Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof

Infliximab and tofacitinib attenuate neutralizing antibody responses against SARS-CoV-2 ancestral and Omicron variants in IBD patients following 3 doses of COVID-19 vaccine

Zhigang Liu, James L. Alexander, Kathy Weitung Lin, VIP study investigators

PII: S0016-5085(22)01184-2
DOI: https://doi.org/10.1053/j.gastro.2022.10.010
Reference: YGAST 65376

To appear in: *Gastroenterology*
Accepted Date: 12 October 2022

Please cite this article as: Liu Z, Alexander JL, Lin KW, VIP study investigators, Infliximab and tofacitinib attenuate neutralizing antibody responses against SARS-CoV-2 ancestral and Omicron variants in IBD patients following 3 doses of COVID-19 vaccine, *Gastroenterology* (2022), doi: https://doi.org/10.1053/j.gastro.2022.10.010.

Infliximab and tofacitinib attenuate neutralizing antibody responses against SARS-CoV-2 ancestral and Omicron variants in IBD patients following 3 doses of COVID-19 vaccine

Zhigang Liu[1,#], James L Alexander[1,2,#], Kathy Weitung Lin[3], VIP study investigators, Tariq Ahmad[4,*], Katrina M Pollock[3,*], Nick Powell[1,2,*]

[1]Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom.

[2]Department of Gastroenterology, Imperial College Healthcare NHS Trust, London, United Kingdom.

[3]Department of Infectious Disease, Faculty of Medicine, Imperial College London, London, United Kingdom.

[4]Royal Devon University Healthcare NHS Foundation Trust, Exeter, United Kingdom.

#Co-first authorship

*Co-senior authorship

CORRESPONDING AUTHOR

Nick Powell, MBChB, PhD, MRCP, Reader in Gastroenterology, Division of Digestive Diseases, Department of Metabolism Digestion and Reproduction, Faculty of Medicine, Imperial College London, Du Cane Road, London, W12 0NN, United Kingdom. Email: npowell@imperial.ac.uk

DECLARATION OF INTERESTS

JLA reports sponsorship from Vifor Pharma for accommodation and travel to the British Society of Gastroenterology annual meeting 2019, outside the submitted work. NAK reports grants from AbbVie, Biogen, Celgene, Celltrion, Galapagos, MSD, Napp, Pfizer, Pharmacosmos, Roche, and Takeda; consulting fees from Amgen, Bristol Myers Squibb, Falk, Janssen, Mylan, Pharmacosmos, Galapagos, Takeda, and Tillotts; personal fees from Allergan, Celltrion, Falk, Ferring, Janssen, Pharmacosmos, Takeda, Tilllotts, and Galapagos; and support for attending meetings from AbbVie, Falk, and Janssen, outside the submitted work. AS has received travel expense support from Janssen. SS reports grants from Takeda, AbbVie, Tillots Pharma, Janssen, Pfizer, and Biogen, and personal fees from Takeda, AbbVie, Janssen, Pharmacocosmos, Biogen, Pfizer, Tillots Pharma, and Falk Pharma, outside the submitted work. ALH reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, AZ, Atlantic, Bristol Myers Squibb, Celltrion, Falk, Galapogos, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire, and Takeda; participation on the Global Steering Committee for Genentech; support for attending meetings from AbbVie, Takeda, and Janssen; and participation on a data safety monitoring board or advisory board for AbbVie, AZ, Atlantic, Bristol Myers Squibb, Galapogos, Janssen, Pfizer, and Takeda. PMI reports grants from Celltrion, Takeda, MSD, Pfizer, and Galapagos, and personal fees from Celltrion, Takeda, Pfizer, Galapagos, Gilead, AbbVie, Janssen, Bristol Myers Squibb, Lilly, and Arena, outside the submitted work. MP receives unrestricted educational grants from Pfizer for genetic analyses to support the IBD BioResource and speaker fees from Janssen. GRJ has received grants from the Wellcome Trust and ECCO; speaker fees from Takeda, Ferring, and Janssen; and support for attending meetings or travel from Ferring. KK reports

payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen and Ferring; support for attending meetings or travel from Janssen and Takeda; and participation on a data safety monitoring board or advisory board for Janssen and PredictImmune. KVP reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, DrFalk, Janssen, PreddictImmune, and Takeda; support for attending meetings or travel from AbbVie, Ferring, Janssen, and Tillotts; and participation on a data safety monitoring board or advisory board for AbbVie, Galapagos, and Janssen. AJK reports consulting fees from Janssen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer and Takeda; support for attending meetings or travel from Janssen, Tillotts, and Norgine; and participation in a data safety monitoring board or advisory board for AbbVie. LCH reports support for attending meetings or travel from AbbVie. CWL reports a Future Leaders Fellow award from UK Research and Innovation; personal consulting fees from Galapagos, AbbVie, Takeda, Pfizer, Janssen, and Iterative Scopes; institutional consulting fees from Trellus Health; personal fees from Galapagos, AbbVie, Takeda, Pfizer, Janssen, GSK, Gilead, Fresenius Kabi, Ferring, and Dr Falk; and support for attending meetings from Galapagos, AbbVie, Takeda, Pfizer, Janssen, GSK, Gilead, Fresenius Kabi, Ferring, and Dr Falk. RJB and DMA are members of the Global T cell Expert Consortium and have consulted for Oxford Immunotec outside the submitted work. JRG reports grants from F Hoffmann-La Roche, Biogen, Celltrion Healthcare, and Galapagos, and non-financial support from Immundiagnostik during the study. TA reports grant funding from Pfizer to his institution to deliver this study; grants from Celltrion, Roche, Takeda, Biogen, and Galapagos; and honoraria for lectures from Takeda and Roche, outside

the submitted work. KMP is the chief, principal or co-investigator for vaccine clinical trials and experimental medicine studies (NCT05007275, NCT04753892, EudraCT 2020-001646-20, NCT04400838, NCT04324606, EudraCT 2017-004610-26, NCT03970993, NCT03816137), is a member of the data safety monitoring board for NCT05249829, has received a fee for speaking from Seqirus and Sanofi Pasteur, and has research funding from the Chan Zuckerberg Initiative, the MRC/UKRI, the Vaccine Task Force, and NIHR Imperial BRC outside the submitted work. NP is the principal investigator on the research grant from Pfizer that funded the VIP study; has received research grants from Bristol Myers Squibb outside the submitted work; reports personal fees from Takeda, Janssen, Pfizer, Galapagos, Bristol Myers Squibb, AbbVie, Roche, Lilly, Allergan, and Celgene, Astra Zeneca outside the submitted work; and has served as a speaker or advisory board member for AbbVie, Allergan, Bristol Myers Squibb, Celgene, Falk, Ferring, Janssen, Pfizer, Tillotts, Takeda, and Vifor Pharma. All other authors declare no competing interests.

CONTRIBUTORS

Imperial College London: Kaixing Le, Xin Zhou, Hajir Ibraheim, Sulak Anandabaskaran, Aamir Saifuddin, Leon R McFarlane, Nikhil Anand, Laura Constable, Rocio Castro Seoane, Andrea D'Mello, Sharmili Balarajah, Lucy C Hicks, Horace R T Williams, Jonathan W Lo, Ailsa L Hart, Daniel M Altmann, Rosemary J Boyton, Julian P Teare

Royal Devon University Healthcare NHS Foundation Trust: Rachel Nice, Claire Bewshea, James R Goodhand, Nicholas A Kennedy, Anna Barnes, John Kirkwood, Marian Parkinson, Helen Gardner-Thorpe

University of Edinburgh: Charlie W Lees, Gareth R Jones, Kate Covil, Lauranne Derikx

King's College London: Francesca Fiorentino, Peter M Irving

University of Cambridge: Miles Parkes, Rachel Linger

Bart's Health NHS Trust: Klaartje Kok, Irish Lee, Bessie Cipriano

St George's Hospital NHS Trust: Kamal V Patel

Hull University Teaching Hospitals NHS Trust: Shaji Sebastian

King's College Hospital: Alexandra J Kent

Imperial College Healthcare NHS Trust: Ijeoma Chukwurah, Sulaimaan Haq, Parita Shah, Stephanie Wilken-Smith, Anitha Ramanathan, Mikin Patel, Lidia Romanczuk, Rebecca King, Jason Domingo, Bridget Knight, Djamila Shamtally, Vivien Mendoza, Joanne Sanchez, Hannah Stark, Louise Bee, Charmaine Estember, Darcy Watkins, Sam Stone, Beatriz Gros Alcalde, Giuseppe Ruocco, Manisha Baden, Graham Cooke, Evgenia Kourampa, Ciro Pasquale, Elena Robisco-Diaz, Suhaylah Bhatti

AUTHOR CONTRIBUTIONS

Conceptualization: NP, KMP, ZL, JLA and RJB.

Investigation, Formal analysis and Validation: ZL, KWL, KL, XZ, LRM, JLA, NA, NAK, HI, SA, IC, SH, PS, SWS, AR, LR, RK, JD, BK, DS, VM, JS, HS, LB, CE, DW, BGA, GR, MB, GC, EK, CP, ERD, AS, LC, RCS, CB, ADM, GRJ, FF, SS, PMI, LCH, HRTW, JWL, AJK, MP, KK, KVP, JPT, RN, AB, DMA, JK, HGT, KC, LD, IL, RJB, ALH, CWL, JRG, SB, RL, TA and NP.

Visualization and Writing: ZL, JLA and NP.

DATA AVAILABILITY

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

ACKNOWLEDGEMENT

Pfizer Ltd provided financial support for the VIP study as an independent research grant. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. This research was supported by the NIHR Biomedical Research Centres in Imperial College London and Imperial College Healthcare NHS Trust and Cambridge (BRC-1215–20014) and the NIHR Clinical Research Facility Cambridge. The NIHR IBD BioResource supported recruitment to this study. The NIHR Exeter Clinical Research Facility that supported this project is a partnership between the University of Exeter Medical School College of Medicine and Health and Royal Devon University Healthcare NHS Foundation Trust. The views expressed in this Article are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. JLA is a recipient of an NIHR Academic Clinical Lectureship (CL-2019–21–502), funded by Imperial College London and The Joyce and Norman Freed Charitable Trust. GRJ is supported by a Wellcome Trust Clinical Research Career Development Fellowship (220725/Z/20/Z). RJB and DMA are supported by UK Research and Innovation (MR/S019553/1, MR/R02622X/1, MR/V036939/1, and MR/W020610/1), the NIHR Imperial Biomedical Research Centre Institute of Translational Medicine & Therapeutics, the Cystic Fibrosis Trust Strategic Research Centre (2019SRC015), NIHR Efficacy and Mechanism Evaluation Fast Track (NIHR134607), NIHR Long Covid (COV-LT2–0027), Innovate UK (SBRI 10008614), and Horizon 2020 Marie

Skłodowska-Curie Innovative Training Network European Training Network (number 860325).

Vaccination is an effective population strategy for preventing severe COVID-19 disease and reducing infection transmission [1]. 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 [2]. Concerns about more transmissible variants are especially pertinent for immunosuppressed individuals, in whom vaccines are less immunogenic and less effective [3]. We and others have shown that patients with IBD (inflammatory bowel disease) established on immunosuppressive drugs, including infliximab (anti-TNF monoclonal antibody) or tofacitinib (a pan JAK-inhibitor), have reduced vaccine-induced humoral responses following two and three doses of COVID-19 vaccination [3-5]. This study aimed to evaluate functional neutralizing antibody responses against SARS-CoV-2 ancestral and Omicron BA.1 variant in an immunosuppressed population of IBD patients.

Between 28th May 2021 and 29th March 2022, 268 participants without evidence of SARS-CoV-2 infection from the VIP cohort [4,5] 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 subjects (n=49). Participants had received either two doses of mRNA vaccine (BNT162b2 or mRNA-1273) or adenovirus vector vaccine (ChAdOx1 nCoV-19) as their primary vaccination schedule and received mRNA vaccine as the third dose. Participant characteristics are shown in Supplementary Table 1.

To evaluate vaccine-induced humoral responses we employed a pseudo-neutralization 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, NT50 titers were significantly lower against Omicron than against the ancestral strain in all study groups, irrespective of the immunosuppressive treatment regimen (**Figure 1A-G**). After two and three vaccine doses, patients treated with infliximab, infliximab/thiopurine combination therapy or tofacitinib mounted significantly lower responses relative to controls. 13 patients could not generate NT50 against the Omicron variant after two doses of vaccine, 7 of which were treated with infliximab monotherapy, comprising 19.44% of this treatment group (**Figure 1B**).

The most compelling rationale to justify a third dose of vaccine would be evidence that low antibody titers following a second vaccine dose were associated with increased risk of SARS-CoV-2 infection. Since lower antibody responses are linked to increased risk of breakthrough infection [6,7], we investigated the risk of breakthrough infection in our cohort according to different thresholds of neutralizing titer (**Figure 1H**). Participants with an NT50 <500 against the SARS-CoV-2 ancestral strain had a 1.6-fold increased odds ratio of breakthrough infection compared to participants with NT50 >500 (P=0.066). After 2 vaccine doses, 45.9% (100/218) of IBD patients had an NT50 >500 against SARS-CoV-2 ancestral strain. After 3 vaccine doses, 85.3% (186) patients reached the NT50 level of 500. While in the healthy controls, 34.7% (17/49) had an NT50 <500 after 2 vaccine doses and 14.3% (7) had breakthrough infections. There was no significant association between NT50 and breakthrough infection in healthy controls. Fortunately, the breakthrough infections in our cohort were mild and 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. Since many mutations exist in the Omicron spike protein, this might lead to a significant escape from immune protection elicited by COVID-19 vaccine designed against SARS-CoV-2 ancestral virus [8]. Recently, FDA approved bivalent omicron-containing vaccines which elicit superior neutralizing antibody responses against the Omicron variant [9]. Preferential use of bivalent 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 pseudo-neutralization assays than the anti-S1 serology assays employed 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 controls as a critical comparison. However, we acknowledge the limitations of this study. Firstly, 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. Secondly, 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.

Figure 1. 50% neutralization titer (NT50) against SARS-CoV-2 ancestral strain and Omicron in IBD patients treated with different immunosuppressive medications and healthy controls after two and three doses of vaccine (A-G). The horizontal bar represents the geometric means. Wilcoxon signed-rank tests with Benjamini-Hochberg correction were performed. The percentage of breakthrough infection in participants stratified by neutralization titer ranges (H). *** p<0.001, **** p<0.0001.

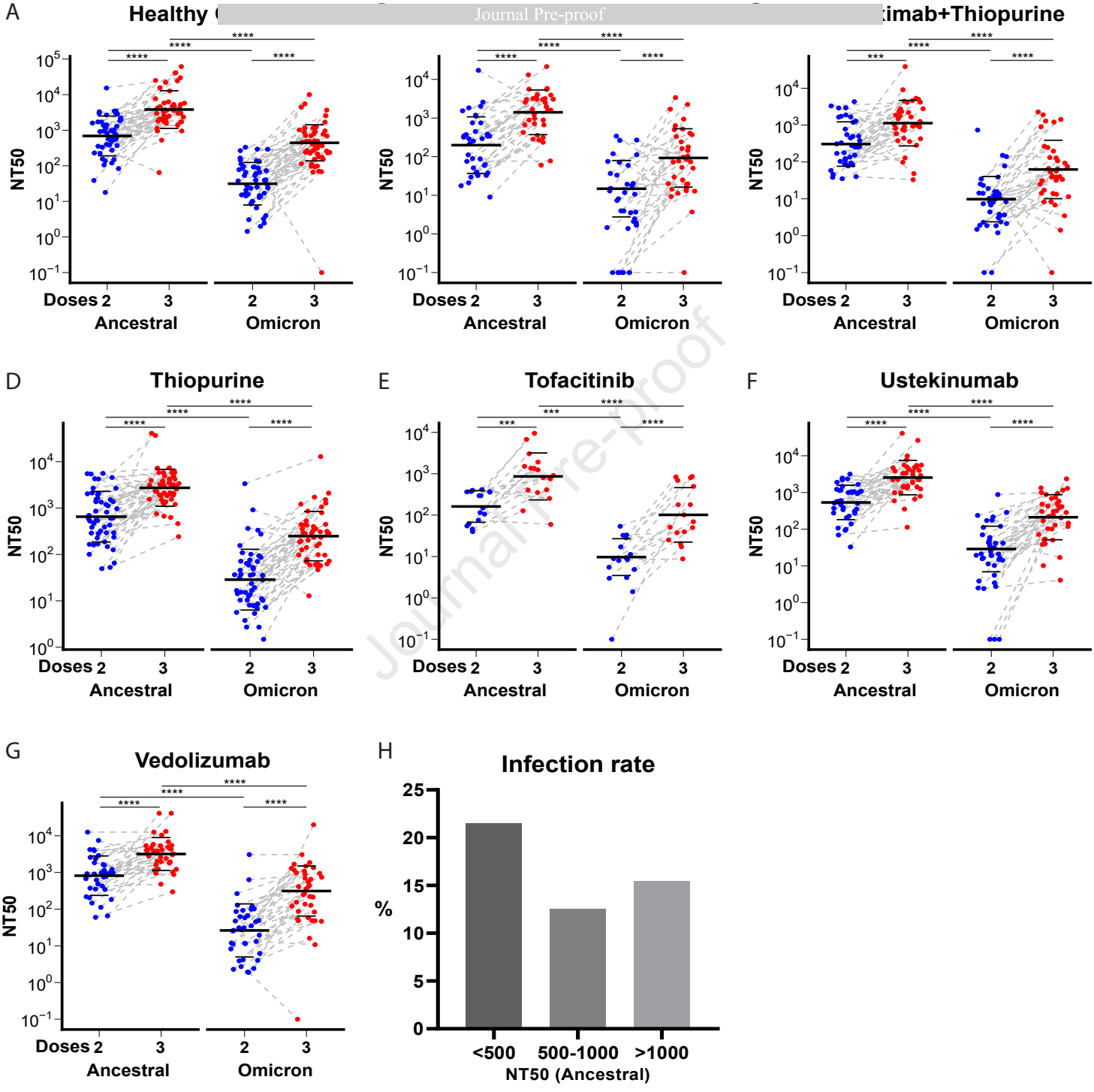
REFERENCES

1. Suthar AB, et al. *BMJ* 2022; **377**: e069317-e069323
2. Altarawneh HN, et al. *New Engl J Med* 2022; **387**: 21-34
3. **Kennedy NA**, **Janjua M**, et al. *Gut* 2022, DOI: 10.1136/gutjnl-2022-327570
4. **Alexander JL**, **Kennedy NA**, et al. *The Lancet Gastroenterology & Hepatology* 2022; **7**: 342-352
5. **Alexander JL**, **Liu Z**, **Muñoz Sandoval D**, **Reynolds C**, et al. *The Lancet Gastroenterology & Hepatology* 2022; **7**: 1005-1015
6. Coppeta L, et al.*Vaccines* 2022; **10**: 141-150
7. Takita M, et al. *Sci Rep* 2022; **12**: 9147-9157

8. Hachmann NP, et al. *N Engl J Med* 2022; **387**: 86-88

9. Chalkias S, et al. *N Engl J Med* 2022; **387**: 1279-1291

Author names in bold designate shared co-first authorship.



Supplementary Methods

VIP (SARS-CoV-2 Vaccination immunogenicity in Immunosuppressed inflammatory bowel disease Patients) is a UK multi-center prospective observational study (registration number: ISRCTN13495664) aimed to evaluate the immunogenicity of COVID-19 vaccination in IBD patients on six different immunosuppressive treatment regimens (infliximab, thiopurine, infliximab and thiopurine combination therapy, ustekinumab, vedolizumab or tofacitinib). Participant recruitment, inclusion and exclusion criteria have been described previously [1]. Participants for the healthy control group were recruited from healthy volunteer databases (National Institute for Health Research National Bioresource, 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 controls 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 controls were not excluded if they had other medical conditions.

In the UK, 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 two doses with 3 – 12 weeks interval between the two 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 2nd vaccine dose and 28–49 days after the 3rd vaccine dose. Participants either received homologous (three doses of mRNA vaccine) or heterologous (two doses of adenovirus vector followed by one 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 employs 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 PCR-confirmed COVID-19 using a cut-off index (COI) of 1. It is reported that anti-N antibody responses following SARS-CoV-2 natural infection are impaired in patients treated with immunosuppressant drugs such as infliximab [2,3]. Results showed that a threshold of 0.12 times the cut-off index provides 100% specificity for determining prior SARS-CoV-2 infection [4]. Therefore, in the current study, anti N equals to or over 0.12 was deemed to have had SARS-CoV-2 infection.

Pseudo neutralization assay

SARS-CoV-2 neutralization assay was conducted using pseudotyped (PSV) viruses. 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 [5]. Participant sera were serially diluted and incubated with PSV viral supernatant for 1 hour. HEK-ACE2 cells were then co-incubated with the sera and PSV for 72 hours

before measurement of the luciferase activity using the Bright-Glo Luciferase assay system (Promega, Madison, WI). NT50 neutralization titers were calculated as the dilution at which relative luminescence was reduced by 50% compared with control. The First WHO International Standard for anti-SARS-CoV-2 immunoglobulin was included as a positive control, which was determined to have an NT50 neutralization titer of approximately 1:3000.

Outcome Measures

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

Secondary outcome was risk of breakthrough infection. SARS-CoV-2 breakthrough infection was defined by participants who reported a PCR or lateral flow test 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 two doses of vaccine [1,4].

Variables

Demographics were recorded as variables: age, gender, ethnicity, comorbidities, height and weight, smoking status, and postcode), IBD disease activity (defined by patient-reported outcomes [PRO2]) [6,7], SARS-CoV-2 symptoms aligned to the 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 [8]. Participants without access to the internet or

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, Vienna, Austria). P values <0.05 with two-detailed test were considered significant. Antibody concentrations are reported as geometric mean and standard deviation. Other continuous data are reported as a median and interquartile range, and discrete data as numbers and percentages unless otherwise stated. Wilcoxon signed-rank test was performed to test the significance of NT50 between ancestral strain and Omicron variant, or 2nd and 3rd vaccine doses. For the univariate analysis comparing NT50 among groups treated with different regimens, Kruskal–the Wallis test with Dunn's posthoc test was performed. Spearman correlations were performed to determine correlations between NT50 against ancestral strain and Omicron variant.

Ethical consideration and role of funders

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

Table 1. Demographics of the cohort in this study. Age, Body-Mass Index and interval days between vaccine doses and blood sample collections were presented as median (IQR). The other variables were presented as percentages within each group.

Characteristics	Control 49 (18%)	Infliximab 36 (13%)	Infliximab + Thiopurine 39 (15%)	Thiopurine 51 (19%)	Tofacitinib 16 (6.0%)	Ustekinumab 39 (15%)	Vedolizumab 38 (14%)
Age	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)
Gender							
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							
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	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							
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							
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							
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 days: 2nd dose to 1st 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)
Interval days: 3rd dose to 2nd 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)
Interval days: 1st to 2nd 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)
Interval days: 2nd to 3rd 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	0 (0%)	1 (2.78%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.70%)
Lung disease	1 (2.08%)	6 (16.67%)	5 (12.82%)	6 (11.76%)	3 (18.75%)	3 (7.69%)	3 (8.11%)
Kidney disease	0 (0%)	2 (5.56%)	0 (0%)	1 (1.96%)	0 (0%)	0 (0%)	1 (2.70%)
Diabetes	1 (2.08%)	3 (8.33%)	0 (0%)	3 (5.88%)	0 (0%)	3 (7.69%)	3 (8.11%)
Cancer	0 (0%)	1 (2.78%)	0 (0%)	1 (1.96%)	0 (0%)	0 (0%)	0 (0%)

References

1. **Alexander JL**, **Kennedy NA**, et al. *The Lancet Gastroenterology & Hepatology* 2022; **7**: 342-352

2. **Kennedy NA**, **Goodhand JR**, et al. *Gut* 2021; **70**: 865-875

3. **Kennedy NA**, **Janjua M**, et al. *Gut* 2022, DOI: 10.1136/gutjnl-2022-327570

4. **Lin SM**, **Kennedy NA**, **Saifuddin A**, **Sandoval, DM**, et al. *Nat Commun* 2022; **13**: 1379-1392

5. Pollock KM, et al. *EClinicalMedicine* 2022; **44**: 101262

6. Khanna R, et al. *Aliment Pharmacol Ther* 2015; **41**: 77-86

7. Jairath V, et al. *Aliment Pharmacol Ther* 2015; **42**: 1200-1210

8. Harris PA, et al. *J Biomed Inform* 2019; **95**: 103208

Author names in bold designate shared co-first authorship.