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Tocilizumab for severe COVID-19 pneumonia

We read with interest the study by Giovanni Guaraldi and colleagues,[1] published in *The Lancet Rheumatology*, which makes an important contribution to the knowledge of the promising therapeutic pathways for severe forms of COVID-19. Unlike antiviral agents, immunomodulatory agents, such as anakinra,[2] tocilizumab,[1] and dexamethasone[3] seem to have become the cornerstone treatment for the cytokine storm that underlies most severe cases of COVID-19. Patients with severe COVID-19 often present with major coagulopathy, with important clinical consequences that have encouraged physicians to progressively modify their anticoagulation treatment regimens for these patients.[4]

To better analyse the level of benefit provided by tocilizumab, Guaraldi and colleagues should specify the number of arterial or venous thromboembolic events observed in their cohort, and specifically detail the proportion of patients receiving therapeutic anticoagulation in both groups. Cohort analyses[5] have shown the major prognostic role of curative anticoagulation in similar patients, making it essential to adjust the analysis for these data.

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1 Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** e474–84.
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We read with interest the study of Giovanni Guaraldi and colleagues[1] on the use of tocilizumab in patients with COVID-19. We congratulate the authors for their effort to assess the effects of tocilizumab in patients with COVID-19, and for the promising results achieved. We wish to suggest a word of caution about the absence of association between the use of tocilizumab and liver injury in their study. Liver function test abnormalities occurred in up to 50% of patients treated with tocilizumab in registration trials, and cases of severe liver injury have been described after tocilizumab licensure.[2,3] Guaraldi and colleagues' study was not designed to assess association between exposure to tocilizumab and liver function test abnormalities. Results of liver function tests were available only in patients admitted to the Modena centre.

We have shown[4] that exposure to tocilizumab was associated with de novo liver function test abnormalities in patients with COVID-19. From that data set, we selected only patients with clinical characteristics similar to those of the patients presented by Guaraldi and colleagues (eg, respiratory rate ≥30 breaths per minute, peripheral blood oxygen saturation <93% in room air, and a PaO_2/FiO_2 ratio of <300 mm Hg). We identified 367 patients, 60 (16%) of whom were treated with tocilizumab. Despite of having a similar extent of liver function test abnormalities at admission (appendix p 2), patients treated with tocilizumab more frequently had a worsening of liver function tests during hospitalisation and had liver function tests that exceeded 3-times the upper limit of normal, compared with those not treated with tocilizumab (52% *vs* 29%, respectively; appendix p 2). Alanine aminotransferase concentrations at days 7 (range 5–9), 14 (12–16), and 21 (19–23) after admission were significantly higher in patients treated with tocilizumab than controls (p<0·05). Although no patient treated with tocilizumab developed acute liver failure, we strongly suggest monitoring liver function tests in patients with COVID-19 who are treated with tocilizumab.

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See **Online** for appendix

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