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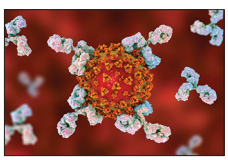
Immunosuppression and SARS-CoV-2 breakthrough infections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Within a year of the introduction of vaccines against SARS-CoV-2, global research efforts had identified that subsets of patients with immune-mediated inflammatory diseases have suboptimal humoral responses after vaccination. Specifically, B cell-depleting therapies, mycophenolate mofetil, and glucocorticoids were found to confer the greatest risk of poor humoral immunity,[1,2] suggesting that patients on these therapies will have the highest risk and severity of breakthrough infections.

Data has emerged confirming these suspicions in patients with immune-mediated inflammatory diseases. The US National COVID Cohort Collaborative consortium found that those who were fully vaccinated on immunosuppression had a 1·25–2·18 times increased risk of breakthrough infection with SARS-CoV-2 after vacciantion.[3] Several case series identified patients taking B cell-depleting therapies, mycophenolate mofetil, methotrexate, and glucocorticoids and those with interstitial lung disease as comprising a very high proportion of those breakthrough cases.[4–6] Furthermore, the absence of anti-spike antibodies 4–6 weeks after the second dose of COVID-19 vaccine is associated with a 3·6 times increase in breakthrough infection compared with presence of robust humoral responses.[7] Thus, risk of breakthrough infection after COVID-19 vaccination among people with immune-mediated inflammatory diseases could correlate with poor antibody responses from specific immunosuppressive medications.

In *The Lancet Rheumatology*, Laura Boekel and colleaguges[8] extend these observations during the second half of 2021 (when the delta [B.1.617.2] variant of SARS-CoV-2 was dominant in Europe) by pooling two large Dutch cohorts: Target-to-B! (T2B!) and the Amsterdam Rheumatology Center COVID study (ARC-COVID). Using electronic case record forms, medical files, and digital questionnaires, they prospectively examined the cumulative incidence of SARS-CoV-2 breakthrough infections (confirmed by PCR or serology) at least 14 days after COVID-19 vaccination between 3207 immunosuppressed patients with immune-mediated inflammatory disease and 1807 immunocompetent controls (comprising healthy controls [n=822] and patients with immune-mediated inflammatory diseases not on immunosuppressants [n=985]). The majority of participants received an mRNA vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]), and the top two immunosuppressants used in the cohorts were methotrexate (992 [31%] of 3207) and TNF inhibitors (929 [29%]). 437 (14%) of 3207 immunosuppressed participants were on either B cell-depleting therapies, mycophenolate mofetil, or S1P receptor modulator therapy.

Boekel and colleagues observed increased crude incidence rates of breakthrough infections among the immunosuppressed patients with immune-mediated inflammatory diseases (8·0 per 1000 person-months) and non-immunosuppressed patients with immune-mediated inflammatory diseases (9·2 per 1000 person-months) compared with healthy controls (6·6 per 1000 person-months). However, in multivariable analyses, no association was seen between immunosuppression and risk of breakthrough infection when compared with the combined controls (odds ratio [OR] 0·88 [95% CI 0·66–1·18). 24 (5%) of 437 participants on B cell-depleting therapies, mycophenolate mofetil, or S1P receptor modulator therapy had a breakthrough infection, compared with 37 (4%) of 992 patients using methotrexate and 49 (5%) of 929 using TNF inhibitors. Interestingly, in post-hoc analyses, specific immunosuppressive class was not associated with risk of breakthrough infection, although the study might have been too small to detect small differences. However, participants with more severe outcomes of breakthrough infections (ie, those who were admitted to hospital *vs* ambulatory care only) were on average older, more likely to be male, and more frequently had obesity, chronic pulmonary disease, diabetes, and cardiovascular disease. Most of the breakthrough infections occurred more than 3 months after vaccination, suggesting either waning immunity or differences in viral epidemiology related to surges in cases. Seropositive participants had reduced odds of breakthrough infections (OR 0·58 [95% CI 0·34–0·98]), concentrated in those with the highest anti-receptor binding domain titres (OR 0·57 [0·28–1·16]); although this was not significant. Finally, those with hybrid immunity (ie, previous SARS-CoV-2 infection before first dose of vaccine) had a lower odds of breakthrough infection (OR 0·34 [0·18–0·56]) than did those without this immunity. Thus, productive humoral responses

appear to confer protection from breakthrough infection.

This is the largest prospective study to investigate clinical outcomes related to breakthrough infection and was adequately sized to investigate specific immunosuppressive medications. Few severe outcomes occurred, and these were more common in the immunosuppressed participants with immune-mediated inflammatory diseases, particularly among those on B cell-depleting therapies. These patients remain susceptible to poor outcomes even after vaccination,[9] so strategies such as pre-exposure prophylaxis or additional vaccine doses should be strongly considered for this population.

Although there were some signals for breakthrough infection in specific patient groups (eg, seronegative status and some comorbidities), the findings of Boekel and colleagues are reassuring to patients who are immunosuppressed. After vaccination, overall rates and clinical severity of breakthrough infections among patients with immune-mediated inflammatory diseases was similar to among healthy controls. How subsequent variants, such as omicron (B.1.1.529) that might confer reduced vaccine effectiveness, will affect infection rates remains unknown. Patients with immune-mediated diseases who are immunosuppressed might have accelerated waning immunity, placing them at risk over time after vaccine receipt. Therefore, quantifying the effect of additional vaccine doses on breakthrough infection with contemporary circulating variants is needed. Finally, although the findings here offer some evidence that humoral responses confer clinical protection, the specific threshold that offers protection remains unclear. Those with absent humoral responses remain at risk for breakthrough infection, but we continue to caution clinicians to not overinterpret anti-spike antibody levels as a surrogate of protection at the individual level.

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*Alfred H J Kim, Jeffrey A Sparks
akim@wustl.edu; @alhkim

Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St Louis, MO 63110, USA (AHJK); Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston, MA, USA (JAS); Department of Medicine, Harvard Medical School, Boston, MA,, USA

1 Boekel L, Steenhuis M, Hooijberg F, et al. Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. *Lancet Rheumatol* 2021; **3:** e778–88.
2 Deepak P, Kim W, Paley MA, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. *Ann Intern Med* 2021; **174:** 1572–85.
3 Sun J, Zheng Q, Madhira V, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. *JAMA Intern Med* 2022; **182:** 153–62.
4 Cook C, Patel NJ, D'Silva KM, et al. Clinical characteristics and outcomes of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases. *Ann Rheum Dis* 2022; **81:** 289–91.
5 Lawson-Tovey S, Hyrich KL, Gossec L, et al. SARS-CoV-2 infection after vaccination in patients with inflammatory rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2022; **81:** 145–50.
6 Liew J, Gianfrancesco M, Harrison C, et al. SARS-CoV-2 breakthrough infections among vaccinated individuals with rheumatic disease: results from the COVID-19 Global Rheumatology Alliance provider registry. *RMD Open* 2022; **8:** e002187.
7 Ahmed S, Mehta P, Paul A, et al. Postvaccination antibody titres predict protection against COVID-19 in patients with autoimmune diseases: survival analysis in a prospective cohort. *Ann Rheum Dis* 2022; published online Feb 8. https://doi.org/10.1136/annrheumdis-2021-221922.
8 Boekel L, Stalman EW, Wieske L, et al. Breakthrough SARS-CoV-2 infections with the delta (B.1.617.2) variant in vaccinated patients with immune-mediated inflammatory diseases using immunosuppressants: a substudy of two prospective cohort studies. *Lancet Rheumatol* 2022; published online April 29. https://doi.org/10.1016/S2665-9913(22)00102-3.
9 Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. *Ann Rheum Dis* 2021; **80:** 1137–46.

Effectiveness of COVID-19 vaccination in immune-mediated inflammatory diseases

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The rapid development of safe and effective COVID-19 vaccines was a hallmark achievement in the pandemic. However, patients with immune-mediated inflammatory diseases were excluded from vaccine clinical trials and might be vulnerable to SARS-CoV-2 breakthrough infection due to immunosuppression and altered immunity.[1,2] Indeed, studies showed lower humoral responses after COVID-19 vaccination in these patients than in healthy controls.[3,4] Although most patients who are immunosuppressed had only a slightly reduced humoral response after COVID-19 vaccination, some medications, such as B cell-depleting therapies, are associated with severely reduced response.[3,4] There had been no previous systematic evaluation to quantify