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GM-CSF in the treatment of COVID-19: a new conductor in the pathogenesis of cytokine storm?



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See [Articles](#) page e465

The outbreak of a new strain of the coronavirus family called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China in December, 2019, has quickly turned into a pandemic that, as of June 10, 2020, accounts for more than 7 million confirmed cases and 400 000 deaths worldwide. COVID-19 has an extremely variable disease course, ranging from asymptomatic or oligosymptomatic patterns to severe interstitial pneumonia that can be complicated with acute respiratory distress syndrome and even death.¹ The rapid evolution of the global health emergency and the scarcity of specific antiviral treatments have immediately focused research towards the identification of a proper management strategy to prevent mortality due to COVID-19. In this respect, improved knowledge about the interaction between SARS-CoV-2 and the immune system has led to the identification of a massive release of pro-inflammatory mediators linked to an aberrant immune response as the main cause of infection evolution towards life-threatening respiratory impairment.² This aberrant immune response closely resembles a similar reaction observed following the oncological use of chimeric antigen receptor (CAR) T cells, known as cytokine release syndrome. A high concentration of interleukin-6 (IL-6) observed in cytokine release syndrome, suggesting a pivotal role of this cytokine in the pathogenesis of this condition, paved the way for use of IL-6 inhibitors to treat this complication.³ Similarly, the anti-IL-6 agent tocilizumab was the first biological drug used in the treatment of severe COVID-19 and is still being tested in several ongoing randomised trials. However, the first published results on this approach are controversial and, so far, have not confirmed the effectiveness of IL-6 blockade.^{4,5} In addition, inhibitors of other pro-inflammatory mediators involved in the development of cytokine release syndrome are being tested as potential treatment targets in COVID-19.⁶

In this scenario, the study published in *The Lancet Rheumatology* by Giacomo De Luca and colleagues⁷ is an important step forward in understanding the pathways implicated in the pathogenesis of life-threatening SARS-CoV-2 infection. The Article reports a prospective analysis aimed at evaluating the effect of mavrilimumab,

a granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor inhibitor, in the treatment of non-mechanically ventilated patients with COVID-19 pneumonia and systemic hyperinflammation. The authors observed that, by day 28 of follow-up, all 13 patients who received mavrilimumab showed clinical improvement compared with 17 (65%) of 26 patients in the control group ($p=0.030$), who received standard care provided at the hospital at the time of the study, including hydroxychloroquine, azithromycin, and lopinavir-ritonavir. Furthermore, no patients who received mavrilimumab died, but seven (27%) patients in the control group died by day 28. The study is certainly affected by some potential limitations. The small sample size, the absence of randomisation, and the short follow-up period might reduce the fully generalisability of observed results. However, the inclusion of an overall well matched control group represents a strength compared with other studies evaluating biological drugs for the same indication. In particular, the results reported by De Luca and colleagues on mavrilimumab seem to be overall more favourable than those observed in similarly designed studies exploring tocilizumab^{4,5} or the IL-1 inhibitor anakinra.⁸ This evidence, if confirmed by larger randomised studies, might lead to a reappraisal of the role of the components involved in the development of cytokine release syndrome. Certainly, GM-CSF has very complex immunological activity, ranging from the well known haematopoietic effect to the more recently demonstrated pro-inflammatory role, which has made it a potential target for the treatment of immune-mediated diseases such as rheumatoid arthritis, spondyloarthritis, and giant-cell arteritis. Undoubtedly, within the inflammatory cascade, this effect can be placed further upstream compared with other cytokines such as IL-1, tumor necrosis factor, and IL-6.⁹ For an example, a Chinese study reported that atypical pathogenic T helper 1-cells expressing GM-CSF have been detected only in patients with more severe COVID-19 compared with both patients with less symptomatic patterns and healthy controls.¹⁰ These findings seem to confirm a crucial and upstream role of GM-CSF in the pathogenesis of SARS-CoV-2-related hyperinflammation. Another point to

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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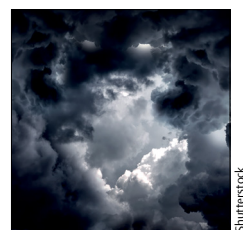
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Can tocilizumab calm the cytokine storm of COVID-19?

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 colleagues⁶ 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