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# Infliximab and Tofacitinib Attenuate Neutralizing Antibody Responses Against SARS-CoV-2 Ancestral and Omicron Variants in Inflammatory Bowel Disease Patients After 3 Doses of COVID-19 Vaccine

Vaccination is an effective population strategy for preventing severe COVID-19 disease and reducing infection transmission.<sup>1</sup> The emergence of new variants, particularly more transmissible strains, such as the omicron variants, has resulted in high infection rates in unvaccinated and vaccinated individuals.<sup>2</sup> Concerns about more transmissible variants are especially pertinent for immunosuppressed individuals, in whom vaccines are less immunogenic and less effective.<sup>3</sup> We and others have shown that patients with inflammatory bowel disease (IBD) established on immunosuppressive drugs, including infliximab (an anti-tumor necrosis factor [TNF] monoclonal antibody) or tofacitinib (a pan-Janus kinase [JAK]-inhibitor), have reduced vaccine-induced humoral responses after 2 and 3 doses of COVID-19 vaccination.<sup>3–5</sup> This study aimed to evaluate functional neutralizing antibody responses against the SARS-CoV-2 ancestral and omicron BA.1 variants in an immunosuppressed population of IBD patients.

Between May 28, 2021, and March 29, 2022, 268 participants without evidence of SARS-CoV-2 infection from the SARS-CoV-2 Vaccination Immunogenicity in Immunosuppressed Inflammatory Bowel Disease Patients (VIP) cohort<sup>4,5</sup> were included in this study. IBD participants were recruited in specific immunosuppressive treatment regimens, including infliximab (n = 36), thiopurines (n = 51), infliximab and thiopurine combination therapy (n = 39), ustekinumab (n = 39), vedolizumab (n = 38), and tofacitinib (n = 16). We additionally recruited healthy, non-IBD control individuals (n = 49). Participants had received either 2 doses of messenger RNA (mRNA) vaccine (BNT162b2 or mRNA-1273) or adenovirus vector vaccine (ChAdOx1 nCoV-19) as their primary vaccination schedule and received an mRNA vaccine as the third dose. Participant characteristics are shown in [Supplementary Table 1](#).

To evaluate vaccine-induced humoral responses, we used a pseudoneutralization assay against the SARS-CoV-2 ancestral strain and omicron BA.1 variant ([Supplementary Methods](#)). Reassuringly, neutralizing antibody titers against ancestral and omicron variants significantly increased after a third dose of vaccine compared to titers after a second dose of vaccine in all treatment groups ([Figure 1A–G](#)). However, 50% neutralization titer (NT50) values were significantly lower against omicron than against the ancestral strain in all study groups, irrespective of the immunosuppressive treatment regimen ([Figure 1A–G](#)). After 2 and 3 vaccine doses, patients treated with infliximab, infliximab/thiopurine combination therapy, or tofacitinib mounted significantly lower responses relative to control individuals. A total of 13 patients could not generate NT50 against the omicron variant after 2 doses of vaccine, 7 of

whom were treated with infliximab monotherapy, making up 19.4% of this treatment group ([Figure 1B](#)).

The most compelling rationale to justify a third dose of vaccine would be evidence that low antibody titers after a second vaccine dose were associated with increased risk of SARS-CoV-2 infection. Because lower antibody responses are linked to increased risk of breakthrough infection,<sup>6,7</sup> we investigated the risk of breakthrough infection in our cohort according to different thresholds of neutralizing titer ([Figure 1H](#)). Participants with an NT50 of <500 against the SARS-CoV-2 ancestral strain had a 1.6-fold increased odds ratio of breakthrough infection compared to participants with an NT50 of >500 ( $P = .066$ ). After 2 vaccine doses, 45.9% (100/218) of IBD patients had an NT50 of >500 against the SARS-CoV-2 ancestral strain. After 3 vaccine doses, 85.3% (186) patients reached the NT50 level of 500. In the healthy control individuals, 34.7% (17/49) had an NT50 of <500 after 2 vaccine doses, and 14.3% (7/49) had breakthrough infections. There was no significant association between NT50 and breakthrough infection in healthy control individuals. Fortunately, the breakthrough infections in our cohort were mild; none of the participants required hospitalization, and there were no deaths.

In this study, neutralizing titers elicited against the omicron variant were generally poor for all individuals and were substantially lower in recipients of infliximab, infliximab/thiopurine combination, or tofacitinib therapy. This raises concerns about whether currently available vaccines will be sufficient to protect against continually evolving SARS-CoV-2 variants, especially in patients established on certain immunosuppressive drugs. Current vaccinations mainly target the ancestral SARS-CoV-2 spike protein. Because many mutations exist in the omicron spike protein, this might lead to a significant escape from immune protection elicited by a COVID-19 vaccine designed against the SARS-CoV-2 ancestral virus.<sup>8</sup> Recently, the US Food and Drug Administration approved bivalent omicron-containing vaccines that elicit superior neutralizing antibody responses against the omicron variant.<sup>9</sup> Preferential use of bivalent

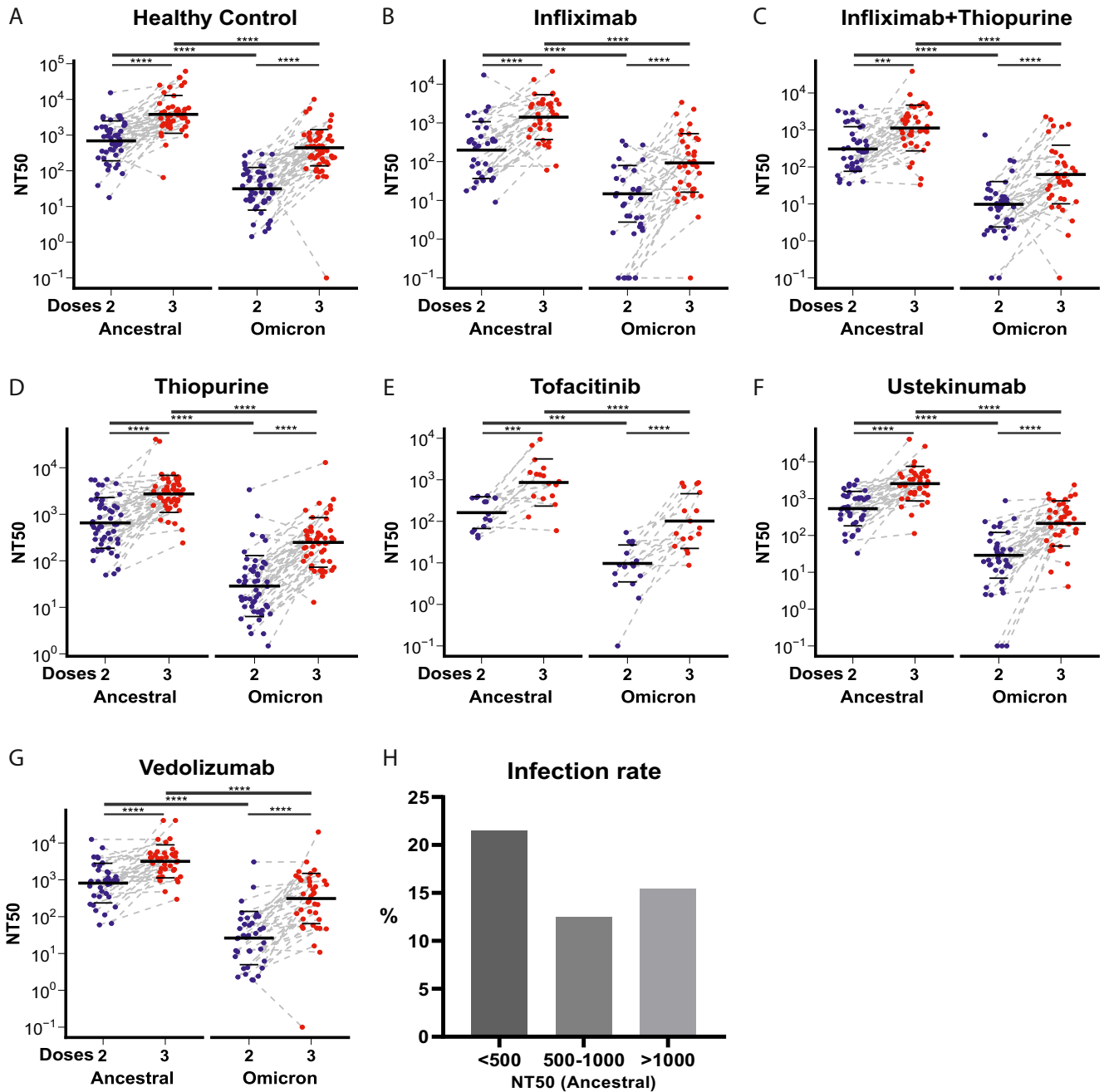
**Abbreviations used in this paper:** IBD, inflammatory bowel disease; JAK, Janus kinase; mRNA, messenger RNA; NT50, 50% neutralization titer; TNF, tumor necrosis factor.

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**Figure 1.** (A–G) NT50 against SARS-CoV-2 ancestral strain and omicron in IBD patients treated with different immunosuppressive medications and healthy control individuals after 2 and 3 doses of vaccine. The horizontal bars represent the geometric mean and standard deviation. Wilcoxon signed-rank tests with Benjamini-Hochberg correction were performed. (H) The percentages of breakthrough infection in participants are stratified by neutralization titer ranges. \*\*\**P* < .001, \*\*\*\**P* < .0001.

vaccines may be especially valuable in IBD patients taking anti-TNF agents or JAK inhibitors.

Our study has important strengths. We have harnessed more robust functional pseudoneutralization assays than the binding antibody measurement used in most other IBD studies. We also actively recruited patients established on the main IBD drug regimens to get a broad view of the impact of different immunosuppressive mechanisms of action on vaccine-induced immunogenicity. We also

prospectively recruited a population of healthy, non-IBD individual as a critical comparison. However, we acknowledge the limitations of this study. First, the sample size for some drug groups, most notably tofacitinib, was small, which might limit the robustness of our findings, although our observations were highly statistically significant. Second, although our study was consistent with a signal for increased risk of breakthrough infection in IBD patients with lower titers of neutralizing antibodies, the study was

underpowered to answer this question definitely, and the results should be regarded with caution.

In summary, we have shown that a third dose of vaccination significantly increases neutralizing antibody responses against the SARS-CoV-2 ancestral and omicron variants, but this response, especially to evolving variants, is substantially lower in patients established on infliximab or tofacitinib. As further mutations in the viral genome accumulate over time, with the attendant risk of immune evasion, it remains important to continue to reappraise vaccination strategy, including the implementation of personalized approaches for some patients, such as those treated with anti-TNF drugs and JAK inhibitors.

The data of this study are available under a transfer agreement from the corresponding author based on a reasonable request.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2022.10.010>.

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## Supplementary Methods

The SARS-CoV-2 Vaccination Immunogenicity in Immunosuppressed Inflammatory Bowel Disease Patients (VIP) study is a UK multicenter prospective observational study aimed at evaluating the immunogenicity of COVID-19 vaccination in IBD patients on 6 different immunosuppressive treatment regimens (infliximab, thiopurine, infliximab and thiopurine combination therapy, ustekinumab, vedolizumab, or tofacitinib). Participant recruitment as well as inclusion and exclusion criteria have been described previously.<sup>1</sup> Participants for the healthy control group were recruited from healthy volunteer databases (National Institute for Health Research National Biobank, Peninsula Research Bank and Healthy Volunteer Panel of the Imperial Clinical Research Facility) and staff working at the university and medical centers involved in the study. Healthy control individuals were included if they did not have a diagnosis of IBD and were not currently being treated with systemic immunosuppressives for any other indication. Healthy control individuals were not excluded if they had other medical conditions.

In the United Kingdom, vaccines were administered to the most clinically vulnerable and then through progressively lower risk and younger age groups from December 2020. Citizens received either the mRNA-based vaccine (BNT162b2 or mRNA-1273) or the adenovirus-vector vaccine (ChAdOx1 nCoV-19) for the first 2 doses with a 3–12-week interval between the 2 doses. From 13 September 2021, patients deemed to be clinically extremely vulnerable, including those with IBD treated with immunosuppressive therapies, were offered a third primary vaccine dose with an mRNA-based vaccine (BNT162b2 or mRNA-1273) at least 8 weeks after their second dose.

Blood samples were collected from participants 53–92 days after the second vaccine dose and 28–49 days after the third vaccine dose. Participants received either homologous (3 doses of mRNA vaccine) or heterologous (2 doses of adenovirus vector followed by 1 dose of mRNA vaccine) vaccination schedules. The study protocol is available online (<https://www.vipstudy.uk>).

### Anti-SARS-CoV-2 Antibody

#### Electrochemiluminescence Assay

The Roche Elecsys anti-SARS-CoV-2 (N) immunoassay is a sandwich electrochemiluminescence immunoassay that uses a recombinant protein of the nucleocapsid antigen for the determination of antibodies against SARS-CoV-2 infection. The manufacturer reports clinical sensitivity and specificity of 99.5% and 99.8%, respectively, >14 days after polymerase chain reaction-confirmed COVID-19 using a cutoff index of 1. It is reported that anti-N antibody responses after SARS-CoV-2 natural infection are impaired in patients treated with immunosuppressant drugs such as infliximab.<sup>2,3</sup> Results showed that a threshold of 0.12 times the cutoff index provides 100% specificity for determining prior SARS-CoV-2 infection.<sup>4</sup> Therefore, in the current

study, individuals with anti-N of  $\geq 0.12$  U/mL were deemed to have had SARS-CoV-2 infection.

### Pseudoneutralization Assay

SARS-CoV-2 neutralization assay was conducted using pseudotyped viruses (PSV). Briefly, pseudotyped SARS-CoV-2 lentiviruses were produced in HEK293T cells using a SARS-CoV-2 spike plasmid, HIV-1 gag-pol plasmid, and a firefly luciferase reporter.<sup>5</sup> Participant sera were serially diluted and incubated with PSV viral supernatant for 1 hour. HEK-ACE2 cells were then cocultured with the sera and PSV for 72 hours before measurement of the luciferase activity using the Bright-Glo Luciferase assay system (Promega). NT50 was calculated as the dilution at which relative luminescence was reduced by 50% compared with control. The First World Health Organization International Standard for anti-SARS-CoV-2 immunoglobulin was included as a positive control, which was determined to have an NT50 of approximately 1:3000.

### Outcome Measures

Our primary outcome was anti-SARS-CoV-2 neutralizing response against ancestral virus and omicron variant after the 2 and 3 doses of anti-SARS-CoV-2 vaccine, stratified by baseline immunosuppressive therapy.

The secondary outcome was risk of breakthrough infection. SARS-CoV-2 breakthrough infection was defined by participants who reported a polymerase chain reaction or lateral flow test result confirming SARS-CoV-2 infection or a concentration of Roche Elecsys anti-SARS-CoV-2 nucleocapsid immunoassay nucleocapsid antibodies in the serum above 0.11 U/mL after 2 doses of vaccine.<sup>1,4</sup>

### Variables

Demographics were recorded as the variables age, sex, ethnicity, comorbidities, height and weight, smoking status, and postcode; IBD disease activity (defined by patient-reported outcomes [PRO2]),<sup>6,7</sup> SARS-CoV-2 symptoms aligned to COVID-19 symptoms study (symptoms, previous testing, and hospital admissions for COVID-19), SARS-CoV-2 test date and results, vaccine schedules (type and date of each vaccination), and date of blood collection. Data were entered electronically into a purpose-designed REDCap database hosted at the Royal Devon University Healthcare NHS Foundation Trust.<sup>8</sup> Participants without access to the Internet or an electronic device completed their questionnaires on paper case record forms that were subsequently entered by local research teams.

### Statistics

A statistical analysis plan was approved by the Study Management Group (available at <https://www.vipstudy.uk/info>). Analyses were undertaken using R 4.1.0 (R Foundation for Statistical Computing). *P* values of <.05 with 2-tailed test were considered significant. Antibody concentrations are reported as the geometric mean and standard deviation.

Other continuous data are reported as a median and interquartile range, and discrete data are reported as number and percentage unless otherwise stated. The Wilcoxon signed-rank test was performed to test the significance of NT50 between the ancestral strain and omicron variant or between the second and third vaccine doses. For the univariate analysis comparing NT50 among groups treated with different regimens, the Kruskal-Wallis test with Dunn post hoc test was performed.

### *Ethical Considerations*

VIP is an investigator-led UK National Institute for Health Research COVID-19 study. Participants were included after providing written informed consent. The study was registered with the International Standard Randomized Controlled Trial Number (ISRCTN, no. 13495664) registry, and the protocol is available online at <https://www.vipstudy.uk>.

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**Supplementary Table 1.** Demographics of the Cohort in This Study

Characteristics	Control	Infliximab	Infliximab +thiopurine	Thiopurine	Tofacitinib	Ustekinumab	Vedolizumab
n (%)	49 (18.28)	36 (13.43)	39 (14.55)	51 (19.03)	16 (5.97)	39 (14.55)	38 (14.18)
Age, y, median (IQR)	38.30 (30.20–54.30)	48.55 (39.30–59.55)	37.30 (30.50–49.85)	46.10 (35.25–56.25)	49.30 (43.12–55.57)	41.80 (33–53.05)	45.50 (36.45–62.45)
Sex, n (%)							
Female	33 (68.75)	17 (47.22)	19 (48.72)	30 (58.82)	2 (12.50)	20 (51.28)	11 (29.73)
Male	15 (31.25)	19 (52.78)	20 (51.28)	21 (41.18)	14 (87.50)	19 (48.72)	26 (70.27)
Ethnicity, n (%)							
Non-White	5 (10.42)	7 (19.44)	5 (12.82)	9 (17.65)	1 (6.25)	4 (10.26)	9 (24.32)
White	43 (89.58)	29 (80.56)	34 (87.18)	42 (82.35)	15 (93.75)	35 (89.74)	28 (75.68)
BMI, kg/m <sup>2</sup> , median (IQR)	22.72 (21.42–24.86)	25.50 (23.46–28.60)	25.24 (22.48–27.28)	24.15 (21.41–26.21)	26.91 (24.32–30.13)	25.58 (22.75–29.33)	24.42 (22.13–27.29)
Vaccine, n (%)							
AstraZeneca	26 (53.06)	16 (44.44)	27 (69.23)	32 (62.75)	13 (81.25)	26 (66.67)	23 (60.53)
Moderna	2 (4.08)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pfizer	21 (42.86)	20 (55.56)	12 (30.77)	19 (37.25)	3 (18.75)	13 (33.33)	15 (39.47)
Diagnosis, n (%)							
Crohn's disease	0 (0)	24 (66.67)	25 (64.10)	21 (41.18)	0 (0)	38 (97.44)	15 (39.47)
IBD unclassified	0 (0)	2 (5.56)	2 (5.13)	1 (1.96)	0 (0)	0 (0)	0 (0)
Ulcerative colitis	0 (0)	10 (27.78)	12 (30.77)	29 (56.86)	16 (100)	1 (2.56)	23 (60.53)
Smoking, n (%)							
Currently	0 (0)	1 (2.78)	2 (5.13)	1 (1.96)	0 (0)	3 (7.69)	4 (10.81)
Not currently	12 (25)	12 (33.33)	11 (28.21)	17 (33.33)	10 (62.50)	13 (33.33)	11 (29.73)
Never	36 (75)	23 (63.89)	26 (66.67)	33 (64.71)	6 (37.50)	23 (58.97)	22 (59.46)
Interval, d, median (IQR)							
Second dose to first blood sampling	80 (78–86)	77.50 (60.75–88)	84 (62–88)	78 (63–85)	79.50 (63.75–89.25)	84.50 (65.25–88)	81 (64–87)
Third dose to second blood sampling	38 (33–42.50)	42 (32–46)	40 (38.50–46.50)	40.50 (30.50–43)	37 (33.50–42)	39.50 (33.75–44.25)	40 (32–42)
First to second vaccine dose	65.50 (56.50–77)	73.50 (68.75–77)	77 (76.25–79)	77 (75–80)	72.50 (62.75–77)	77 (70.25–79)	77 (71–80)
Second to third vaccine dose	174.50 (154.50–184.75)	176 (167–185)	171 (151.50–184.50)	176 (163–187)	171.50 (152–179)	177 (152.50–189)	189 (179–196)
Heart disease, n (%)	0 (0)	1 (2.78)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.70)
Lung disease, n (%)	1 (2.08)	6 (16.67)	5 (12.82)	6 (11.76)	3 (18.75)	3 (7.69)	3 (8.11)
Kidney disease, n (%)	0 (0)	2 (5.56)	0 (0)	1 (1.96)	0 (0)	0 (0)	1 (2.70)
Diabetes, n (%)	1 (2.08)	3 (8.33)	0 (0)	3 (5.88)	0 (0)	3 (7.69)	3 (8.11)
Cancer, n (%)	0 (0)	1 (2.78)	0 (0)	1 (1.96)	0 (0)	0 (0)	0 (0)

IQR, interquartile range.