Response to 'Neither earlier not late tocilizumab improved outcomes in the intensive care unit patients with COVID-19 in a retrospective cohort study' by Moiseev et al

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We read with interest the letter from Moiseev *et al*[1] on our COVID High-intensity Immunosuppression in Cytokine storm syndrome study.[2] In our study, we have used an immunosuppressive strategy composed by glucocorticoids in the first line, followed, in case of insufficient response, by tocilizumab in patients with COVID-19-associated cytokine storm syndrome (CSS). Moiseev *et al* share with us the results of their study in which they have treated patients with COVID-19 with tocilizumab. In a retrospective study, the authors compared the outcomes of patients treated with tocilizumab with those of patients not treated with it. Patients could receive tocilizumab in the presence of bilateral pneumonia involving at least 50% of lung tissue and requiring respiratory support, particularly if associated with an increased C-reactive protein, but the final treatment decision was at the discretion of the treating clinician. No difference was seen in the in-hospital mortality between patients treated with tocilizumab and those not treated. We agree with the authors that their results, at first sight, do not seem promising for tocilizumab in COVID-19, but it is too early to draw definite conclusions. Moiseev's retrospective study will likely suffer from bias by indication: it was a physician, not a trial protocol or treatment protocol, who decided patients being candidates for tocilizumab, and undoubtedly, the physicians prioritised the more severe patients, while the less severe ones did not receive tocilizumab (TCZ) but had an inherently lower risk to die. Further, differences in other risk factors for mortality (eg, diabetes and coronary artery disease) between the treated and non-treated, although not statistically significant, preclude a fair judgement.

We truly think we need more data to better understand the potential role of tocilizumab in the treatment of COVID-19, particularly of COVID-19-associated CSS. As mentioned by Moiseev *et al*, the COVACTA trial was a negative trial with tocilizumab, but all patients with COVID-19 were treated, without a selection based on patients with the most severe COVID-19 (namely those with CSS).[3] It remains enigmatic whether such a selection would have led to different results. The CORIMUNO-TOCI French study reported positive results, still only in the form of a press release and we anxiously await the study publication.[4] Recently, the press release of another trial with tocilizumab, the EMPACTA trial, reported meeting its primary endpoint, showing that patients with tocilizumab plus standard care were 44% less likely to progress to mechanical ventilation or death compared with patients who received placebo plus standard of care (HR 0.56; 95% CI 0.32–0.97).[5] All in all, there are contradictory results and more clarity is needed about the role of tocilizumab in COVID-19, particularly in COVID-19-associated CSS.

REFERENCES

1 Moiseev S, Avdeev S, Karovaikina E. Neither earlier nor late tocilizumab improved outcomes in the intensive care unit patients with COVID-19 in a retrospective cohort study. *Ann Rheum Dis* 2023;82:e3.
2 Ramiro S, Mostard RLM, Magro-Checa C, *et al*. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the chiC study. *Ann Rheum Dis* 2020;79:1143–51.
3 Press release COVACTA study. Available: https://www.roche.com/investors/updates/inv-update-2020-07-29.htm [Accessed 15 Oct 2020].
4 Press release CORIMUNO-TOCI study. Available: https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19 [Accessed 15 Oct 2020].
5 Press release EMPACTA trial. Available: https://www.roche.com/investors/updates/inv-update-2020-09-18.htm [Accessed 15 Oct 2020].