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.

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Anti–SARS-CoV-2 Antibody Responses in Patients With IBD Treated With Biologics: Are We Finding CLARITY?

Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. Gut 2021;70:865-875.

Kennedy NA, Lin S, Goodhand JR Contributors to the CLARITY IBD study, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. Gut 2021;70:1884-1893.

After first emergence in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has proven to be an unprecedented worldwide health challenge. By August of 2021, more than 200 million confirmed cases and 4 million deaths had been reported to the World Health Organization. This threat has been countered with an extraordinary vaccine development response, including novel strategies using messenger RNA (mRNA) platforms and adenoviral vectors, with more than 4 billion vaccine doses delivered to date. However, questions have arisen surrounding the impact of immunosuppressive medication commonly used in inflammatory bowel disease (IBD) on antibody responses and protective immunity after both SARS-CoV-2 infection and vaccination. Particular concern surrounds the impact of tumor necrosis factor (TNF) antagonist drugs on vaccination efficacy, driven by existing data suggesting that this class of drugs may impair immunity after influenza, pneumococcal, and viral hepatitis vaccination (J Crohn's Colitis 2021;15:1376–1386).

CLARITY IBD has sought to address these questions through a United Kingdom multicenter prospective observational cohort study, comparing the impact of the TNF antagonist infliximab with the gut selective anti-integrin vedolizumab, with or without concurrent immunomodulators, on SARS-CoV-2 serologic response after infection and vaccination. Vedolizumab-treated patients were chosen as the reference cohort because vedolizumab is also administered in hospital with a similar dosing schedule and has not been associated with attenuated serologic responses to vaccination.

In the first publication of this consortium, rates of seroconversion after symptomatic and proven SARS-CoV-2 infection were compared between 4685 infliximab-treated and 2250 vedolizumab-treated patients. Seroprevalence of anti–SARS-CoV-2 antibodies was measured using the Roche Elecsys electrochemiluminescence immunoassay targeted against the SARS-CoV-2 nucleocapsid (N). Although both symptomatic and proven infection rates were similar across the two cohorts and reassuringly uncommon, the seroprevalence of anti–SARS-CoV-2 antibodies was significantly lower in infliximab-treated vs vedolizumab-treated patients (3.4% vs 6%; $P < .0001$), even after propensity matched analysis. Moreover, patients treated with infliximab had a lower seroconversion rate of anti–SARS-CoV-2 antibodies (48% vs 83%; $P = .00044$) after infection and lower magnitude of antibody reactivity (median 0.8 cut off index [0.2–5.6] vs 37.0 [15.2–76.1]; $P < .0001$). The seroconversion rate ($P = .046$) and anti–SARS-CoV-2 reactivity ($P = .035$) were further reduced by combination infliximab and immunomodulator (IM).

After their first publication, the CLARITY IBD consortium went on to assess the anti–SARS-CoV-2 antibody levels and seroconversion rates in 865 infliximab-treated and 428 vedolizumab-treated patients after at least one dose of the BNT162b2 mRNA (Pfizer/BioNTech) vaccine or the ChAdOx1 adenoviral vector (Oxford/AstraZeneca) vaccine. To determine antibody responses specific to vaccination, the Roche Elecsys anti–SARS-CoV-2 spike (S) immunoassay was used alongside the nucleocapsid (N) immunoassay, with a positive spike immunoassay but negative nucleocapsid immunoassay result consistent with vaccination without previous infection. Anti–SARS-CoV-2 spike (S) antibody levels were lower in infliximab-treated patients compared with vedolizumab-treated patients after either vaccine (BNT162b2 geometric mean 6.0 U/mL [±5.9] vs 28.8 U/mL [±5.4], $P < .0001$; ChAdOx1 geometric mean 4.7 U/mL [±4.9] vs 13.8 U/mL [±5.9], $P < .0001$); again, concomitant IM use was also independently associated with lower antibody levels. The lowest rates of seroconversion (threshold of 15 U/mL) were seen in patients treated with concurrent

infliximab and IM after either BNT162b2 (27.1%) or ChAdOx1 vaccine (20.2%), with highest rates in those who received vedolizumab monotherapy (BNT162b2 74.7% and ChAdOx1 57.3%). IM use was independently associated with lower antibody levels. However, seroconversion rates after a single dose of either vaccine were significantly higher after prior SARS-CoV-2 infection in both infliximab (81.7%) and vedolizumab-treated patients (91.7%) and in a small cohort of 27 patients who had received two doses of BNT162b2 vaccine, infliximab (17/20; 85%) and vedolizumab (6/7; 86%).

The authors concluded that infliximab-treated patients showed an impaired immunologic response to SARS-CoV-2 infection or single-dose vaccination. However, vaccination after SARS-CoV-2 infection, or a second dose of the BNT16B2 vaccine, led to seroconversion in the majority.

Comment. The potential risks of SARS-CoV-2 infection to patients with IBD on immunosuppressive medication have been a source of concern and great debate within the IBD community, both for patients and physicians. It is worth acknowledging the outstanding efforts that have allowed for large collaborative studies to rapidly generate much needed data that have provided guidance throughout these challenging times. While the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) database (Gut 2021;70:725–732) has provided important data and reassurance on the use of most IBD medications and SARS-CoV-2 disease course, CLARITY IBD has sought to inform the impact of one of the most widely used biologics, infliximab, on immunity after infection or vaccination. The data presented by CLARITY IBD suggest that infliximab-treated patients may mount lower antibody responses either after infection or the initial inoculation of two of the currently available SARS-CoV-2 vaccines. These results may have important practical implications, and merit close reflection.

One very important aspect to consider is the correlation between the measured antibody levels and protective immunity because clinical outcomes were not assessed. It is still not clearly defined what level of neutralizing antibodies, or other immune marker, correlates best with SARS-CoV-2 vaccine efficacy. Notably a neutralizing antibody assay was not used in the first paper (Nat Med 2021;27:1205–1211). Anti–SARS-CoV-2 spike (S) concentrations, as measured in the second article, correlate closely with neutralization assays and the threshold used for seroconversion ($\geq$15 U/mL) appears highly predictive of neutralizing potential. However, there may be a weaker correlation with anti–SARS-CoV-2 nucleocapsid (N) concentrations, which is of potential importance in the first article. Importantly, low or absent antibodies do not necessarily imply lower protection because other immune mechanisms triggered by both infection and vaccination may be important in protection against SARS-CoV-2, including cellular immunity, and, in particular, virus-specific B- and T-cell responses (BMJ 2020;371:m4838). Intriguingly, recent data from CLARITY IBD, available as a preprint (Research Square 2021; https://doi.org/10.21203/rs.3.rs-755879/v1), suggests no significant difference in T-cell responses between infliximab- and vedolizumab-treated patients after one or two doses of either vaccine, and reassuringly most patients who did not mount an antibody response appear to show a detectable T-cell response. The lack of healthy controls, matched at least for age and comorbidities, represents a limitation of CLARITY IBD that should be acknowledged. Notably, immune responses may vary after infection or vaccination, with antibody levels decaying over time even in healthy individuals. Moreover, additional host factors undoubtedly impact on immunity, such as genetics, nutritional state, age and microbiota (J Crohn's Colitis 2021;15:1376–1386). Indeed, in the present study, age $\geq$60 years, current smoking, and white ethnicity were all associated with lower antibody levels after either vaccine. Crohn's disease was also associated with lower antibody levels, although this finding had not been previously demonstrated in vaccine studies.

It must also be emphasized that due to the delayed second dose strategy adopted by the United Kingdom, only a small number of patients (27) who received two vaccine doses were included, and thus the primary analysis was of an incomplete vaccination strategy, which may not tell the full story. Vaccination after infection or a second vaccine dose did lead to seroconversion in most patients, and this is a reassuring message to be transmitted to patients. Further supportive data for the efficacy of double vaccination comes from the International study of COVID-19 Antibody Response Under Sustained immune suppression in IBD (ICARUS-IBD) (Gastroenterology 2021;161:715-718.e4) where both the BNT162b2 mRNA and the mRNA-1273 (Moderna) vaccines were assessed in 26 patients with IBD: 8 TNF antagonist monotherapy-treated, 12 vedolizumab, 2 ustekinumab, and 4 on no medication. All patients developed anti–SARS-CoV-2 spike antibody levels consistent with presumed protection. Therefore, an important practical point is that timely administration of the second dose should be actively sought in this patient population.

The emergence of certain SARS-CoV-2 mutations in late 2020, termed "variants of concern," which may show reduced neutralization by postvaccination serum, provide significant further challenges both to the definition and achievement of protective immunity (Nat Rev Microbiol 2021;19:409-424). It is clear, therefore, that undertaking a definitive assessment of immunity would require a broad panel of immunologic assays, performed at multiple time points and potentially against multiple viral mutations, encompassing antibody response, B- and T-cell activation and lymphoproliferation, and cytokine response. However such comprehensive assays would be impractical to perform at scale and we still lack sufficient understanding of correlates of protection to be certain how the results would inform vaccine effectiveness. These complexities in defining protective immunity, together with a lack of standardization of commercially available assays, are major reasons why antibody testing to guide vaccination strategy is not currently recommended.

A number of important questions remain unanswered, such as whether these data on infliximab can be

extrapolated to the other TNF antagonists used in IBD (adalimumab, golimumab, and certolizumab), which show variable TNF binding affinities. Although adalimumab also attenuates influenza and pneumococcal vaccination response in IBD, little is known about the effect of golimumab and certolizumab. A study of patients with rheumatoid arthritis (RA) suggested certolizumab monotherapy may not impair antibody response to influenza and pneumococcal vaccination, whereas combination therapy with methotrexate does. Data for other advanced therapies used in IBD are also needed. Reassuringly, a recent study of influenza vaccination in 15 ustekinumab-treated patients with Crohn's disease found no impairment of antibody or T-cell response when compared with healthy controls (Vaccines 2020;8:455). However, in RA the oral JAK inhibitor tofacinitib was associated with impaired response to pneumococcal vaccination, although response to influenza vaccination was preserved (Ann Rheumatic Dis 2016;75:687–695). It is also unknown whether vaccination timing should be adjusted around scheduling of immunosuppressive medication to boost vaccine efficacy. In CLARITY IBD, the impact of timing of biological infusion on vaccination efficacy could not be assessed because follow-up blood tests were taken at time of infusion, which was 8 weekly for the majority. Currently no US or UK IBD guidelines recommend the adjustment of SARS-CoV-2 vaccine delivery around the timing of immunosuppressive medications, or the interruption of medication. However, US guidelines in RA have suggested that medication, including tofacitinib and methotrexate, may be briefly interrupted in patients with well-controlled disease in the hope of enhancing vaccine efficacy, while acknowledging that more research is needed (Arthritis Rheum 2021;73:e30–e45). Finally, the serologic response to single-dose vaccines, such as Ad26.COV-2S (Janssen), in patients on immunosuppressive medication is currently unknown.

There is considerable research interest in how SARS-CoV-2 vaccination efficacy may be boosted in the immunocompromised. This need is further underlined by data from the same CLARITY IBD preprint, suggesting a potentially significant decay of antibody levels within just 4 months of a second vaccine dose in infliximab- but not vedolizumab-treated patients (Research Square 2021; https://doi.org/10.21203/rs.3.rs-755879/v1). The provision of a third dose or of an additional "booster dose" shows particular promise as a strategy to overcome attenuated vaccine response. A randomized trial of a third dose of the mRNA-1273 vaccine (Moderna) in 120 immunosuppressed transplant recipients led to significantly higher immunogenicity, although follow-up was short at 4 months, with greater SARS-CoV-2 neutralization and virus specific T-cell counts demonstrated and no major safety concerns (N Engl J Med 2021;385:1244-1246). Higher dosing is a further potential strategy to be explored; patients with IBD receiving TNF antagonist monotherapy demonstrated significantly greater antibody levels after high-dose versus standard-dose influenza vaccine (Inflamm Bowel Dis 2020;26:593–602). A heterologous prime-boost strategy (mix and match strategy) is also of interest, where separate vaccines that potentially offer complementary stimulation of different immune pathways are offered sequentially to enhance immunogenicity, while use of adjuvants are also under consideration.

In summary, although studies such as CLARITY IBD raise important concerns about the efficacy of SARS-CoV-2 vaccination in subgroups of patients with IBD, there is great hope that ongoing intensive research will allow us to overcome these challenges, and provide evidence on how to best protect our patients from this vaccine-preventable disease. In the end, it is worth emphasizing that IBD medications, and specifically TNF antagonists, particularly if used in monotherapy, have not been shown to be associated with more severe SARS-CoV2 infection, and that, notwithstanding the need for continued work in the setting of vaccination, their benefits clearly outweigh their risks.

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Clinical Guidelines for the Management of IBD

> Like they say, you can learn more from a guide in one day than you can in three months fishing alone.
> –Mario Lopez

Because an increasing number of effective therapies are available for the treatment of inflammatory bowel disease