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.

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

approach has not been that effective. Targeting individual pro-inflammatory cytokines (eg, interleukin [IL]-1 and IL-6) has shown some survival benefit but, again, the effect has been rather underwhelming.[3,4] Somewhere in between these two approaches, Janus kinase (JAK) inhibitors disrupt signalling downstream from receptors that bind multiple cytokines. Different small molecule JAK inhibitors target different kinases associated with various cytokine receptors, and ruxolitinib preferentially targets JAK1 and JAK2, which signal downstream of numerous pro-inflammatory cytokines, including IL-6 and interferon-γ.[5] In *The Lancet Rheumatology*, MeiLan Han and colleagues[6] report results from a randomised, double-blind, placebo-controlled trial of ruxolitinib to treat patients with COVID-19 (RUXCOVID).

In the RUXCOVID trial, 432 patients with COVID-19 were randomly assigned (2:1) to ruxolitinib (5 mg twice daily for 2 weeks) plus standard of care or placebo plus standard of care. The primary endpoint was a composite of death and requirement for invasive ventilation or intensive care by day 29. 34 (12%) of 284 ruxolitinib-treated patients and 17 (12%) of 144 placebo-treated patients met the composite endpoint (odds ratio 0·91, 95% CI 0·48–1·73; p=0·77), but the median time to recovery was 1 day faster in the ruxolitinib group, although this difference was not statistically significant (hazard ratio 1·10, 95% CI 0·89–1·36). Han and colleagues concluded that ruxolitinib showed no benefit for the overall study population and that a larger clinical trial is necessary to show potential benefit in subgroups of patients with COVID-19 who showed potential improvement with ruxolitinib.

The RUXCOVID trial is another failed attempt to treat the hyperinflammation associated with COVID-19 with immunomodulatory therapy. These results differ from a trial that showed some COVID-19 survival benefit for another JAK1/2 inhibitor, baricitinib, when used in combination with the antiviral remdesivir.[7] Less than 8% of patients with COVID-19 in the RUXCOVID trial received remdesivir, which might have contributed to this disparity in findings.[6] Additionally, only slightly more than half of the patients in the RUXCOVID study received dexamethasone, which is now standard of care for patients admitted to hospital with COVID-19, and might allow for anti-cytokine approaches to be beneficial.[3,4] Another JAK inhibitor, tofacitinib, showed a COVID-19 survival benefit in conjunction with standard of care (89% of patients received glucocorticoids).[8] Thus, JAK inhibitors, which inhibit signalling from multiple cytokines and are intermediate between glucocorticoid-induced broad immunosuppression and targeted cytokine approaches, appear to have a role in treating patients admitted to hospital with COVID-19.


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So, why is that some cytokine inhibitors, including different JAK inhibitors, show benefit for patients admitted to hospital with COVID-19, and others do not? Trial design, including patient selection, different standard of care regimens, and timing of therapies, could be critical.[9] The lack of benefit of ruxolitinib for patients with COVID-19 in the RUXCOVID trial[6] is somewhat surprising, given the ability of ruxolitinib to benefit a wide variety of patients with cytokine storm syndrome.[10] Therefore, the combination of glucocorticoids and ruxolitinib could be crucial to optimise therapy for patients with cytokine storm syndrome.[10] Moreover, as the optimal inflammatory features of COVID-19 were relatively unknown at the time of the RUXCOVID trial, patient selection did not include features such as high C-reactive protein, hyper-ferritinaemia, or elevated pro-inflammatory cytokine concentrations, but rather relied strictly on clinical criteria. Patients with COVID-19 with hyperinflammatory states are more likely to benefit from anti-cytokine therapies. Interestingly, ruxolitinib lowered IL-2RA levels, a marker of hyperinflammation,[1] in the RUXCOVID trial.

Although some laboratory markers (eg, IL-2RA, ferritin, D-dimers, C-reactive protein, and IL-6) of more standard varieties of cytokine storm syndrome[1] are elevated in patients with COVID-19, the degree of elevation is often modest, and only subsets of patients with COVID-19 meet traditional criteria for cytokine storm syndrome. Unsurprisingly, established treatment approaches used for cytokine storm syndrome[1] before the SARS-CoV-2 pandemic are notably less effective in treating the imperfect cytokine storm associated with COVID-19. Although there has been clear progress in dampening the cytokine storm associated with COVID-19, prevention of developing COVID-19 through highly effective and safe vaccines remains a priority.

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COVID-19 vaccine acceptance over time in patients with immune-mediated inflammatory rheumatic diseases

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Before the global distribution of COVID-19 vaccines, we observed substantial concerns among non-immunocompromised people about the lack of long-term research or the occurrence of adverse events after vaccination, and concerns among patients with immune-mediated inflammatory rheumatic diseases about interactions with their underlying autoimmune disease or immunosuppressive treatment regimens.[1] Our findings have since been replicated,[2,3] but there is as yet no data on how patients' thoughts and behaviour have evolved as vaccines were distributed, or data that compare COVID-19 vaccine coverage between patients with rheumatic immune-mediated inflammatory diseases and healthy controls.

In this Comment, we aim to describe the evolution of COVID-19 vaccination willingness over time in patients with immune-mediated inflammatory rheumatic diseases compared with controls, to evaluate motives for getting or not getting vaccinated against COVID-19, changes in psychosocial wellbeing after receiving a COVID-19 vaccination, and perspectives towards additional COVID-19 vaccinations. Questionnaires were sent to patients and controls included in an ongoing prospective cohort study (Netherlands Trial Register, trial ID NL8513) that was set up at the start of the COVID-19 pandemic to compare the severity of COVID-19 between patients with immune-mediated inflammatory rheumatic diseases and healthy controls. Between April 26, 2020, and March 1, 2021 all adult patients (aged ≥18 years) with an immune-mediated inflammatory rheumatic disease from the Amsterdam Rheumatology and Immunology Center (Amsterdam, Netherlands) were digitally invited to participate in the study.[4] Patients were asked, but not obliged, to recruit their own healthy control participant who was of the same sex and similar age (age difference <5 years). All participants provided written informed consent.

See **Online** for appendix

Data were collected via online questionnaires distributed via email.[4] Demographic data, including age, sex, height, weight, smoking status, disease type, ethnicity, and educational level, were collected at baseline. Information on patients' perspectives on COVID-19 vaccinations were collected in some, but not all, follow-up questionnaires of the study: in December, 2020, before the start of the Dutch vaccination programme; in April and May, 2021, shortly before the application of the COVID-19 vaccination passport; and in August and September, 2021, when the whole Dutch population had been given the chance to get a COVID-19 vaccination. A complete overview of the study surveys, including the content, is presented in the appendix (pp 12–17). Participants who completed at least two questionnaires that assessed their perspective on COVID-19 vaccination were included in the analyses.

In total, 1927 consecutive patients with immune-mediated inflammatory rheumatic diseases and 811 controls were included for analyses. The questionnaires sent in December, 2020, were completed