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CORRESPONDENCE

Response to Drs de Grooth and Parienti

To the Editor—We appreciate very much the updated trial-level surrogacy analysis by Drs de Grooth and Parienti and their insightful comments concerning individual- and trial-level surrogacy.

In their letter, Drs de Grooth and Parienti suggested that a direct comparison of their trial-level results with individual-level results from our study over the same time frame (day 5 of follow-up) would be of interest. Unfortunately, a reanalysis in our study of quantitative SARS-CoV-2 RNA levels in anterior nasal swabs at day 5 (rather than day 3) for predicting subsequent hospitalization/death is not possible, as the ACTIV-2 study did not collect swabs at day 5. Of note, however, the beneficial effects of amubarvimab plus romlusevimab (a mAb treatment) vs placebo were evident by day 3 in lowering RNA levels and reducing hospitalization/death [1].

Overall, our results provide strong support of an association between RNA levels and subsequent hospitalization/death in the natural history setting (ie, among placebo recipients) [2]. However, insufficient evidence in our study regarding the predictiveness of RNA levels achieved at 3 days following mAb treatment on subsequent hospitalization/death certainly merits further evaluation in other mAb studies.

In terms of pandemic response, we agree that the meta-regression type of analysis undertaken by Parienti and de Grooth [3] is potentially valuable for (1) underpinning whether a treatment might be active against a new SARS-CoV-2 variant or (2) guiding what candidate treatments to take forward to phase 3 evaluation for a future pandemic. The approach evaluates what we describe in the HIV setting as "concurrent" surrogacy [4, 5] in that many hospitalizations/deaths may occur over the same time frame (eg, 5–7 days) as that when RNA changes are being assessed. Hence, RNA measurements may be influenced by treatments received during any hospitalization prior to measurement and may be missing due to hospitalization or death. There are also statistical complexities in analyzing values below the assay lower limit of quantification [6]. Despite these issues, their meta-regression shows an association across trials between treatment effects (vs control) on risk of hospitalization/death and corresponding effects on changes in quantitative RNA. Another meta-regression analysis available as a medRxiv preprint [7] also shows such an association, including at day 3 as well as day 5, in a different but overlapping set of trials. The ability to show associations was undoubtedly helped by the substantial effect of some treatments (ie, observed reductions in risk of hospitalization/death of ≥70%). These various issues highlight the need in any future pandemic to plan to (1) comprehensively identify trials with relevant biomarker and clinical outcome data that should be included in surrogacy analyses (recognizing that there might be quicker publication of trials with positive vs negative results) and (2) access participant-level data to standardize outcome definitions and statistical analysis methods. Addressing these needs will be especially important in the setting of treatments that are less effective than those achieved against SARS-CoV-2.

Notes

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