Letters

Serological responses to three doses of SARS-CoV-2 vaccination in inflammatory bowel disease

We read with interest the article by Kennedy *et al*, which demonstrated adequate serological responses to two-dose regimens of SARS-CoV-2 vaccination in individuals with IBD.[1] However, a decay in antibody levels has been shown in the IBD population after two vaccine doses, with anti-tumour necrosis factor (anti-TNF) therapies associated with a more rapid decline.[2–4] Despite recommendations for three-dose vaccine regimens for individuals with IBD,[5] the uptake has been low in this population.[6] We examined the serological response following three doses of mRNA SARS-CoV-2 vaccines in persons with IBD, the factors associated with antibody titres and the decay of antibody titres over time.

Adults aged 18 years or older with a confirmed diagnosis of IBD who received three doses of an mRNA SARS-CoV-2 vaccine (Pfizer-BioNTech BNT162b2 mRNA (Comirnaty) or NIH-Moderna mRNA-1273 (Spikevax)) were recruited from 25 June 2021 to 6 January 2022. Serum samples were drawn at least 1 week following the third dose of vaccine and processed by Alberta Precision Laboratories using the Abbott SARS-CoV-2 IgG II Quant assay to detect antibodies to the S1 subunit of the spike protein (anti-S). The threshold for seroconversion was defined as ≥50 AU/mL for anti-S antibodies. Age, sex, vaccination date and type, IBD type, and IBD medications at time of vaccination were collected through medical chart review. Vaccine schedule between second and third vaccine doses was defined as 'scheduled' for 4–18 weeks between dose administration and 'delayed' for >18 weeks. Prior history of COVID-19 was defined by either nucleocapsid seroconversion or molecular-confirmed diagnosis of SARS-CoV-2 infection via PCR.[7]

Geometric mean titres (GMTs) with associated 95% CIs were used to report anti-S concentrations. Multivariable linear regression was used to determine the effect of independent predictors determined *a priori* on log-transformed anti-S concentration. Exponentiated coefficients represented the fold change (FC) associated with each binary covariate and the FC in log anti-S concentration per unit change for continuous variables.[2]

Table 1 Number of patients with sample proportion, stratified geometric mean titres (GMTs) and exponentiated coefficients of multivariable linear regression model per characteristic

Variable	Number of patients, n (%)	Seroconversion rate, n/N (%)	GMT (95% CI)	Fold change (95% CI)
Age	N/A	N/A	N/A	0.92 (0.82 to 1.02)
Per decade				
Sex				
Male	99 (42.7)	98/99 (99.0)	12 947 (10 588 to 15 306)	0.97 (0.72 to 1.30)
Female	133 (57.3)	133/133 (100.0)	15 933 (13 297 to 18 569)	
IBD type, n (%)				
Crohn's disease	180 (77.6)	180/180 (100.0)	14 835 (12 695 to 16 975)	0.84 (0.60 to 1.19)
UC/IBD-Undetermined	52 (22.4)	51/52 (98.1)	14 049 (10 680 to 17 417)	
Medication, n (%)*				
No immunosuppressives†	16 (6.9)	16/16 (100.0)	13 556 (8142 to 18 971)	–
Anti-TNF only	90 (38.8)	90/90 (100.0)	12 861 (9915 to 15 807)	0.78 (0.43 to 1.40)
Immunomodulators only	6 (2.6)	6/6 (100.0)	13 904 (0 to 28 581)‡	0.77 (0.28 to 2.15)
Vedolizumab only	21 (9.0)	21/21 (100.0)	18 326 (10 785 to 25 867)	1.65 (0.80 to 3.38)
Ustekinumab only	45 (19.4)	45/45 (100.0)	21 038 (16 875 to 25 200)	1.69 (0.90 to 3.17)
Combination therapy	48 (20.7)	48/48 (100.0)	12 449 (8735 to 16 164)	0.66 (0.35 to 1.24)
Oral corticosteroids	6 (2.6)	5/6 (83.3)	2320 (0 to 5728)‡	0.07 (0.03 to 0.20)
Vaccine type, n (%)				
Pfizer	211 (91.0)	210/211 (99.5)	14 690 (12 724 to 16 657)	0.62 (0.37 to 1.02)
Moderna	21 (9.0)	21/21 (100.0)	14 341 (10 670 to 18 022)	
Vaccine schedule				
Scheduled	122 (52.6)	120/121 (99.2)	13 520 (11 128 to 15 913)	0.78 (0.59 to 1.05)
Delayed	110 (47.4)	110/110 (100.0)	15 922 (13 147 to 18 696)	
Prior COVID-19				
Yes	22 (9.5)	22/22 (100.0)	23 470 (16 372 to 30 569)	1.97 (1.22 to 3.18)
No	210 (90.5)	209/210 (99.5)	13 736 (11 898 to 15 573)	
Time after vaccine				
Per week	N/A	N/A	N/A	0.88 (0.85 to 0.92)

*IBD medications were classified in the following mutually exclusive groups: A. No immunosuppressive therapies including no medical treatment, use of 5-aminosalicylic acid (oral or topical), and/or oral budesonide; B. immunomodulator monotherapy (azathioprine, 6-mercaptopurine or methotrexate); C. anti-TNF monotherapy (infliximab, adalimumab, or golimumab, originator or biosimilar); D. vedolizumab monotherapy; E. ustekinumab monotherapy; F. combination therapy, defined as any combination of two or more of anti-TNF, immunomodulators, vedolizumab, ustekinumab or tofacitinib; or G. oral corticosteroids, defined as prednisone at any dose alone or in conjunction with any other medication.
†Indicates reference group.
‡Lower bound of CIs that are negative are reported as 0.

In total, 232 participants (mean age 52.7 years;42.7% male) with IBD and three doses of an mRNA vaccine were included (table 1). The seroconversion rate among this sample was 99.6% and the GMT was 14 569 AU/mL (95% CI 12 846 to 16 472 AU/mL). Multivariable linear regression identified significantly increased log anti-S concentration for prior SARS-CoV-2 infection (FC: 1.97 (95% CI 1.22 to 3.18)) and decreased log anti-S concentration for corticosteroid use (FC: 0.07 (95% CI 0.03 to 0.20)) (table 1). Antibodies decayed by 12% per week (95% CI 8% to 15%) following third dose vaccination (figure 1). Age, sex, IBD type, vaccine type and vaccine schedule were not associated with anti-S concentration. Our data can be viewed in an online dashboard (https://kaplan-gi.shinyapps.io/COVID_Serology/) using the Shiny: Web Application Framework for R package.[8]

A three-dose SARS-CoV-2 vaccination regimen for individuals with IBD has been proposed based on impaired serological responses to two-dose regimens.[3 5] Our study demonstrates near complete seroconversion and high antibody titres following a three-dose mRNA vaccine regimen, similar to an American cohort of individuals with IBD that demonstrated a robust antibody response following an extra dose from the initial vaccine series.[9] Antibody responses following three doses are consistently high across all IBD therapies for maintenance of remission, including biologic and immunomodulator therapies. In contrast, prednisone use at the time of vaccine dosing was associated with lower antibody responses.

Our study also indicated significant decay of antibody titres over time

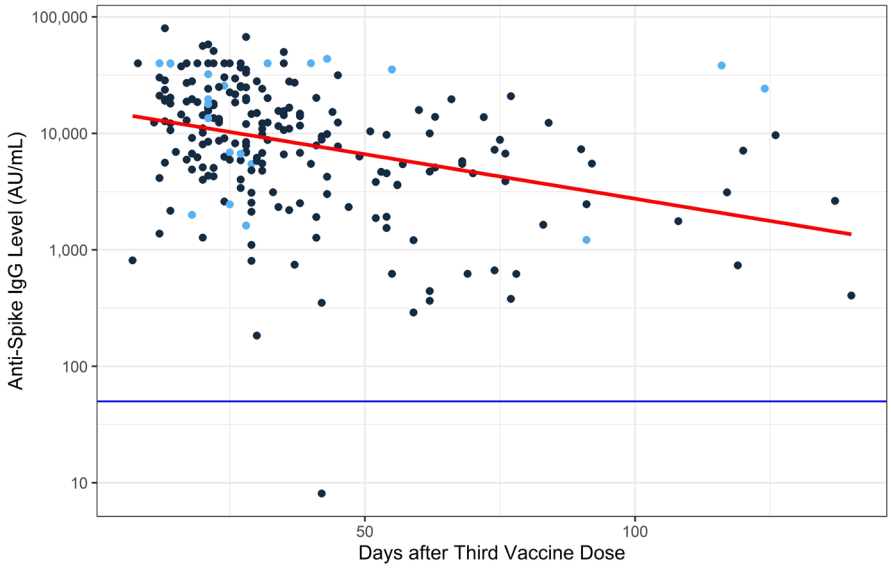

Figure 1 Concentration of antibodies to the S1 subunit of the spike protein (anti-S) by days after third-dose vaccination. Blue points represent individuals with prior SARS-CoV-2 infection. Solid red line represents the line of best fit for linear relationship between anti-S concentration (AU/mL) and time after vaccination. Solid blue line represents the threshold for positive seroconversion (50 AU/mL). Serological data from this study are available in an open access online interactive ShinyApp: https://kaplan-gi.shinyapps.io/COVID_Serology/

following third-dose vaccination at a rate of 12% per week. While these data support widespread implementation of a three-dose vaccine regimen, future studies are necessary to determine if additional doses will be required to maintain sufficient antibody levels over time.

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Contributors GGK has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. GGK, CM, JQ, JK, GT, RP conceived and designed the study. GGK, CM, RP, NS, MH, RJI, AM were responsible for clinical data. JK, GT, were responsible for serological data. JQ, GGK, SC, LH analysed the data. JQ and GGK drafted the manuscript. All authors interpreted the data and provided critical revisions of the manuscript for important intellectual content. All authors have approved the final draft of the manuscript.

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