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.

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Serious infection with tofacitinib in patients with rheumatoid arthritis: the importance of context

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We read with interest Ajinkya Pawar and colleagues' Article on the risk of hospital admission for serious infection in patients with rheumatoid arthritis after initiating either tofacitinib or biologic disease-modifying antirheumatic drugs (bDMARDs),[1] and Ennio Giulio Favalli's accompanying Comment.[2] Pawar and colleagues compare tofacitinib with seven bDMARDs in 130 718 patients with rheumatoid arthritis across three US medical insurance databases.[1] We noted several misleading statements that we believe do not reflect all the data and warrant your readers' attention.

Pawar and colleagues state in their summary that their study "found potential differences between tofacitinib and several bDMARDs in the risk of admission to hospital for serious infection".[1] However, significant differences were seen only for tofacitinib versus etanercept. When tofacitinib was compared with other bDMARDs, the incidence of serious infection was similar (adalimumab and certolizumab) or differed numerically but not significantly (abatacept, golimumab, tocilizumab, and infliximab). With the exception of infliximab, the observed differences each favoured the bDMARD in the comparison. These results were not made clear in the summary. The authors mention that, similar to tofacitinib trials, they observed "higher numbers of serious infection events in patients aged 65 years or older enrolled in the Medicare database than in younger patients from commercial databases" but do not explicitly state that this was also true for bDMARDs. Furthermore, incidence of serious infections with tofacitinib was not significantly different to that of bDMARDs in the older population and was significantly higher only when compared with etanercept in younger groups.

Favalli, in his Comment,[2] mentions that data from an ad-hoc analysis of an ongoing Phase 3b/4 trial (NCT02092467; data cut-off: August, 2019; database not locked; data subject to change) show "a significantly higher risk of serious and fatal infections in older patients (>65 years) treated with tofacitinib compared with tumour necrosis factor inhibitors" (TNFi), but we believe the commentary presents insufficient data for contextualisation. The incidence of serious infections was indeed increased in patients aged 65 years or older compared with younger patients, and this increase was greater with tofacitinib than with TNFi—but more so for tofacitinib 10 mg twice per day than for tofacitinib 5 mg twice per day, the widely approved dose.[3] The Comment refers to TNFi, giving the impression of a comparison with a broad group of drugs, yet only etanercept and adalimumab were studied.[3] It is important to assess the risk of serious infections with tofacitinib in the context of additional clinical and real-world data.

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

The Tocilizumab in Patients with Severe COVID-19 Pneumonia (TESEO) study by Giovanni Guaraldi and colleagues[1] provides vital information regarding the benefits of tocilizumab in severe pneumonia due to COVID-19. However, certain aspects of the study warrant deliberation in greater detail.

By contrast with the pharmacokinetic and pharmacodynamic bioequivalence data available from non-COVID settings,[2] use of 324 mg of subcutaneous tocilizumab in patients with COVID-19 was found to be as efficacious as intravenous tocilizumab at a cumulative dose of 16 mg/kg. The difference in the therapy costs resulting from these cumulative doses (and the consumables involved in intravenous administration) could have substantial implications from a pharmacoeconomic point of view. Anecdotal signals of efficacy in COVID-19 have been reported previously with a single 162 mg dose of subcutaneous tocilizumab.[3] Dose optimisation of subcutaneous tocilizumab could thus be explored in future studies, as it has the potential to further reduce the cost of therapy.

Since short-term use of tocilizumab is not bereft of serious adverse events,[4] many of which are dose dependent, a comparative safety analysis of the subcutaneous tocilizumab group (which had a much lower cumulative

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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