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.

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.

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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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immunosuppressive therapy was associated with poorer outcomes in patients who were hospitalised for COVID-19. The data, which were extracted from electronic medical records up to June, 2021 and therefore largely before the introduction of COVID-19 vaccination, included 16 494 adults who were taking some form of immunosuppressive therapy and 206 081 who were not. Patients on immunosuppressants more frequently had comorbidity, so unadjusted analyses unsurprisingly showed a greater risk of mechanical ventilation (9% *vs* 6%) and in-hospital death (14% *vs* 9%) in these patients. When propensity score matching was performed, however, immunosuppression was not associated with death; in fact, a reduced risk of mechanical ventilation was observed. These associations were unchanged by a range of sensitivity and subgroup analyses, except those examining rituximab, in which the risk of in-hospital death was increased in patients treated with the drug for either autoimmune disease or cancer. Although provisos exist in the interpretation of these data, as is the case for most retrospective real-world cohorts, the best attempts to remove confounders have shown no clear risk profile in patients on immunosuppressive therapies, apart from that associated with rituximab.

The most plausible mechanism whereby rituximab impacts outcomes is through blunted humoral immunity. This makes mechanistic sense and is also supported by the RECOVERY trial, which showed that those who were seronegative for anti-SARS-CoV-2 antibodies benefited from treatment with monoclonal antibodies directed at the virus, whereas those who were seropositive did not.[9] The potential contribution of cell-mediated immunity should also be noted but has not yet been explored fully. What do all these data mean for patients and their doctors faced with a scenario in which rituximab is a good therapeutic option?

Patients and clinicians have two potential paths. For those who proceed to treatment with rituximab, we must find the safest approach. This might ideally involve COVID-19 vaccinations before initiating rituximab and adherence to public health measures, such as wearing face coverings and shielding from high-transmission exposures, but all of these strategies are likely to be challenging in practice. It is also not clear how the risk to patients with some pre-existing immunity to SARS-CoV-2 before rituximab might vary from those without such immunity; data on this will help to further our understanding of the pathophysiology of COVID-19 and help us make better decisions for individual patients.

Of course, with the right strategy, the impact of B-cell depletion might be mitigated, and rituximab might not need to be a therapeutic pariah. If vaccination can induce sufficient and sustained humoral immunity before rituximab is needed, rituximab could plausibly be far less risky, particularly if B-cell repertoire diversity can combat subtle spike protein mutations. However, questions about the optimal strategy for individual patients remain unanswered. When should rituximab be timed relative to vaccine administration? What improvements will additional vaccine boosters confer? How important is having some cell-mediated immunity in patients treated with rituximab? If patients develop COVID-19, is seropositivity for antiviral antibodies an appropriate marker for protection in these patients, or should they be given anti-SARS-CoV-2 monoclonals or small molecules regardless? Clearly, there is much further work to be done.

A key component of therapeutic strategies involving rituximab is likely to be post-exposure prophylaxis, either with neutralising monoclonal antibodies, based on the evidence of efficacy with this approach using casirivimab and imdevimab,[10] or emerging small molecule antiviral therapies. If patients become infected with SARS-CoV-2, one might advocate for the early use of virus-neutralising monoclonal antibodies if available, based on currently available data and in line with the aforementioned RECOVERY data.[9] Furthermore, pre-exposure prophylaxis might be appropriate for those identified to be at the highest risk (clinically or serologically), with long-acting monoclonal antibodies a logistical possibility. These interventions are potentially lifesaving for those who can access them but, in a glaring issue of equity, much of the world cannot.

The other path leads to rheumatologists being forced to use alternative therapies. Whereas in rheumatoid arthritis, rituximab is one of a large number of choices, in many other potential indications, it stands alone as first-line therapy. The detriment from choosing an inferior option, such as azathioprine for the maintenance of ANCA-associated vasculitis, will need to be balanced against potentially improved outcomes with COVID-19. This equation will vary with new SARS-CoV-2 variants, changing epidemiology, and between individual patients; currently, such a complex decision lacks data to inform it.

As we enter this next endemic stage of the pandemic, the flurry of intuition must be replaced by data, and we must determine the optimal solutions for our patients: solutions that encompass both good rheumatic disease outcomes and good COVID-19 outcomes. Without robust data on vaccination responses in a range of rituximab treatment scenarios and outcomes from strategies such as post-exposure prophylaxis, we will only be able to guess at the best approaches. We must do better than that.

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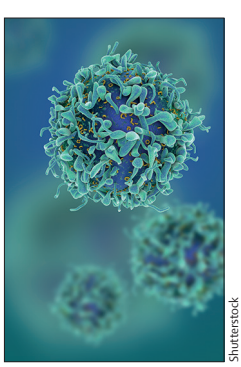
Immunity after COVID-19 vaccinations in immunocompromised patients with psoriasis

COVID-19 vaccination is paramount to reduce morbidity and mortality of SARS-CoV-2 infection, but immunosuppressive treatment prescribed to patients with immune-mediated inflammatory diseases might reduce the efficacy of COVID-19 vaccines in these patients. Studies that measure both humoral and cellular immune responses to vaccination are important to fully understand effects of immunosuppressive agents on COVID-19 vaccine immunogenicity.

In *The Lancet Rheumatology*, Satveer Mahil and colleagues[1] evaluated the development of humoral and cellular immunity against the SARS-CoV-2 spike glycoprotein in 67 patients with psoriasis and 15 healthy controls after the second dose of the COVID-19 vaccine BNT162b2 (Pfizer-BioNTech). All patients had well controlled psoriasis and were receiving monotherapy with methotrexate (n=14), tumour necrosis factor (TNF) inhibitors (n=19), interleukin (IL)-17 inhibitors (n=14), or IL-23 inhibitors (n=20); no patients paused their medication during the vaccination period. A key aspect of the study was that participants received the second BNT162b2 vaccine dose according to an extended interval of up to 12 weeks between doses, compared with the standard 3–4 week interval. After the second dose, patients and controls had similar titres of neutralising antibody against wild-type SARS-CoV-2 and two SARS-CoV-2 variants of concern: the alpha and delta variants. These data are reassuring and important as it is becoming increasing clear that neutralising antibody titres correlate with protection against symptomatic COVID-19,[2] and because breakthrough infections in vaccinated individuals are mainly caused by variants of concern.[3]

Another finding of Mahil and colleagues was that total IgG antibody titres against SARS-CoV-2 were numerically lower (albeit not significantly so) in patients treated with methotrexate (median half maximal effective concentration 1751 [IQR 468–4976])



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