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.

Antibody Response Six Months after SARS-CoV-2 mRNA Vaccination in Patients with Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) are recommended to receive vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), regardless of their immunosuppression status. Immunosuppressive medications represent a mainstay of therapy in moderate to severe IBD; however, their impact on the SARS-CoV-2 vaccine response remains unclear. Studies thus far have shown that patients with IBD on various therapies had detectable antibody responses after standard vaccinations.[1-5] To date, one study has examined the kinetics of antibody response at 3 months after vaccination in patients with IBD, but data beyond this time point are not yet available.[6] The aim of this study was to assess anti-spike antibody response 6 months after completion of standard SARS-CoV-2 vaccination in patients with IBD. Secondarily, we observed antibody kinetics over 6 months in a subset of patients post-vaccination.

Patients with IBD who received SARS-CoV-2 vaccination with either Pfizer, Moderna, or Johnson & Johnson (J&J), and who were 18 years old and older were included. Participants provided informed consent prior to study entry. Transplant patients, those with prior COVID-19 infection, and those who received additional vaccine doses were excluded. An electronic questionnaire was used to collect baseline demographics and clinical characteristics. Antibody titers were measured at 1, 3, and 6 months after completion of vaccine series using the Roche Elecsys anti-SARS-CoV-2 enzyme immunoassay (positive $\geq$0.8 U/mL, ceiling of 250 U/mL with later expansion to 2500 in U/mL in April 2021). The assay tests for antibodies against the spike protein receptor binding domain (RBD). As in our previous studies, low-positive antibody response was defined as anti-RBD pan Ig 0.8 to 50 units/mL; high antibody response was defined as anti-RBD pan Ig >50 units/mL based on plasma neutralizing capacity in COVID-19 convalescent patients as well as a modeling study across SARS-CoV-2 vaccine trials.[7-9] This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540).

Of 75 patients with antibody titers at 6 months, 78% were female, with a median age of 45 years (interquartile range, 38–58 years) (Table 1). Forty-three patients (57.3%) received Pfizer and 32 (42.7%) received Moderna. The majority of patients (n = 68; 90.7%) were on immunosuppressive medications; tumor necrosis factor-α (TNF-α) inhibitors were the most commonly prescribed therapy (n = 38; 50.7%). Twenty-nine patients (38.7%) were on combination therapy with TNF-α inhibitors and thiopurines, corticosteroids, or methotrexate.

All 75 patients had a detectable antibody response at 6 months following SARS-CoV-2 vaccination, with 59 of 75 patients (78.7%) having a high-positive antibody response. Of those with low-positive antibody response at 6 months, 12 of 16 patients (75%) were on TNF-α inhibitors; 10 (63%) of these 16 patients were on TNF-α inhibitor monotherapy.

In examining the association of TNF-α inhibitors with antibody response, 12 of 38 patients (31.6%) on TNF-α inhibitors had low-positive antibody response, whereas 26 of 38 (68.4%) had high-positive antibody titers at 6 months. In contrast, nearly all participants on vedolizumab (6/6; 100%), tofacitinib (2/2; 100%), and ustekinumab (15/17; 88.2%) had high-positive antibody response. A greater proportion of patients on TNF-α inhibitors, either monotherapy or combination therapy, had low-positive antibody titers as compared with those on other immunosuppressive agents (12/16; 75% vs 4/16; 25%; $P = .048$ [Fisher exact test]). A similar proportion of patients with low-positive and high-positive antibody response at 6 months were on glucocorticoids (5/16; 31.2% vs 18/59; 30.5%).

To assess for stability of antibody response, we compared 1- and 6-month antibody levels among the 45 patients with paired results. Most patients (37/45; 82.2%) with high antibody response at 1 month maintained high antibody response at 6 months (Supplementary Table 1). Of the 8 patients with high-positive antibody titers at 1 month that waned to low-positive at 6 months, 6 of 8 (75%) were on TNF-α inhibitors, and 6 of 8 (75%) received the Pfizer vaccine series (Supplementary Table 2). There was one report of a breakthrough COVID-19 infection 2 months after vaccination; this patient received the Moderna vaccine and reported an immunosuppressive regimen including intravenous immune globulin, glucocorticoids, and mesalamine.

This is the first study assessing antibody response 6 months after standard SARS-CoV-2 vaccination in patients with IBD. All patients had detectable antibodies at

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Table 1. Demographic and Clinical Characteristics of Patients With IBD After SARS-CoV-2 Vaccination, Stratified by Anti-SARS-CoV-2 RBD Antibody Response After 6 Months

	Overall[a] (N = 75)	Low-positive[a] (n = 16)	High-positive[a] (n = 59)
Age, *years*	45 (38–58)	41 (38–53)	47 (38–59)
Female	55 (73.3)	9 (56.3)	46 (78.0)
Non-white	6 (8.0)	1 (6.3)	5 (8.5)
Hispanic/Latino[b]	5 (6.7)	0 (0)	5 (8.5)
Immunosuppressive therapy included in regimen[c]			
Hydroxychloroquine[d]	1 (1.3)	0 (0)	1 (1.7)
Mycophenolate[e]	1 (1.3)	0 (0)	1 (1.7)
Methotrexate	5 (6.7)	1 (6.3)	4 (6.8)
Thiopurine[f]	11 (14.7)	1 (12.5)	9 (15.2)
TNF inhibitor[g]	38 (50.7)	12 (75.0)	26 (44.1)
TNF inhibitor monotherapy	24 (32.0)	10 (62.5)	14 (23.7)
Tofacitinib	2 (2.7)	0 (0)	2 (3.4)
Ustekinumab	17 (22.7)	2 (12.5)	15 (25.4)
Vedolizumab	6 (8.0)	0 (0)	6 (10.2)
Corticosteroids			
Budesonide	6 (8.0)	1 (6.3)	5 (8.5)
Systemic corticosteroids[h]	17 (22.4)	4 (25.0)	13 (22.0)
Combination therapy			
TNF inhibitor and thiopurine or methotrexate	8 (10.7)	2 (12.5)	6 (10.2)
TNF inhibitor and systemic steroid	10 (13.3)	1 (6.3)	6 (10.2)
Other combination therapy[i]	11 (14.7)	2 (12.5)	9 (15.3)
Medication held[b,j]			
Yes	3 (21.4)	1 (33.3)	2 (18.2)
No	11 (78.6)	2 (66.6)	9 (81.8)
Vaccine type			
Pfizer	43 (57.3)	11 (68.8)	32 (54.2)
Moderna	32 (42.7)	5 (31.3)	27 (45.8)
RMD diagnosis[k]	15 (20.0)	2 (12.5)	13 (22.0)
Days from dose 2 to 6-month testing[l]	179 (165–202)	179 (164–214)	179 (165–199)

Note: Data are presented as number (%) or median (interquartile range).
IBD, Inflammatory bowel disease; RBD, receptor binding domain; RMD, rheumatic and musculoskeletal diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.
[a]The percentages in these columns are shown as percentage of each category in the overall column. Negative antibody response was defined per manufacturer data as Roche Elecsys anti-RBD pan Ig <0.8 units/mL. Low-positive antibody response was defined as anti-RBD pan Ig 0.8–50 units/mL. High-positive antibody response was defined as anti-RBD pan Ig >50 units/mL.
[b]The denominators for these categories differ from the total N as 1 participant answered "prefer not to answer" for Hispanic/Latino, and 62 did not respond to the question about holding medications prior to vaccination.
[c]Patients could select >1 medication, thus n>76
[d]Hydroxychloroquine includes hydroxychloroquine and chloroquine.
[e]Mycophenolate includes mycophenolic acid and mycophenolate mofetil.
[f]Thiopurine includes azathioprine and 6-mercaptopurine.
[g]TNF inhibitors include adalimumab, certolizumab, etanercept, golimumab, and infliximab.
[h]Systemic corticosteroid includes prednisone and prednisone equivalents.
[i]Other combination therapy includes 2 or more drugs listed above, excluding 5-ASAs. Regimens in this category included adalimumab and budesonide (n = 2), budesonide, systemic corticosteroid, and vedolizumab (n = 1), methotrexate, systemic corticosteroid, and ustekinumab (n = 1), budesonide and ustekinumab (n = 1), azathioprine and ustekinumab (n = 2), azathioprine and ustekinumab (n = 2), adalimumab and ustekinumab (n = 1), mycophenolate and systemic corticosteroid (n = 1).
[j]Participants were surveyed with the question "Did you hold doses of your immunosuppressive medication(s) in the 2 weeks before receiving the vaccine?"
[k]Participants also have diagnosis of systemic lupus erythematosus, Sjögren's syndrome, myositis, systemic sclerosis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease associated arthritis, polyarteritis nodosa, Behcet's syndrome, polymyalgia rheumatica, temporal arteritis, eosinophilic granulomatosis polyangiitis, granulomatous polyangiitis, Henoch-Schonlein purpura, microscopic polyangiitis, or Takayasu arteritis.
[l]Calculated as days from first dose to testing for the patient who received the J&J vaccine. All 76 patients had antibody titers measured at 6 months, 63 patients had antibody titers measured at 3 months, and 46 patients had antibody titers measured at 1 month.

6 months, with the majority (78.7%) having a high-positive antibody response. A recent study demonstrated a reduced humoral response in patients treated with TNF-α inhibitor monotherapy compared with healthy controls, and although our findings suggest that those on TNF-α inhibitors are more likely to have a lower antibody response at 6 months compared with patients on other immunosuppressive agents, a larger sample size to allow adjustment for confounding factors is required for further evaluation.[10] Limitations of this study include small sample size and lack of racial and ethnic diversity. There were only a few participants included on vedolizumab, ustekinumab, or tofacitinib, which limits our assessment of antibody formation while on those medications. Due to small numbers, we were unable to control for vaccine, type, age, and comorbidity. In addition, the dosing of corticosteroids was not available. We included patients without prior known COVID-19 infection, but as we did not complete anti-nucleocapsid testing, asymptomatic infection at any point in the study cannot be excluded.

Despite these limitations, this is the first available data on 6-month antibody response to SARS-CoV-2 vaccination in patients with IBD. Our findings are reassuring for patients with IBD receiving immunosuppressive therapy in that all patients in our study mounted an immune response to the SARS-CoV-2 vaccine. Although the clinical significance of quantitative antibody titers is unknown, this data can help guide clinicians' recommendations on timing of SARS-CoV-2 vaccine booster doses.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.12.045.

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Conflicts of interest
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Supplementary Table 1. Anti-spike Antibody Response 6 Months Following 2-dose SARS-CoV-2 Vaccine in Patients With IBD, Stratified by Antibody Response 1 Month After 2-dose mRNA Vaccine Series

		Antibody response after 6 months		
		Low-positive	High-positive	Totals (1 month)
Antibody response after 1 month	High-positive	8 (17.8)	37 (82.2)	45 (100)
	Totals (6-month)	8 (17.8)	37 (82.2)	45 (100)

Note: Data are presented as number (%).
Note: Negative antibody response was defined per manufacturer data as Roche Elecsys anti-RBD pan Ig <0.8 units/mL. Low-positive antibody response was defined as anti-RBD pan Ig 0.8–50 units/mL. High-positive antibody response was defined as anti-RBD pan Ig >50 units/mL.
IBD, Inflammatory bowel disease; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary Table 2. Clinical Characteristics of 8 Patients With High-positive Antibody Response at 1 Month, Which Waned to Low-positive Antibody Response at 6 Months Following 2-dose SARS-CoV-2 Vaccination

Age, years	Sex	Vaccine	1-month titer, U/mL	3-month titer, U/mL	6-month titer, U/mL	Therapy
41	F	Pfizer	>250	30.0	7.1	Azathioprine Infliximab Corticosteroid[a]
38	F	Pfizer	96.6	19.4	17.7	Budesonide Ustekinumab
26	F	Pfizer	>250	110.5	24.3	Adalimumab
54	M	Moderna	441.1	36.1	10.2	Infliximab
64	M	Pfizer	88.3	27.3	6.7	Infliximab
34	M	Pfizer	92.0	55.1	9.6	Azathioprine Corticosteroid[a] Ustekinumab
43	M	Pfizer	616.7	68.7	26.4	Infliximab
39	M	Moderna	219.6	–	16.5	Infliximab Methotrexate

F, Female; M, male; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
– Denotes missing data.
[a]Corticosteroid includes prednisone and prednisone equivalents.