The misleading "pooled effect estimate" of crude data from observational studies at critical risk of bias: the case of tocilizumab in coronavirus disease 2019 (COVID-19) reply
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Citation

Version: Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).
Tleyjeh expressed concerns regarding a possible effect of “immortal time bias” on the pooled estimate. We agree that “immortal time bias” is an important potential source of bias. Therefore, we re-evaluated the included papers for differences in duration of symptoms or start of mechanical ventilation [5] between the TCZ and control group. This difference could serve as a landmark [8]. Patients in the control group who died before the landmark, as is visible in the Kaplan-Meier and other figures, were excluded from the analysis. Comparing the results from the landmark method with the non-landmark method on the same set of studies [3–5, 9] gave similar results and did not change the conclusion: a pooled RR of .12 (95% CI, .05–.27) for the landmark method and a pooled RR of .094 (95% CI, .03–.31) for the non-landmark method. Although there are apparent limitations to this method, it does provide some insight regarding this bias.

For our rapid review of the analyses are based on the literature until the end of June 2020 and indicated that patients with coronavirus disease 2019 (COVID-19) may benefit from TCZ treatment based on observational studies and that this effect appears to be modified by co-medication. Acknowledging the limitations of observational studies, as we did in our paper, the published results of randomized controlled trials are awaited to provide more definitive answers as to whether or not TCZ could benefit patients with COVID-19.

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases • 2021;72(12):e1154–5 © The Authors 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/ciaa1735

Reply to Tleyjeh

To the Editor—We thank Professor Tleyjeh for his letter [1] and we appreciate the opportunity to address the concerns that may have risen regarding our paper [2].

Tleyjeh expressed concerns regarding the use of unadjusted data in the meta-analysis. We discussed this issue in our paper and also provided the individual adjusted estimates of the studies that reported them. All these adjusted estimates confirmed the lower mortality for the Tocilizumab (TCZ) group: hazard ratio, 0.035 [3]; hazard ratio, 0.38 [4]; hazard ratio, 0.58 [5]; and odds ratio, 0.78 [6]. The pooled estimate of these adjusted analyses is .39 (95% confidence interval [CI] .21–.76), which is similar to the pooled estimate of crude data and does not change the conclusion: Risk Ratio (RR), .27 (95% CI, .12–.59).

Tleyjeh expressed concerns regarding inclusion of studies in the meta-analysis that, in his view, are at critical risk of bias. Indeed, we did not exclude studies based on risk-of-bias assessment. This approach allowed us to explore the impact of risk of bias on the results in sensitivity analyses and also gave us sufficient studies to explore other possible sources of heterogeneity (eg, co-medication). As indicated in our paper, the results remained the same when restricted to studies with the highest quality. Similarly, when we re-did the analysis for the studies Tleyjeh indicated to be of moderate risk of bias [4–6], the pooled RR is .25 (95% CI, .063–1.02), which is very similar to the RR of .27 (95% CI, .12–.59) of the full analysis. It should also be mentioned that the reliability is low for such risk-of-bias assessment tools, so different reviewers may classify studies differently, which could be problematic when studies are excluded based on their presumed risk of bias [7].
Impact of Tocilizumab on the Mortality of Patients With Coronavirus Disease 2019

To the Editor—We read with great interest the meta-analysis by Malgie et al [1] who showed that mortality was 12% lower for coronavirus disease 2019 (COVID-19) patients treated with tocilizumab compared with COVID-19 patients who were not treated with tocilizumab. Although this is an encouraging finding during the COVID-19 pandemic, this finding was based on a meta-analysis of observational studies and requires additional confirmation by randomized, controlled trials (RCTs). Recently, several RCTs [2–4] that investigated the usefulness of tocilizumab for severe COVID-19 patients have been published. However, the findings of these studies seem controversial [5]. Stone et al’s study showed tocilizumab was not effective in preventing death in moderately ill hospitalized patients with COVID-19 [2], while Hermine et al found that tocilizumab may reduce death by day 14 but not mortality by day 28 [3]. Therefore, we did a meta-analysis of these RCTs to provide updated data and clarify one critical issue, that is, the impact of tocilizumab on the mortality of severe COVID-19 patients.

RCTs that compared the clinical efficacy of tocilizumab and other alternative agents or placebo in the treatment of COVID-19 patients were identified through a systematic search of PubMed through 22 October 2020. The results of 28- or 30-day mortality were extracted for the analysis of primary outcome. In addition, data regarding the risk of adverse events (AEs), particularly serious infection, were collected in order to evaluate this secondary outcome. All statistical analyses were performed using Review Manager version 5.3.

Overall, 5 RCTs [2–4, 6, 7] fulfilled the inclusion criteria and were included in this meta-analysis. A total of 1310 patients were enrolled in this study, including 827 and 483 patients who received tocilizumab and a comparator, respectively. The 28- or 30-day mortality among tocilizumab was 11.97% (n = 99), which was similar to that for the control group (10.35%, n = 50). No significant difference was found between these 2 groups in the pooled analysis of 5 RCTs [2–4, 6, 7] (odds ratio [OR], 1.10; 95% confidence interval [CI], .76–1.60; I² = 0; Figure 1). In addition, there was no significant difference between tocilizumab and comparator in terms of serious AEs in the pooled analysis of 3 RCTs [2–4] (OR, 0.83; 95% CI, .50–1.38; I² = 0). Furthermore, the tocilizumab group was associated with a lower rate of serious infection compared with the control group (OR, 0.57; 95% CI, .36–.89; I² = 21) in the pooled analysis of 5 RCTs [2–4, 6, 7].

In contrast to Malgie et al’s finding [1], we did not find the additional mortality benefit of tocilizumab for COVID-19 patients. Our findings are supported by stronger evidence than that from previous meta-analyses [1, 8] for the following reasons. First, our findings were based on the meta-analysis of RCTs with low heterogeneity. Second, in the leave-one-out sensitivity analysis, no single study had a substantial influence on the mortality analysis. Therefore, without additional data from ongoing RCTs, our findings indicated that the impact of tocilizumab on the mortality of COVID-19 patients was minimal.

Regarding another concern of risk of tocilizumab-associated infection, our finding was consistent with Malgie et al’s finding [1]. The risk of serious infection in the tocilizumab group was similar to the risk in the control group. In addition, no significant difference regarding the risk of serious AEs was observed between the tocilizumab and control groups. Thus, this should suggest that tocilizumab would be a safe agent in the treatment of COVID-19 patients.

In conclusion, tocilizumab does not provide mortality benefit for severe COVID-19 patients, but it is as tolerable as other comparators. Additional recommendations for use of tocilizumab for COVID-19 patients should be made after additional evidence is gained from ongoing RCTs.

Note
Potential conflicts of interest. All authors: No reported conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.