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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Humoral response following SARS-CoV-2 vaccination: not all immunosuppressants are created equal

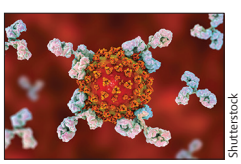
It is well established that many patients on immunosuppression have an attenuated humoral response to SARS-CoV-2 vaccination.[1,2] Indeed, people with immune dysregulation have a higher risk of SARS-CoV-2 breakthrough infection despite vaccination than do immunocompetent people.[3] As understanding of the SARS-CoV-2 vaccine response among immunosuppressed populations evolves, a hierarchy among agents is emerging, with recipients of lymphocyte-depleting therapies, such as rituximab and mycophenolate mofetil, at greatest risk of a reduced immune response.[1,2]

A study in *The Lancet Rheumatology* by Luuk Wieske and colleagues adds to existing evidence that humoral responses after standard vaccination (defined as two-dose ChAdOx1 nCoV-19 [Oxford–AstraZeneca], BNT162b2 [Pfizer–BioNtech], CX-024414 [Moderna], or single-dose Ad.26.COV2.S [Janssen]) are suboptimal among patients with immune-mediated inflammatory diseases treated with anti-CD20 therapy, sphingosine 1-phosphate receptor (S1P) modulator, or mycophenolate mofetil combination therapies.[4] Similar rates of seroconversion were observed among patients treated with other immunosuppressants, although antibody titres were moderately reduced compared with controls. Given findings of a preserved recall response in these patients, the authors conclude that reduced antibody titres are unlikely to translate to loss of short-term protection. However, we believe that this conclusion might be premature in the absence of clinical outcome data, and more importantly, studies have demonstrated the correlation between antibody titres and breakthrough infections.[5] Moreover, recent data have highlighted that significantly higher antibody concentrations are required to overcome immune evasion induced by variants of concern,[6] further underlining the potential role of antibody titres in guiding strategies for infection prevention.

Although Wieske and colleagues did evaluate differential response between monotherapies and combination therapies, absence of dosing information limits additional insights into the role of immunosuppressive intensity in blunting humoral responses. In addition, the dose of both mycophenolate mofetil and glucocorticoid, as well as the degree of rituximab exposure, is important, particularly considering findings that glucocorticoids independently blunt antibody responses.[1] Moreover, two-dose vaccination with mRNA vaccines has been shown to elicit greater humoral responses compared with the Ad.26.COV2.S vaccine in patients with immune-mediated inflammatory diseases, whereas the CX-024414 vaccine induces greater humoral immunogenicity and is associated with lower rates of breakthrough infections than the BNT162b2 vaccine in immunocompetent people;[7] data pertaining to differential immunogenicity between vaccine platforms would be useful to inform clinical decision making.

Wieske and colleagues provide valuable insights into humoral responses following an additional mRNA vaccine dose; they report increased seroconversion among patients on mycophenolate mofetil combination therapy, but limited effects in those on anti-CD20 therapy and S1P modulators. A temporary hold of mycophenolate mofetil in the perivaccination period augments humoral responses in patients with immune-mediated inflammatory diseases and solid organ transplant recipients,[8,9] and it is unclear whether mycophenolate mofetil dosing was modulated in this study to facilitate increased seroconversion. In addition, heterologous boosting is associated with lower COVID-19 incidence rates than homologous boosting in immunocompetent people,[10] and assessment for different responses in these groups would be beneficial to guide the choice of optimal additional dose vaccine platform.

Wieske and colleagues suggest that antibody testing alone to determine additional vaccine doses is



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inappropriate among patients treated with anti-CD20 therapy or S1P modulators. We agree that there is a need for a reliable, accessible assessment of cellular responses, particularly among these patients. An association between seronegative status and breakthrough infections in patients with immune-mediated inflammatory diseases has been demonstrated,[5] and among patients with COVID-19, monoclonal antibody therapy reduced 28-day mortality in seronegative patients but not in those who were seropositive at baseline. Thus, there is still merit in assessing antibody status to determine therapeutic and preventive strategies in these patient groups.

Data on the humoral response to additional dose vaccination in patients with immune-mediated inflammatory diseases are scarce, and Wieske and colleagues are commended for their robust study design. However, many questions remain for immunosuppressed patients. Both the mechanism and intensity of immunosuppression are integral in mediating the SARS-CoV-2 vaccine response; however, it appears that the vaccine platform, use of heterologous additional doses, and modulation of perivaccination immunosuppression have roles in optimising the immune response. Although the role of antibody testing remains to be defined, it should be considered a useful tool in the armamentarium of the rheumatologist to inform risk mitigation strategies, as well as the allocation of immune prophylaxis in patients at high risk.

In conclusion, we acknowledge the contribution of this study; the findings add credence to existing data that the type and intensity of immunosuppressive therapy is of major relevance for humoral responses following SARS-CoV-2 vaccination and highlight the continued need for non-medical and medical countermeasures, including additional vaccine doses, in immunosuppressed patients. We also emphasise the need for further analyses and studies to define the phenotype of patients with immune-mediated inflammatory diseases who have a poor response, as well as the potential role of antibody testing to facilitate the protection of our most vulnerable patients.

We declare no competing interests.

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No perfect therapy for the imperfect COVID-19 cytokine storm

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More than 2 years into the pandemic, almost 6 million people have died from COVID-19 worldwide. Many people who succumbed to the virus had cytokine storm syndrome, a dysregulated immune response to the pathogen.[1] Progress toward treating COVID-19 has been substantial on several fronts, including rapidly developed safe and effective vaccines, and various antiviral therapies (eg, monoclonal antibody therapies, protease inhibitors, and nucleoside analogues). Antiviral approaches are particularly effective early during infection, but cytokine targeted therapies have shown benefit during later stages of illness, when hyperinflammation is present.

The most promising treatment for COVID-19 hyperinflammation is glucocorticoids when given to patients admitted to hospital with COVID-19 who require oxygen.[2] Nonetheless, this broadly immunosuppressive