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with glucocorticoids.<sup>1</sup> Case reports have been published in which improvement or worsening of visual symptoms was reported in the context of tocilizumab treatment,<sup>10</sup> and more experience is needed to elucidate whether tocilizumab in the absence of glucocorticoids might facilitate vascular occlusion, either mechanistically or by masking subclinical activity.

In conclusion, the results of the GUSTO study are relevant although quite preliminary due to the study design. However, the pathogenesis of giant cell arteritis is too complex and incompletely understood to assume that blocking a single cytokine pathway will be enough to suppress the full-blown inflammatory process sustained by a highly redundant cytokine network. Remission induction by potent, wide-spectrum drugs such as glucocorticoids still seems to be necessary in patients with giant cell arteritis, although the results of the GUSTO study suggest that dose and duration of glucocorticoids currently used could be further reduced when pathways associated with relapsing disease, such as IL-6 signalling, are simultaneously blocked.

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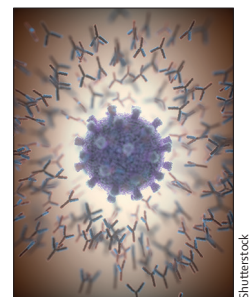
## Impact of methotrexate on first-dose COVID-19 mRNA vaccination



The current approach to COVID-19 vaccination of patients with immune-mediated inflammatory diseases is largely extrapolated from existing data relating to other vaccines. It is well recognised that methotrexate impairs humoral responses to both influenza and pneumococcal vaccines,<sup>1,2</sup> and a temporary discontinuation of therapy for 2 weeks enhances influenza vaccine immunogenicity in patients with rheumatoid arthritis.<sup>3</sup> These data were used as a surrogate for COVID-19 vaccination responses, prompting the American College of Rheumatology (ACR) to recommend temporary interruption of methotrexate for 1 week after each vaccine dose.<sup>4</sup> The degree to which this pause will translate to enhanced

COVID-19 vaccine responses is unclear, but data are rapidly accumulating.

In *The Lancet Rheumatology*, Satveer Mahil and colleagues report on both the humoral and cellular immune responses to the first dose of the COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) in a prospective longitudinal cohort of patients with dermatologist-confirmed psoriasis.<sup>5</sup> The patients from this cohort were unique in that they were largely in remission and were treated with methotrexate or other targeted biological monotherapy without concurrent use of glucocorticoids. In addition to assessing serological conversion, Mahil and colleagues addressed the key components of the adaptive immune response to vaccination, including



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T-cell responses and neutralising antibody responses. The humoral response to vaccination is well represented in the literature due to convenience and accessibility of antibody measurement. Seroconversion, or presence of IgG antibody specific to the SARS-CoV-2 spike protein, has been the main outcome measure used to assess COVID-19 vaccine responses in clinical trials and major studies so far. However, it is increasingly recognised that deeper immunophenotyping with rigorous assessment of humoral and cellular immunity will be needed to accurately evaluate COVID-19 vaccine immunogenicity.

The main finding of the study by Mahil and colleagues was a disparity between humoral and cellular immunogenicity of the BNT162b2 vaccine in patients treated with methotrexate. They report that cellular immunity, including T helper 1 and follicular T-cell responses, were similar in healthy controls and patients taking all classes of immunosuppression. Notably, however, they reported only a 47% (95% CI 21–73; seven of 15 patients) seroconversion rate in patients receiving methotrexate, along with correlating lower levels of antibody neutralisation (median 50% inhibitory dilution 129 [IQR 40–236]) compared with healthy controls (317 [213–487],  $p=0.0032$ ). The rate of serological conversion was quite low, contrasting with a previous study in which most patients taking methotrexate showed adequate humoral responses after the first dose of BNT162b2 vaccine.<sup>6</sup> Larger prospective studies have recently shown considerable immunogenicity induced by two doses of BNT162b2 vaccine in patients treated with methotrexate,<sup>7,8</sup> although data on cellular responses were not included. Notably, adherence to methotrexate was confirmed in all patients in the study by Mahil and colleagues, without any pause in the vaccination period, which could account for some of the disparities in the seroconversion rate. Consistent with existing data, Mahil and colleagues showed that targeted biological therapies, including tumour necrosis factor inhibitors, anti-interleukin (IL)-23 or anti-IL-17 agents, did not affect vaccine responses.<sup>6–8</sup>

Data on cellular responses to COVID-19 vaccination in patients with immune-mediated inflammatory diseases are scarce, and Mahil and colleagues are to be commended for their robust study design. However, their finding of preserved cellular response in most patients taking methotrexate contradicts that of Haberman and colleagues,<sup>9</sup> who showed ameliorated humoral and cellular response to two doses of BNT162b2 in patients treated

with methotrexate. The cause for this disparity is unclear and warrants additional investigation in larger samples of patients. In addition, the effect of peri-vaccination modification of therapy remains to be defined.

Last, methotrexate is a widely used therapy across many immune-mediated inflammatory diseases, and this study focused on patients with psoriasis; patients with other diseases were not included, and the authors did not examine the effect of other immunosuppressant regimens on the response to the first dose of the BNT162b2 vaccine. There is a growing body of evidence to suggest that lymphocyte-depleting agents such as mycophenolate, rituximab, and glucocorticoids, and the B-cell incompetence that results, are the primary factors associated with an attenuated humoral response to COVID-19 vaccines.<sup>6,7,9</sup> Further studies are required to assess both cellular and humoral response to COVID-19 vaccines across a heterogeneous population of patients with immune-mediated inflammatory diseases.

In immunocompetent patients, mRNA vaccines have elicited a strong antibody response, even after a single dose.<sup>10</sup> Previous studies have suggested that patients taking methotrexate have robust humoral responses; however, Mahil and colleagues report low rates of seroconversion in their sample of 17 patients. Although it is encouraging that cellular responses appear to be preserved even in patients with poor humoral responses, these findings are not consistent across study groups. During this period of clinical uncertainty, patients might remain vulnerable, especially after the first dose, and should engage in risk mitigation strategies.

Furthermore, given the promising findings after two-dose vaccination, we believe that both doses of the BNT162b2 vaccine should be administered per the approved schedule to reduce the burden of COVID-19 in this vulnerable population. Patients receiving immunosuppressive therapies should be prioritised for the regular schedule of vaccination (ie, not a prolonged interval between doses) and should be aware of the potential for suboptimal vaccine responses, even after completion of the vaccine series. With the spectre of variants looming, vaccination will allow patients to achieve maximum protection and reduce the burden of COVID-19. In the interim, there is a need for ongoing vigilance in observing non-pharmacological preventive measures in these patients.

We declare no competing interests.

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## Defining COVID-19-associated hyperinflammatory syndrome in specific populations



Among the unique characteristics of COVID-19 is a predilection to elicit a maladaptive immune response leading to excessive inflammation and organ injury.<sup>1</sup> This complication of severe COVID-19 is associated with poor outcomes, shares characteristics with other cytokine storm or hyperinflammatory syndromes,<sup>2</sup> and is the target for a variety of immunomodulatory therapeutics. Defining this syndrome and identifying which patient populations are at highest risk of developing hyperinflammation are high clinical priorities.

Identifying this risk is particularly important in patients with underlying systemic rheumatic diseases for several reasons. First, patients with these diseases often have an elevated inflammatory setpoint and might be more likely to develop secondary hyperinflammatory syndromes.<sup>3</sup> Second, immunomodulatory therapies used in patients with systemic rheumatic diseases might variably affect susceptibility to COVID-19 and its associated hyperinflammatory syndrome. For example, some therapies, such as tumour necrosis factor inhibitors, have been posited to temper complications associated with COVID-19 hyperinflammation.<sup>4</sup> Alternatively, drugs that impair humoral immunity, such as anti-CD19 monoclonal antibodies or non-selective antiproliferative drugs, might prolong the active virological phase of COVID-19, leading to perpetuated lung injury, persistent or relapsing

inflammation, and poor outcomes.<sup>5</sup> Finally, the interaction between systemic inflammation and immunomodulatory therapy and COVID-19 prognosis is further complicated by the high prevalence of chronic diseases in patients with systemic rheumatic diseases that independently increase risk for poor outcomes in COVID-19.<sup>6</sup>

In *The Lancet Rheumatology*, Tiffany Hsu and colleagues<sup>7</sup> report hyperinflammatory features and outcomes in patients with systemic rheumatic diseases admitted to hospital with severe COVID-19 compared with contemporaneous comparators without rheumatic diseases matched by age, sex, and date of initial PCR positivity for SARS-CoV-2. The authors compared levels of laboratory biomarkers, as well as the COVID-19-associated hyperinflammatory syndrome (cHIS) criteria, an ordinal diagnostic scale based on existing diagnostic criteria for other hyperinflammatory disorders and adapted to features unique to COVID-19.<sup>2</sup> Demographics and comorbid conditions were similar between patients with a rheumatic disease and comparators, with the exception of chronic kidney disease and interstitial lung disease, which were more common in patients. Body-mass index, which is an important contributor to poor outcomes of COVID-19, was similar between groups.

Hsu and colleagues' data showed that patients with systemic rheumatic diseases had higher expression

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