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.

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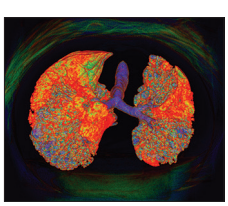
Increased risk of severe COVID-19 outcomes in patients with rheumatoid arthritis and interstitial lung disease

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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outcomes from COVID-19.[2,3] However, at present, it remains impossible to estimate the degree to which rheumatoid arthritis, the associated interstitial lung disease, and the medication that these patients require for their disease individually contribute towards this increased risk. The number of patients on each specific drug was too small for reliable statistical analysis in this study. Understanding which drugs are safe to use during the pandemic is a complex but key issue for clinicians managing patients with rheumatoid arthritis-related interstitial lung disease, as some drugs used, or proposed, for the treatment of rheumatoid arthritis-related interstitial lung disease have also been trialled in the treatment of COVID-19 pneumonia, which shares overlapping clinical features with acute-onset interstitial lung disease in patients with rheumatoid arthritis.[4]

Glucocorticoids, interleukin (IL)-6 inhibitors, and Janus kinase (JAK) inhibitors have been shown to have potential benefit in the treatment of patients with acute pneumonia from COVID-19.[5] Although oral prednisone is no longer considered standard treatment for rheumatoid arthritis-related interstitial lung disease, there is some evidence for the efficacy of IL-6 and JAK inhibitors in this condition.[6] By contrast, there is concern that rituximab might increase the risk of mortality in patients with acute COVID-19,[7] despite being associated with improved outcomes in the management of rheumatoid arthritis-related interstitial lung disease.[8] The data available from the admittedly small numbers of participants from Figueroa-Parra and colleagues supports the evidence that rituximab increases the risk of mortality in patients with COVID-19 in suggesting that worse outcomes might have been associated with rituximab therapy, whereas reduced risk of mortality might have been accorded to those on JAK inhibitors.[1]

There is good evidence that the subset of interstitial lung disease is a major determinant of prognosis of rheumatoid arthritis-related interstitial lung disease. Patients with rheumatoid arthritis-related interstitial lung disease with a usual interstitial pneumonia pattern on imaging have a four-fold increased risk of death compared with those with non-specific interstitial pneumonia.[9] Furthermore, the extent of lung involvement, as assessed by imaging, is an additional determinant of prognosis.[10] Neither of these variables were assessed in the study by Figueroa-Parra and colleagues, making it difficult to predict whether the adverse outcomes of COVID-19 in people with rheumatoid arthritis-related interstitial lung disease are confined to those with extensive usual interstitial pneumonia or whether they apply to all patients with interstitial lung disease.

Women with rheumatoid arthritis appeared to be at considerably higher risk of severe COVID-19 (HR 2·03 [1·62–2·55] compared with women without rheumatoid arthritis) than were men with rheumatoid arthritis (1·23 [0·88–1·74] compared with men without rheumatoid arthritis).[1] This increased risk might appear counterintuitive given that interstitial lung disease develops more frequently in men. However, the respiratory reserve is usually greater in men, and obesity, which increases the risk of adverse outcomes, might be more common in women. Other known risk factors for interstitial lung disease in people with rheumatoid arthritis analysed in this study included age, smoking, and seropositivity. Increased articular disease activity is also associated with interstitial lung disease; however, this study was unable to assess the potential influence of disease activity on outcomes due to its retrospective design. Clinicians treating patients with rheumatoid arthritis-related interstitial lung disease need to balance their enthusiasm to reduce the activity of disease in the joints and lungs against the potential increased risk of severe COVID-19 from immunosuppression.

It is important to note that this study was done in the first 15 months of the COVID-19 epidemic. As a result, only 21 (4%) of the patients included had the opportunity to receive vaccination before enrolment. The risk of developing severe COVID-19 in patients with rheumatoid arthritis-related interstitial lung disease is likely to be reduced by vaccination (as this study recognises), and repeating this study in a vaccinated rheumatoid arthritis population could provide valuable guidance for clinicians and public health physicians.

The key message from this Article is that people with rheumatoid arthritis are at higher risk of developing severe COVID-19, and that, for those with interstitial lung disease, the risk appears especially high. However, several factors remain unknown, including the degree of vaccination that attenuates the risks of severe COVID-19 and how much of the risk is due to the disease rather than drugs used to treat it. Detailed answers to these questions are essential for clinicians if they are to offer patients accurate evidence-based advice. Additional data on the potential contributions of high disease

activity and interstitial lung disease subtype could also be provided in a large prospective study designed to address these issues in a vaccinated rheumatoid arthritis population with detailed therapeutic documentation.

I declare no competing interests.

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Preventive medicine in rheumatology: COVID-19 and its lessons for better health outcomes

The COVID-19 pandemic not only persists but represents a substantive ongoing threat to patients on immunosuppressive therapies. Advances in antiviral therapies and vaccines have led to substantially reduced risk, of both infection and adverse outcomes, for people who can access them,[1] but the risk is ongoing as new variants emerge. In this continuing battle, some approaches, such as glucocorticoids, will persist in their original form and some will become irrelevant, such as older neutralising monoclonal antibodies.[2] Many strategies, such as vaccines and antivirals, will sit between these two extremes, in need of constant revision of strategy to deliver protection. In this race to deliver new solutions relevant to current threats, patients who are immunosuppressed need us to not only continually assess effective strategies for them, but also think carefully about their application in practice.

In *The Lancet Rheumatology*, Malcolm Risk and colleagues[3] report the findings of their study of COVID-19 vaccine effectiveness in patients on immunosuppressants during the omicron (B.1.1.529 variant)-dominant wave of the pandemic. Among 168 414 patients from the US state of Michigan during the first omicron peak (December, 2021, to March, 2022), the 5609 patients who were taking immunosuppressive mediations had increased risk of adverse outcomes compared with those who were not immunosuppressed. Patients taking immunosuppressive disease-modifying antirheumatic drugs (hazard ratio 2·32, 95% CI 1·23–4·38; p=0·0097) and those taking glucocorticoids (2·93, 1·77–4·86; p<0·0001) were at increased risk of hospitalisation due to COVID-19 compared with those who were not immunosuppressed, a finding that is consistent with both initial studies and two more recent large studies.[4–6]

Poorer outcomes have been observed consistently in multiple, rigorous, large datasets of varied origin and context, suggesting that COVID-19 remains a risk that disproportionately impacts patients who are immunosuppressed. Importantly, though, the study by Risk and colleagues[3] shows that, even in the era of the omicron variant, preventive therapy still mitigates this risk: patients who received three doses of either available mRNA vaccine derived significant benefit over those who received two doses (50% [95% CI 31 to 64] vaccine effectiveness against SARS-CoV-2 infection for three doses of the BNT162b2 vaccine; p<0·0001; *vs* 13% [–19 to 39] for two doses; p=0·43; compared with those who were unvaccinated). However, protection against hospitalisation due to COVID-19 was similar between patients who received three doses and those who received two doses (87% [95% CI 74 to 93] vaccine effectiveness with three doses of either mRNA vaccine

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