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LETTER

A Response to: Letter to the Editor Regarding Combination of Tocilizumab and Steroids to Improve Mortality in Patients with Severe COVID-19 Infection: A Spanish, Multicenter, Cohort

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DIGITAL FEATURES

To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14308061.

Dear Editor,

We appreciate the interest in our manuscript [1], and thank Dr. Janapala et al. [2] for the letter, and the Editor for giving us the opportunity to respond.

In response to Dr. Janapala, we would like to note that we are fully aware of the limitations of retrospective observational studies and the risk of bias derived from diverse factors, but mainly from differences in baseline characteristics between groups. Nevertheless, there are different strategies that can be implemented to minimize these limitations and increase the robustness of the conclusions reached. In our study [1], specifically to avoid bias derived from differences between groups and account for potential confounders, we have used a well-established and scientifically sound methodology, the inverse probability of the treatment weights (IPTW) technique. The details, and some key scientific references on which these methods rely on, are provided in our manuscript. The IPTW technique generates a pseudo-population in which the two groups are balanced across baseline covariates. Any reader can therefore check the baseline comparability in Table 1 of our manuscript, and confirm that all variables achieved a $< |11\%|$ standardized difference (STD), except for the interleukin-6 (IL-6). The latter remained unbalanced since the amount of missingness did not allow us to compensate for that observed. The IPTW analysis for assessment of the study outcomes has been based on this well-balanced population.

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Dr. Janapala et al. might have misunderstood the methodology, focusing on the raw data instead of the IPTW analysis for assessing baseline comparability. Also, by no means have we substantiated the baseline comparability on a hypothetical lack of statistical significance but on small STD. Please note that, in fact, no *p* values have been provided for the IPTW baseline comparability.

With regard to the time from the onset of symptoms of COVID-19 to the inclusion of patients in the study (day 0 for the control group), it is noted that, as a matter of fact, the mean (SD) results are also provided in Table 1, and for the IPTW analysis were 10.41 (4.71) and 10.12 (5.42) for the tocilizumab and the control group, respectively. The median [25th–75th percentiles] were not reported in the manuscript but they were also similar: 10 [7–13] and 9 [6–13] for tocilizumab and the control group, respectively. Notably, the STD were − 0.2%, which may be considered very small on the STD scale, thus ruling out any potential impact of this variable on the study outcomes.

Finally, concerning the use of medicinal drugs other than the study treatment of interest (tocilizumab), we would like to point out that all these treatments were used in the context of clinical practice, and all of them were used concomitantly with tocilizumab (and not instead of). At the time of the analysis of our study, continuous evidence became available regarding the lack of efficacy of hydroxychloroquine, azithromycin, and lopinavir/ritonavir in the treatment of COVID-19, so it was not considered appropriate to carry out a subgroup analysis to account for the potential influence of these drugs, as they had already proved to be ineffective.

Additionally, the hypothesis of our study was to evaluate the efficacy of tocilizumab as anti-inflammatory and immunomodulatory therapy in patients with COVID-19 who are purportedly in the inflammatory phase of the disease, where steroids would have a similar and potentially synergic role. This, together with the positive results that had been reported for steroids, led us to consider it appropriate to analyze the effect of combined use of steroids plus tocilizumab therapy.

In conclusion, in spite of the fact that our study is an observational one and, as such, has the inherent limitations thereof, our findings raised the need to conduct appropriate randomized clinical studies to confirm results. We are pleased to see that consistent benefits have been shown in several published randomized controlled studies, e.g., the RECOVERY trial [3], which has recently demonstrated that tocilizumab is an effective treatment for hospitalized patients with COVID-19 who have hypoxia and evidence of inflammation, where the benefits of tocilizumab were clearly seen among those also receiving treatment with a systemic corticosteroid.

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Disclosures. Belén Ruiz-Antorán, Aránzazu Sancho López, Ferrán Torres and Ana Fernández-Cruz have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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