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Tocilizumab for severe COVID-19 pneumonia - Authors' reply 2

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Dr Jain et al underline that TESEO cohort found no difference in efficacy of subcutaneous (SC) tocilizumab (TCZ) formulation, in comparison to intravenous (IV) route and advocate for its use due to an approximatively 6-fold cost reduction. However, we argue that IV administration has other advantages, i.e. the pharmacokinetic profile that is more linear and predictable, while proteolytic degradation of the SC formulation could be variable. Additionally, elevated levels of IL-6 may downregulate the hepatic cytochromes [1]. This may promote enhanced drug exposure as it has been recently postulated for darunavir [2]. Consistently, we believe that prospective pharmacokinetic studies comparing different administration routes are needed to address both appropriate dose-finding and safety. A formal cost-effectiveness analysis should also be considered.

We agree that the optimal time for TCZ administration in COVID-19 is critical. While a beneficial effect of TCZ on mortality was shown in observational studies, a recent randomized trial did not confirm these results. Besides unmeasured confounding, the case-mix of the target population, number of doses, timing of the intervention are other possible reasons for the conflicting results between observational and randomized studies. Assuming that a causal link could be established, the question when is best to start TCZ should be addressed in a randomized study. The emulation of such a trial in the observational setting requires sophisticated methodology beyond those used in our parental paper and a collaborative study with a much larger sample size. A simple correlation analysis is unlikely to produce the answer that we need.

Regarding the need for monitoring patients with severe renal impairment, chronic kidney disease was found in 14 participants at hospital admission and 7 of these (50%) received TCZ. The primary endpoint was observed in 4/7 (57%) in TCZ in addition to standard of care (SoC) and in 3/7 (43%) in SoC group (p=1.0). All but one (who was treated with TCZ) of the 7 participants who experienced the endpoint have died. Therefore, our data, although limited, suggest that TCZ use was not harmful in this subgroup.

To conclude, the challenge of appropriate TCZ use lays on the prediction of the progression of respiratory failure in people who develop a cytokine storm. This is typically accompanied by "respiratory crush" is unlikely to be captured by chest radiology. A recent study demonstrated little benefit with this regard [3]. We can rely on a machine learning algorithms which provides a trustworthy 48 hours prediction of severe respiratory failure, with satisfactory accuracy [4].

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