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Protecting the vulnerable: SARS-CoV-2 vaccination in immunosuppressed patients with interstitial lung disease

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Interstitial lung diseases (ILDs) comprise a vast array of conditions that can be responsive or non-responsive to immunosuppression. When immunosuppression is used, most commonly in connective tissue disease-associated ILD, hypersensitivity pneumonitis, and sarcoidosis, the clinician and patient have to navigate carefully between too much and too little modulation of the immune system. The COVID-19 pandemic is a threat to this equilibrium, with uncertainty about the risks of SARS-CoV-2 infection for these patients and concerns around vaccine efficacy and safety.

In the largest analysis to date, the presence of various ILDs conferred an approximately 50% increase in the risk of death from COVID-19.[1] Individuals with fibrotic and more advanced disease are at a higher risk of severe illness and mortality from COVID-19 than are controls matched for age, sex, and comorbidities.[2–5] However, there are few data relating to COVID-19 specifically in people with ILDs using immunosuppression.

Established risk factors for severe COVID-19, such as diabetes, hypertension, and obesity, are prevalent among patients with ILDs who are immunosuppressed. In Drake and colleagues' European ILD cohort,[2] in which almost a third of patients were receiving some form of immunosuppression before SARS-CoV-2 infection, the data do not allow an assessment of the effect of immunosuppression on outcomes. A French report,[3] indicated no association between severe COVID-19 infection and background corticosteroids or immunosuppression in patients with ILDs, although the sample size was small and the risk is likely to differ according to the immunosuppressive agent being used. Information from rheumatological cohorts is conflicting, although the evidence is generally suggestive of an increased likelihood of severe disease. Specifically, background corticosteroid therapy, particularly in doses of more than 10 mg prednisolone per day, might confer an increased risk.[3,6–8] Treatment with rituximab has also been associated with worse COVID-19 outcomes in patients with rheumatic diseases.[8,9]

Although definitive data on the risk posed by the combination of ILD, immunosuppression, and autoimmune disease are not yet available, it is important to minimise the chance of SARS-CoV-2 infection (and hence severe COVID-19 disease) in such populations, which should be prioritised for vaccination. A major concern is the effect of immunosuppressive treatment on the development of effective immune responses after vaccination. Primary data to inform patients with ILDs using immunosuppression are not available. Evidence can be extrapolated from the rheumatological and transplant literature, with most current information limited to studies on mRNA vaccines (appendix pp 1–3). A markedly lower immunogenicity of SARS-CoV-2 mRNA vaccines has been observed in patients receiving corticosteroids (independent of dose), mycophenolate,[10] B-cell depleting therapies (including rituximab), or combination immunosuppression compared with those not on treatments or immunocompetent controls.[11] Compared with detectable antibody (seropositivity) of 98% in immunocompetent controls, only 65% of people using any dose of prednisolone were seropositive after two doses of mRNA vaccines (BNT162b2 or mRNA-1273).[11] A 36-times reduction in anti-Spike protein immunoglobulin G (IgG) and SARS-CoV-2 neutralisation titres was found in people receiving B-cell depleting therapy.[11] Vaccine immunogenicity is also reduced in people using methotrexate.[11,12] By contrast, anti-tumour necrosis factor therapies appear not to have a substantial effect on the generation of a humoral response to SARS-CoV-2 vaccination.[11,12] Reduced or absent serological responses to mRNA vaccines are reported in recipients of solid organ transplants, who often use multiple immunosuppressive agents, particularly in those receiving antimetabolite therapies (mycophenolate or azathioprine).

The humoral immune response is needed to clear infection, as shown by the occurrence of severe and protracted disease with anti-CD20 therapy and primary antibody deficiency.[13] However, how impaired seroconversion affects COVID-19 disease outcomes if an individual is infected after vaccination is not yet known. Cell-mediated immunity is also required for viral clearance and is generated in response to SARS-CoV-2 vaccination. This response might be important in protecting immunosuppressed patients with ILDs who

are not mounting an antibody response, although further work is needed to confirm this.

The American College of Rheumatologists' guidance on SARS-CoV-2 vaccination advises against delaying vaccination for almost all immunosuppressive therapies.[14] In the case of rituximab, the college suggests that the optimal vaccination timing might be 4 weeks before the next scheduled dose, and that rituximab should be delayed 2–4 weeks after the second vaccination where feasible. Withholding methotrexate or delaying cyclophosphamide for 1 week after vaccination has been proposed to improve vaccine efficacy in patients receiving these treatments. Whether this strategy is effective is unknown, because most of the data are inferred from influenza vaccination. Of note, patients with ILDs receiving rituximab or cyclophosphamide often have severe or rapidly progressive disease, and it might not be possible to delay the next dose of treatment in someone requiring urgent immunosuppression. Patients who might require these drugs at some point in the future, including those with idiopathic inflammatory myopathy-associated or systemic sclerosis-associated ILDs, should be encouraged to have the vaccine at the earliest opportunity.

Another strategy to improve vaccine responsiveness is to reduce immunosuppression around the time of vaccination. However, in patients with ILDs, the risk of disease progression to irreversible fibrosis should be weighed against the possible increased vaccine efficacy after immunosuppressant dose reduction. Further prospective work in people on immunosuppression, including those with underlying ILDs, is urgently required. Many studies are currently recruiting to address this knowledge gap, although none specifically in patients with ILDs.

There is no reason to suggest that patients who are immunosuppressed are at any greater risk of vaccine-related complications. Patients should be reassured that none of the currently available vaccines includes a live replication-competent virus, nor is there evidence of a link between immunosuppression and the thrombosis with thrombocytopenia syndrome observed with some vaccines. The possibility of an acute ILD exacerbation after SARS-CoV-2 vaccination is a potential concern. Although there have been no published reports of this complication, vigilance is still warranted.

It is important not to become complacent about other precautionary measures. These measures include personal protective approaches, an awareness of physical distancing, and encouragement of mass vaccination in the general population. Immunocompetent household contacts should be strongly encouraged to receive a SARS-CoV-2 vaccine. In the future, patients with ILDs who are immunosuppressed could benefit from research into vaccination approaches to boost effectiveness, including extra doses or mixing of vaccines. For example, in a population of recipients of a solid-organ transplant, a third dose of the BNT162b2 mRNA vaccine was associated with the development of anti-Spike protein IgG in 44% of those who were seronegative after the conventional two doses,[15] suggesting that a similar approach could be used in immunosuppressed patients with ILDs who do not mount seropositivity. Also, the use of monoclonal antibodies directed against SARS-CoV-2 spike protein is being studied as a means of providing prophylactic passive immunisation (NCT04625725).

There is little current evidence for routine SARS-CoV-2 antibody testing before or after vaccination. Patients with ILDs should continue to be vaccinated as per local guidance and targeted for enrolment in vaccine clinical trials, recognising that the approach to vaccination might change in the months and years to come. If infection does nevertheless occur in patients who are immunosuppressed and unable to generate humoral immune responses, treatment with antibody-based therapies (with or without remdesivir) shows promise and might be more effective in those who are immunosuppressed than in the general population.[13,16]

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