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.

Tocilizumab for severe COVID-19 pneumonia

Authors' reply

In the TESEO retrospective observational study, we showed that tocilizumab was able to reduce the need for invasive mechanical ventilation, or death, or both, by 39% and overall mortality by 62%.[1] Nevertheless, much still needs to be learned, possibly from upcoming randomised clinical trials, to better understand the role of tocilizumab in different clinical and epidemiological settings. Our study elicited several questions regarding the effect of tocilizumab outside the respiratory system, particularly its impact on thromboembolic events, its safety profile with regard to liver injury, and selection of patients for tocilizumab treatment in a personalised medicine approach.

We thank Jean-Jacques Mourad and Philippe Azria for raising a question about the observed number of arterial or venous thromboembolic events in our cohort. In the subset of 354 patients in the Modena cohort, all patients received low molecular weight heparin at a prophylactic dose; therefore, we were unable to evaluate the association between heparin use and risk of thromboembolic events. In our study, thromboembolic events were seen in ten (8%) of 132 patients in the tocilizumab group and two (1%) of 222 patients in the standard of care group. These events were reported by clinical suspicion or CT findings, and when they occurred they prompted a switch from prophylactic to therapeutic doses of heparin. Enoxaparin was administered subcutaneously at 4000 UI per day in the prophylactic group, and at 70 UI/kg twice a day in the therapeutic group. The risk of thromboembolic events in patients treated with tocilizumab versus standard of care, after adjusting for sex, age, comorbidity, and duration of symptoms, was an adjusted odds ratio of 0·65 (95% CI 0·09–4·89; p=0·675). Thus, tocilizumab treatment was not associated with the risk of thromboembolic events in our population. Nevertheless, our study was not powered to address a possible modulating effect of tocilizumab on immunothrombosis,[2] a major (but not the only) driver of thromboembolism.[3]

We thank Salvatore Piano and colleagues for suggesting a word of caution regarding the use of tocilizumab and liver injury. The extent of liver function test abnormalities observed during hospitalisation in patients, both those treated with tocilizumab and those in the control group, in the TESEO Modena cohort are shown in the appendix. Our results are similar to the findings of Piano and colleagues, but we also showed a few outliers. The overall difference in mean alanine aminotransferase (ALT) concentration between the tocilizumab group and standard of care group was significant by ANOVA Fisher test (p<0·0001). Of note, given the quadratic nature of the relationship, the mixed linear model originally done failed to detect this difference in the ALT trend over time between treatment groups. Nevertheless, the increase of ALT in these patients might reflect multiple mechanisms of liver injury beyond tocilizumab toxicity, such as microthrombosis or reactivation of herpes viruses (HSV1 in particular), variables that were not accounted for in this simple unadjusted analysis.

Brian Lipworth and colleagues advocate for a personalised endotype-driven approach to facilitate earlier identification of patients with COVID-19 who might benefit from treatment with tocilizumab or glucocorticoids. We have developed a data-driven predictive model that provides a reliable 48 h prediction of severe respiratory failure, with an accuracy of 84%, which also minimises the false-negative rate.[4] The best performing model required approximately 20 variables, which included interleukin-6, C-reactive protein, and blood gas analyses. Of note, the identification of sick patients (relating to prediction) cannot be confused with the identification of patients who will benefit from the use of tocilizumab, or with questions regarding what intervention is needed to prevent severe complications of COVID-19, which need to be evaluated in the context of counterfactual predictions.[5] Lipworth and colleagues also suggest that the effect of tocilizumab in our analysis could have been due to more prevalent concomitant use of glucocorticoids in these patients, compared with those treated with standard of care; however, our estimates were adjusted for post-baseline use of glucocorticoids. It should also be noted that the optimal time for tocilizumab use in the clinical course of COVID-19 remains to be elucidated.

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See Online for appendix

We declare no competing interests.

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