason to suspect that those exposed to sirolimus would have differential treatment of their potential skin cancers as compared with unexposed individuals.

Although we agree that the effects of sirolimus have been demonstrated in vitro, the in vivo clinical trial referenced by the authors of the commentary was conducted among those with a history of SCC.[3] Rather than focusing on secondary prevention of SCCs, we focused on primary prevention after transplantation and included all SOTRs, regardless of their SCC history, which may explain the differences in our findings. Trends identified in other skin cancers, such as Kaposi sarcoma,[4,5] cited by the authors, may not apply to SCCs. We thank the authors for raising some important points and allowing us to further clarify our findings.

Disclosure:

Dr Asgari has received grant funding from Pfizer and Valeant Pharmaceuticals; the research topic was not relevant to this work. Ms Arron, Ms Warton, Dr Quesenberry, and Dr Weisshaar have no conflicts of interest to declare.

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