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Article

Patients with Inflammatory Bowel Disease on anti-Tumor Necrosis Factor Therapy Might be Predisposed to SARS-CoV-2 Variants Infection Even after Receiving a Third mRNA Vaccine Dose

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Abstract. Management of inflammatory bowel disease (IBD) often relies on biological and immunomodulatory agents for remission through immunosuppression, raising concerns regarding the SARS-CoV-2 vaccine's effectiveness. The emergent variants have hindered the vaccine neutralization capacity, and whether the third vaccine dose has the capacity to neutralize SARS-CoV-2 variants in this population remains unknown. This study aims to evaluate the humoral response of SARS-CoV-2 variants in patients with IBD 60 days after the third vaccine dose [BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)].56 su bjects with IBD and 12 healthy subjects were recruited. 90% of patients with IBD (49/56) were receiving biologics and/or immunomodulatory therapy. 24 subjects with IBD did not develop effective neutralizing capability against the Omicron variant. 70% (17/24) of those subjects were receiving anti-Tumor Necrosis Factor therapy [10= adalimumab, 7= infliximab], two of them had a history of COVID-19 infection, and one subject did not develop immune neutralization against three other variants: Gamma, Epsilon, and Kappa. All subjects in the control group developed detectable antibodies and effective neutralization against all seven SARS-CoV-2 variants. Our study shows that patients with IBD might not be protected against SARS-CoV-2 variants, and larger studies are needed to evaluate optimal immunity.

Keywords: COVID-19 variants, COVID-19 vaccine, IBD, ulcerative colitis, Crohn's disease, anti-TNF

Introduction

As the coronavirus pandemic is evolving, more questions and challenges have arisen. COVID-19 disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with a 2-3% fatality rate [1]. Vaccination against this virus has shown successful outcomes in reducing symptomatic COVID-19 infection, hospitalizations, and mortality [2]. Yet, the characterization of the vaccine's efficacy among immunocompromised patients is still unclear. Patients with inflammatory bowel disease (IBD) are part of this immunocompromised population. As is well known, clinical trials for the vaccines

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against COVID-19 excluded immunosuppressed patients [3]. Thus, whether these vaccines can induce an adequate and long-lasting immune response against the virus in this population is not fully addressed. Inflammatory bowel diseases, including Crohn's disease (CD) and ulcerative colitis (UC), are complex, chronic, and costly conditions characterized by an immune-mediated inflammatory response in the gastrointestinal (GI) tract. Although the etiology is unknown, it is thought to be multifactorial, including environmental triggers, gut microbiota, and immune dysregulation in genetically susceptible individuals [4]. Management of these diseases often relies on immunomodulatory and biological agents to achieve and maintain clinical, biochemical, and endoscopic remission in these patients, placing these individuals vulnerable to bacterial and viral infections [5]. These drugs also impair the protective immune response elicited by various vaccines [3]. For instance, it has been shown that infliximab reduces immunity to hepatitis B, hepatitis A, pneumococcal, and influenza vaccinations [6].

The emergence of SARS-CoV-2 variants has posed a significant concern in the general community, especially in patients with dysregulated immune responses and comorbidities. Mutations modifying the spike protein structure can consequently alter the protein and the human ACE-2 receptor interaction, further changing immune response and threatening the efficacy of vaccines against variants [7]. The administration of the third dose of mRNA COVID-19 vaccine has been promoted to boost the immune response against SARS-CoV- 2 rapidly appearing variants [8].

Recent evidence showing the efficacy of COVID-19 immunization on patients with IBD has suggested that they can reach seroconversion against the virus after two doses of mRNA- COVID-19 vaccine [9]. However, with the emergent SARS-CoV-2 variants, whether this third vaccine dose can provide the same efficacy remains unknown. In this study, we report the results of the humoral immune response against seven SARS-CoV-2 variants of concern in patients with IBD on biological and/or immunomodulatory therapies 60-days after receiving three doses of mRNA- COVID-19 vaccine.

2. Materials and Methods

Patients ≥ 21 years of age diagnosed with CD or UC exposed and unexposed to biologic and/or immunomodulatory therapy were recruited between October 2021 and May 2022 at the University of Puerto Rico IBD Clinics. Patients with Hermansky- Pudlak syndrome and pregnant women were excluded from the study. Blood samples were collected at 60 ± 7 days after receiving the third dose of mRNA COVID-19 vaccine [BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)]. We measured anti-Spike IgG levels with an indirect in-house ELISA for the semi-quantitative determination of human IgG antibody class [10, 12]. Briefly, 96 well microplates were coated overnight at 4°C with 2µg/mL of recombinant SARS-CoV-2 S1-RBD (GenScript, New Jersey, USA) protein in carbonate-bicarbonate buffer. After washing and blocking, samples (serum or plasma) were diluted 1:100 and incubated at 37°C for 30 min. Following a washing step, horseradish peroxidase (HRP) labeled-mouse anti-human IgG-Fc (GenScript, New Jersey, USA) was added and incubated for 30 min at 37°C. After washing, the substrate solution was added; the reaction was stopped with 10% HCl and the absorbance was measured at 492nm (A492) using a

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Multiskan FC reader (Thermo Fisher Scientific). Samples with A492 > 0.499 were considered positive. For the neutralizing activity we used cPassTM SARS-CoV-2 neutralization antibody detection kit (GenScript, New Jersey, USA) to measure inhibitory capability based on the ability of the antibodies to target host ACE2 receptor and viral receptor-binding domain (RBD) interaction. Serum or plasma samples were diluted according to manufacturer's instructions and incubated with a soluble SARS-CoV2 receptor binding domain (RBD-HRP) antigen for 30 minutes, mimicking a neutralization reaction. Following incubation, samples were added to a 96 well plate coated with human ACE-2 protein. Since this is an inhibition assay, color intensity is inversely proportional to the amount of neutralizing antibodies present in samples [10-11].

This test was performed on SARS-CoV-2 Wild type and seven SARS-CoV-2 variants of concern: Alpha, Beta, Gamma, Epsilon, Kappa, Delta, and Omicron. A result of ≥ 30% in a surrogate virus neutralization test (sVNT%) demonstrated an effective viral variant neutralization capacity. Results were stratified by the mechanism of action of the specific immunosuppressive therapy and compared to a healthy control group. Informed consent was obtained from all subjects involved in the study.

Statistical Analysis

Analyses were performed using *Intellectus Statistics* online software (Clearwater, Florida, United States). Categorical data items were summarized using frequency counts and percentages, while continuous quantitative variables were described as mean ± standard deviation (SD). The comparative analysis two-tailed Mann-Whitney two-sample was performed among the two cohorts, patients with IBD and the control group, to evaluate statistical differences in the mean values for anti-Spike IgG Levels and sVNT% of the SARS-CoV-2 variants of concern. There were 56 observations in participants with IBD and 12 observations in controls. In addition, we evaluated differences in IgG levels and sVNT% among patients with IBD stratified by their current medication by conducting a Kruskal-Wallis test. Post-hoc analyses were completed for statistically significant differences with Pairwise comparisons. Statistical significance for all analyses was set at alpha <0.05.

Ethical Statement

This study was approved by the University of Puerto Rico Medical Sciences Campus IRB (protocol: #1250121). Volunteers in the control group were participating in the IRB-approved clinical protocol "Molecular Basis and Epidemiology of Viral infections circulating in Puerto Rico", Pro0004333.

3. Results

56 subjects with IBD, 5 unexposed and 51 exposed to biological and/or immunomodulatory drugs, and 12 healthy controls are reported. Blood samples were examined 60 ± 7 days after the third vaccine dose in the IBD subjects and 60 ± 10 days after the third dose in the controls. 82% (46/56) of subjects with IBD had a diagnosis of CD, 61% were males (34/56), and the mean age was 42. The majority of the subjects were receiving anti-TNF therapy (30/56), and one was on concomitant oral corticosteroids. All subjects with

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IBD developed detectable antibodies after 60 ± 7 days. Twenty-four (24) subjects with IBD did not develop effective neutralizing capability against the Omicron variant. Seventy percent (17/24) of those subjects were receiving anti-TNF therapy [10= adalimumab, 8= infliximab], two of them had a history of COVID-19 infection, and one subject did not develop immune neutralization against three other variants: Gamma, Epsilon, and Kappa. In the healthy controls, only one subject had a prior history of COVID-19 infection, and all developed detectable antibodies and effective humoral responses against all seven variants of SARS-CoV-2.

When analyzed by non-parametric tests, participants with IBD showed statistically lower values of sVNT% for the Gamma, Epsilon, Kappa, Delta, and Omicron variants when compared to healthy controls (p=0.015, <0.001, <0.001, 0.014, 0.031, respectively), as detailed in Table 1 and Figure 1 (a). Data of anti-Spike IgG levels and sVTN% between the control group and patients with IBD was stratified by biological/immunomodulatory treatment, as seen in Figure 2. We found statistical differences in the sVNT% values for SARS- CoV-2 Wild type (p=0.008), and Beta (p=0.029), Gamma (p=0.001), Epsilon (p<0.001), Kappa (p<0.001), Delta (p=0.018), and Omicron (p=0.007), variants, mainly between controls and patients receiving anti-TNF therapy, detailed in Table 2 and Figure 1 (b).

Table 1. Summary Statistics Table for Interval/Ratio of anti-Spike IgG levels and sVNT% against SARS-CoV-2 variants in patients with IBD vs. control, and p-value for the two-Tailed Mann-Whitney Test**.**

Variable	Mean	SD	n	Min	Max	p-value
Anti-Spike IgG Levels						
IBD	3,393.95	1,711.59	56	100.00	6,254.00	0.177
Control	4,235.67	941.32	12	2,327.00	5,281.00	
Wild Type sVNT%						
IBD	95.25	3.80	56	70.00	97.84	0.114
Control	96.18	0.18	12	95.76	96.50	
Alpha sVNT%						
IBD	94.38	9.01	56	41.63	98.30	0.326

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Control	96.93	0.19	12	96.47	97.18	
Beta sVNT%						
IBD	90.12	10.17	56	40.13	98.41	0.243
Control	94.23	1.00	12	91.57	94.98	
Gamma sVNT%						
IBD	89.32	15.73	56	14.59	98.28	**0.015**
Control	96.80	1.69	12	91.81	97.73	
Epsilon sVNT%						
IBD	93.61	9.85	56	28.47	98.18	**<0.001**
Control	97.95	0.07	12	97.82	98.08	
Kappa sVNT%						
IBD	92.78	12.78	56	18.02	98.20	**<0.001**
Control	97.93	0.15	12	97.51	98.07	
Delta sVNT%						
IBD	95.28	7.93	56	47.12	98.46	**0.014**
Control	98.18	0.11	12	97.99	98.35	
Omicron sVNT%						
IBD	45.20	38.40	56	0.00	97.15	**0.031**
Control	72.00	25.38	12	31.94	97.30	

Descriptive values and Two-tailed Mann-Whitney two-sample rank-sum test p-value result

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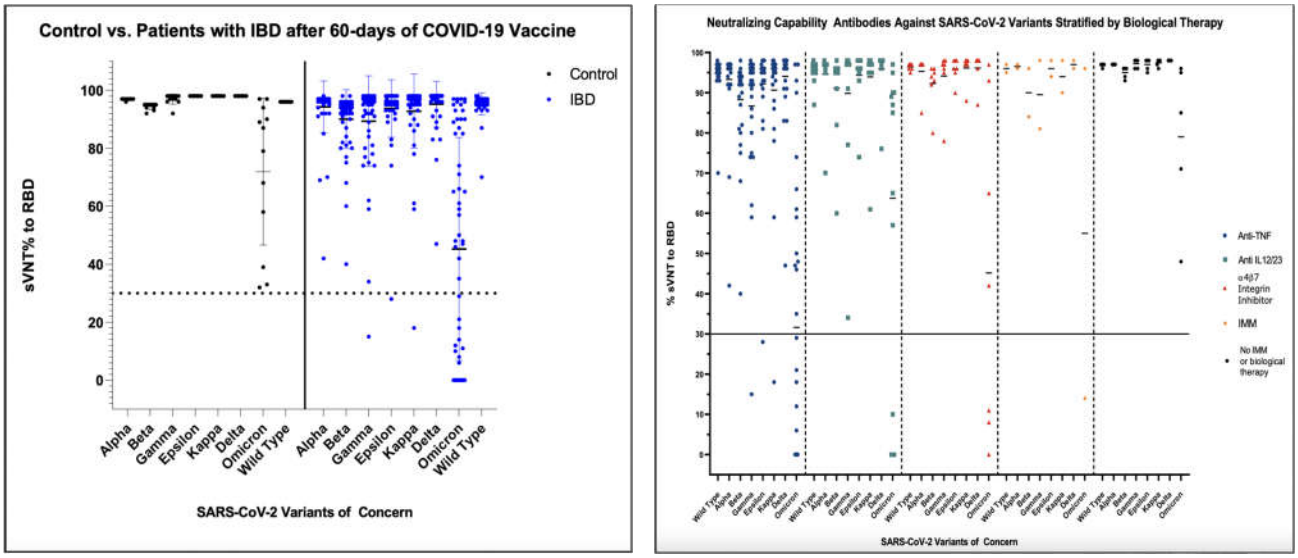

(**a**) (**b**)

Figure 1. (**a**) Patients with IBD developed a limited humoral neutralization against SARS-CoV-2 variants after a third mRNA vaccine dose. (**b**) Patients with IBD receiving anti-TNF do not develop an effective neutralization capacity against SARS-CoV-2, especially against Omicron.

Table 2. Kruskal-Wallis Rank Sum Test for anti-Spike IgG levels and sVNT% stratified by therapy vs. control, and Pairwise Comparisons for the Mean Ranks.

Variable Levels	*Mean*	*SD*	n	*p-value*
Anti-Spike IgG Levels				
Anti-TNF	2,789.98	1,663.38	30	.055
IL12/23 Inhibitors	3,957.58	1,686.53	12	
Integrin $\alpha_4\beta_7$ Inhibitor	3,962.14	1,664.47	7	
Non-Biologic	4,448.00	1,167.81	7	
Controls	4,235.67	941.32	12	
Wild Type sVNT%				
Anti-TNF	94.67	4.78	30	**0.008**
IL12/23 Inhibitors	95.31	2.95	12	
Integrin $\alpha_4\beta_7$ Inhibitor	96.40	0.73	7	
Non-Biologic	96.49	0.74	7	
Controls	96.18	0.18	12	

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However, results indicated that none of the individual pairwise comparisons were significantly different.

Alpha sVNT%				
Anti-TNF	93.32	11.11	30	0.072
IL12/23 Inhibitors	94.81	7.81	12	
Integrin $\alpha_4\beta_7$ Inhibitor	95.51	4.45	7	
Non-Biologic	97.01	0.55	7	
Controls	96.93	0.19	12	
Beta sVNT%				
Anti-TNF	88.32	11.61	30	**0.029**
IL12/23 Inhibitors	91.03	10.54	12	
Integrin $\alpha_4\beta_7$ Inhibitor	92.66	5.74	7	
Non-Biologic	93.76	4.44	7	
Controls	94.23	1.0	12	

However, results indicated that none of the individual pairwise comparisons were significantly different.

Gamma sVNT%				
Anti-TNF	86.68	17.20	30	**0.001**
IL12/23 Inhibitors	89.76	18.74	12	
Integrin $\alpha_4\beta_7$ Inhibitor	93.99	7.38	7	
Non-Biologic	95.16	6.28	7	
Controls	96.80	1.69	12	

Pairwise Comparison	Obs. Diff.	Critical Diff.
Anti-TNF vs Non-Biologic	23.74	23.30
Anti-TNF vs Controls	23.53	18.96

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The results of the multiple comparisons indicated significant differences between the following variable pairs: Anti TNF-Non-Biologic and Anti TNF-Controls

Epsilon sVNT%				
Anti-TNF	92.13	12.64	30	**< 0.001**
IL12/23 Inhibitors	94.17	6.61	12	
Integrin $\alpha_4\beta_7$ Inhibitor	95.87	2.66	7	
Non-Biologic	96.70	1.45	7	
Controls	97.95	0.07	12	

Pairwise Comparison	Obs. Diff.	Critical Diff.
Anti-TNF vs Controls	33.68	18.96
IL12/23 Inhibitors vs Controls	29.46	22.66

The results of the multiple comparisons indicated significant differences between the following variable pairs: Anti TNF-Controls and IL12/23 Inhibitors-Controls

Kappa sVNT%				
Anti-TNF	90.73	15.92	30	**< 0.001**
IL12/23 Inhibitors	93.87	10.48	12	
Integrin $\alpha_4\beta_7$ Inhibitor	96.10	3.55	7	
Non-Biologic	96.34	2.77	7	
Controls	97.93	0.15	12	

Pairwise Comparison	Obs. Diff.	Critical Diff.
Anti-TNF vs Controls	35.60	18.96
IL12/23 Inhibitors vs Controls	26.92	22.66

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The results of the multiple comparisons indicated significant differences between the following variable pairs: Anti TNF-Controls and IL12/23 Inhibitors-Controls

Delta sVNT%				
Anti-TNF	94.16	9.81	30	**0.018**
IL12/23 Inhibitors	96.11	6.43	12	
Integrin $\alpha_4\beta_7$ Inhibitor	96.23	4.31	7	
Non-Biologic	97.68	0.84	7	
Controls	98.18	0.11	12	

Pairwise Comparison	Obs. Diff.	Critical Diff.
Anti-TNF vs Controls	19.87	18.96

The results of the multiple comparisons indicated significant differences between Anti-TNF-Controls

Omicron sVNT%				
Anti-TNF	31.60	34.57	30	**0.007**
IL12/23 Inhibitors	63.64	38.24	12	
Integrin $\alpha_4\beta_7$ Inhibitor	45.10	40.67	7	
Non-Biologic	72.03	30.95	7	
Controls	72.00	25.38	12	

Pairwise Comparison	Obs. Diff.	Critical Diff.
Anti-TNFvs Controls	20.38	18.96

The results of the multiple comparisons indicated significant differences between Anti-TNF-Controls

4. Discussion

The data about the efficacy of a third vaccine dose of COVID-19 against SARS-CoV-2 variants in patients with IBD is scarce. Our results demonstrate that humoral immune response after the third vaccine dose in patients with IBD on anti-TNF therapy might not be protective against SARS-CoV-2 variants, particularly against Omicron. We show that participants with IBD had statistically lower values of sVNT% for the Gamma, Epsilon, Kappa, Delta, and Omicron variants compared to healthy controls. Differences are evident in the sVNT% values for SARS-CoV-

2 Wild type, along with Beta, Gamma, Epsilon, Kappa, Delta, and Omicron variants, mainly between controls and patients receiving anti-TNF therapy.

Our findings after three doses of the vaccine against the Omicron variant are comparable with organ transplant recipients receiving immunosuppressive therapy [13] and other groups with autoimmune inflammatory disease receiving anti-TNF therapy after two vaccine doses [14]. The mechanism of how anti-TNF decreases immune response from vaccines is not fully understood, yet it is known that TNF influences important cellular behavior such as migration and proliferation and thus anti-TNF drugs may interfere with germinal centers to induce an adequate humoral immune response [15].

These results are limited by the small sample in both cohorts and the short follow-up period included in the analysis. Among other limitations in our analysis were differences in gender and age between the participants with IBD and controls. In the control group, the female gender was predominant (p=0.030) and the subjects were also younger [control: 24 years vs. IBD: 36 years (p=0.050)]. Nevertheless, this would not explain our findings.

Our data suggest that patients with IBD (especially those on biological medications) might benefit from an additional vaccine dose to produce vaccine-induced antibodies with a stronger and more effective neutralizing capability. Patients receiving anti-TNF may have less vaccine protection than those treated with other biologics, as seen in our findings. In this report, we present a snapshot of the rapid evolution of the SARS-CoV-2 variants that keep changing our current understanding of the viral behavior in response to the vaccine. More prospective studies with a larger sample and longer time frames are needed to ensure the optimal immunity for these high-risk patients.

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Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Puerto Rico-School of Medicine (protocol number. #1250121 and approval date: 31-march-2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Data supporting the reported results are stored by the authors and are available upon request.

Conflicts of Interest: The authors declare no conflict of interest.

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