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Impact of Inflammatory Bowel Disease Therapies on Durability of Humoral Response to SARS-CoV-2 Vaccination



Immunization against the spike protein of SARS-CoV-2 reduces transmission^{1,2} and severe outcomes. However, little is known regarding the impact of immune-mediated diseases and immunosuppressive medications on the efficacy of vaccination. Vaccination immunity is transient, with breakthrough cases increasing at longer time intervals since the last dose.^{3,4} Although there are data on SARS-CoV-2 vaccine on early seroconversion in patients with inflammatory bowel disease (IBD),⁵ no data in the same cohort exist describing the durability of these antibodies over time. We sought to investigate the impact of IBD and its therapies on postvaccination antibody response and kinetics of immunogenicity decline, because these findings may better inform clinical guidelines and recommendations on precautions and booster vaccination.

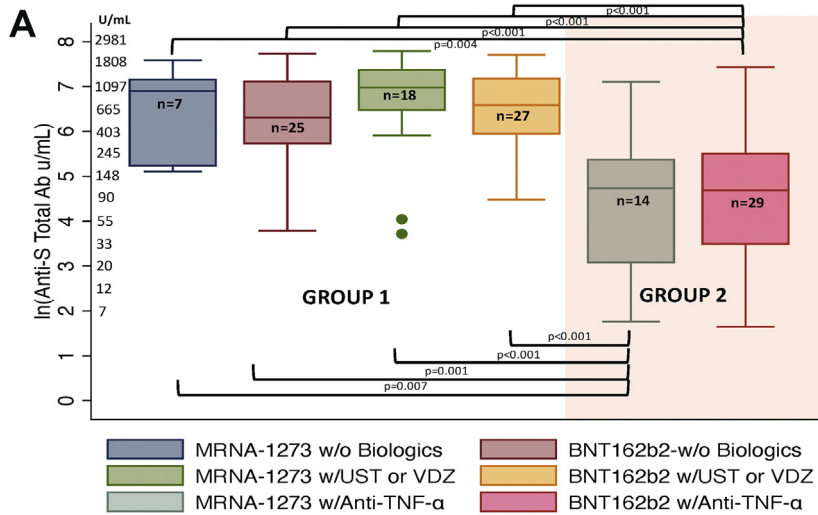
Within a prospectively followed cohort of 195 patients with IBD who underwent 1 anti-S total Ab titer test at a nonpredetermined time, between April 15 and October 19, 2021, 185 had measured titers following both doses of the BNT162b2 (Pfizer, BioNTech; 60%; n = 111) or mRNA-1273 (Moderna; 35.1%; n = 65) vaccines, and 9 (4.6%) the JNJ-78436735 vaccine (Janssen Pharmaceutical Companies; excluded from analyses because of low sample size). All vaccine doses were given at recommended dosing intervals. We divided the patients into 2 main medication groups: vedolizumab (VDZ)/ustekinumab (UST)/mesalamine/budesonide/no therapy as group 1 and those on anti-tumor necrosis factor (TNF)- α \pm immunomodulators as group 2. There were 7 patients on corticosteroids (prednisone \geq 20 mg/day or equivalent within 30 days of dose 1) and 7 on tofacitinib, which we excluded from main analyses given low sample sizes. VDZ, UST, and mesalamine/budesonide/no therapy were grouped together to improve sample size because antibody titer trends among all 3 were similar on preliminary analysis (Supplementary Figure 1A). Furthermore, there was no difference in testing interval distribution between VDZ/UST and mesalamine/budesonide/no therapy. Median time between dose #2 and titer measurement was 126 days (interquartile range, 89–162), similarly distributed between mRNA vaccines ($P = .799$) and within vaccine-medication groups ($P = .403$; Supplementary Figure 1B). Among 169 mRNA-vaccine recipients, 46 had qualitative results ($>2500 \mu\text{mL}$, $>250 \mu\text{mL}$, $<0.4 \mu\text{mL}$) and were included only in dichotomous analyses.

We included patients with quantitative titers without prior history of COVID-19 (n = 121) in titer decay analyses. Geometric mean titer of anti-S total Ab among all patients was $306 \mu\text{mL}$ (95% confidence interval, 234–401). The overall mean $\log_e(\text{anti-S total Ab})$ was 5.72 (95% confidence interval, 5.45–5.99) without significant differences between vaccines (BNT162b2 5.83 ± 1.61 vs mRNA-1273 5.67 ± 1.51 ; Student t test; $P = .6$). One breakthrough COVID-19 infection was observed in a 69 year old with severely active Crohn's disease treated with infliximab, 3 weeks after a titer of $13 \mu\text{mL}$ (measured 57 days after BNT162b2 dose #2). Patient characteristics and perivaccination disease activity approximated by surrogate markers (albumin, C-reactive protein, fecal calprotectin) are described in Supplementary Table 1.

Comparisons of mean $\log_e(\text{anti-S total Ab})$ across subgroups revealed significant differences between medication groups 1 and 2, in both BNT162b2 and mRNA-1273 recipients (Figure 1A). Comparisons among 4 arbitrarily selected titer thresholds, at different time-points and overall, showed significantly lower proportions of patients in group 2 that mounted anti-S total Ab above each threshold, with statistically significant difference persisting up to anti-S total Ab $\geq 300 \mu\text{mL}$ for at least 4 months after dose #2, whereas comparisons after 6 months exhibited large numerical differences without reaching statistical significance because of sample size (Figure 1B).

There was significant decay observed in group 2 (n = 42; exponentiated decay coefficient [EDC] 1.8%/day; $P = .012$; estimated half-life, 38 days) and it was significantly faster (Δ -slope $P = .045$) than group 1 (n = 74; $P = .058$; EDC 0.05%/day; estimated half-life, 153 days), as shown in Figure 1C.

Figure 1D shows the differences between the 2 mRNA vaccines among patients receiving anti-TNF- α antagonist monotherapy, with graphical evidence of greater decay in BNT162b2 (n = 25; EDC 2.4%/day; $P = .002$; half-life, 28 days) compared with mRNA-1273 (n = 10; EDC 0.9%/day; $P = .188$; half-life, 76 days), and slope difference approaching significance ($P = .109$), despite relatively low sample size.



B Comparison across Medication Groups in BNT162b2 and mRNA-1273 recipients at different titer cutoffs and time intervals

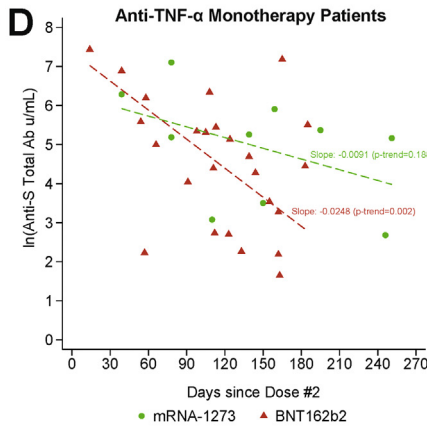
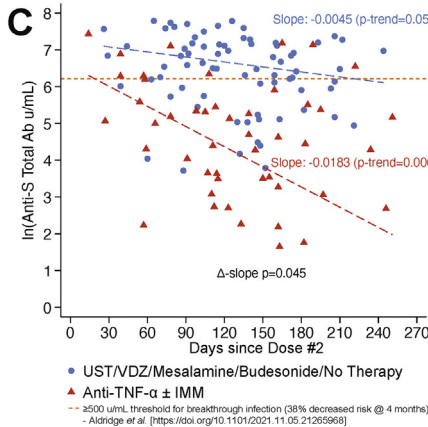
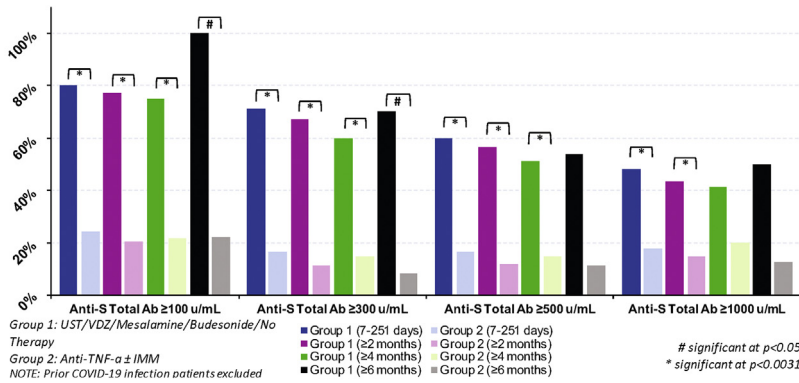


Figure 1. (A) Titer comparison across medication-vaccine groups in BNT162b2 and mRNA-1273 recipients with IBD. One-way analysis of variance of $\log_e(\text{anti-S total Ab})$ means across the groups revealed significant difference between medication groups 1 and 2, in BNT162b2 and mRNA-1273 recipients. (B) Comparison across medication groups in BNT162b2 and mRNA-1273 recipients with IBD at different titer cutoffs and time intervals. Comparisons among 4 arbitrarily selected titer thresholds at different timepoints and overall, showing significantly lower proportions of patients in group 2 mounting an anti-S total Ab titer above each threshold, with statistically significant difference persisting up to anti-S total Ab $\geq 300 \mu\text{mL}$ for at least 4 months after dose #2, whereas comparisons after 6 months exhibited large numerical differences without reaching statistical significance because of sample size. (C) BNT162b2 and mRNA-1273 recipients with IBD (excluding prior COVID-19). Robust linear regression lines fitted for each medication group. Group 1 (VDZ/UST/mesalamine/budesonide/no therapy) showed a near-significant decreasing trend. Group 2 (anti-TNF- α /CS/IMM) had significant linear decay in $\ln(\text{anti-S total Ab})$, and significantly faster than group 1. Most patients in group 1 were below the $500 \mu\text{mL}$ (orange-dotted line) threshold for breakthrough infection protection, as described by Aldridge et al.⁶ (D) Patients on anti-TNF- α antagonists (excluding IMM/CS/prior COVID-19). Robust linear regression lines fitted for each vaccine group, among patients exclusively on anti-TNF- α antagonists. Both vaccines had significant linear decay in $\ln(\text{anti-S total Ab})$. CS, systemic corticosteroids; IMM, immunomodulators.

Four patients (2.3%; mean age, 63.3 years) had undetectable antibodies (measurement days: 7, 34, 104, 181; 3 BNT162b2, 1 mRNA-1273). Two of the BNT162b2 patients (1 on UST) and the mRNA-1273 patient (on UST and 6-mercaptopurine) were also receiving tacrolimus after solid-organ transplant. The fourth patient (BNT162b2, titer at day #181) was on adalimumab and on dialysis for end-stage renal disease.

These data demonstrate robust immunogenicity among patients with IBD to SARS-CoV-2 vaccination,

with the notable exception of those on simultaneous transplant immunosuppressants, and are the first data to describe the kinetics of immunogenicity decay in this cohort. Although our cohort had only 1 vaccinated patient develop COVID-19, our breakthrough infection rate is likely underestimated because there was no predetermined testing at prespecified intervals, potentially missing asymptomatic carriers. Patients on anti-TNF- α \pm immunomodulators had lower titers and more rapid decay than those on no immunosuppression/VDZ/UST.

Our findings are in line with the findings of Edelman-Klapper et al,⁵ where at a 4-week follow-up period, anti-TNF- α patients exhibited significantly lower anti-S IgG titers, together with lower neutralizing and inhibitory functions of anti-S IgG, when compared with non-anti-TNF- α -treated patients. Recent data by Aldridge et al,⁶ using the same titer assay, showed that a >500 μmL cutoff conferred 38% lower risk for breakthrough infection in the community setting ($n = 197/8858$; 2.2%; median follow-up, 4 months). Furthermore, earlier studies have shown that anti-S antibodies correlate with both neutralizing antibody titers⁷ and T-cell response,⁸ allowing extrapolation of the clinical usefulness of anti-S antibodies in conferring immunity against SARS-CoV-2. Additionally, initial titer response has been suggested to positively impact long-term immunity.⁹ The previously discussion, together with our findings, suggest that most patients with IBD still carry a theoretical risk of breakthrough infection after vaccination, but especially those on anti-TNF- α agents ($<20\%$ with anti-S total Ab ≥ 500 μmL at ≥ 2 months after dose #2). Furthermore, among the anti-TNF- α -treated patients, titer decay was 2.7 times faster in BNT162b2 vaccine recipients compared with the mRNA-1273 vaccine, thus potentially exposing to earlier breakthrough-infection risk. We thus agree that augmented vaccine dosing regimens as recommended by the Centers for Disease Control and Prevention¹⁰ may be needed for patients with IBD, especially those on anti-TNF- α agents and possibly BNT162b2 recipients, although more data are needed to confirm the latter.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click [here](#).

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Reprint requests

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Conflicts of interest

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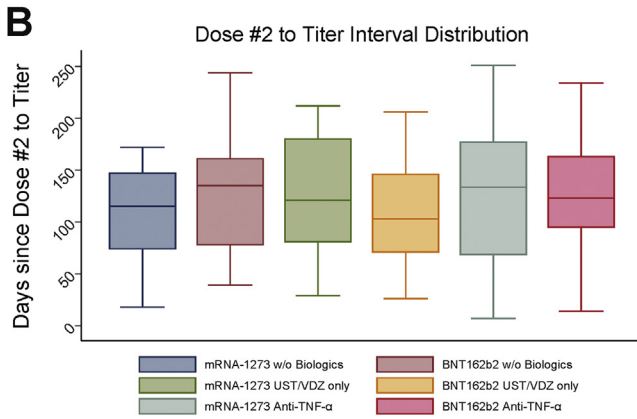
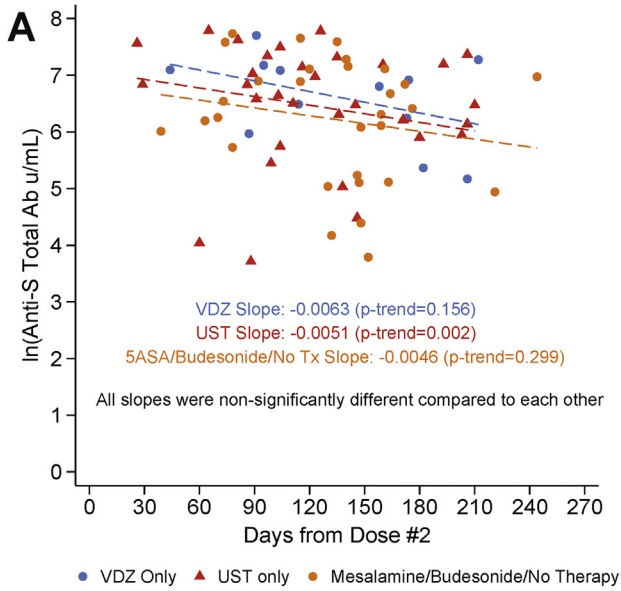
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Supplementary Methods

Data were collected retrospectively using the DataMart Inflammatory Bowel Disease (IBD) database of New York-Presbyterian Hospital Weill Cornell Medicine, from April 1, 2021 to October 19, 2021. We collected all patients with IBD who had “SARS-CoV-2 Semi-Quantitative Total Antibody Spike” test (LabCorp test #164090, an electrochemiluminescence immunoassay). The data were then quality controlled via manual chart review. The study was approved by the institutional review board.

Missing values were not imputed because of sample size limitation ($n = 185$), to ensure data validity. Continuous variables were analyzed using the Student t test and Mood medians test for normally and non-normally distributed data, respectively. Categorical variables were analyzed using chi-square or Fisher

exact tests. Multiple comparisons were done using 1-way analysis of variance, with Bonferroni correction to adjust for alpha-error inflation. The main outcome of interest, anti-S total Ab titer, was presented as a geometric mean titer or log-transformed (with base e), given its log-normal distribution and to allow linear modelling on its otherwise nonnormally distributed residuals should be left untransformed. Robust linear regression, which is robust to potential outliers and thus allowing to include all available data, was used to fit linear trends among various comparison groups to assess the linear $\ln(\text{anti-S total Ab})$ decay since dose #2 of vaccination. By extension, the exponentiated decay coefficients represent the percent change from the geometric mean titer. STATA MP version 15 was used for all analyses (Stata Corp, College Station, TX). All comparisons were deemed significant a priori at $P < .05$, unless otherwise stated.



Supplementary Figure 1. (A) Days since dose #2 among non-anti-TNF- α medication groups. Preliminary analysis of slopes and intercepts (ie, theoretical immediate post-vaccination titers) was nonsignificantly different among UST only, VDZ only, and mesalamine/budesonide/no therapy groups. (B) Days since dose #2 distribution between vaccine-medication groups. The median time between second dose and titer measurement was 126 days (interquartile range, 89–162) and similarly distributed between mRNA vaccines ($P = .799$) and within vaccine-medication groups ($P = .403$).

Supplementary Table 1. Characteristics of IBD Patients Who Received mRNA-Vector Vaccines

Variable	mRNA-1273 n = 65 (36.9%)	BNT162b2 n = 111 (63.1%)	Overall n = 176	P value
Age at dose #1, y	47.5 ± 17.4 (43; 33–63)	47.1 ± 15.3 (47; 33–59)	47.3 ± 16.0 (47; 33–60.5)	.890
Female	42 (64.6)	77 (69.4)	119 (67.6)	.515
Prior history of COVID-19	6 (9.2)	10 (9)	16 (9.1)	.961
Crohn's disease	43 (66.2)	69 (62.7)	112 (64)	.648
Ulcerative colitis extent				
E1	1 (4.6)	(0)	1 (1.6)	.345
E2	9 (40.9)	20 (50)	29 (46.8)	
E3	12 (54.6)	20 (50)	32 (51.6)	
Ulcerative colitis severity				
S0	3 (13.6)	7 (17.5)	10 (16.1)	.971
S1	8 (36.4)	15 (37.5)	23 (37.1)	
S2	4 (18.2)	6 (15)	10 (16.1)	
S3	7 (31.8)	12 (30)	19 (30.7)	
Crohn's disease classification				
A1	5 (11.6)	10 (14.7)	15 (13.5)	.026
A2	23 (53.5)	49 (72.1)	72 (64.9)	
A3	15 (34.9)	9 (13.2)	24 (21.6)	
L1	10 (23.3)	27 (39.7)	37 (33.3)	.073
L2	8 (18.6)	11 (16.2)	19 (17.1)	.741
L3	25 (58.1)	30 (44.1)	55 (49.6)	.150
L4	2 (4.7)	1 (1.5)	3 (2.7)	.314
B1	17 (100)	30 (96.8)	47 (97.9)	.454
B2	18 (100)	20 (95.2)	38 (97.4)	.348
B3	11 (100)	20 (95.2)	31 (96.9)	.462
Perianal disease	7 (100)	12 (92.3)	19 (95)	.452
Biologics/SM within 3 mo of dose #1				
No biologic/SM	20 (30.8)	35 (31.5)	55 (31.3)	.474
IFX/ADA/CTZ	14 (21.5)	33 (29.7)	47 (26.7)	
UST	22 (33.9)	25 (22.5)	47 (26.7)	
VDZ	6 (9.2)	14 (12.6)	20 (11.4)	
Tofacitinib	3 (4.6)	4 (3.6)	7 (4)	
Prednisone ≥20 mg/day within 30 days of 1st dose	4 (6.2)	3 (2.7)	7 (4)	.258
Immunomodulators	11 (16.9)	7 (6.3)	18 (10.2)	.025
Anti-TNF-α + IMM	2 (14.3)	2 (6.1)	4 (8.5)	.355

Supplementary Table 1. Continued

Variable	mRNA-1273 n = 65 (36.9%)	BNT162b2 n = 111 (63.1%)	Overall n = 176	P value
Vaccination-related data				
Above median anti-S total Ab (≥ 477 μmL)	46 (70.8)	66 (59.5)	112 (63.6)	.132
Vaccine nonresponder	1 (1.5)	3 (2.7)	4 (2.3)	.617
Titer testing interval (days since dose #2)	131 \pm 60 (145; 81–174)	124 \pm 51 (123; 91–161)	126 \pm 54 (126; 89–162)	.441
Anti-S total Ab titer (μmL) (n = 128)	759.8 \pm 713.0 (GM: 340) (593; 107–1256)	610.6 \pm 601.8 (GM: 291) (445; 140–982)	659.6 \pm 641.5 (GM: 305) (477; 125–1107)	.225
ln(anti-S total Ab) titer (μmL) (n = 128)	5.83 \pm 1.61 (6.38; 4.67–7.14)	5.67 \pm 1.51 (6.10; 4.94–6.88)	5.72 \pm 1.54 (6.17; 4.82–7.01)	.661
Disease activity markers				
Any albumin < 3.5 mg/dL (from 60 d before dose #1 up to titer date)	15 (25.4)	15 (16.3)	30 (19.9)	.171
Mean albumin (g/dL; from 60 d before dose #1 up to titer date) (n = 151)	3.91 \pm 0.45 (3.9; 3.7–4.2)	4.06 \pm 0.47 (4.2; 3.85–4.4)	4.00 \pm 0.47 (4.1; 3.8–4.3)	.042
Any FCP ≥ 250 $\mu\text{g/g}$ (from 60 d before dose #1 up to titer date)	16 (57.1)	17 (50)	33 (53.2)	.575
Mean FCP ($\mu\text{g/g}$; from 60 d before dose #1 up to titer date) (n = 62)	397.2 \pm 471.2 (291; 77–492)	447.1 \pm 671.6 (205; 43–437)	424.6 \pm 585.6 (239; 66.5–486)	.741
Any CRP ≥ 1 mg/dL (from 30 d before dose #1 up to titer date)	18 (40)	12 (16.4)	30 (25.4)	.004
Mean CRP (mg/dL; from 30 d before dose #1 up to titer date) (n = 59)	1.02 \pm 1.84 (0.4; < 0.04 –1.3)	0.68 \pm 1.72 (< 0.04 ; < 0.04 –0.4)	0.81 \pm 1.77 (< 0.04 ; < 0.04 –0.80)	.309

NOTE. Values are n (%) or mean \pm SD (median; IQR).

ADA, adalimumab; anti-S, anti-spike; CRP, C-reactive protein; CTZ, certolizumab; FCP, fecal calprotectin; GM, geometric mean; IBD, inflammatory bowel disease; IFX, infliximab; IMM, immunomodulators; IQR, interquartile range; ln, natural logarithm; SD, standard deviation; SM, small molecule; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.