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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Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19

See Online for appendix

Few effective therapeutic options are available for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. IL-6 receptor blockade has been proposed as one potential therapeutic strategy, and more than 40 clinical trials of anti-IL-6 receptor antibodies (including tocilizumab and sarilumab) in the setting of SARS-CoV-2 infection are underway (appendix p 2). Early evidence from observational studies and open-label, uncontrolled trials has suggested that IL-6 receptor blockers might confer benefit, particularly in patients with severe COVID-19.[1]

Human genetics enables the investigation of potential opportunities for drug repurposing. We leveraged large-scale human genetic data to investigate whether IL-6 receptor blockade might confer therapeutic benefit in COVID-19. A genetic instrument consisting of seven genetic variants in or close to *IL6R* (pairwise $r^2 \leq 0{\cdot}1$; appendix pp 8–9) was recently shown to be associated with altered concentrations of C-reactive protein, fibrinogen, circulating IL-6, and soluble IL-6 receptor, concordant with known effects of pharmacological IL-6 receptor blockade (appendix p 4).[2] We investigated the effect of these *IL6R* variants on risk of hospitalisation for COVID-19 and other SARS-CoV-2-related outcomes using data from the COVID-19 Host Genetics Initiative (appendix pp 2–3, 10).[3]

Based on data from UK Biobank, the *IL6R* variants were confirmed to be associated with lower serum C-reactive protein concentrations (appendix pp 5–6). Meta-analysis of scaled estimates identified a lower risk of rheumatoid arthritis (odds ratio 0·93 per 0·1 SD lower C-reactive protein; 95% CI 0·90–0·96, p<0·0001; appendix pp 5–6), supporting this established indication for IL-6 receptor inhibitors (eg, tocilizumab and sarilumab), as well as a lower risk of coronary heart disease (0·96; 0·95–0·98, p<0·0001), which has previously been linked to genetic variation in *IL6R*.[4] The *IL6R* instrument was also associated with a lower risk of hospitalisation for COVID-19 (0·88; 0·78–0·99, p=0·03; appendix pp 5–6). We found a consistent association when using a population-based control group (ie, all non-cases; 0·91; 0·87–0·96, p=0·0005; appendix pp 5–6).

On evaluation of further SARS-CoV-2-related outcomes, we detected an association of the *IL6R* instrument with risk of SARS-CoV-2 infection (0·92; 0·89–0·95, p<0·0001 using a population-based control group; appendix pp 5–6), but no evidence of association with death or need for respiratory support. The results of the main analysis were robust to various sensitivity analyses (appendix p 7).

Our findings show that *IL6R* variants mimicking therapeutic inhibition of IL-6 receptor are associated with a lower risk of hospitalisation for COVID-19, a phenotype that is associated with disease severity (eg, requiring supplemental oxygen is a typical reason for hospitalisation). This result suggests that pharmacological blockade of IL-6 receptor might be expected to lead to reduced COVID-19 severity. We also found an association with lower risk of SARS-CoV-2 infection; although this finding might suggest that IL-6 receptor blockade lowers susceptibility to SARS-CoV-2 infection, these phenotypes could be biased by symptom severity (ie, individuals with more severe symptoms might be more likely to present for testing, to be offered testing, or to have a positive test). The lack of association with very severe COVID-19 requiring respiratory support or leading to death might be relevant in the context of the announced failure of sarilumab in a phase 3 randomised controlled trial in patients with COVID-19 requiring mechanical ventilation.[5] However, the genetic analysis with very severe COVID-19 was based on relatively few cases (n=536), limiting robust inference, and the EMPACTA randomised controlled trial reported a lower risk of progressing to mechanical ventilation or death in patients with COVID-19 pneumonia who received tocilizumab compared with patients who received placebo (hazard ratio 0·56; 95% CI 0·32–0·97, p=0·035).[6]

Our results serve as genetic evidence for the potential efficacy of IL-6 receptor blockade in COVID-19 and support the study of IL-6 receptor inhibitors in randomised controlled trials. On their own, these data should not be used to influence clinical care. Ongoing, large-scale randomised controlled trials of IL-6 receptor inhibitors will be instrumental in identifying the potential settings, including stage of disease and potential pharmacogenetic subgroups, in which these agents might be effective.

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1 Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* 2020; published online Aug 14. https://doi.org/10.1016/S2665-9913(20)30277-0.

2 Georgakis MK, Malik R, Gill D, et al. Interleukin-6 signaling effects on ischemic stroke and other cardiovascular outcomes: a mendelian randomization study. *Circ Genom Precis Med* 2020; **13:** e002872.

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.

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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.
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.

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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:** 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).

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