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Suspending methotrexate for 2 weeks after COVID-19 vaccination


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People with inflammatory arthritis treated with immune-suppressing drugs are members of a large, clinically vulnerable patient group that is at increased risk of hospitalisation and death from COVID-19.[1] Effective vaccination against COVID-19 has improved disease outcomes worldwide but there have been concerns about the effectiveness of vaccinations in immunosuppressed individuals because of lowered COVID-19 vaccine-induced immunity.[2]

In *The Lancet Rheumatology,* Teny Grace Skaria and colleagues[3] report the results of two clinical trials—MIVAC I and II—that investigated the effect of a 2-week hold of methotrexate treatment on COVID-19 vaccine immunogenicity using an antibody against the spike antigen in the receptor binding domain (S1-RBD).[3] The study showed that withholding methotrexate after each of the two doses of ChAdOx1 nCov19 vaccine, and after only the second dose, led to approximately two-times higher antibody titres 4 weeks after the second vaccine dose compared with methotrexate continuation. Withholding methotrexate only after the second vaccine dose rather than after both doses appeared to be as effective, and did not increase the risk of arthritis flares (withholding methotrexate after both doses did show a significant association with disease flare). A positive effect of a temporary hold in methotrexate on vaccine-induced immunity has been shown with three different COVID-19 vaccine technologies[4,5] and the influenza vaccine.[6,7] However, these studies were relatively small, with short follow-up periods, and were not designed to assess the effect of withholding methotrexate on the risk of infections or their complications. Nevertheless, the consistency of effect across different vaccines makes the findings relevant to patient care and should be considered when planning future vaccinations against COVID-19 or influenza in this population.

In the MIVAC I and II studies,[3] patients with previous COVID-19 were excluded from random assignment and analysis to provide a homogeneous population to test the effect of the interventions on antibody levels. This strategy differs from a previous study that included all patients regardless of previous COVID-19 status to provide more real-world evidence.[4] The two MIVAC trials addressed slightly different interventions but are complementary. The population in these studies was heterogeneous but reflective of the clinical population with well-controlled rheumatoid arthritis (>90% patients in the studies) and psoriatic arthritis with low disease activity. A substantial proportion of patients were taking immune-suppressing disease-modifying anti-rheumatic drugs (DMARDs) with around 10%, 3%, and 1% prescribed leflunomide, tofacitinib, and anti-TNF, respectively. This observation raises the potential for a future exploratory subgroup analysis to investigate the effect of a temporary suspension in methotrexate treatment on COVID-19 vaccine-induced immunity in the context of additional immunosuppression.

The absence of an incremental effect on vaccine-induced immunity from holding methotrexate after the first ChAdOx1 nCov19 vaccine dose is intriguing. This finding might be due to relatively low serological immunogenicity after the first vaccine dose in this population—in the context of low immunogenicity, holding methotrexate for 2 weeks after vaccination might not have had a detectable immune-boosting effect. This finding might not hold true in the context of other vaccine technologies (eg, mRNA). Nevertheless, patients who are unvaccinated against COVID-19 or those who have received one dose of ChAdOx1 nCov19 vaccine and are intending to complete their primary vaccination series using ChAdOx1 nCov19 vaccine ought to consider skipping methotrexate for 2 weeks after the second vaccine dose.

Beyond this study, there remain unanswered questions. There have not been any detailed T-cell or memory B-cell immunity studies to examine the underlying mechanisms. There are various other immunosuppressant medications. Similar concerns exist as to their effect on vaccine immunogenicity, but there are no strong data on other drugs at present, and it is difficult to extrapolate from methotrexate. Nevertheless, the American College of Rheumatology recommend a break from immunosuppressive DMARDs for 1–2 weeks after COVID-19 vaccination based on expert opinion.[8]

This study adds to the literature showing that a temporary hold of methotrexate improves the

response to primary and booster vaccinations against COVID-19.[3-5] This issue is important given that the COVID-19 pandemic is ongoing globally. As a result of emerging evidence,[4] the British Society of Rheumatology have changed their guidance to support a temporary hold of methotrexate after vaccination.[9]

Further COVID-19 booster vaccinations are planned for high-risk individuals in many countries. As patients with rheumatic diseases are recommended to get both influenza and COVID-19 vaccinations regularly, it is reasonable to organise these vaccines to be administered together, allowing patients to take a single 2-week break from their drug treatment (in consultation with their specialist) after vaccination rather than risk multiple periods off treatment.[10] Future research is needed to provide additional evidence on the benefits and risks of holding other immunosuppressant drugs in the context of vaccination to best protect rheumatology patients.

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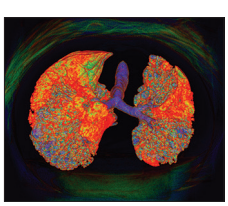
Increased risk of severe COVID-19 outcomes in patients with rheumatoid arthritis and interstitial lung disease

Patients with chronic autoimmune disorders are naturally at higher risk of infection, and immunosuppressive therapy increases this risk. The COVID-19 pandemic in many ways provided a perfect storm for patients with rheumatoid arthritis, especially for those with systemic complications such as interstitial lung disease. In the absence of evidence, their responsible clinicians had no way of knowing whether continuing immunosuppressive therapy increased or reduced survival during the pandemic. The Article by Gabriel Figueroa-Parra and colleagues[1] in *The Lancet Rheumatology* shows that patients with rheumatoid arthritis are at increased risk of severe COVID-19 (ie, hospitalisation or death after COVID-19) compared with matched comparators without rheumatoid arthritis (hazard ratio [HR] 1·75 [95% CI 1·45–2·10]). When examining phenotypic features of rheumatoid arthritis, patients with rheumatoid arthritis-related interstitial lung disease had an even greater risk (HR 2·50 [1·66–3·77]) for severe outcomes than those without rheumatoid arthritis following infection with SARS-CoV-2.[1] These data add to previous evidence that patients with interstitial lung disease are at increased risk of adverse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