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.

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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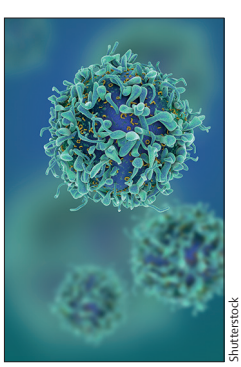
Immunity after COVID-19 vaccinations in immunocompromised patients with psoriasis

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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compared with controls (2749 [86–4770]; p=0·20), a trend that has also been observed in other studies.[3] This finding might be important because initial lower antibody titres might reduce the longevity of protection against COVID-19, as antibody titres and cross-neutralising activity to variants of concern decline over time.[4] However, Frey and colleagues observed that SARS-CoV-2 antibody titres could increase up to 3 months after a second COVID-19 vaccination in a subset of patients, primarily those treated with lymphodepleting therapies (ie, azathioprine, mycophenolate, or methotrexate),[5] which suggests that some immunosuppressive therapies might delay, rather than fundamentally impair, antibody development. As Mahil and colleagues and others[3] measured the antibody response within the first month after a second vaccination, the lower antibody titres reported in these studies might be an underestimation of the humoral immune response generated in patients receiving methotrexate. Additionally, the magnitude of antibody response after COVID-19 vaccination differs greatly between individuals, regardless of the presence of an underlying autoimmune disease or treatment with immunosuppressive agents, and the quantity of antibodies required to prevent symptomatic infection is still unknown.[2] Studies that assess effects of immunosuppressive agents on clinical outcome measures (ie, symptomatic COVID-19 breakthrough infections) are therefore urgently needed to establish associations between (neutralising) antibody titres and protection against COVID-19, and subsequently, to justify clinical recommendations that are thus far based only on laboratory findings (ie, temporary treatment discontinuation of methotrexate at the time of COVID-19 vaccination).

Although neutralising antibodies are reported as the most important surrogate marker for the development of protection against (severe) symptomatic COVID-19,[2] it is increasingly recognised that cellular immunity mediated by T cells also plays an important role in both short-term and long-term protection against the disease.[6,7] However, due to the functional heterogeneity of T cells, the role of cellular immunity, especially in patients treated with immunosuppressive therapy, is still incompletely understood.

Mahil and colleagues sought to improve on this knowledge gap by comparing T-cell responses after the first and second dose of the BNT162b2 vaccine in their cohort of patients with psoriasis treated with methotrexate or biologics and healthy controls. They assessed both T helper (Th)1 cell responses (based on production of interferon-γ and IL-2) and T follicular helper (Tfh) cell responses (IL-21), which is unique compared with other studies that mostly measured only Th1 cell function. These data are an important contribution to the literature because both Th1 and Tfh cells have been shown to contribute to protection against COVID-19. Th1 cells support and enhance cytotoxic ($CD8^+$) T cells that aid in protection against COVID-19 by killing infected cells,[6] and Tfh cells coordinate and sustain humoral immunity.[7] Mahil and colleagues observed that numerical levels of total T-cell responses and individual Th1 and Tfh responses did not significantly differ between patients and controls after both the first and second vaccination, whereas a significant increase of T-cell responses after a second vaccine dose occurred only in controls. Absence of boosting of cellular immunity has been shown previously, specifically for patients receiving methotrexate,[3] and at a larger scale for patients with immune-mediated inflammatory diseases who received various immunosuppressive agents.[8] Additionally, Picchianti-Diamanti and colleagues[9] reported that patients treated with IL-6 inhibitors or abatacept had diminished T-cell responses compared with healthy controls after two doses of BNT162b2. Therefore, the findings of Mahil and colleagues and others[3,9] suggest that the longevity of protection against COVID-19 might be impaired in patients treated with targeted immunosuppression, given the fundamental role of T cells in sustaining and promoting both cellular and humoral immunity. However, the exact mechanisms that underly the reported immunoinhibitory effects of individual immunosuppressive agents, especially TNF, IL-23, and IL-17 inhibitors, and how the reported laboratory findings translate to clinical outcome measures, remain unclear and warrant further research.

In conclusion, the findings of Mahil and colleagues on antibody development after COVID-19 vaccination in patients treated with methotrexate or targeted immunosuppressive agents are reassuring, whereas their observation of absence of boosting of T-cell responses might indicate that durable cellular and humoral immunity is impaired in some patients

receiving these drugs. Studies with clinical outcome measures in immunocompromised patients are needed and are important to warrant clinical decisions regarding additional booster vaccinations or temporary treatment discontinuation at the time of vaccination.

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Uricaemia as a surrogate endpoint in gout trials and the treat-to-target approach for gout management

Gout is believed to be the best understood and treatable type of inflammatory arthritis. Monosodium urate crystals that deposit as a result of long-term hyperuricaemia are pathogenic and cause flares, tophi, and bone erosion. Flares are the most frequent and disabling manifestation of gout and are thought to be triggered by monosodium urate crystals moving from their site of deposition on cartilage into the joint space, allowing interaction with cells of the synovial lining and activation of the NLRP3 inflammasome.[1]

Therefore, rheumatology societies have unanimously recommended a treat-to-target serum urate approach for the management of gout that aims to reduce serum urate concentration to below the monosodium urate saturation point, to dissolve pathogenic crystals.[2–4] However, the first months of effective urate lowering therapy are associated with an increased risk of flares, which are believed to result from mobilisation of monosodium urate crystals within joints following partial dissolution of articular deposits. Furthermore, crystal depletion is a long process, which is why cessation of gout flares is usually not seen within 12 months of starting urate lowering therapy, the most common duration of gout drug trials. This delay in the positive effects of urate lowering has led to some uneasiness in accepting low uricaemia as a robust surrogate endpoint.

The study in *The Lancet Rheumatology* by Lisa K Stamp and colleagues[5] brings reassurance on the validity of decreasing serum urate concentration to less than 6 mg/dL (360 µmol/L) as a surrogate endpoint in gout trials. This post-hoc analysis of two trials that mostly used allopurinol—the most widely used urate lowering therapy—involved a total of 588 patients with gout and showed that achieving a serum urate concentration of less than 6 mg/dL (which is recommended by most rheumatology societies) during the first year of urate lowering therapy drastically reduced the risk of flares during the second year of continued treatment (adjusted odds ratio [OR] 0·29 [95% CI 0·17–0·51], p<0·0001).

Stamp and colleagues also explored the effects of reaching 5 mg/dL (300 µmol/L) and 7 mg/dL (420 µmol/L) serum urate targets. Although no formal comparison was made, achieving a 5 mg/dL target appeared to show a similar reduction in the risk of flares during the second year (adjusted OR 0·31 [0·17–0·59], p<0·0001) compared to achieving the 6 mg/dL target. The lower 5 mg/dL target has been advocated for the management of severe, tophaceous


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