Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

dose) versus the intravenous tocilizumab group would be interesting. A potential divergence in these two groups, if identified, could go a long way in optimising the current use of tocilizumab in COVID-19.

Considering the complex, pleiotropic biology of interleukin (IL)-6 and the concomitant cis (anti-inflammatory) and trans (pro-inflammatory) blockade with tocilizumab, timing of initiation of therapy becomes key.[5] Initiation very early in the disease course might blunt protective antiviral responses and cause worsening of disease. A correlation of the composite primary outcome with the time of treatment initiation in the tocilizumab group could thus be attempted to tease out the ideal timing of initiation of therapy.

Since the use of tocilizumab has not yet been studied in patients with severe renal impairment and close monitoring is advised (as per manufacturer instructions), it would be interesting to assess if its use in the seven study patients with chronic renal insufficiency resulted in greater, or unanticipated, adverse events or efficacy. Finally, therapeutic efficacy in severe COVID-19 pneumonia seems incomplete without a discussion of the chest radiology.

We declare no competing interests.

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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.

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