Tocilizumab in COVID-19: finding the optimal route and dose

Authors' reply

We thank Siddharth Jain and colleagues for their interest in our Article;[1] they underline that in the Tocilizumab in Patients with Severe COVID-19 Pneumonia (TESEO) cohort, there was no difference in efficacy of the subcutaneous tocilizumab formulation compared with the intravenous route, and they advocate for use of the subcutaneous formulation due to an approximately six-times cost reduction. However, we argue that intravenous administration has other advantages—eg, a pharmacokinetic profile that is more linear and predictable compared with the subcutaneous formulation, for which proteolytic degradation can be variable. Additionally, elevated levels of interleukin (IL)-6 might downregulate hepatic cytochromes,[2] which could promote enhanced drug exposure, as has been recently postulated for darunavir.[3] 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 determining the optimal time for tocilizumab administration in patients with COVID-19 is crucial. While a beneficial effect of tocilizumab on mortality has been shown in observational studies, a recent randomised trial (NCT04320615) did not confirm these results. Besides unmeasured confounding, the case mix of the target population, number of doses, and the timing of the intervention are other possible reasons for the conflicting results between observational and randomised studies. Assuming that a causal link could be established, the question of when it is best to start tocilizumab treatment should be addressed in a randomised study. Emulation of such a trial in an observational setting would require sophisticated methodology beyond that used in our study,[1] as well as a collaborative setting 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, in the TESEO cohort, chronic kidney disease was found in 14 participants at hospital admission, seven (50%) of whom received tocilizumab.[1] The primary endpoint of invasive ventilation or death was observed in four (57%) of seven patients in the tocilizumab plus standard care group and in three (43%) of seven patients in the standard care group (p=1·0). Of the seven patients who experienced the endpoint, all but one (who was treated with tocilizumab) have died. Therefore, our data, although limited to few patients, suggest that tocilizumab use was not harmful in this subgroup.

To conclude, the challenge of appropriate tocilizumab use rests on the prediction of progression of respiratory failure in people who develop a cytokine storm. This is typically accompanied by so-called respiratory crush, which is unlikely to be captured by chest radiology. Indeed, a recent study showed little benefit with this regard.[4] To identify these patients, it might be possible to rely on a machine learning algorithm that we recently developed, which provides a trustworthy 48-h prediction of severe respiratory failure, with satisfactory accuracy.[5]

We declare no competing interests.

Giovanni Guaraldi, Jovana Milic, Alessandro Cozzi-Lepri, Federico Pea, Cristina Mussini
giovanni.guaraldi@unimore.it

Department of Infectious Diseases, Azienda Ospedaliero-Universitaria Policlinico of Modena, Modena 41124, Italy (GG, CM); Department of Surgical, Medical, Dental and Morphological Sciences (GG, JM, CM) and Clinical and Experimental Medicine PhD Program (JM) University of Modena and Reggio Emilia, Modena, Italy; Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, London, UK (AC-L); and Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria Della Misericordia, University of Udine, Udine, Italy (FP)

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