OBSERVATIONS: BRIEF RESEARCH REPORTS

Antibody Responses After SARS-CoV-2 mRNA Vaccination in Adults With Inflammatory Bowel Disease

Background: The effects of immunosuppression on responses to SARS-CoV-2 vaccine are unclear given that patients receiving immune-modifying therapies, who constitute 2.8% of commercially insured adults, were underrepresented in vaccine trials (1). Fewer than half of organ transplant recipients receiving antimetabolite therapies developed antibodies after 2 doses of mRNA vaccine (2). Patients with inflammatory bowel disease (IBD) receiving infliximab were less likely than those receiving vedolizumab to develop antibodies after 1 dose of BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine (3), although other researchers have shown that seroconversion occurs in most patients with IBD after 2 doses of mRNA vaccine (4, 5).

Objective: To contextualize these findings relative to nonimmunosuppressed persons by assessing responses after mRNA vaccination in adults with IBD receiving various medication regimens.

Methods: We assessed antibody titers in adults with IBD who received mRNA SARS-CoV-2 vaccination who were referred from 18 U.S. gastroenterology practices and a social media campaign (January to July 2021). Participants completed baseline surveys detailing medical history at the time of vaccination. Local

Table. Participant Characteristics, Seropositivity, and GMTs, by Medication Class

Characteristic	Overall	No Immunosuppressive Therapies (Reference)	Anti-Integrin	Anti-IL-12/23	Immunomodulator Monotherapy*	Anti-TNF Monotherapy	JAK Inhibitor	Anti-TNF Combination Therapy†	Corticosteroids
Patients, *n*	582	92	80	119	12	183	7	50	35
Mean age (SD), *y*	44.4 (14.6)	47.0 (14.8)	46.9 (16.0)	45.8 (15.1)	45.2 (10.8)	41.5 (13.6)	45.7 (12.2)	41.5 (12.6)	42.7 (13.5)
Male sex, *n (%)*	198 (34.3)	33 (35.9)	30 (37.5)	43 (36.1)	5 (41.7)	53 (29.6)	2 (28.6)	21 (42.0)	9 (25.7)
Person of color, *n (%)*	39 (6.7)	4 (4.3)	4 (5.0)	7 (5.9)	3 (25.0)	14 (7.7)	0 (0.0)	4 (8.0)	3 (8.6)
Latinx ethnicity, *n (%)*	21 (3.6)	4 (4.3)	1 (1.2)	2 (1.7)	1 (8.3)	4 (2.2)	1 (14.3)	2 (4.0)	6 (17.1)
Ulcerative/indeterminate colitis, *n (%)*	197 (33)	55 (60)	35 (44)	13 (11)	6 (50.0)	51 (28)	6 (86)	17 (34.0)	14 (40)
Crohn disease, *n (%)*	385 (66)	37 (40)	45 (56)	106 (89)	6 (50.0)	132 (72)	1 (14)	33 (66)	21 (60)
Vaccine type: mRNA-1273 (Moderna), *n (%)*	240 (41.2)	34 (37.0)	32 (40.0)	52 (43.7)	7 (58.3)	75 (41.0)	4 (57.1)	21 (42.0)	15 (42.9)
Vaccine type: BNT162b2 (Pfizer–BioNTech), *n (%)*	342 (58.8)	58 (63.0)	48 (60.0)	67 (56.3)	5 (41.7)	108 (59.0)	3 (42.9)	29 (58.0)	20 (57.1)
Positive‡ after dose 1, *n/N (% [95% CI])*	55/113 (49 [49–58])	16/22 (73 [50–89])	7/12 (58 [28–85])	13/23 (57 [34–77])	1/2 (50 [1–99])	11/29 (38 [21–58])	1/2 (50 [1–99])	4/10 (40 [12–74])	1/11 (9 [0–41])
Positive‡ after dose 2, *n/N (% [95% CI])*	82/89 (92 [84–97])	13/13 (100 [75–100])	8/8 (100 [63–100])	20/22 (91 [71–99])	1/1 (100 [3–100])	27/28 (96 [82–100])	1/1 (100 [3–100])	8/8 (100 [63–100])	4/8 (50 [16–84])
Positive‡ after week 2, *n/N (% [95% CI])*	545/552 (98 [97–99])	85/87 (98 [92–100])	75/76 (99 [93–100])	113/114 (99 [95–100])	12/12 (100 [74–100])	175/177 (99 [96–100])	7/7 (100 [59–100])	49/49 (100 [93–100])	26/27 (96 [81–100])
GMT after dose 1 (95% CI) (*n* = 113)	50 (30–83)	191 (59–617)	129 (32–525)	69 (23–204)	115 (3–3891)	26 (9–72)	40 (1–1288)	20 (6–76)	6 (2–21)
GMT after dose 2 (95% CI) (*n* = 89)	2042 (1348–3090)	302 (25–3631)	1445 (776–2692)	3020 (1175–7763)	309 (NA–NA)	2818 (1445–5495)	–	2455 (1318–4571)	25 119 (NA–NA)
GMT at week 2 (95% CI) (*n* = 115)	10 233 (7762–13 490)	8318 (2692–25 704)	15 136 (7763–29 512)	20 893 (15 136–28 840)	5754 (1950–16 982)	9120 (5495–15 136)	2399 (NA–NA)	9772 (5623–16 982)	2630 (776–8913)
GMT at week 8 (95% CI) (*n* = 366)	3236 (2818–3715)	5370 (4074–7080)	5888 (4266–8128)	4266 (3236–5623)	3311 (1622–6761)	2570 (2042–3236)	2399 (676–8511)	1380 (1000–1905)	1202 (724–1995)
GMT at week 16 (95% CI) (*n* = 171)	1445 (1148–1820)	1738 (977–3090)	2884 (1622–5129)	2951 (2042–4266)	2239 (661–7586)	759 (550–1047)	1698 (955–3020)	776 (251–2399)	1479 (331–6607)

GMT = geometric mean titer; IL = interleukin; NA = not applicable; TNF = tumor necrosis factor-α.
* 6-mercaptopurine, azathioprine, or methotrexate.
† With immunomodulator.
‡ IgG(S) > 50 AU/mL.

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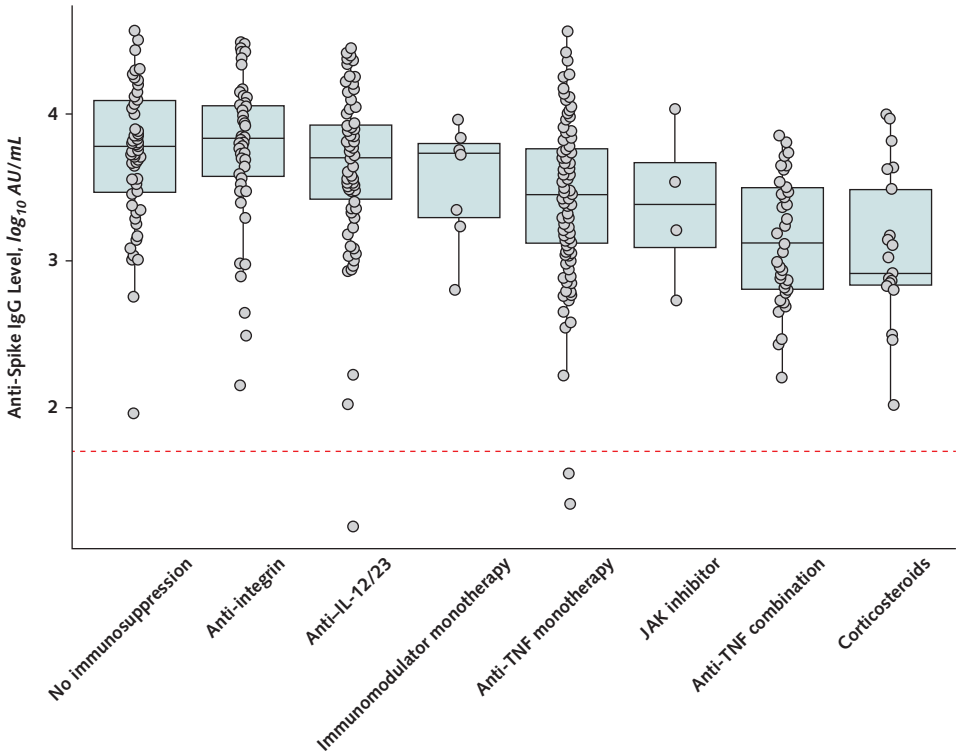
Figure. Week 8 anti-spike IgG (log



10) **levels, by medication class.** The dotted line represents the threshold for a positive antibody result (50 AU/mL [Abbott Labs]). IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis factor-α.

participants at Cedars-Sinai Medical Center were offered antibody assessments after dose 1 (from 5 days after dose 1 until the day of dose 2); after dose 2 (from 2 to 13 days after dose 2); and at 2 weeks (14 to 29 days), 8 weeks (30 to 84 days), and 16 weeks (85 to 140 days) after dose 2; geographically distant participants were offered at-home sampling using Tasso-SST (Tasso) at 8 weeks. We analyzed plasma antibodies to the receptor-binding domain of the spike protein S1 subunit (IgG(S)) and to the viral nucleocapsid protein (IgG(N)) using the SARS-CoV-2 IgG-II and SARS-CoV-2 IgG assays, respectively (Abbott Labs). We defined an IgG(S) level of 50 AU/mL or higher as a positive result. Qualitatively positive responses were determined after dose 1, after dose 2, and after week 2 (14 to 140 days after dose 2). We excluded recipients of the Ad26.COV2 vaccine (Johnson & Johnson), those with prior COVID-19 defined by a positive IgG(N) result at any time point, and those who did not receive both mRNA doses. Participants provided electronic informed consent, and the Cedars-Sinai institutional review board approved the study. Geometric means and CIs were calculated for log-transformed antibody titers.

Findings: The study included 582 participants (mean age, 44 years; 55% female) (**Table**); 342 (59%) received BNT162b2, and 240 (41%) received mRNA-1273 (Moderna). The proportions of participants receiving no immune suppression, anti-integrin therapy, anti–interleukin-12/23 therapy, immunomodulator monotherapy, anti–tumor necrosis factor monotherapy, Janus kinase inhibition, anti–tumor necrosis factor therapy combined with an immunomodulator, and systemic corticosteroids were 15.8%, 13.7%, 20.4%, 2.1%, 31.4%, 1.2%, 8.6%, and 6.0%, respectively. Those receiving systemic corticosteroids were included in the corticosteroids category regardless of concomitant medications. Four participants were missing medication data. We obtained 854 samples for antibody assessments from 582 participants, including 113 after the first dose, 89 after the second dose, 115 at 2 weeks, 366 at 8 weeks, and 171 at 16 weeks.

Overall, 49% of participants had positive levels of antibodies after the first dose, 92% after the second dose, and 99% after week 2. Quantitative levels numerically increased from dose 1 to week 2 then decreased at subsequent time points. The **Figure** shows quantitative levels at week 8 by medication regimen.

Discussion: Our study has several important findings. First, 99% of participants had detectable antibodies after 2 weeks regardless of medication regimen. Second, quantitative levels peaked at week 2 and decreased across all groups over subsequent time points. Third, mean quantitative levels at 8 weeks were the highest in the "no immunosuppression" group, as well as among those treated with anti-integrin and anti–interleukin-12/23, and lowest among those treated with anti–tumor necrosis factor combination therapy or corticosteroids; however, our study was not powered to assess differences across medication subgroups.

These findings showing seroconversion across medication groups are consistent with those seen in other IBD studies (4, 5). In contrast, transplant recipients have lower rates of seroconversion, likely related to B-cell–depleting medications and combined

therapies. Whether biologic and small-molecule therapies accelerate waning of titers over time is not yet known, but our results may reassure patients receiving these medications that initial humoral responses to mRNA vaccines are generally robust.

Limitations include lack of racial diversity and a tertiary center focus that may diminish generalizability. Further characterization of immunity over time may inform future vaccination strategies for patients with IBD receiving biologic and small-molecule therapies.

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References

1. Wallace BI, Kenney B, Malani PN, et al. Prevalence of immunosuppressive drug use among commercially insured US adults, 2018-2019. JAMA Netw Open. 2021;4:e214920. [PMID: 34014329] doi:10.1001/jamanetworkopen.2021.4920
2. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA. 2021;325:2204-2206. [PMID: 33950155] doi:10.1001/jama.2021.7489
3. 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;70:1884-1893. [PMID: 33903149] doi:10.1136/gutjnl-2021-324789
4. Wong SY, Dixon R, Martinez Pazos V, et al; ICARUS-IBD Working Group. Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. Gastroenterology. 2021;161:715-718.e4. [PMID: 33887219] doi:10.1053/j.gastro.2021.04.025
5. Kappelman MD, Weaver KN, Boccieri M, et al; PREVENT-COVID Study Group. Humoral immune response to messenger RNA COVID-19 vaccines among patients with inflammatory bowel disease. Gastroenterology. 2021;161:1340-1343.e2. [PMID: 34144046] doi:10.1053/j.gastro.2021.06.016