Effectiveness and Safety of COVID-19 Vaccines in Patients With Inflammatory Bowel Disease

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Abstract: Vaccines against SARS-CoV-2 are important for protection from COVID-19; however, patients with immune-mediated conditions and patients taking immunosuppressive medications, including patients with inflammatory bowel disease (IBD), were excluded from studies demonstrating the safety and efficacy of these vaccines. This article provides an overview of the research and recommendations currently published on vaccines against COVID-19 in adult populations with IBD, including studies evaluating effects of commonly used medications. COVID-19 vaccines are strongly recommended for patients with IBD. Messenger RNA (mRNA) and adenovirus vector vaccines are safe in patients with IBD, and reports of severe reactions or IBD flares are rare. Studies assessing antibody response, T-cell immunity, and real-world experience demonstrate positive outcomes for mRNA and adenovirus vector vaccines in patients with IBD, although mRNA vaccines may have a slight advantage. Studies assessing inactive COVID-19 vaccines are still needed. Immunosuppressive therapies used in IBD, especially tumor necrosis factor antagonists, combination therapy, and corticosteroids, may reduce antibody responses and durability, but the impact on infection, hospitalizations, and death requires further evaluation. Educating patients with this evidence-based information will likely help to reduce concerns and vaccine hesitancy.

Keywords
Inflammatory bowel disease, COVID-19, vaccines, immunosuppression

Vaccines against SARS-CoV-2 are important for protection from COVID-19. Currently, 3 types of vaccines are available for widespread use: messenger RNA (mRNA) vaccines (Pfizer and Moderna), adenovirus vector vaccines (Janssen/Johnson & Johnson [thereafter referred to as Janssen in this article], AstraZeneca, Sputnik, and CanSino), and inactive COVID-19 vaccines (Sinopharm and Sinovac). Although clinical trials demonstrated safety and efficacy in the general population, patients with immune-mediated conditions and patients taking immunosuppressive medications, including patients with inflammatory bowel disease (IBD), were excluded.[1] Hence, safety and efficacy were incompletely addressed for these populations. Moreover, one study found that vaccine efficacy against COVID-19–related

hospitalizations was lower for patients with immunocompromising conditions (90% vs 63%).[2] Although patients with IBD are overall not at increased risk for severe illness or poorer outcomes from COVID-19,[1,3] providing patients with safe, effective defenses is nonetheless critical. This article provides an overview of the research and recommendations currently published on COVID-19 vaccines in adult patients with IBD. Effects of medications are also addressed.

General Vaccine Concerns in Inflammatory Bowel Disease

Patients with IBD are recommended to receive most vaccines.[4] However, research on vaccines against other pathogens has demonstrated differences in immune response in patients with IBD, and blunted vaccine immune response and faster waning of antibodies have been observed in patients taking commonly used therapies.[5] Attenuated immune responses to influenza vaccines have previously been documented in patients with IBD, especially patients receiving infliximab.[1] Similar findings for hepatitis B vaccines suggested that tumor necrosis factor (TNF) blockade decreases T-cell response. Yet for other vaccines, such as pneumococcal vaccines, there may be limited to no differences in immune responses between patients with IBD and the general population. For some vaccines, higher doses have successfully improved immune responses in patients with IBD, although for other vaccines boosters were not effective. How these precedents apply to COVID-19 vaccines is important.

In general, vaccines are considered safe in patients with IBD. In this population, adverse events (AEs) from vaccination are usually local site reactions, including pain, swelling, or erythema. Although less common, when systemic reactions occur, such as myalgias, arthralgia, fatigue, chills, or headache, they tend to be mild.[6] A systematic review found that after vaccination with influenza, pneumococcal, herpes zoster, or hepatitis B vaccines, the incidence of local AEs, systemic events, and IBD flares was 24%, 16%, and 2%, respectively, in patients with IBD.[6]

The only vaccine mechanism that is not safe for patients with IBD is live vaccine.[4] There is concern that because of interactions with immunosuppressive medications, live pathogens may replicate and paradoxically cause sickness.[7,8] Currently, none of the vaccines against COVID-19 are live vaccines.

Recommendations for Patients With Inflammatory Bowel Disease

Various groups have established recommendations on vaccination against COVID-19 for patients with IBD. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) published its position in January 2021 and included all vaccine types.[4] At the time, Pfizer, Moderna, AstraZeneca, Janssen, Sinovac, Sputnik, Sinopharm, and Novavax vaccines were all being studied. The IOIBD recommended vaccination against COVID-19 at the earliest opportunity and did not think that vaccination should be impacted by disease activity or specific drug therapy, including induction and maintenance therapies. Further, the IOIBD advised against delaying vaccination because of use of immunosuppressive drugs and against stopping medications in preparation for vaccination. mRNA vaccines were considered safe. Although it was thought that patients with IBD could develop immune protection, the IOIBD suggested counseling about possible decreased vaccine efficacy with immune-modifying medications, especially corticosteroids. Vaccination was not thought to cause an IBD flare. Among members of the IOIBD, it was agreed upon, but less strongly, that patients with IBD on immune-modifying medication regimens should be prioritized along with other immunocompromised groups.

The Crohn's & Colitis Foundation (CCF) largely agreed with the IOIBD. Additionally, the CCF was supportive of patients receiving additional doses if they were on immunosuppressive therapies.[9] The CCF followed guidelines from the US Centers for Disease Control and Prevention stating that patients on immunosuppressive and/or immunomodulatory therapies interested in extra doses should receive the same vaccine at earliest 28 days after completing the series, but noted that mixing had been approved by the US Food and Drug Administration. Therefore, most patients with IBD, aside from patients on no medications or mesalamines only, qualified for an early booster. Furthermore, the CCF did not recommend serologic tests to monitor antibodies before or after vaccination.

The British Society of Gastroenterology (BSG) Inflammatory Bowel Disease section first published recommendations in January 2021.[10] Recommendations were consistent with the IOIBD and CCF guidelines but focused on vaccines available in the United Kingdom (Pfizer, AstraZeneca, Moderna, and later Janssen). In addition, the BSG indicated that complete vaccine series were advised for patients with IBD regardless of prior COVID-19 exposure, but suggested waiting 4 weeks after acute infection. Patients were advised against delaying or avoiding vaccination because of active IBD unless activity was severe or required hospitalization, in which case a brief delay was recommended to distinguish AEs from IBD vs from vaccination. Furthermore, when possible, reducing systemic steroids was recommended. The BSG suggested waiting at least 7 days after COVID-19 vaccines before

administering other vaccines. Later updates provided reassurance regarding risk for venous thromboembolism with the AstraZeneca vaccine.[11] Because risks were considered small and vaccination was a priority for patients with IBD, many of whom are immunosuppressed, patients were still encouraged to seek vaccination with any vaccine type offered to them. Only patients younger than 40 years with otherwise low risk for COVID-19 who could easily access another vaccine were advised to find an alternative vaccine.[12] Another update addressed third doses as part of the primary vaccination series (to be given 8 weeks after the second dose) and booster doses, which are additional beyond the completed primary series and given 6 months after the second dose.[13] A third primary dose was recommended for all patients on immunosuppressive medications (including all biologics, Janus kinase [JAK] inhibitors, thiopurines, methotrexate, and corticosteroids) regardless of medication dose and for patients with IBD who were particularly vulnerable as long as they were age-eligible for vaccination.

Finally, experts stated that vaccination is important even if medications may cause blunted responses, as any amount of protection is beneficial.[5] Furthermore, they urged vaccination against other infectious diseases, especially against pathogens targeting the respiratory system, such as influenza for all patients and pneumococcus for patients who are over 60 years old or who are taking immunosuppressive medications.

Attitudes Toward Vaccination

Most patients with IBD expressed interest in receiving vaccines against COVID-19, with internationally reported rates of intent ranging from 53.6% to 92.6.%.[14-18] Reasons for wanting vaccination included belief in vaccines' ability to protect against infection, a sense of community responsibility, interests in protecting the vulnerable, a desire to return to normal life, and hopes for achieving herd immunity.[16,18]

Patients with IBD who were hesitant to receive a COVID-19 vaccine cited safety as a central reason. Studies have suggested that between 15% and 52% of patients were concerned about AEs,[14,16,18] one-third to two-thirds were worried about long-term safety,[14,18] and one-half were concerned that vaccination might negatively affect their IBD course.[16] Patients were interested in learning how others tolerated the vaccine before receiving it themselves[14] and were willing to wait months for information about AEs, especially for mRNA vaccines.[15,17] Other reasons included concern about vaccine development process and time line, worry about previous allergic reactions, interest in choices for vaccines offered, and distrust of pharmaceutical companies.[18]

Studies have found that intention to undergo vaccination was correlated with IBD requiring management with medications, other comorbidities, older household members, experience with severe COVID-19 in close friends or family, prior vaccination against influenza, and, in one study, male sex.[16,17] In a study among patients taking biologics, vaccination rates were higher among women and patients over 50 years old.[19] Importantly, one study found that advice from patients' gastroenterologists was associated with intention to vaccinate,[16] and another study found that more than 80% of patients with IBD who were hesitant reported that their provider's recommendation was important in their decision.[14] Even among the hesitant, many patients still thought that COVID-19 vaccines would be important for their health and were interested in learning more about safety and efficacy in patients with their disease and medications. Smaller studies found educational materials to be successful in assisting patients to make informed decisions, and many patients afterward reported that they would likely get vaccinated.[20] As the data on COVID-19, vaccines, and treatments change, attitudes toward vaccination may continue to shift. Health care professionals will likely have a central role in communicating these messages with patients and the public.

COVID-19 Vaccine Safety in Patients With Inflammatory Bowel Disease

Safety data for COVID-19 vaccines among patients with IBD are growing. The first published study, by Botwin and colleagues, evaluated AEs after the Pfizer and Moderna vaccines in 246 patients with IBD.[21] Overall, 39% of patients had AEs after the first dose (D1), with 38% having local site reactions. There were more events after the second dose (D2), with 62% of patients reporting any event and 56% experiencing local site reactions. After each dose, the most common systemic AEs were fatigue, malaise, headache, dizziness, fever, chills, and gastrointestinal symptoms, all more common after D2 than D1. Similarly, there were more severe AEs after D2 (in 10% of patients, vs 3% after D1), but only 2 hospitalizations, whereas there were 3 hospitalizations after D1. Increased frequency of AEs was associated with younger age and inversely associated with being on TNF antagonists, integrin antagonists, interleukin antagonists, and JAK inhibitors.

Hadi and colleagues also assessed the safety of mRNA vaccines in patients with IBD.[22] Among 5562 vaccinated patients with IBD, approximately one-third had received 1 dose. Fewer than 10 patients developed immediate AEs (anaphylaxis or poisoning) after vaccination. Special AEs of interest, which included acute myocardial infarction,

coagulopathies, thromboses, neuropathies, myocarditis, pericarditis, transverse myelitis, and appendicitis, among others, occurred more often in patients with IBD (2% vs 0.8% in controls), but this was not significant in analyses with propensity score matching. The same was true for all-cause hospitalization in 30 days (0.95% in patients with IBD vs 0.48% in controls). Furthermore, there were no differences in the number of patients with steroid prescriptions 30 days after vaccination or in the incidence of special AEs of interest among patients on biologics, immunomodulators, both, or neither, nor between patients with Crohn's disease (CD) and patients with ulcerative colitis (UC).

Edelman-Klapper and colleagues' study in 185 patients with IBD reported on AEs after the Pfizer vaccine only.[23] After D1, they reported local site swelling and pain in 78% of patients, and headache, fatigue, and muscle soreness each in less than 15% of patients. After D2, local symptoms, headache, fatigue, muscle soreness, and shivering were reported by approximately 70%, 25%, 25%, 15%, and 12%, respectively. However, the authors reported no severe AEs. There was no association between AEs and use of TNF antagonists or serologic measurements of TNF antagonist drug levels. IBD activity was found to be the same before and after vaccination with each dose. Lev-Tzion and colleagues' study had longer follow-up than Edelman-Klapper and colleagues' study and followed patients for a mean of 12 weeks after D2 with the Pfizer vaccine.[24] Lev-Tzion and colleagues found no differences in IBD flares in the first 40 days after vaccination, but patients who were vaccinated had more flares afterward (44% vs 34% of unvaccinated patients). However, after matching for the number of flares in the past 2 years and the time since most recent flare, this difference was no longer statistically significant.

The safety of adenovirus vector vaccines in patients with IBD has also been evaluated. One study by Weaver and colleagues assessed response to the Pfizer, Moderna, and Janssen vaccines among 3316 patients, 161 of whom received Janssen.[25] With Janssen, the most common AEs were tenderness (58%), pain (48%), and redness (12%) for local reactions, and fatigue (66%), headache (59%), and muscle aches (39%) for systemic reactions. After 1 dose, 1% of patients receiving the Pfizer vaccine, 2% of patients receiving the Moderna vaccine, and 0% receiving the Janssen vaccine experienced severe injection site reactions, of whom 1, 0, and 0 required medical attention, respectively; in addition, 2%, 3%, and 9% experienced severe systemic reactions, respectively, of whom 5, 4, and 0 required medical attention, respectively. More patients with Janssen had no local reactions after D1 (29%, vs 14% for Pfizer and 9% for Moderna), but fewer had no systemic reactions (22%, 45%, and 40%, respectively). Across all vaccine types, after D1, interleukin antagonist use was negatively associated with severe local site reactions. Female sex, vaccine type, and TNF antagonists were associated with severe systemic reactions. Prior COVID-19 was associated with both severe local and systemic reactions. After D2 with mRNA vaccines, younger age, female sex, TNF antagonists, and integrin antagonists were associated with severe systemic reactions, and the Moderna vaccine was associated with more severe systemic and local reactions than the Pfizer vaccine. Although 12%, 12%, and 11% of patients reported increased bowel frequency, extraintestinal manifestations, and abdominal pain after vaccination, respectively, only 2.1% of patients had an IBD flare (2.5% for Pfizer, 1.8% for Moderna, and 0.6% for Janssen). In a different study of patients who received the Pfizer, Moderna, or AstraZeneca vaccines, there were no differences in the fecal calprotectin or serum C-reactive protein levels measured before vaccination and 8 weeks after completion of a vaccine series.[26]

There are currently no known studies evaluating safety of the inactivated COVID-19 vaccines in patients with IBD.

Efficacy of COVID-19 Vaccines in Patients With Inflammatory Bowel Disease

Many studies have demonstrated vaccine efficacy in patients with IBD. Studies that focus on antibody response, T-cell response, and real-world effectiveness are described. Antibody tests, their cutoff levels for seroconversion to positive antibody response, and antibody titers are summarized in the Table.

Data on antibody response to vaccines against COVID-19 in patients with IBD have been promising, especially in studies of mRNA vaccines. A study by Melmed and colleagues reporting response to the Pfizer and Moderna vaccines found that 49% of 113 patients were positive for antibodies after D1, 92% of 89 patients were positive after D2, and 99% of 115 patients were positive 2 weeks after D2.[27] Wong and colleagues' study of 26 patients found that 84.6% of patients who completed both mRNA doses had antibody titers high enough to qualify for convalescent plasma donation, and 100% of patients were positive for antibodies.[28] Even after D1, antibody titers were similar between patients with and without IBD, and 2 of 3 patients with prior infection had high levels after D1. Levine and colleagues' study of 19 patients who completed an mRNA vaccine series found that 18 patients had seroconverted, with 17 patients showing the highest levels measurable on the assay used.[29] Further, 17 patients in this study were on biologics, and the only patient who did not seroconvert was a 78-year-old receiving adalimumab, prednisone, and sulfasalazine.

Table. Antibody Titers and Seroconversion Values

Study	Laboratory Test Used	Seroconversion Cutoff Value	Antibody Titers	Comments/ Additional Notes	Time Frame
Edelman-Klapper et al[23]	Abbott Laboratories SARS-CoV-2 IgG II Quantitative assay	50 AU/mL	Control: D1: 1039 AU/mL D2: 10,979 AU/mL Patients with IBD not on TNF antagonists: D1: 710 AU/mL D2: 8320 AU/mL Patients with IBD on TNF antagonists: D1: 340 AU/mL D2: 3787 AU/mL	Measured as geometric mean concentrations in patients receiving Pfizer Differences were significant in patients taking TNF antagonists compared with patients not taking TNF antagonists and compared with controls	First dose evaluated 14-21 days after inoculation Second dose evaluated 21-35 days after inoculation
Cerna et al[26]	Abbott Laboratories SARS-CoV-2 IgG II Quantitative assay	50 AU/mL	Infliximab monotherapy: 1454.90 AU/mL Infliximab combination therapy: 509.60 AU/mL Adalimumab monotherapy: 2504.96 AU/mL Adalimumab combination therapy: 603.20 AU/mL Vedolizumab monotherapy: 1750.00 AU/mL Vedolizumab combination therapy: 1131.90 AU/mL Ustekinumab monotherapy: 1988.98 AU/mL Ustekinumab combination therapy: 2123.40 AU/mL Tofacitinib: 1709.50 AU/mL Thiopurine monotherapy: 2774.95 AU/mL	Median levels reported	8 weeks after second vaccine dose
Melmed et al[27]	Abbott Laboratories SARS-CoV-2 IgG II Quantitative assay	50 AU/mL	After D1: Overall: 50 AU/mL No therapy: 191 AU/mL JAK inhibitor: 40 AU/mL Immunomodulator monotherapy: 115 AU/mL Integrin antagonist: 129 AU/mL IL-12/23 antagonist: 69 AU/mL TNF antagonist: 26 AU/mL Combination therapy: 20 AU/mL Corticosteroids: 6 AU/mL After D2: Overall: 2042 AU/mL No therapy: 302 AU/mL JAK inhibitor: Not reported Immunomodulator monotherapy: 309 AU/mL Integrin antagonist: 1145 AU/mL IL-12/23 antagonist: 3020 AU/mL TNF antagonist: 2818 AU/mL Combination therapy: 2455 AU/mL Corticosteroids: 25,119 AU/mL 2 weeks after D2: Overall: 10,233 AU/mL No therapy: 8318 AU/mL JAK inhibitor: 2399 AU/mL Immunomodulator monotherapy: 5754 AU/mL Integrin antagonist: 15,136 AU/mL IL-12/23 antagonist: 20,893 AU/mL TNF antagonist: 9120 AU/mL Combination therapy: 9772 AU/mL Corticosteroids: 2630 AU/mL 8 weeks after D2: Overall: 3236 AU/mL No therapy: 5370 AU/mL JAK inhibitor: 2399 AU/mL Immunomodulator monotherapy: 3311 AU/mL Integrin antagonist: 5888 AU/mL IL-12/23 antagonist: 4266 AU/mL TNF antagonist: 2570 AU/mL Combination therapy: 1380 AU/mL Corticosteroids: 1202 AU/mL 16 weeks after D2: Overall: 1445 AU/mL No therapy: 1738 AU/mL JAK inhibitor: 1698 AU/mL Immunomodulator monotherapy: 2239 AU/mL Integrin antagonist: 2884 AU/mL IL-12/23 antagonist: 2951 AU/mL TNF antagonist: 759 AU/mL Combination therapy: 776 AU/mL Corticosteroids: 1479 AU/mL	Levels measured using geometric means Study not powered to assess differences by medical therapy	Time frames as listed

(Table continues on following page)

Table. *(Continued)* Antibody Titers and Seroconversion Values

Study	Laboratory Test Used	Seroconversion Cutoff Value	Antibody Titers	Comments/ Additional Notes	Time Frame
Wong et al[28]	Siemens Healthineers SARS-CoV-2 total Ig assay (for RBD of S protein)	Index value of 1	Titers displayed in figures in original manuscript without specific levels reported		Levels after 1 and 2 mRNA vaccine doses assessed in study (up to 12 weeks)
	Siemens Healthineers SARS-CoV-2 IgG assays (for anti-RBD IgG)	Index value of 1	Titers displayed in figures in original manuscript without specific levels reported		
	Mount Sinai in-house ELISA test for IgG against full length S protein	Titer of 100 cutoff 4-fold increase from baseline was significant	Titers displayed in figures in original manuscript without specific levels reported		
Levine et al[29]	Roche ELISA assays for spike domain antibodies	0.80 units/mL	Specific titers not reported	17/19 patients with titers >250.00 U/mL (highest measurement)	Levels after 2 mRNA vaccine doses
Kappelman et al[30]	LabCorp Cov2Quant IgG assay	1.0 μg/mL	Overall: 28.6 μg/mL TNF antagonist: 15.1 μg/mL Combination therapy with TNF antagonist: 11.5 μg/mL Vedolizumab: 45.2 μg/mL Ustekinumab: 34.6 μg/mL Immunomodulator therapy: 24.0 μg/mL Mesalamine/sulfasalazine, budesonide, or no medications: 44.2 μg/mL	Percent seroconverted: Overall: 95% TNF antagonist: 94% Combination therapy with TNF antagonist: 88% Vedolizumab: 100% Ustekinumab: 97% Immunomodulator therapy: 95% Mesalamine/sulfasalazine, budesonide, or no medications: 94%	Levels after 2 mRNA vaccine doses (8 weeks)
Kappelman et al[31]	LabCorp Cov2Quant IgG assay	1.0 μg/mL is positive (equivalent to 25 IU/mL WHO International Standard)	mRNA vaccines (Pfizer, Moderna): Mean: 29.8 μg/mL Median: 17 μg/mL Adenovirus vector vaccine (Janssen): Mean: 4.18 μg/mL Median: 2.7 μg/mL Prior COVID-19 infection and vaccine: Mean: 82.4 μg/mL Median: 39 μg/mL		Mean 67 days after D2
Caldera et al[32]	LabCorp Cov2Quant IgG assay	Not specified in this study	Overall: Control: 118 μg/mL IBD (all): 31 μg/mL Within IBD cohort: Pfizer: 22 μg/mL Moderna: 38 μg/mL Taking biologics: 26 μg/mL Not taking biologics: 57 μg/mL Any immunosuppression: 26 μg/mL No immunosuppression: 59 μg/mL	Median antibody titers Vedolizumab was included in the no-immunosuppression group	In patients with IBD, 28-35 days after D2 In controls, 30 days after D2
Pozdnyakova et al[33]	Abbott Laboratories SARS-CoV-2 IgG II Quantitative assay	50 AU/mL	2 weeks: Moderna: $10^{4.20}$ AU/mL Pfizer: $10^{3.92}$ AU/mL Janssen: $10^{1.96}$ AU/mL 8 weeks: Moderna: $10^{3.72}$ AU/mL Pfizer: $10^{3.41}$ AU/mL Janssen: $10^{2.65}$ AU/mL	Differences in Janssen vs Pfizer and Moderna were significant	Levels after completing vaccine series, 2-8 weeks
Reuken et al[34]	Liaison SARS-CoV-2 Trimerics IgG CLIA	13 AU/mL or 33.8 BAU/mL	3 weeks after D1 (Pfizer or AstraZeneca): IBD: 57.2 BAU/mL Control: 105.0 BAU/mL After D2 (all Pfizer 2nd doses): IBD: 1119 BAU/mL Control: 1570 BAU/mL	Differences between IBD and control groups were not significant	Time frames as indicated

(Table continues on following page)

Table. *(Continued)* Antibody Titers and Seroconversion Values

Study	Laboratory Test Used	Seroconversion Cutoff Value	Antibody Titers	Comments/ Additional Notes	Time Frame
Kennedy et al[35]	Roche Elecsys anti–SARS-CoV-2 spike immunoassay	15 U/mL	No prior infection, D1 (monotherapy, combination therapy): Pfizer + infliximab: 6.0 U/mL, 4.4 U/mL Pfizer + vedolizumab: 28.8 U/mL, 16.7 U/mL AstraZeneca + infliximab: 4.7 U/mL, 4.2 U/mL AstraZeneca + vedolizumab: 13.8 U/mL, 10.0 U/mL No prior infection, D2: Pfizer + infliximab: 158 U/mL Pfizer + vedolizumab: 562 U/mL Prior infection, D1: Pfizer + infliximab: 191 U/mL Pfizer + vedolizumab: 1865 U/mL AstraZeneca + infliximab: 185 U/mL AstraZeneca + vedolizumab: 752 U/mL	Geometric mean titers measured Differences between infliximab and vedolizumab were significant. Differences after 2 doses compared with 1 dose were significant	Within 10 weeks of D1, shortly after D2
Lin et al[38]	Roche Elecsys anti–SARS-CoV-2 spike immunoassay	15 U/mL	No prior infection: Pfizer + infliximab: 547.5 U/mL Pfizer + vedolizumab: 3980.4 U/mL AstraZeneca + infliximab: 4189.3 U/mL AstraZeneca + vedolizumab: 781.5 U/mL Prior infection: Pfizer + infliximab: 1811.3 U/mL Pfizer + vedolizumab: 10079.6 U/mL AstraZeneca + infliximab: 575.1 U/mL AstraZeneca + vedolizumab: 2595.1 U/mL	Geometric mean titers measured after second vaccine doses Differences between infliximab and vedolizumab were significant	Up to 18 weeks after D2

AU, arbitrary unit; BAU, binding antibody units; CLIA, chemiluminescent immunoassay; D1, first dose; D2, second dose; ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; mRNA, messenger RNA; RBD, receptor-binding domain; TNF, tumor necrosis factor; WHO, World Health Organization.

Two larger studies by Kappelman and colleagues in patients with IBD who completed a 2-dose series with mRNA vaccines found that 95% to 96% of patients had detectable antibodies.[30,31] Although the overall antibody response rate was high for patients with mRNA vaccines, the second study found that the odds of not developing antibodies was 2.1 times greater in patients receiving the Pfizer vaccine than in patients receiving the Moderna vaccine, and antibody titers were lower in the Pfizer vaccine group.[31] Other factors associated with lower likelihood of having detectable antibodies and lower antibody titers were older age and longer time from second vaccine dose. Caldera and colleagues also found that patients who received the Moderna vaccine developed higher titers than patients who received the Pfizer vaccine.[32]

Several studies have evaluated adenovirus vector vaccines. In the second study by Kappelman and colleagues, 81% of the 94 patients receiving the Janssen vaccine had detectable antibodies approximately 3 months after vaccination.[31] A study by Pozdnyakova and colleagues compared antibody levels after inoculation with a single dose of the Janssen vaccine to titers after receiving both doses of the Pfizer or Moderna vaccine.[33] This study found antibody responses in patients receiving any of the 3 vaccines, with 90% of patients receiving the Janssen vaccine seroconverting, 99% of patients receiving the Pfizer vaccine seroconverting, and 100% of patients receiving the Moderna vaccine seroconverting. Longer time between inoculation and antibody testing was associated with lower antibody levels. Antibody levels were also lower in patients receiving the adenovirus vector vaccine (compared with the mRNA vaccines) after 2 and 8 weeks, with levels highest with the Moderna vaccine at both time points. Notably, only 12 patients in this study had received the adenovirus vector vaccine.

Reuken and colleagues similarly evaluated antibody responses in patients with IBD vs controls.[34] Participants had received either the AstraZeneca or Pfizer vaccine for D1. After D1, patients with IBD had lower rates of seroconversion (71.4% vs 85.1%) and lower antibody levels; however, these differences were not statistically significant. Although patients with IBD had responses similar to controls, the authors did not specify differences between patients receiving adenovirus vector and mRNA vaccines; hence, few conclusions can be drawn about the adenovirus vector vaccines specifically. Notably, after second doses with a Pfizer vaccine in patients receiving either AstraZeneca or Pfizer first doses, seroconversion rates were 91.7% in patients with IBD and 100% in controls. Additionally, antibody levels had increased and were not statistically different than controls, although mean antibody levels were still numerically lower in the IBD

group. Among patients with IBD, antibody titers after D2 in patients who seroconverted after the second dose were similar to antibody titers after D1 in patients who seroconverted after the first dose. Kennedy and colleagues' study also did not analyze differences between adenovirus vector and mRNA vaccines (specifically, AstraZeneca vs Pfizer) but reported numerically lower seroconversion rates and antibody levels in the AstraZeneca group compared with the Pfizer group after D1.[35] For both vaccines, there were lower antibodies in patients who were older than 60 years, smoked cigarettes, and were white. For the Pfizer vaccine only, lower titers were seen in patients with CD. For both vaccines, there were higher seroconversion rates in patients with prior COVID-19 infection. Overall, the seroconversion rate after D2 was above 85%.

In addition to humoral immunity and antibody response, the value of T-cell immunity is increasingly being recognized. Whereas antibody activity may only be detectable for a limited amount of time, T cells are thought to be associated with longer-term immunity.[34] Moreover, it is unclear whether antibody levels alone indicate the ability to neutralize or be protected from the virus, as other arms of the immune system, including cellular immunity, may have essential roles.[1] After D1, Reuken and colleagues' study found a similarly increased T-cell response in patients with IBD and controls.[34] The response was further enhanced after D2. This finding may be reassuring for patients with IBD, as it suggests that they likely form the same long-lasting immunity from T cells as the general population.

Data from real-world experiences of patients with IBD further encourage optimism regarding effectiveness of COVID-19 vaccines, especially mRNA vaccines. Khan and colleagues' study among patients with IBD in the US Department of Veterans Affairs system found that vaccination with 2 mRNA doses was 80.4% effective against infection.[36] Meanwhile, vaccination with 1 dose was only 25.1% effective, emphasizing the importance of a complete mRNA series. Interestingly, this study did not find differences in rates of severe infection or all-cause mortality; however, a total of only 6 severe infections and 11 deaths were reported among more than 7300 patients. Hadi and colleagues' study found no differences in infection rates between the general population and patients with IBD after vaccination with at least 1 mRNA vaccine dose, with subsequent infection rates of 0.28% and 0.36%, respectively.[22] Among patients with IBD, of 19 postvaccination infections, 14 were diagnosed within 1 month of the first vaccine. No difference was found between patients with CD and UC. In a study from Israel by Ben-Tov and colleagues, rates of COVID-19 infection more than 7 days after D2 with the Pfizer vaccine was 0.19% in patients with IBD compared with 0.15% in matched controls.[37] After 14 days, these rates dropped to 0.14% and 0.10%, respectively, with no statistically significant differences at either time point. However, patients with CD had a higher risk relative to patients with UC (hazard ratio [HR] of 3.56 after 7 days, 3.38 after 14 days). Of the 23 patients with IBD who were infected after vaccination, only 9 were symptomatic, 2 were hospitalized, and 1 died. Lev-Tzion and colleagues' study, also in Israel among patients receiving the Pfizer vaccine, demonstrated similar results, with 0.3% of patients developing COVID-19 infections after vaccination in both the IBD and non-IBD patient cohorts.[24] The authors found no difference in time to infection after vaccination. Lastly, Weaver and colleagues' study of patients receiving the Pfizer, Moderna, and Janssen vaccines reported that only 16 participants developed COVID-19 after vaccination, 10 of whom were infected after D1, 15 of whom were symptomatic, and none of whom were hospitalized.[25] The authors did not report infections by vaccine type.

Among studies evaluating COVID-19 vaccines in patients with IBD, studies from Edelman-Klapper and colleagues, Caldera and colleagues, and Cerna and colleagues showed the greatest differences between patients with IBD and the general population, although the findings were reassuring overall. Edelman-Klapper and colleagues' study in patients receiving the Pfizer vaccine found that 14 of 185 patients with IBD did not seroconvert after D1, and all 73 control patients seroconverted.[23] Of the patients who did not seroconvert, 4 patients were receiving TNF antagonist monotherapy, 1 patient was receiving combination therapy with a TNF antagonist and immunomodulator, 1 patient was receiving a TNF antagonist and steroids, 2 patients were receiving JAK inhibitors, 1 patient was receiving vedolizumab (Entyvio, Takeda), and 1 patient was receiving ustekinumab (Stelara, Janssen). Additionally, this study found lower neutralizing antibodies in patients with IBD compared with controls after D1 and D2. Nevertheless, the study found that all patients with IBD had seroconverted after D2. Older age was also associated with poorer vaccine response. In Caldera and colleagues' study of patients receiving Pfizer or Moderna vaccines, 3% (4 patients) did not have measurable antibodies 1 month after completing a 2-dose series, and all of the healthy controls seroconverted and had higher titers compared with patients with IBD.[32] However, the 4 patients who did not seroconvert were all on immunosuppressive medications, and none of the control patients were on immune medications. Moreover, significantly more of the control patients had received the Moderna vaccine, which the study found was associated with higher antibody titers. Finally, in Cerna and colleagues' study from the Czech Republic in patients

receiving the Pfizer, Moderna, or AstraZeneca vaccines, 11 patients with IBD who had received the AstraZeneca vaccine did not have measurable antibodies, and all control patients receiving this vaccine had seroconverted.[26] Furthermore, the authors found that in the group vaccinated with the AstraZeneca vaccine, antibody levels were lower in the IBD group compared with the controls. Nevertheless, the authors found that 97.8% of patients with IBD seroconverted. Across all vaccines, patients with prior COVID-19 infection had higher antibody levels, and older patients had lower titers.

Overall, these studies demonstrate vaccine protection against COVID-19, both through serology and real-world experiences. Future studies, especially those evaluating adenovirus vector and inactive COVID-19 vaccines, are still needed.

Inflammatory Bowel Disease Medication Impact on Vaccine Effectiveness

The majority of studies have demonstrated reduced immunity from COVID-19 vaccines in patients on immune-suppressing and/or immune-modifying medications.[23,26-28,30-35,38] The therapies most commonly identified in studies evaluating antibodies up to 3 months after completing a vaccine series were TNF antagonists, combination therapy, and corticosteroids.[23,26-28,30-32,35] Additionally, a study of 48 patients found lower titers in patients on integrin antagonists.[28] There was no association found between antibody titers and drug levels or troughs of biologics[23,26] or between antibody titers and the timing of administration of biologics.[23,28] In studies evaluating the persistence of antibodies over time, waning antibodies were found in patients receiving TNF antagonists and combination therapy.[27,38] This may suggest increased risk for infection in patients taking these medications over time, although risks of hospitalization and death are unknown. However, 3 studies evaluating infection rates found no differences between patients receiving various medications,[24,36,37] as did a study of 28 patients evaluating antibody levels.[34] Another study on infection rates reported few cases in patients receiving biologics, immunomodulators, or both, but did not provide quantitative analyses or comparisons to patients not taking these medications.[22] Data from studies reporting differences between medical therapies are presented.

Two key papers from the CLARITY IBD study directly compared the antibody responses in patients receiving vedolizumab to those in patients receiving infliximab. The first study evaluated patients who received 1 dose of the Pfizer or AstraZeneca vaccine.[35] The study found that patients taking infliximab had lower antibody titers than patients taking vedolizumab in both the Pfizer and AstraZeneca groups. In the infliximab group only, antibody titer levels were even lower in patients with concurrent immunomodulator use. Importantly, in a small subgroup receiving a second vaccine dose, antibody levels increased in patients taking both medications. There were no differences in seroconversion rates, with 3 of 20 patients receiving infliximab and 1 of 6 receiving vedolizumab failing to seroconvert.

The second study evaluated persistence of antibodies up to 18 weeks after completing a vaccines series.[38] Overall, 6.1% of patients receiving infliximab failed to seroconvert, compared with 1.3% of patients receiving vedolizumab. In the infliximab group, antibodies were found to be 4 to 5 times lower than in the vedolizumab group, and they decreased significantly faster (HR, 2.95); in infliximab-treated patients, a 4-fold decrease in antibodies occurred at 14 weeks and 18 weeks in patients receiving the AstraZeneca and Pfizer vaccines, respectively, whereas vedolizumab-treated patients and patients without IBD sustained antibodies through 16 weeks. For patients on both biologics, antibody levels were higher in patients with prior infection and were sustained at 14 weeks. For patients receiving the Pfizer vaccine, thiopurines and methotrexate were further associated with lower titers. However, this study found no differences in T-cell responses between patients treated with infliximab and vedolizumab, with 19.6% and 19.2% without detectable response, respectively.

Consistent with the first CLARITY IBD study, Edelman-Klapper and colleagues' study of patients receiving the Pfizer vaccine found that antibody levels were up to 3 times lower in patients taking TNF antagonists compared with patients not taking TNF antagonists and healthy controls.[23] No differences were observed among patients treated with other IBD medications. Additionally, there was less binding inhibition by antibodies in patients treated with TNF antagonists compared with controls, and patients on TNF antagonists had significantly lower antibody neutralization activity after D2 (79%, vs 97% in controls and 96% in patients not taking TNF antagonists).

The first study by Kappelman and colleagues reported titers but did not analyze for statistical significance.[30] This study found similar titers in patients receiving vedolizumab and patients receiving mesalamine/sulfasalazine, budesonide, or no medications. Patients receiving ustekinumab and immunomodulators had slightly lower titers, and patients receiving TNF antagonist monotherapy and combination therapy had the numerically lowest antibody titers. However, in the second study, when assessing statistical significance in multivariate models, the authors found that the odds of not developing an antibody response were 4.2 times greater in patients taking combination

therapy with TNF antagonists, and antibody levels were lower in patients taking TNF antagonists (as part of monotherapy and combination therapy).[31] Treatment with budesonide and oral corticosteroids was also associated with lower antibody titers. Meanwhile, patients taking mesalamine and ustekinumab were less likely not to have an antibody response to vaccination (odds ratios of 0.3 and 0.2, respectively).

As in the first study by Kappelman and colleagues, Melmed and colleagues' study reported antibody titers in patients on different medical therapies after completing mRNA vaccine series but did not analyze for statistical significance.[27] The study reported antibody titers at 2, 8, and 16 weeks after D2. At 8 weeks, patients taking integrin antagonists had the highest titers, even greater than patients on no immunosuppression. Patients taking TNF antagonists had the lowest titers among those taking biologics, and patients taking combination therapy and corticosteroids had the lowest titers overall. At 16 weeks, patients taking integrin antagonists, interleukin antagonists, and immunomodulators had higher titers than patients on no immunosuppressive medications. Patients on TNF antagonists, both for monotherapy and combination therapy, had the lowest titers, even lower than patients taking corticosteroids. Across all groups, antibodies waned between 8 and 16 weeks.

Conclusion

COVID-19 vaccines are strongly recommended for patients with IBD. Positive outcomes have been demonstrated for mRNA vaccines and adenovirus vector vaccines, although mRNA vaccines may have a slight advantage. The Moderna vaccine may have some additional protection compared with the Pfizer vaccine, but more studies are needed to confirm these findings. Few studies have assessed inactive COVID-19 vaccines. Current evidence suggests that immunosuppressive therapies used in IBD may reduce antibody responses and durability, especially TNF antagonists, combination therapy, and corticosteroids. Effects on T cells require further evaluation. Real-world experience data indicate that patients with immunocompromising conditions, including IBD, may be less protected against hospitalization after vaccination; however, studies assessing the impact of medications on infection, hospitalizations, and death in vaccinated persons are still needed. Educating patients using this evidence-based information will likely help to alleviate concerns and reduce vaccine hesitancy.

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References

1. Wellens J, Colombel JF, Satsangi JJ, Wong SY. SARS-CoV-2 vaccination in IBD: past lessons, current evidence, and future challenges. *J Crohns Colitis*. 2021;15(8):1376-1386.

2. Tenforde MW, Self WH, Naioti EA, et al; IVY Network Investigators; IVY Network. Sustained effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults—United States, March-July 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(34):1156-1162.

3. Crohn's & Colitis Foundation. COVID-19 vaccines: position statements. https://www.crohnscolitisfoundation.org/coronavirus/vaccine-position-statements#vaccinepositionstatement. Updated August 18, 2021. Accessed December 30, 2021.

4. Siegel CA, Melmed GY, McGovern DP, et al; International Organization for the Study of Inflammatory Bowel Disease (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut*. 2021;70(4):635-640.

5. Melmed GY, Rubin DT, McGovern DPB. Winter is coming! Clinical, immunologic, and practical considerations for vaccinating patients with inflammatory bowel disease during the coronavirus disease-2019 pandemic. *Gastroenterology*. 2021;160(3):639-644.

6. Desalermos A, Pimienta M, Kalligeros M, et al. Safety of immunizations for the adult patient with inflammatory bowel disease—a systematic review and meta-analysis [published online November 24, 2021]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izab266.

7. Rubin LG, Levin MJ, Ljungman P, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):309-318.

8. Manser CN, Maillard MH, Rogler G, Schreiner P, Rieder F, Bühler S. Vaccination in patients with inflammatory bowel diseases. *Digestion*. 2020;101(suppl 1):58-68.

9. Crohn's & Colitis Foundation. COVID-19 vaccine additional dose: position statement. https://www.crohnscolitisfoundation.org/coronavirus/vaccine-position-statements#additionaldosestatement. Updated August 18, 2021. Accessed December 30, 2021.

10. Alexander JL, Moran GW, Gaya DR, et al; Inflammatory Bowel Disease section of the British Society of Gastroenterology and the Inflammatory Bowel Disease Clinical Research Group. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. *Lancet Gastroenterol Hepatol*. 2021;6(3):218-224.

11. Alexander JL, Powell N; British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group. SARS-CoV-2 vaccination in immunosuppressed patients with inflammatory bowel disease: should our approach change? *Lancet Gastroenterol Hepatol*. 2021;6(7):528-529.

12. British Society of Gastroenterology. BSG Inflammatory Bowel Disease section and Clinical Research Group position statement on SARS-CoV2 vaccination. https://www.bsg.org.uk/covid-19-advice/british-society-of-gastroenterology-inflammatory-bowel-disease-section-and-ibd-clinical-research-group-position-statement-on-sars-cov2-vaccination/. Updated September 23, 2021. Accessed December 30, 2021.

13. Alexander JL, Selinger CP, Powell N; British Society of Gastroenterology

Inflammatory Bowel Disease section and the Inflammatory Bowel Disease Clinical Research Group. Third doses of SARS-CoV-2 vaccines in immunosuppressed patients with inflammatory bowel disease. *Lancet Gastroenterol Hepatol*. 2021;6(12):987-988.
14. Dalal RS, McClure E, Marcus J, Winter RW, Hamilton MJ, Allegretti JR. COVID-19 vaccination intent and perceptions among patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2021;19(8):1730-1732.e2.
15. Giannini EG, Demarzo MG, Bodini G. Elevated adherence to vaccination against SARS-CoV-2 among patients with inflammatory bowel disease. *J Crohns Colitis*. 2021;15(12):2142-2143.
16. Crispino F, Brinch D, Carrozza L, Cappello M. Acceptance of SARS-CoV-2 vaccination among a cohort of IBD patients from southern Italy: a cross-sectional survey. *Inflamm Bowel Dis*. 2021;27(11):e134-e135.
17. Walldorf J, von Arnim U, Schmelz R, et al. SARS-CoV-2 vaccination in patients with inflammatory bowel disease—fear and desire. *Inflamm Bowel Dis*. 2021;27(11):1858-1861.
18. Caron B, Neuville E, Peyrin-Biroulet L. Inflammatory bowel disease and COVID-19 vaccination: a patients' survey [published online May 12, 2021]. *Dig Dis Sci*. doi:10.1007/s10620-021-07040-z.
19. Shehab M, Zurba Y, Al Abdulsalam A, Alfadhli A, Elouali S. COVID-19 vaccine hesitancy among patients with inflammatory bowel disease receiving biologic therapies in Kuwait: a cross-sectional study. *Vaccines (Basel)*. 2021;10(1):55.
20. Hudhud D, Caldera F, Cross RK. Addressing COVID-19 vaccine hesitancy in patients with IBD [published online September 24, 2021]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izab241.
21. Botwin GJ, Li D, Figueiredo J, et al. Adverse events after SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *Am J Gastroenterol*. 2021;116(8):1746-1751.
22. Hadi YB, Thakkar S, Shah-Khan SM, Hutson W, Sarwari A, Singh S. COVID-19 vaccination is safe and effective in patients with inflammatory bowel disease: analysis of a large multi-institutional research network in the United States. *Gastroenterology*. 2021;161(4):1336-1339.e3.
23. Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, et al; REsponses to COVid-19 vaccinE IsRaeli IBD group (RECOVER). Lower serologic response to COVID-19 mRNA vaccine in patients with inflammatory bowel diseases treated with anti-TNFα. *Gastroenterology*. 2022;162(2):454-467.
24. Lev-Tzion R, Focht G, Lujan R, et al. COVID-19 vaccine is effective in inflammatory bowel disease patients and is not associated with disease exacerbation [published online December 23, 2021]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2021.12.026.
25. Weaver KN, Zhang X, Dai X, et al. Impact of SARS-CoV-2 vaccination on inflammatory bowel disease activity and development of vaccine-related adverse events: results from PREVENT-COVID [published online December 6, 2021]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izab302.
26. Cerna K, Duricova D, Lukas M, et al. Anti-SARS-CoV-2 vaccination and antibody response in patients with inflammatory bowel disease on immune-modifying therapy: prospective single-tertiary study [published online November 29, 2021]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izab301.
27. Melmed GY, Botwin GJ, Sobhani K, et al. Antibody responses after SARS-CoV-2 mRNA vaccination in adults with inflammatory bowel disease. *Ann Intern Med*. 2021;174(12):1768-1770.
28. Wong SY, Dixon R, Martinez Pazos V, Gnjatic S, Colombel JF, Cadwell K; ICARUS-IBD Working Group. Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. *Gastroenterology*. 2021;161(2):715-718.e4.
29. Levine I, Swaminath A, Roitman I, Sultan K. COVID-19 vaccination and inflammatory bowel disease: desired antibody responses, future directions, and a note of caution. *Gastroenterology*. 2022;162(1):349-350.
30. Kappelman MD, Weaver KN, Boccieri M, Firestine A, Zhang X, Long MD; PREVENT-COVID Study Group. Humoral immune response to messenger RNA COVID-19 vaccines among patients with inflammatory bowel disease. *Gastroenterology*. 2021;161(4):1340-1343.e2.
31. Kappelman MD, Weaver KN, Zhang X, et al. Factors affecting initial humoral immune response to SARS-Cov-2 vaccines among patients with inflammatory bowel diseases [published online December 29, 2021]. *Am J Gastroenterol*. doi:10.14309/ajg.0000000000001619.
32. Caldera F, Knutson KL, Saha S, et al. Humoral immunogenicity of mRNA COVID-19 vaccines among patients with inflammatory bowel disease and healthy controls. *Am J Gastroenterol*. 2022;117(1):176-179.
33. Pozdnyakova V, Botwin GJ, Sobhani K, et al. Decreased antibody responses to Ad26.COV2.S relative to SARS-CoV-2 mRNA vaccines in patients with inflammatory bowel disease. *Gastroenterology*. 2021;161(6):2041-2043.e1.
34. Reuken PA, Andreas N, Grunert PC, Glöckner S, Kamradt T, Stallmach A. T cell response after SARS-CoV-2 vaccination in immunocompromised patients with inflammatory bowel disease [published online August 11, 2021]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjab147.
35. Kennedy NA, Lin S, Goodhand JR, et al; Contributors to the CLARITY IBD study. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut*. 2021;70(10):1884-1893.
36. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 vaccination in a veterans affairs cohort of patients with inflammatory bowel disease with diverse exposure to immunosuppressive medications. *Gastroenterology*. 2021;161(3):827-836.
37. Ben-Tov A, Banon T, Chodick G, et al. BNT162b2 messenger RNA COVID-19 vaccine effectiveness in patients with inflammatory bowel disease: preliminary real-world data during mass vaccination campaign. *Gastroenterology.* 2021;161(5):1715-1717.e1.
38. Lin S, Kennedy NA, Saifuddin A, et al. Covid-19 vaccine-induced antibodies are attenuated and decay rapidly in infliximab treated patients. Nature Portfolio. Preprint posted online July 30, 2021. doi:10.21203/rs.3.rs-755879/v1. Research Square. https://www.researchsquare.com/article/rs-755879/v1. Accessed December 30, 2021.