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.

3 COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur J Hum Genet* 2020; **28:** 715–18.
4 Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes MV, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012; **379:** 1214–24.
5 Regeneron. Regeneron and Sanofi provide update on Kevzara (sarilumab) phase 3 U.S. trial in COVID-19 patients. July 2, 2020. https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-kevzarar-sarilumab-phase-3 (accessed July 8, 2020).
6 Business Wire. Genentech's phase III EMPACTA study showed actemra reduced the likelihood of needing mechanical ventilation in hospitalized patients with COVID-19 associated pneumonia. Sept 18, 2020. https://www.businesswire.com/news/home/20200917006062/en/Genentech%E2%80%99s-Phase-III-EMPACTA-Study-Showed-Actemra-Reduced-the-Likelihood-of-Needing-Mechanical-Ventilation-in-Hospitalized-Patients-With-COVID-19-Associated-Pneumonia (accessed Sept 18, 2020).

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.

J-JM reports personal fees from Servier, Mylan, and Pfizer, outside the submitted work. PA declares no competing interests.

**Jean-Jacques Mourad, Philippe Azria*
jjmourad@ghpsj.fr

Department of Internal Medicine, Groupe Hospitalier Paris Saint-Joseph, Paris 75014, France (J-JM, PA)

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.
2 Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020; **2:** e393–400.
3 The Recovery Collaborative Group. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.
4 Zhai Z, Li C, Chen Y, et al. Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines. *Thromb Haemost* 2020; **120:** 937–48.
5 Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020; **765:** 122–24.

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.

SP, RV, and PA report grants from Cassa di Risparmio di Padova e Rovigo (Cariparo) during the study. PA also reports personal fees from Biovie, Grifols, Sequana Medical, and grants from Boehringer Ingelheim, outside the submitted work. COVID-LIVER study group members are listed in the appendix (p 3).

**Salvatore Piano, Roberto Vettor, Paolo Angeli, on behalf of the COVID-LIVER study group*
salvatore.piano@unipd.it

Unit of Internal Medicine and Hepatology, Department of Medicine, University and Hospital of Padova, Padova 35100, Italy

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:** 474–84.
2 National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: clinical and research information on drug-induced liver injury. 2012. https://www.ncbi.nlm.nih.gov/books/NBK548243/ (accessed June 28, 2020).

See **Online** for appendix

Published **Online** August 17, 2020 https://doi.org/10.1016/S2665-9913(20)30282-4

Published **Online** August 17, 2020 https://doi.org/10.1016/S2665-9913(20)30284-8

3 Genovese MC, Kremer JM, van Vollenhoven RF, et al. Transaminase levels and hepatic events during tocilizumab treatment: pooled analysis of long-term clinical trial safety data in rheumatoid arthritis. *Arthritis Rheumatol* 2017; **69:** 1751–61.
4 Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. *Liver Int* 2020; published online June 11. https://doi.org/10.1111/liv.14565.

Published **Online** August 17, 2020 https://doi.org/10.1016/S2665-9913(20)30283-6

Severe COVID-19 manifests as a viral-induced autoimmune multiorgan disease with pneumonia, and associated cytokine-mewdiated hyperinflammation and coagulopathy.[1] A key pro-inflammatory cytokine involved in COVID-19 is interleukin-6 (IL-6), which induces synthesis of C-reactive protein (CRP) by hepatocytes.

We read with interest the observational study by Giovanni Guaraldi and colleagues,[2] in which baseline concentrations of IL-6 and CRP, as well the PaO_2/FiO_2 ratio, were higher in patients who received tocilizumab compared with patients who received standard of care in the Modena cohort. Moreover, 76% of patients treated with tocilizumab received concomitant glucocorticoids.[2] Preliminary unpublished data, from a Roche press release, regarding the COVACTA trial (NCT04320615) in severe COVID-19 pneumonia have revealed futility for tocilizumab compared with placebo for the primary end point after 4 weeks with no difference in mortality or need for ventilation.

For the **Roche press release** see https://www.roche.com/investors/updates/inv-update-2020-07-29.htm

Herold and colleagues[3] reported on patients with severe COVID-19, showing that once IL-6 concentrations exceeded 80 pg/mL, the median time to mechanical ventilation was 1·5 days (range 0–4 days), and for CRP concentrations above 97 mg/mL, the median time to mechanical ventilation was 0 days (range 0–4 days). In another study,[4] a composite score comprising SaO_2/FiO_2 ratio, and concentrations of CRP and IL-6 on admission, predicted clinical deterioration within 3 days of hospital admission, with an area under the receiver operating curve of 0·88.[4]

Published **Online** August 17, 2020 https://doi.org/10.1016/S2665-9913(20)30285-X

Another possibility for escalating treatment in patients with severe COVID-19 is to use medium-dose systemic glucocorticoids to non-selectively suppress the cytokine cascade. In one study,[5] treatment with dexamethasone at 6 mg/day in 2014 patients, compared with usual care in 4321 patients, resulted in a 35% relative reduction in mortality in ventilated patients and a 20% relative reduction in patients requiring oxygen alone.

Taken together, these observations suggest that it is time to adopt a personalised endotype-driven approach to facilitate earlier identification of patients with COVID-19 who might benefit from such selective or non-selective cytokine suppression.

CRWK reports personal fees from AstraZeneca, Chiesi, and Circassia, outside the submitted work. BJL and RC declare no competing interests.

*Brian J Lipworth, Rory Chan, Chris RuiWen Kuo
b.j.lipworth@dundee.ac.uk

Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, Dundee, Scotland, UK (BJL, RC, CRWK)

1 Lipworth B, Chan R, Lipworth S, RuiWen Kuo C. Weathering the cytokine storm in susceptible patients with severe SARS-CoV-2 infection. *J Allergy Clin Immunol Pract* 2020; **8:** 1798–801.
2 Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** 474–84.
3 Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020; **146:** 128–36.
4 Vultaggio A, Vivarelli E, Virgili G, et al. Prompt predicting of early clinical deterioration of moderate-to-severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study. *J Allergy Clin Immunol* 2020; published online June 19. https://doi.org/10.1016/j.jaip.2020.06.013.
5 The Recovery Collaborative Group. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.

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