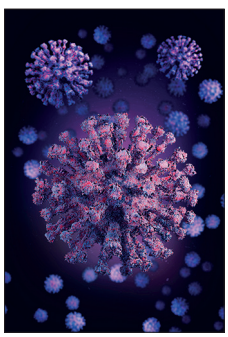
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Who, what, and when—effective therapy for severe COVID-19



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Published Online
November 17, 2021
https://doi.org/10.1016/
S2665-9913(21)00353-2

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The COVID-19 pandemic is ongoing, and the SARS-CoV-2 delta variant has resulted in disease resurgence. As many as 20% of people infected with SARS-CoV-2 suffer from hyperinflammatory COVID-19, resulting in hospitalisation with COVID-19 pneumonia.[1] Although old age and comorbidities (eg, diabetes, obesity, and hypertension) are risk factors for severe COVID-19, the delta variant has affected young, often previously healthy, individuals, some of whom have to be admitted to intensive care units. Although broad immunosuppression with glucocorticoids has been life-saving,[2] defining those with hyperinflammatory COVID-19 who might benefit from targeted approaches to dampening proinflammatory cytokines has been challenging.[3] Early during the pandemic, concentrations of serum interleukin (IL)-6 were noted to be elevated in patients with severe COVID-19, and multiple clinical trials have explored therapeutic monoclonal antibodies to IL-6 or the IL-6 receptor. Although individual trials have yielded conflicting results, meta-analyses suggest that blockade of IL-6 signalling might enhance survival for patients with severe COVID-19.[4]

In *The Lancet Rheumatology*, Xavier Mariette and colleagues, on behalf of the CORIMUNO-19 Collaborative group,[5] explore the IL-6 receptor monoclonal antibody sarilumab for treatment of moderate-to-severe COVID-19 pneumonia using a multi-centric, open-label, Bayesian randomised, adaptive trial approach.

Mariette and colleagues enrolled 148 adults hospitalised for COVID-19 on more than 3L/min oxygen but not requiring high-flow oxygen or mechanical ventilation (WHO Clinical Progression Scale [CPS] score of 5). The patients were randomly assigned to sarilumab or usual care, and 29 (20%) of 144 patients also received glucocorticoids (the trial occurred before the publication of RECOVERY[2]). The primary outcomes were a WHO-CPS score higher than 5 on day 4 and survival without high-flow oxygen or mechanical ventilation on day 14. There was no difference in either outcome between the two groups. 18 (26%) of 68 patients in the sarilumab group had a WHO-CPS score greater than 5 at day 4 versus 20 (26%) of 76 in the usual care group (median posterior absolute risk difference 0·2%; 90% credible interval −11·7 to 12·2), and at day 14, 25 (37%) patients in the sarilumab and 26 (34%) patients in the usual care group needed ventilation or died (median posterior hazard ratio 1·10; 90% credible interval 0·69–1·74). There was a higher total number of adverse events in the sarilumab group than in the usual care group, but no significant difference in the number of serious adverse events. Limitations of the study include its small sample size, unmasked design, and no standardisation of usual care.

Although the results of various clinical trials are mixed as to the benefit of IL-6 inhibition in treating severe COVID-19, there are likely subsets of individuals who will benefit from this therapy. Perhaps, similar to those who improve with glucocorticoids, those with the most severe disease, as defined by respiratory support, will best benefit.[2] Alternatively, those with high concentrations of serum IL-6 or IL-6-responsive C-reactive protein might receive the most aid from IL-6 blockade. Nonetheless, meta-analyses have reported that the survival advantage seen for IL-6 inhibition was in those with supplemental oxygen requirement but not those requiring invasive mechanical ventilation.[4] Moreover, the benefit afforded by IL-6 pathway disruption was only noted in those on concomitant glucocorticoid therapy.[4] Thus, co-administration of glucocorticoids and timing (requiring oxygen but before invasive mechanical ventilation) of IL-6 receptor monoclonal antibody treatment are probably crucial factors in improving the outcome of patients with severe COVID-19.

In addition to patient selection and the timing of drug administration, deciding which specific targeted anti-cytokine approach to use in treating severe COVID-19 remains a conundrum. Although IL-6 inhibition has received the most attention, blockade of IL-1, granulocyte-macrophage colony stimulating factor, interferon-gamma, and others (eg, tumour necrosis factor) are being explored as COVID-19 treatments. In a trial of the anti–interleukin-1β antibody canakinumab, although survival was greater in those receiving the study drug than in those receiving placebo, the study drug did not significantly improve outcomes in patients with COVID-19 pneumonia.[6] Recently, blockade of IL-1-α and IL-1-β signalling with the recombinant human IL-1 receptor antagonist, anakinra, was shown to improve survival in

patients with COVID-19 with elevated concentrations of soluble urokinase-type plasminogen activator receptor (suPAR).[7] Similar to the recent IL-6 inhibition trials, the benefit of anakinra was identified in the setting of glucocorticoid standard-of-care therapy.

Since broad immunosuppression with glucocorticoids is probably harmful before supplemental oxygen is required, because it perhaps allows for increased viral replication, there is an unmet need to prevent the development of severe COVID-19 in at-risk individuals infected with SARS-CoV-2. For targeted anti-cytokine approaches that probably do not benefit those with severe lung disease or acute respiratory distress syndrome, earlier treatment of COVID-19 might be beneficial. As we are not at the stage of precision medicine for hyperinflammatory COVID-19,[8] choosing the appropriate anti-cytokine approach is difficult. An intermediate option might be polycytokine targeting with the use of Janus kinase inhibitors.[9] However, until well-designed comparative effectiveness studies are done, the question of which immunomodulatory agent to use in conjunction with glucocorticoids for treatment of severe COVID-19, in which patients, and at what time point of illness will remain unanswered.

RQC reports grants and personal fees from Sobi, personal fees from Novartis, personal fees from Pfizer during the conduct of the study. DAK declares no competing interests.

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What does endemic COVID-19 mean for the future of rituximab?

It may have been a stalwart of rheumatological therapy for 20 years, but rituximab has not fared well during the COVID-19 pandemic. Whereas the observational outcome data have been reassuring for the use of almost all other disease-modifying anti-rheumatic drugs, the same cannot be said of rituximab. Multiple rheumatological cohorts[1,2] have shown that the drug is associated with worsened morbidity and mortality after COVID-19, and similar outcomes have been seen with B-cell depleting therapies in patients with multiple sclerosis.[3,4] Additionally, the protective effect of COVID-19 vaccination is probably threatened by concomitantly administered rituximab, hindering the most viable solution to address this pandemic.[5]

It is unfortunate that the COVID-19 pandemic has occurred at a time when the potential utility of rituximab has been shown across multiple diseases, including in the maintenance of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, in primary Sjögren's syndrome, and even as proof-of-concept in diseases such as systemic sclerosis[6] and polymyalgia rheumatica.[7] Additionally, for some patients with orphan conditions, off-label rituximab remains one of very few therapeutic options. At a time in which much of the world is benefiting from more affordable rituximab biosimilars, we might ordinarily be heralding this as rituximab's golden era. The persistence of COVID-19 as an issue has instead dampened enthusiasm for rituximab in contemporary practice.

In *The Lancet Rheumatology*, Kathleen M Andersen and colleagues further extinguish any doubt around concerns about COVID-19 in patients treated with rituximab.[8] They used the US National COVID-19 Cohort Collaborative (N3C) to examine whether

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Published **Online**
November 15, 2021
https://doi.org/10.1016/S2665-9913(21)00362-3

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