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.

consider is the favourable safety profile of mavrilimumab observed both in the study by De Luca and colleagues and in the entire drug development programme for rheumatoid arthritis, for which the reported incidence of serious infections was negligible.[9] In particular, some concerns could arise from the involvement of GM-CSF in the clearance of the alveolar surfactant by resident macrophages and the development of pulmonary proteinosis in cases of congenital deficit of this mediator. However, no such complication has ever been reported throughout the development programme of all GM-CSF inhibitors.[9]

In conclusion, GM-CSF receptor blockade is certainly a potential option for the treatment of more severe subsets of COVID-19, and more extensive studies are warranted to confirm the role of GM-CSF in the pathogenesis of cytokine release syndrome.

We declare no competing interests.

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Can tocilizumab calm the cytokine storm of COVID-19?

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a global pandemic, with ongoing regional COVID-19 outbreaks across the world. For many patients, COVID-19 manifests simply as a viral respiratory syndrome, but a subset of patients develops a life-threatening course with significant and prolonged systemic inflammation.[1] Increasing data show that many severe COVID-19 cases have features of cytokine storm syndrome, including characteristics of acute respiratory distress syndrome and macrophage activation syndrome, such as hyperferritinaemia, systemic hyperinflammation, and multi-organ system dysfunction.[2] Indeed, several early reports highlighted that patients with severe disease had clinical and laboratory features of hyperinflammation and cytokine storm, including elevated levels of interleukin-6 (IL-6).[3,4] Based on these observations and the encouraging results of an early case series using tocilizumab (a recombinant humanised monoclonal antibody against the IL-6 receptor),[5] clinicians facing rising numbers of patients with COVID-19 have increasingly turned to cytokine-directed therapies for critically ill patients.

In *The Lancet Rheumatology*, Giovanni Guaraldi and colleagues[6] report the results of the TESEO study, a large, multicentre, retrospective cohort study of tocilizumab for severe COVID-19 pneumonia. The study included 544 patients with confirmed COVID-19 and severe respiratory symptoms (defined as tachypnea, hypoxemia, poor oxygenation, and lung infiltrates of more than 50%) at three centres in the Emilia-Romagna region of Italy. 179 (33%) of these patients received tocilizumab (intravenous or subcutaneous) and standard of care therapy, and 365 (67%) patients with similar respiratory symptoms received only standard of care therapy (supplemental oxygen, hydroxychloroquine, azithromycin, combination antiretrovirals, and low molecular weight heparin). The primary outcome was a composite of death or progression to invasive mechanical ventilation. At day 14 from hospital admission, 22·6% (95% CI 16·2–29·0) of tocilizumab patients had the primary outcome,


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See Articles page e474

compared with 36·5% (30·7–42·2) of patients receiving standard of care. 13 (7%) of 179 patients treated with tocilizumab died, compared with 73 (20%) of 365 who received standard of care. When adjusted for age, gender, recruiting centre, duration of symptoms, and Subsequent Organ Failure Assessment (SOFA) score, tocilizumab treatment showed a hazard ratio for death alone of 0·38 (95% CI 0·17–0·83; p=0·015). Similar numbers of patients received intravenous and subcutaneous tocilizumab, on the basis of local availability, and no significant difference in the outcomes or side-effect profile were found according to the route of administration. Regarding safety, more secondary infections were diagnosed in the tocilizumab group (24 [13%]) than in the standard of care group (14 [4%]), which has also been seen in randomised trials of tocilizumab.[7] The present study included one patient receiving tocilizumab who died from acute liver failure due to herpes simplex virus 1 reactivation.

This study is the largest of its kind reported thus far and represents a crucial addition to the literature regarding tocilizumab in COVID-19. It is also an impressively rigorous effort undertaken at the height of the pandemic in northern Italy, with patients enrolled in a systematic manner with informed consent, standardised data collection, and predefined study outcomes. Dosing was also standardised at either 8 mg/kg (up to 800 mg) administered twice intravenously, or 162 mg administered subcutaneously in two simultaneous doses (81 mg in each thigh). These doses were based on pharmacokinetic data and were intended to mimic peak plasma concentration. Finally, patients receiving tocilizumab were compared with a contemporaneous cohort of controls with the same inclusion and exclusion criteria. The primary limitation of this study, and all cohort studies, is that the patients and controls were not randomly chosen, thus introducing both measurable and unknown potential biases. Patients were offered tocilizumab treatment mainly on the basis of availability of the drug, but potentially also because of both demographic and disease-specific factors. Indeed, the patients treated with tocilizumab were younger, and in Modena (where more granular clinical data was available), they were more likely to have comorbidities. Treated patients also had worse baseline oxygenation and SOFA scores, and those in Modena had more severe markers of cytokine storm, including higher C-reactive protein, IL-6, and lactate dehydrogenase concentrations, and worse thrombocytopenia. However, the authors adjusted results for several of the key variables and found no differences based on these strata.

This study adds key new information to our understanding of tocilizumab in COVID-19. Previous studies of tocilizumab in COVID-19 have largely been encouraging, but either did not have a matched comparator group,[5,8] did not match to contemporaneous controls,[9] or were small and probably underpowered for key safety and efficacy outcomes.[10,11] This study provides strong evidence that tocilizumab might prevent intubation and death in adults with severe COVID-19 pneumonia. These findings are also in agreement with emerging evidence that, in the setting of COVID-19-induced cytokine storm, immunosuppressive treatments might be most helpful earlier in the disease: after the onset of severe disease but before florid respiratory failure.[9] The precise group of patients who might benefit from tocilizumab and the optimal biomarkers for identifying cytokine storm in the setting of COVID-19 remain unknown. The most crucial question concerns the relative utility of tocilizumab treatment versus other non-specific immunomodulatory agents (including corticosteroids) and other cytokine-directed therapies, which is the focus of multiple ongoing randomised trials.

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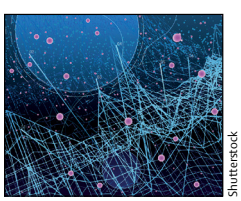
Making a big impact with small datasets using machine-learning approaches



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See **Articles** page e485

As comprehensive electronic medical records increasingly capture more data points from large-scale clinical cohorts, machine-learning approaches have been applied to identify patterns that would otherwise be challenging to ascertain with traditional statistical methods. Although we often think of machine learning for analysis of large, complex datasets, in *The Lancet Rheumatology*, George Robinson and colleagues[1] successfully applied machine-learning algorithms to derive information from a small dataset in a rare disease. Using blood from 67 patients with juvenile-onset systemic lupus erythematosus (SLE), the authors identified dysregulation in multiple immune cell subsets using a combination of balanced random forest, sparse partial least squares-discriminant analysis, and traditional logistic regression, which was subsequently validated using ten-fold cross-validation. They found an immune signature specific to juvenile-onset SLE, which was further stratified into four different immune profile cluster groups that were associated with disease activity over time. These unique immune profiles could be useful in predicting prognosis and response to treatment in juvenile-onset SLE. Development of a personalised approach to therapy is especially relevant because children tend to receive more intensive drug therapy and accrue more end-organ damage than patients with adult-onset SLE.[2]

The findings of this study not only contribute to our current understanding of juvenile-onset SLE, but they also outline a potential future machine-learning roadmap for untangling the complex immunological underpinnings of other rheumatic conditions. The data density in this analysis comes not from the cohort size, but rather from detailed analysis of peripheral blood mononuclear cells (PBMCs) by flow cytometry. Subsequently, machine-learning algorithms were applied, and this strategy might be particularly useful for studying other rheumatic conditions such as vasculitis, myositis, or systemic sclerosis, which are relatively rare and highly heterogeneous, making accrual of multiple, large clinical cohorts challenging. Nevertheless, the absence of an external validation dataset is an important limitation because it might result in problematic model overfitting and inappropriate generalisation. The generalisability issue is magnified when a small training dataset is used or when baseline parameters have highly skewed distributions, one of the recognised limitations of methods such as random forest. In this example, Robinson and colleagues acknowledge that their cohort consisted of few black patients and few patients with severely active disease, collected from a single centre. Although their findings are highly novel, readers should be cautious in the interpretation as advanced statistical methods are an inadequate replacement for external validation.

How will Robinson and colleagues' findings change clinical practice? Our current methods for classifying patients with juvenile-onset SLE and other rheumatic diseases remains relatively crude.[3] Accordingly, our ability to identify subgroups of patients who are likely to have disease progression over time or to predict which patients might respond to a specific medical therapy is limited. Robinson and colleagues highlight two potential future directions for the field. First, we need to improve the classification of patients on the basis of their biological, rather than clinical, disease profiles. Identification of unique patient subgroups who have different clinical outcomes using PBMCs would represent an important advance over current classification methods that require multiple longitudinal assessments. Second, classification of patients according to their immunological signature might allow targeting of specific pathways that maximise therapeutic response and minimise off-target side-effects.