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# Working towards a comprehensive appraisal of vaccine-induced immunity against SARS-CoV-2 in IBD

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In *The Lancet Gastroenterology & Hepatology*, Zhigang Liu and colleagues,[1] on behalf of the CLARITY-IBD study investigators, report on the effect of different immunomodulating treatments commonly prescribed to patients with inflammatory bowel disease (IBD) on serological responses against the highly transmissible SARS-CoV-2 omicron (B.1.1.529) variants (BA.1 and BA.4 and BA.5 [hereafter BA.4/5]). In this prospective, multicentre, cohort study, functional neutralising antibody responses against SARS-CoV-2 wild-type and omicron BA.1 and BA.4/5 variants after three doses of SARS-CoV-2 vaccine were investigated in 1288 patients with IBD without previous SARS-CoV-2 infection, and who were treated with either infliximab (n=871) or vedolizumab (n=417) recruited from infusion units across the UK. The median age of patients was 46·1 years (IQR 33·6–58·2) and 612 (47·5%) of 1288 were female, 663 (51·5%) were male, 1209 (93·9%) were White, and 46 (3·6%) were Asian. The investigators found that patients treated with infliximab had significantly lower neutralising antibodies against all investigated SARS-CoV-2 variants than did those being treated with vedolizumab, irrespective of the primary vaccination schedule. Additionally, they found that breakthrough SARS-CoV-2 infections were associated with lower neutralising antibody titres against the BA.4/5 variant in patients being treated with infliximab and in those being treated with vedolizumab. These trends remained present after adjusting for potentially confounding patient characteristics (eg, age, concomitant use of immunomodulators and corticosteroids, and comorbidities) with inverse probability of treatment weighting, a statistical method used to correct for such characteristics by reducing the bias of potentially unweighted estimators.[2] The findings of this study have important implications for patients with IBD, supporting the prioritisation of second-generation, bivalent booster vaccinations for patients who are treated with infliximab, who generally have lower neutralising antibody titres against the SARS-CoV-2 BA.1 and BA.4/5 omicron variants than those treated with vedolizumab.

Continued assessment of the effect of immunomodulating treatment on the antiviral immune response is essential, especially when considering the ongoing spread of novel dominant SARS-CoV-2 variants caused by viral mutation drift driving global infection rates. The study of Liu and colleagues[1] highlights the consequences of infliximab and vedolizumab therapy for neutralising antibody responses against omicron BA.1 and BA.4/5 variants for patients with IBD; however, similar efforts for other immunosuppressive agents like methotrexate and JAK inhibitors are also important, because these treatments are likely to affect vaccine-induced immunity against SARS-CoV-2.[3] More real-world evidence is required to inform vaccine prioritisation in the foreseeable future. Such information would aid in substantiating personalised vaccination strategies for specific subgroups of patients with IBD—eg, across different

disease activity states, disease complications, and the presence of relevant comorbidities.

An important point of discussion relates to focusing on specific immunological domains when assessing the immune response after vaccination. Liu and colleagues[1] focused on the humoral immune response through examination of functional neutralising antibody responses. Although this functional neutralising capacity reflects efficient protection against SARS-CoV-2 infection, it only partially informs on immunological protection.[4,5] T-cell-mediated immunity against SARS-CoV-2 is at least equally important in combating the infection when neutralising antibody concentrations decay. Further study of cellular immune responses could provide important additional insights. A flow cytometry approach could already be sufficient to enumerate and phenotypically characterise variant-specific T cells (eg, using IFN-γ release assays or ELISpot assays on cryopreserved peripheral blood mononuclear cells). Previously, the CLARITY-IBD study investigators reported no significant differences in quantities of anti-spike T-cell fractions or IFN-γ-producing T cells in patients with IBD treated with infliximab versus vedolizumab after one or two doses of SARS-CoV-2 vaccine.[4] Similarly, the VIP study reported similar T-cell concentrations among patients with IBD treated with infliximab or vedolizumab,[3] and some other studies have found augmented anti-SARS-CoV-2 T-cell fractions in patients with IBD treated with TNF antagonists.[6,7] By contrast, a study investigating anti-SARS-CoV-2 serological responses after a third vaccine dose in patients with IBD treated with biologics reported reduced T-cell-mediated IFN-γ concentrations in those treated with TNF antagonists compared with those not treated with such agents.[8] Likewise, two other studies reported reduced IFN-γ secretion in vaccinated patients treated with TNF antagonists, whereas those not treated with TNF antagonists had T-cell responses similar to controls without IBD.[9,10] These observations could be explained by a potential reduction in T-cell functionality or specificity in the absence of quantitative alterations in relevant T-cell subsets. As such, a comprehensive appraisal of qualitative T-cell responses, neutralising antibody responses, and the risk of breakthrough infections deserves attention in future studies, assessing which domains are most relevant for guiding vaccination prioritisation in patients with IBD receiving immunomodulating treatment.

The efforts of Liu and colleagues in identifying patient subgroups at risk of reduced neutralising capacity against the dominating SARS-CoV-2 omicron variants are important and can only be applauded. However, more in-depth and mechanistic assessment of waning vaccine-induced immunity is warranted to secure improved vaccine immunogenicity for patients with IBD.

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