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Contemplation of treatment tapering or discontinuation in some patients with rheumatoid arthritis is remarkable and a measure of how far treatments have advanced. However, further work to address outstanding questions on who should taper and how best to do it is still required.

I declare no competing interests.

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## B cells: more than just for antibodies in SARS-CoV-2 vaccine responses

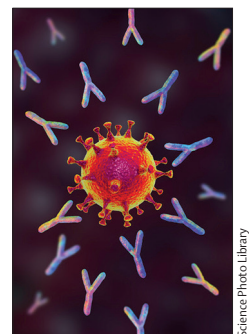


The emergence of SARS-CoV-2 has increased the risks of immunosuppressive therapies needed to treat chronic inflammatory diseases, such as glucocorticoids, methotrexate, and B-cell-depleting therapies.<sup>1</sup> Effective vaccines against SARS-CoV-2 provide a central instrument to reduce the risk of severe COVID-19 and death; however, immunosuppressive therapies can blunt vaccine responses.<sup>2</sup> A crucial question, therefore, is which forms of immunosuppression impair vaccine responses, particularly in response to novel platforms such as mRNA-based vaccines.

In a study in *The Lancet Rheumatology*, Laura Boekel and colleagues<sup>3</sup> measured seroconversion rates against the receptor-binding domain of the SARS-CoV-2 spike protein in 632 patients with autoimmune diseases, including rheumatoid arthritis, spondyloarthritis, juvenile idiopathic arthritis, vasculitis, Sjogren's syndrome, and multiple sclerosis, as well as in 289 healthy controls. A key aspect of this study was that investigators measured antibody responses after both the first and the second dose of the vaccine and stratified the analysis by previous SARS-CoV-2 infection. Boekel and colleagues showed reduced immunogenicity associated with methotrexate use (43 [30%] of 144 patients seroconverted) or CD20 B-cell-depleting therapies (one [6%] of 18 patients seroconverted) when compared with healthy controls (154 [73%] of 210 controls seroconverted) after the

first vaccination in participants who had not been previously infected with SARS-CoV-2. However, a second vaccination resulted in comparable rates of seroconversion for those taking methotrexate (17 [94%] of 18) and healthy controls (38 [95%] of 40), but not for patients on B-cell-depleting therapies (three [43%] of seven). By contrast, patients taking methotrexate with a previous SARS-CoV-2 infection had an excellent rate of seroconversion (22 [96%] of 23) after a single vaccination. In accordance with previous observations,<sup>4</sup> these data suggest that while methotrexate might blunt the antibody response to a single dose of vaccine, this effect can be overcome by repeated immunisation.

Although reduced antibody responses after B-cell depletion is predictable, what is less well understood is whether T-cell responses would be altered as well. In another study in *The Lancet Rheumatology*, Matthias Moor and colleagues<sup>5</sup> took a more detailed look at responses to mRNA vaccines against SARS-CoV-2 by examining both T-cell and B-cell responses simultaneously in 96 patients with a treatment history of CD20 B-cell-depleting therapies and 29 healthy controls. Similar to Boekel and colleagues,<sup>3</sup> Moor and colleagues<sup>5</sup> found that B-cell-depleting therapy was associated with poor antibody response to the vaccines with a seroconversion rate of 49% (47 of 96 patients) after the second vaccine dose. Additionally, Moor and colleagues found that the



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rate of T-cell responses to SARS-CoV-2 spike protein, by interferon- $\gamma$  release assay, were also diminished in the setting of B-cell-depleting therapies compared with healthy controls (20% vs 75%). Thus, B-cell-depleting therapies not only weaken humoral immunity but might also impair cellular immune responses to vaccination.

The association between poor seroconversion and concurrent use of B-cell-depleting therapies seen in both studies has also been observed in other contemporaneous reports.<sup>6-9</sup> However, what factors predict a poor antibody response have not yet been clarified. To address this knowledge gap, Moor and colleagues measured several laboratory covariates to determine the characteristics associated with optimal antibody responses. The investigators identified four factors that were associated with high antibody titres after immunisation in patients on B-cell-depleting therapies: higher numbers of circulating B cells and CD4 T cells, higher concentrations of IgM, and a longer time since the last infusion of B-cell-depleting agent. By contrast with IgM, circulating concentrations of IgG did not correlate with higher titres of anti-SARS-CoV-2 spike protein after vaccination. Although not a direct measure of the anti-SARS-CoV-2 antibody response, the numbers of circulating B cells and IgM concentration probably serve as an indirect surrogate for the size of the naive B-cell compartment that potentially contains antibody-secreting cells elicited by vaccination. This premise has been reported in a preprint article.<sup>10</sup> Additionally, the number of circulating CD4 T cells likely reflects the potential help that CD4 T cells provide to B cells to optimise antibody responses after vaccination.

The correlation between time since last infusion and antibody titre seen by Moor and colleagues has also been independently observed in patients treated with rituximab, with recovery of seroconversion gradually returning 6 months after the last infusion.<sup>2,9</sup> By contrast, in a study of patients treated with ocrelizumab, correlation with time since last treatment was not found; however, all patients had received B-cell-depleting therapies within 6 months of their SARS-CoV-2 vaccination.<sup>2</sup> Thus, these data raise the possibility that delaying repeat infusions of B-cell-depleting therapies by 6–12 months (when clinically feasible) might facilitate stronger antibody responses after vaccination.

Two previous studies in patients treated with rituximab found that T-cell responses to SARS-CoV-2 vaccination

were present regardless of a productive antibody response.<sup>7,8</sup> Although these results might appear to conflict with the current study results, there was a key methodological difference in the study approaches. The previous studies used an ELISpot assay to assess T-cell responses, which is a highly sensitive assay to measure the number of T cells that recognise a given antigen; whereas Moor and colleagues measured the total amount of interferon- $\gamma$  released after stimulation, which integrates the number of reactive T cells with the amount of interferon- $\gamma$  produced per cell. Thus, a reconciliation of both findings suggests the possibility that the number of vaccine-elicited T cells remains unchanged in patients on B-cell-depleting therapies, but that the quality of the T cells in their ability to produce interferon- $\gamma$  is impaired. This finding highlights a key role of B cells in promoting cellular immunity.

In summary, the collective findings of Boekel and colleagues<sup>3</sup> and Moor and colleagues<sup>5</sup> show the deleterious effect of B-cell-depleting therapies on protective immunity. Whether additional vaccine doses can overcome the detrimental effects of these therapies to generate effective humoral immunity requires further study.

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## Cutaneous vasculitis following COVID-19 vaccination



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Vaccines against SARS-CoV-2 represent a pivotal and effective countermeasure to contain the COVID-19 pandemic. Four vaccines are approved by the European Medicines Agency: two messenger RNA-based vaccines encoding the spike protein of SARS-CoV-2 (BNT162b2, Pfizer-BioNTech; mRNA-1273, Moderna) and two adenoviral vector-based vaccines encoding the spike protein (ChAdOx1 nCoV-19, AstraZeneca; Ad.26.COV2.S, Janssen).<sup>1</sup>

As of Sept 23, 2021, more than 83 million vaccine doses were administered in Italy, with approximately a fifth of recipients receiving ChAdOx1 nCoV-19 vaccine.<sup>2</sup> Here, we report three cases of cutaneous vasculitis developing in previously healthy individuals shortly after vaccination with ChAdOx1 nCoV-19.

The clinical features of the patients are summarised in the appendix (p 1). Briefly, patient 1 was a 57-year-old man with a history of hypertension but no previous personal or family history of autoimmunity. Purpura developed 14 days following the first vaccine dose, initially affecting the lower limbs and rapidly spreading to the abdomen, torso, and head (figure). He received treatment with 1 mg/kg prednisone, which led to progressive resolution of skin lesions over 3 weeks. Patient 2 was a 58-year-old man, whose previous medical history was also unremarkable with no history of autoimmunity. Purpura developed 7 days following the second dose of vaccine, spreading from the lower limbs to the abdomen and trunk (appendix p 2). He received 0.5 mg/kg prednisone, to no clinical benefit, and then 1 mg/kg prednisone, with progressive resolution of skin lesions over 10 days. Patient 3 was a 53-year-old woman with no underlying health conditions or history of autoimmunity. Purpura developed 6 days following the first dose, affecting

the lower and upper limbs. She received treatment with 1 mg/kg prednisone, which led to a progressive resolution of skin lesions over 2 weeks.

All cases were investigated for laboratory abnormalities or organ involvements that are typically associated with small-vessel vasculitis. However, laboratory tests showed only non-specific increases in erythrocyte sedimentation rate and C-reactive protein (CRP); anti-neutrophil cytoplasmic antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, rheumatoid factor, cryoglobulins, antinuclear antibodies, anti-DNA, C3, C4, IgA, and serology for hepatitis B virus and hepatitis C virus were negative or normal. Chest imaging (ie, x-ray or CT), urinalysis, and a search for stool blood were also negative. A 5 mm skin punch biopsy was performed in patient 3, which showed only a mild lymphocytic perivascular infiltrate (appendix p 3). A histological diagnosis of leukocytoclastic vasculitis could not be formally confirmed in the absence of neutrophils, yet disruption of the vessel wall, or fibrinoid necrosis, the

See Online for appendix



Figure: Purpura in patient 1