Crohn's and Colitis Canada
Crohn et Colite Canada

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Secrétariat du Comité consultatif national de l'immunisation
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Cher Monsieur/Madame,

En mars 2020, Crohn et Colite Canada a formé un groupe de travail dénommé « COVID-19 & Maladie inflammatoire de l'intestin (MII) » dirigé par les Drs Eric Benchimol et Gil Kaplan, et comprenant des experts des maladies infectieuses et des MIIs, des représentants de patients ainsi que des leaders communautaires. Le groupe de travail se réunit régulièrement pour analyser des lignes directrices et donner des conseils fondés sur des évidences scientifiques aux personnes présentant des MII afin de les protéger et de maintenir leur maladie sous contrôle pendant la pandémie.

Après avoir examiné la récente publication CLARITY IBD du Royaume-Uni au sujet des personnes vivant avec des MIIs, le groupe de travail COVID-19 & MII vous demande de reconsidérer le report de la deuxième dose pour les personnes sous traitement immunosuppresseur.

L'étude CLARITY IBD montre, une plausibilité biologique substantielle, que les individus présentant des MIIs sous immunosuppresseurs (tels que l'azathioprine, le méthotrexate et des agents biologiques comme l'infliximab) devraient recevoir leur deuxième dose de vaccin comme indiqué dans les essais cliniques randomisés du fabricant (3 semaines après la première dose du vaccin Pfizer à ARNm ; 4 semaines après la première dose du vaccin Moderna à ARNm et vaccin et celui d'Oxford-AstraZeneca à adénovirus).

Sur la base des observations de l'étude CLARITY IBD, le groupe de travail COVID-19 & MII craint qu'une dose unique du vaccin puisse être moins efficace chez les patients avec des MIIs immunodéprimés :

- Les personnes présentant des MIIs sous thérapies d'immunosuppression montrent une réponse anticorps anti-SRAS-CoV-2 beaucoup plus faible et pourraient être moins protégées après une dose de vaccin;
- Un nombre important de personnes MII n'a pas établi de réponse anticorps adéquate suite à la première dose du vaccin. Par exemple, seulement un quart des patients sous infliximab ont présenté une réponse anticorps anti-SRAS-CoV-2 adéquate après la première dose de vaccin;
- Les personnes utilisant des immunomodulateurs (azathioprine ou méthotrexate) avec l'infliximab ou le vedolizumab ont eu une réponse anticorps plus faible en réponse à une dose de vaccin par rapport à celles sous infliximab ou vedolizumab seul;
- Et la majorité des personnes ayant des MIIs ont monté une réponse anticorps adéquate après avoir reçu leur deuxième dose de vaccin, quels que soient les médicaments qui leur ont été prescrits.

Le groupe de travail COVID-19 & MII demande donc au comité consultatif national de l'immunisation d'inclure les patients MII sous traitement immunosuppresseur sur la liste des exceptions pour les intervalles de dosage prolongés. Les ministères provinciaux de la Santé devraient permettre aux patients MII de recevoir la deuxième dose de leur vaccin au moment indiqué par les fabricants.

Pour votre référence, la publication est jointe à cette lettre. Si vous avez des questions, n'hésitez pas à communiquer avec Crohn et Colite Canada à research@crohnsandcolitis.ca

Merci de votre considération.

Sincèrement,

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Original research

Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab

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ABSTRACT

Objective Antitumour necrosis factor (anti-TNF) drugs impair protective immunity following pneumococcal, influenza and viral hepatitis vaccination and increase the risk of serious respiratory infections. We sought to determine whether infliximab-treated patients with IBD have attenuated serological responses to SARS-CoV-2 infections.

Design Antibody responses in participants treated with infliximab were compared with a reference cohort treated with vedolizumab, a gut-selective anti-integrin α4β7 monoclonal antibody that is not associated with impaired vaccine responses or increased susceptibility to systemic infections. 6935 patients were recruited from 92 UK hospitals between 22 September and 23 December 2020.

Results Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups. Seroprevalence was lower in infliximab-treated than vedolizumab-treated patients (3.4% (161/4685) vs 6.0% (134/2250), p<0.0001). Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; OR 0.66 (95% CI 0.51 to 0.87), p=0.0027) and immunomodulator use (OR 0.70 (95% CI 0.53 to 0.92), p=0.012) were independently associated with lower seropositivity. In patients with confirmed SARS-CoV-2 infection, seroconversion was observed in fewer infliximab-treated than vedolizumab-treated patients (48% (39/81) vs 83% (30/36), p=0.00044) and the magnitude of anti-SARS-CoV-2 reactivity was lower (median 0.8 cut-off index (0.2–5.6) vs 37.0 (15.2–76.1), p<0.0001).

Conclusions Infliximab is associated with attenuated serological responses to SARS-CoV-2 that were further blunted by immunomodulators used as concomitant therapy. Impaired serological responses to SARS-CoV-2 infection might have important implications for global public health policy and individual anti-TNF-treated patients. Serological testing and virus surveillance should be considered to detect suboptimal vaccine responses, persistent infection and viral evolution to inform public health policy.

Trial registration number ISRCTN45176516.

Significance of this study

What is already known on this subject?

- Antitumour necrosis factor (anti-TNF) drugs are effective treatments for immune-mediated inflammatory diseases (IMIDs); however, by suppressing immune responses, they impair vaccine effectiveness and increase susceptibility to serious infection.
- In the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were subject to the most restrictive public health measures.
- Registry studies have not reported an increased risk of adverse outcomes from SARS-CoV-2 in patients treated with anti-TNF therapies. However, the impact of these therapies on serological responses and subsequent immunity to SARS-CoV-2 infection remains unknown.

What are the new findings?

- Rates of symptomatic and proven SARS-CoV-2 infection were similar between infliximab-treated and vedolizumab-treated patients with IBD.
- Seroprevalence, seroconversion and the magnitude of anti-SARS-CoV-2 antibody reactivity was significantly attenuated in infliximab-treated patients compared with vedolizumab-treated patients.
- Concomitant immunomodulator use with a thiopurine or methotrexate further blunted serological responses to SARS-CoV-2 infection in infliximab-treated patients, with only a third of patients having detectable anti-SARS-CoV-2 antibodies.

Significance of this study

How might it impact on clinical practice in the foreseeable future?

- For the individual anti-TNF-treated patient, lower rates of seroconversion and reduced anti-SARS-CoV-2 antibody reactivity levels may increase their susceptibility to recurrent COVID-19.
- Impaired serological responses might lead to chronic nasopharyngeal colonisation that may act as a reservoir to drive persistent transmission and the evolution of new SARS-CoV-2 variants.
- Serological testing and virus surveillance should be considered to detect suboptimal vaccine responses, persistent infection and viral evolution to inform public health policy.
- If attenuated serological responses following vaccination are also observed, then modified immunisation strategies will need to be designed for millions of patients worldwide.

INTRODUCTION

Induction of protective immunity following SARS-CoV-2 infection and/or vaccination is critical to suppress transmission. By suppressing immune responses, biological and immunosuppression therapies may lead to chronic SARS-CoV-2 infection and have recently been implicated in the evolution and emergence of novel variants.[1–3]

Immune-mediated inflammatory diseases (IMIDs) including IBD, the inflammatory arthritides and psoriasis affect about 3%–7% of Western populations.[4 5] Drugs targeting tumour necrosis factor (TNF) are the most frequently prescribed biological therapies used in the treatment of IMIDs with over 2 million patients receiving treatment worldwide.[6] However, anti-TNF drugs impair protective immunity following pneumococcal,[7] influenza[8] and viral hepatitis[9] vaccinations and increase the risk of serious infection, most notably with respiratory pathogens.[10] Consequently, in the early phase of the COVID-19 pandemic, patients with IMIDs treated with anti-TNF drugs were advised to follow strict social distancing measures, and some, depending on the severity of their condition, were advised to shield.[11] Data from disease-specific registries are reassuring, however, citing similar rates and risk factors for SARS-CoV-2 infection, hospitalisation and outcomes to background populations.[12–14] Whether anti-TNF drugs impair serological responses and subsequent immunity to SARS-CoV-2 infection is unknown.

We hypothesised that anti-SARS-CoV-2 antibody responses would be impaired following SARS-CoV-2 infection in patients with IBD treated with infliximab, a commonly prescribed anti-TNF drug. To test this hypothesis, we compared antibody responses in patients with IBD treated with infliximab with a reference cohort treated with vedolizumab. Vedolizumab is a gut-selective anti-integrin α4β7 monoclonal antibody, administered in hospital with the same dosing schedule as infliximab and is not associated with increased susceptibility to systemic infection or attenuated serological responses to vaccination.[15]

Objectives

We aimed to define, in patients with IBD, whether biological class, concomitant use of an immunomodulator and/or social distancing measures impact:

1. Seroprevalence of SARS-CoV-2.
2. Subsequent seroconversion in patients with infection confirmed by prior PCR testing.
3. Magnitude of anti-SARS-CoV-2 reactivity.

METHODS

Patient and settings

ImpaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY (CLARITY) IBD is a UK wide, multicentre, prospective observational cohort study investigating the impact of infliximab and vedolizumab and/or concomitant immunomodulators (thiopurines or methotrexate) on SARS-CoV-2 acquisition, illness and immunity in patients with IBD.

Consecutive patients were recruited at the time of attendance at infusion units from 92 National Health Service (NHS) hospitals across the UK (see online supplemental table S1) between 22 September 2020 and 23 December 2020.

The eligibility criteria were:

1. Age 5 years and over.
2. Diagnosis of IBD.
3. Current treatment with infliximab or vedolizumab for 6 weeks or more, with at least one dose of drug received in the past 16 weeks.

Patients were excluded if they had participated in a SARS-CoV-2 vaccine trial.

Here we report the seroprevalence of anti-SARS-CoV-2 antibodies at entry to the CLARITY IBD study.

Outcome measures

The primary outcome was the proportion of participants with a positive anti-SARS-CoV-2 antibody test. Secondary outcomes were the proportion of participants with a positive anti-SARS-CoV-2 antibody following a positive PCR test to SARS-CoV-2 and the magnitude of the anti-SARS-CoV-2 antibody reactivity.

Variables

Variables recorded by participants included demographics (age, sex, ethnicity, comorbidities, height and weight, smoking status and postcode), IBD disease activity (PRO2),[16 17] IBD-related quality of life (IBD control),[18] mental well-being (Patient Health Questionnaire depression scale[19] and General Anxiety Disorder Assessment),[20] SARS-CoV-2 outcomes aligned to the COVID-19 symptoms study[21] (symptoms, previous testing and hospital admissions for COVID-19) and social distancing behaviour during the lockdown periods. During lockdown, the population of the UK was instructed to adhere to restrictions on social and professional activities with specific advice to vulnerable groups to undertake more extreme social exclusion measures referred to as shielding.[11]

Study sites completed data relating to IBD history (age at diagnosis, disease duration and phenotype according to the Montreal classifications,[22] previous surgeries and duration of current biological and immunomodulator therapy).

Wherever possible, data were entered electronically into a purpose-designed REDCap database hosted at the Royal Devon and Exeter NHS Foundation Trust.[23] At sites without access to electronic devices or the internet, participants completed their questionnaires on paper case record forms that were subsequently entered by local research teams.

Case definition

Cases were defined according to the recently published WHO framework.[24] In brief, this framework uses symptoms and the results of nucleic acid amplification testing to determine whether patients are suspected, probable or confirmed cases of COVID-19. Participants who reported fever and cough, or anosmia/ageusia or any three or more of the following symptoms: fever, cough, general weakness/fatigue, myalgia, sore throat, coryza, dyspnoea, and altered mental status were

Table 1 Baseline characteristics stratified by biological therapy

Variable	Infliximab	Vedolizumab	Overall	P value
Age (years)	37.1 (27.2–50.6)	43.8 (31.9–58.6)	39.0 (28.7–53.2)	<0.0001
Sex				
Female	45.5 (2134/4685)	48.3 (1087/2250)	46.4 (3221/6935)	0.089
Male	54.3 (2546/4685)	51.5 (1159/2250)	53.4 (3705/6935)	
Intersex	0.0 (1/4685)	0.0 (1/2250)	0.0 (2/6935)	
Prefer not to say	0.1 (4/4685)	0.1 (3/2250)	0.1 (7/6935)	
Ethnicity				
White	88.5 (4143/4683)	88.2 (1981/2247)	88.4 (6124/6930)	0.20
Asian	6.6 (308/4683)	7.6 (171/2247)	6.9 (479/6930)	
Mixed	2.2 (104/4683)	2.3 (51/2247)	2.2 (155/6930)	
Black	1.8 (82/4683)	1.2 (27/2247)	1.6 (109/6930)	
Other	1.0 (46/4683)	0.8 (17/2247)	0.9 (63/6930)	
Diagnosis				
Crohn's disease	66.6 (3121/4685)	36.8 (828/2250)	56.9 (3949/6935)	0.00050
UC	31.1 (1457/4685)	60.1 (1353/2250)	40.5 (2810/6935)	
IBD unclassified	2.3 (107/4685)	3.1 (69/2250)	2.5 (176/6935)	
Duration of IBD (years)	7.0 (3.0–15.0)	9.0 (4.0–16.0)	8.0 (3.0–15.0)	<0.0001
Age at IBD diagnosis (years)	26.3 (18.9–37.5)	30.4 (21.6–44.1)	27.6 (19.8–39.8)	<0.0001
Immunomodulators at recruitment	56.3 (2639/4685)	18.8 (424/2250)	44.2 (3063/6935)	<0.0001
5-ASA at recruitment	22.2 (1039/4685)	35.2 (791/2250)	26.4 (1830/6935)	<0.0001
Steroid use in 2020	14.2 (664/4685)	21.9 (492/2250)	16.7 (1156/6935)	<0.0001
BMI	24.4 (21.5–28.1)	24.9 (22.0–28.4)	24.5 (21.7–28.2)	0.044
Heart disease	2.1 (97/4685)	5.0 (113/2250)	3.0 (210/6935)	<0.0001
Diabetes	3.4 (158/4685)	6.8 (154/2250)	4.5 (312/6935)	<0.0001
Lung disease	12.6 (588/4685)	16.7 (375/2250)	13.9 (963/6935)	<0.0001
Kidney disease	0.9 (42/4685)	2.1(47/2250)	1.3 (89/6935)	<0.0001
Cancer	0.2 (11/4685)	1.7 (39/2250)	0.7 (50/6935)	<0.0001
Smoker				
Yes	11.5 (538/4684)	9.2 (206/2249)	10.7 (744/6933)	0.00050
Not currently	28.5 (1333/4684)	34.4 (773/2249)	30.4 (2106/6933)	
Never	60.1 (2813/4684)	56.5 (1270/2249)	58.9 (4083/6933)	
Meets clinical criteria for suspected or probable COVID-19	8.3 (389/4685)	8.9 (201/2250)	8.5 (590/6935)	0.38
Tested with PCR for SARS-CoV-2	36.5 (1712/4685)	39.0 (877/2250)	37.3 (2589/6935)	0.050
Positive PCR for SARS-CoV-2	5.2 (89/1712)	4.3 (38/877)	4.9 (127/2589)	0.39
Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample	5.3 (81/1537)	4.4 (36/809)	5.0 (117/2346)	0.43
Hospitalised for confirmed COVID-19	0.2 (8/4685)	0.2 (5/2250)	0.2 (13/6935)	0.77
Shielding behaviour April–July				
I remained in my house or garden	35.2 (1647/4681)	33.3 (749/2248)	34.6 (2396/6929)	0.41
I only left the house for exercise on my own or with members of my household	38.5 (1804/4681)	39.9 (897/2248)	39.0 (2701/6929)	
I encountered people from outside of my household but *maintained social distancing*	24.4 (1142/4681)	24.6 (554/2248)	24.5 (1696/6929)	
I encountered people from outside of my household but *did not maintain social distancing*	1.9 (88/4681)	2.1 (48/2248)	2.0 (136/6929)	
Exposure to documented cases of COVID-19	11.4 (533/4683)	10.7 (240/2250)	11.1 (773/6933)	0.39
PHQ8	4.0 (1.0–8.0)	5.0 (1.0–9.0)	4.0 (1.0–9.0)	0.018
GAD-7	3.0 (0.0–7.0)	3.0 (0.0–7.0)	3.0 (0.0–7.0)	0.12
Income deprivation score	0.099 (0.057–0.168)	0.095 (0.056–0.160)	0.097 (0.57–0.165)	0.24
Active disease (PRO2)	6.7 (303/4534)	12.6 (272/2166)	8.6 (575/6700)	<0.0001
IBD Control 8	13.0 (10.0–16.0)	13.0 (9.0–16.0)	13.0 (9.0–16.0)	0.024
IBD Control VAS	80.0 (66.0–93.0)	79.0 (61.0–91.0)	80.0 (65.0–92.0)	0.00022

Values shown are medians (IQR) and percentages (proportions) as appropriate.
5-ASA, 5-aminosalicylate; BMI, body mass index; GAD-7, General Anxiety Disorder Assessment; PHQ8, Patient Health Questionnaire depression scale; PRO2, Patient Reported Outcome; VAS, visual analogue scale.

considered suspected/probable COVID-19 cases. We omitted the GI symptoms because patients with active IBD may suffer anorexia, nausea, vomiting and diarrhoea. We linked our data by NHS number or Community Health Index to Public Health England, Scotland and Wales who archive dates and results of all SARS-CoV-2 PCR tests undertaken in the UK. Confirmed cases were those participants with a positive PCR test to SARS CoV-2.

Table 2 Seroprevalence to anti-SARS-CoV-2, stratified by baseline characteristics

Variable	Seroprevalence	P value
Biological therapy		
Infliximab	3.4 (161/4685)	<0.0001
Vedolizumab	6.0 (134/2250)	
Biological/immunomodulator therapy		
Infliximab with immunomodulator	3.0 (78/2639)	0.00050
Infliximab without immunomodulator	4.1 (83/2046)	
Vedolizumab with immunomodulator	4.5 (19/424)	
Vedolizumab without immunomodulator	6.3 (115/1826)	
Sex		
Female	4.3 (137/3221)	1.0
Male	4.3 (158/3705)	
Intersex	0.0 (0/2)	
Prefer not to say	0.0 (0/7)	
Ethnicity		
White	3.5 (217/6124)	0.00050
Asian	9.2 (44/479)	
Mixed	7.7 (12/155)	
Black	13.8 (15/109)	
Other	11.1 (7/63)	
Diagnosis		
Crohn's disease	3.2 (128/3949)	0.00050
UC	5.5 (155/2810)	
IBD unclassified	6.8 (12/176)	
Immunomodulators at recruitment		
No	5.1 (198/3872)	<0.0001
Yes	3.2 (97/3063)	
5-ASA at recruitment		
No	3.9 (198/5105)	0.012
Yes	5.3 (97/1830)	
Steroid use in 2020		
No	4.0 (232/5779)	0.031
Yes	5.4 (63/1156)	
Heart disease		
No	4.3 (287/6725)	0.86
Yes	3.8 (8/210)	
Diabetes		
No	4.2 (280/6623)	0.57
Yes	4.8 (15/312)	
Lung disease		
No	4.4 (260/5972)	0.34
Yes	3.6 (35/963)	
Kidney disease		
No	4.3 (294/6846)	0.19
Yes	1.1 (1/89)	
Cancer		
No	4.3 (293/6885)	1.0
Yes	4.0 (2/50)	
Smoker		
Yes	2.2 (16/744)	0.00050
Not currently	3.4 (71/2106)	
Never	5.1 (207/4083)	
Meets clinical criteria for suspected or probable COVID-19		
No	2.5 (158/6345)	<0.0001
Yes	23.2 (137/590)	
Tested with PCR for SARS-CoV-2		
No	2.9 (128/4346)	<0.0001
Yes	6.5 (167/2589)	
Positive PCR for SARS-CoV-2		
No	3.8 (93/2462)	<0.0001
Yes	58.3 (74/127)	
Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample		
No	3.8 (85/2229)	<0.0001
Yes	59.0 (69/117)	
Hospitalised for confirmed COVID-19		
No	4.1 (285/6922)	<0.0001
Yes	76.9 (10/13)	
Shielding behaviour April–July		
I remained in my house or garden	3.8 (92/2396)	0.0020
I only left the house for exercise on my own or with members of my household	3.9 (104/2701)	
I encountered people from outside of my household but *maintained social distancing*	4.9 (83/1696)	
I encountered people from outside of my household but *did not maintain social distancing*	11.0 (15/136)	
Exposure to documented cases of COVID-19		
No	3.1 (192/6160)	<0.0001
Yes	13.3 (103/773)	
Active disease (PRO2)		
No	4.3 (266/6125)	0.67
Yes	3.8 (22/575)	

Values shown are percentages (proportions).
5-ASA, aminosalicylates; PRO2, patient-reported outcome.

Laboratory methods

Laboratory analyses were performed at the Academic Department of Blood Sciences at the Royal Devon and Exeter NHS Foundation Trust. We used the Roche Elecsys Anti-SARS-CoV-2 immunoassay to detect antibodies to SARS-CoV-2 in serum samples.[25] This sandwich electrochemiluminescence immunoassay uses a recombinant protein of the nucleocapsid antigen for the determination of antibodies against SARS-CoV-2. The electrochemiluminescence signal from a negative and positive calibrator is assigned a value of 0.8 and 1.2, respectively, and a cut-off is set at a signal equivalent to 1. The electrochemiluminescence signal from the reaction product of the sample is compared with the cut-off signal and expressed as positive when ≥1.0 or negative when <1, as well as quantitatively in the form of a cut-off index (COI; calculated by sample signal/cut-off signal).

In house assay validation experiments demonstrated the intra-assay and interassay coefficient of variation were 2.2% and 7.0%, respectively. No effect was observed on recovery of anti-SARS-CoV-2 antibodies following four freeze/thaw cycles. SARS-CoV-2 antibodies were stable in uncentrifuged blood and serum at ambient temperature for up to 7 days permitting postal transport from research sites to the central laboratory. No analytical interference was observed for the detection of anti-SARS-CoV-2 with infliximab or vedolizumab up to 10 000 mg/L and 60 000 mg/L, respectively, or with antidrug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL, respectively.

Study size

Limited data are available regarding the risk of SARS-CoV-2 in patients with IBD to inform sample size calculations.

The following assumptions were made to determine our sample size:

- Proportion of patients treated with each drug(s): vedolizumab: 30% (20% with concomitant immunomodulator), infliximab: 70% (60% with concomitant immunomodulator).
- Seroprevalence of SARS-CoV-2 in the background population: 0.05.
- OR for SARS-CoV-2 seropositivity with immunomodulator use: 0.8.
- OR SARS-CoV-2 seropositivity for infliximab versus vedolizumab: ≤0.7.
- Attrition rate: 20%.

We calculated that a sample size of 6970 patients would provide 80% power for the comparison of infliximab versus vedolizumab, controlling for immunosuppressant status in a multivariable logistic regression model at the 0.05 significance level.

Ethical consideration and roles of funders

CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public health study funded by the Royal Devon and Exeter NHS Foundation Trust, Hull University Teaching Hospital NHS Trust and by unrestricted educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH(Switzerland), Celltrion Healthcare (South Korea) and Galapagos NV (Belgium).

None of our funding bodies had any role in study design, data collection or analysis, writing or decision to submit for publication. Patients were included after providing informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The protocol is available online at https//www.clarityibd.org. The study was registered with the ISRCTN registry.

Statistics

Statistical analyses were undertaken in R V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two tailed, and p values<0.05 were considered significant. We included participants in the primary analysis if they had completed the patient questionnaire and had an anti-SARS-CoV-2 serology result at visit 1. We included patients with missing clinical data in analyses for which they had data and have specified the denominator for each variable. Continuous data were reported as median and IQR, and discrete data as numbers and percentages, unless otherwise stated. We used patients' postcodes to assign them to one of the ten UK administrative regions and present seroprevalence rates mapped to these regions. We also used postcodes to derive participants' income and employment deprivation scores using combined English and Welsh data from 2019[26] and Scottish data from 2020.[27] Univariable analyses, using Fisher's exact and Mann-Whitney U tests were used to identify demographic, disease and treatment related factors associated with SARS-CoV-2 seropositivity. A priori, we included age, sex, ethnicity, region, income deprivation score, comorbidity, body mass index and social distancing measures that are known to affect SARS-CoV-2 acquisition and COVID-19 outcomes[28] alongside IBD diagnosis, biological therapies, immunomodulator and 5-aminosalicylate use. We used multivariable logistic regression models to identify factors independently associated with seropositivity.

We undertook Fisher's exact and Mann-Whitney U tests to compare the rates of, and time to, seroconversion in infliximab-treated and vedolizumab-treated patients with confirmed COVID-19 and to identify factors associated with failure of seroconversion in infliximab-treated patients. We explored the magnitude of antibody reactivity using density plots, stratified by drug exposure among participants with a positive PCR to anti-SARS-CoV-2 at least 2 weeks prior to measurement of serology.

We conducted sensitivity analyses using propensity matching to account for significant differences in baseline variables between infliximab-treated and vedolizumab-treated patients using the MatchIt package.[29] Patients were matched exactly on diagnosis, immunomodulator use and cancer and then using optimal matching, on age, comorbidities, ethnicity and presence of active disease.

RESULTS

Patient characteristics

Between 22 September 2020 and 23 December 2020, 7226 patients were recruited from 92 UK hospitals. Serum samples and completed questionnaires were available in 96.0% (6935/7226) patients. Of these, 67.6% (4685/6935) were treated with infliximab and 32.4% (2250/6935) were treated with vedolizumab. Participant characteristics are shown in table 1.

Adherence to social distancing measures during the UK lockdown period between April and July 2020 and exposure to COVID-19 cases were similar between infliximab and vedolizumab treated patients (table 1). Fewer infliximab-treated patients were tested by PCR for SARS-CoV-2 (36.5% (1712/4685) vs 39.0% (877/2250), p=0.050). There were no differences between the proportions of infliximab-treated and vedolizumab-treated patients who: reported symptoms of suspected or probable COVID-19 (8.3% (389/4685) vs 8.9% (201/2250), p=0.38); tested positive by PCR for SARS-CoV-2 (5.2% (89/1712) vs 4.3% (38/877), p=0.39); or were hospitalised with confirmed COVID-19 (0.2% (8/4685) vs 0.2% (5/2250), p=0.77).

Seroprevalence of anti-SARS-CoV-2 antibodies in anti-TNF and vedolizumab-treated patients

Overall, the seroprevalence of anti-SARS-CoV-2 antibodies was 4.3% (295/6935, 95% CI 3.8% to 4.8%). The proportion of patients with a positive anti-SARS-CoV-2 antibody test was lower in infliximab-treated than vedolizumab-treated patients (3.4% (161/4685) vs 6.0% (134/2250), p<0.0001) (table 2).

Seropositivity was also associated with younger age, non-white ethnicity, UK region, higher income deprivation score, having never smoked, UC, no concomitant immunomodulator use, recent steroid use, exposure to confirmed cases of COVID-19, reported symptoms of suspected or probable COVID-19, and social distancing measures during the UK government's lockdown period (tables 2 and 3, See online supplemental figure S1).

Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; OR 0.66 (95% CI 0.51 to 0.87), p=0.0027) and immunomodulator use (OR 0.70 (95% CI 0.53 to 0.92), p=0.012) were independently associated with lower seropositivity (figure 1). Conversely, non-white ethnicity, several UK regions, higher income deprivation score and non-adherence to social distancing measures were independently associated with an increased risk of SARS-CoV-2 seropositivity. There was no significant interaction between the effect of infliximab (vs vedolizumab) and immunomodulator use (OR for interaction term 1.03 (95% CI 0.57 to 1.92), p=0.92). In our propensity matched analysis, we confirmed lower seroprevalence in infliximab-treated compared with vedolizumab-treated patients 3.9% (67/1704) versus 6.2% (105/1707) p=0.0037 (online supplemental table S2).

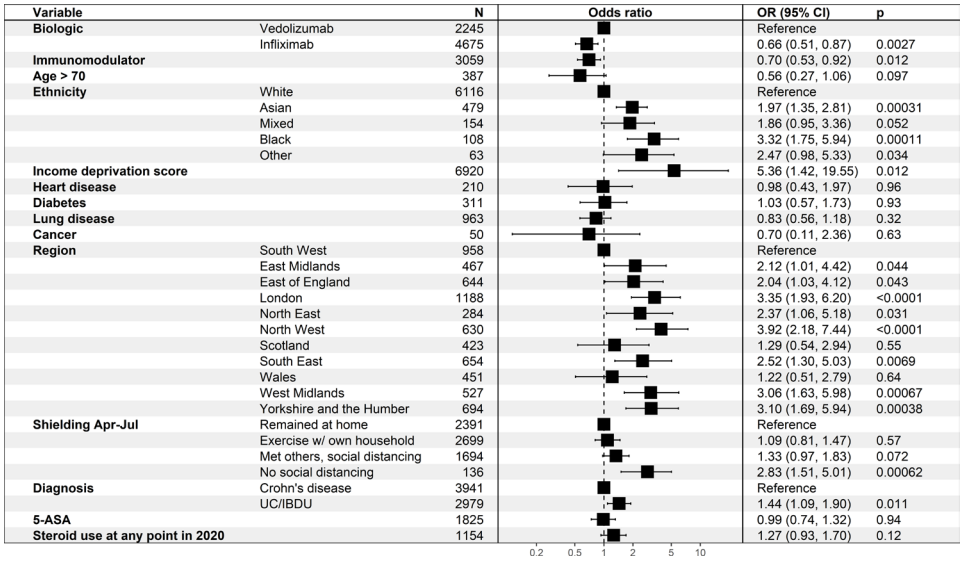

Figure 1 Forest plot showing the coefficients from a multivariable logistic regression model of associations with a positive anti-SARS-CoV-2 antibody. abbreviations: 5-ASA, 5-aminosalicylates; IBDU, IBD unclassified.

Seroconversion in patients with confirmed SARS-CoV-2 infection

Sensitivity analyses in participants with confirmed SARS-CoV-2 infection demonstrated that fewer infliximab-treated than vedolizumab-treated patients had seroconverted (48% (39/81) vs 83% (30/36), p=0.00044). The magnitude of anti-SARS-CoV-2 reactivity was lower in patients with previous PCR-confirmed SARS-CoV-2 infection treated with infliximab than with vedolizumab (median 0.8 COI (0.2–5.6) vs 37.0 (15.2–76.1), p<0.0001; figure 2). This difference was also seen restricting our analyses to participants whose antibody reactivity results were above the threshold (1 COI) for seropositivity (p<0.0001; see online supplemental figure S2).

Failure of seroconversion was associated with concomitant immunomodulator use. In patients treated with infliximab alone, the seroconversion rate was 60% (24/40) and in patients treated with infliximab and immunomodulator combination therapy, the rate was 37% (15/41, p=0.046). There was also a significant difference in the magnitude of anti-SARS-CoV-2 reactivity (p=0.035; see online supplemental figure S3). The median interval from a positive PCR test to serological testing at recruitment in infliximab-treated patients was 32 days (IQR 20–54) and for vedolizumab-treated patients was 40 days (IQR 24–83) (p=0.082). An increase in anti-SARS-CoV-2 antibody reactivity was observed 4 weeks after a positive PCR test in vedolizumab-treated patients (47.2 COI (IQR 24.1–113.0) vs 14.5 COI (IQR 0.4–30.7), p=0.0079) but not infliximab-treated patients (0.7 COI (IQR 0.2–7.5) vs 1.1 COI (IQR 0.4–4.5), p=0.70) (figure 3).

Table 3 Baseline characteristics, stratified by baseline anti-SARS-CoV-2 antibody status

Variable	Positive	Negative	P value
Age (years)	36.3 (26.9–50.6)	39.2 (28.7–53.3)	0.017
Duration of IBD (years)	7.0 (3.0–15.0)	8.0 (3.0–15.0)	0.25
Age at IBD diagnosis (years)	26.4 (19.8–36.4)	27.6 (19.8–40.0)	0.12
BMI	24.7 (21.7–28.1)	24.5 (21.7–28.3)	0.75
PHQ8	4.0 (1.0–8.0)	4.0 (1.0–9.0)	0.40
GAD-7	2.0 (0.0–6.0)	3.0 (0.0–7.0)	0.050
Income deprivation score	0.120 (0.666–0.204)	0.097 (0.056–0.163)	<0.0001
IBD Control 8	13.0 (10.0–16.0)	13.0 (9.0–16.0)	0.32
IBD Control VAS	79.0 (67.0–92.0)	80.0 (65.0–92.0)	0.61

Values shown are medians (IQR).
BMI, body mass index; GAD-7, General Anxiety Disorder Assessment; PHQ8, Patient Health Questionnaire depression scale; VAS, visual analogue scale.

DISCUSSION

We have shown that infliximab-treated patients have attenuated serological responses to SARS-CoV-2 infection with lower seroprevalence, seroconversion and antibody reactivity. Similar rates of symptomatic and proven SARS-CoV-2 infection and hospitalisations between infliximab-treated and vedolizumab-treated patients suggest that our findings cannot be explained by differences in acquisition or severity of infection alone. Rather, infliximab seems to be directly influencing the serological response to infection. Concomitant immunomodulator use with a thiopurine or methotrexate further blunted serological responses to both drugs with fewer than half of patients (37%) having

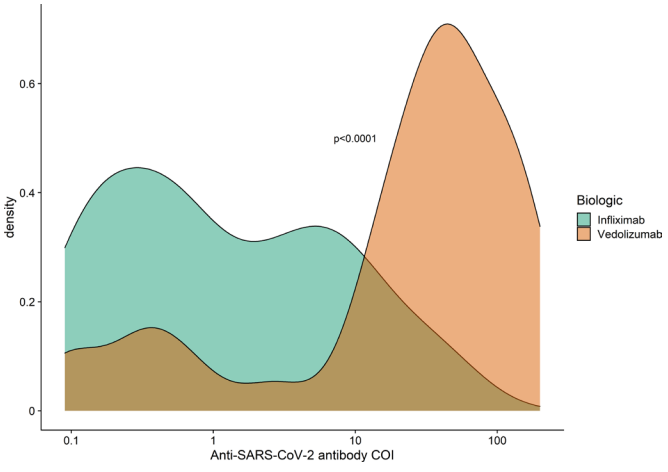

Figure 2 Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy among participants who had a positive PCR to anti-SARS-CoV-2 at least 2 weeks prior to their serology sample. COI, cut-off index.

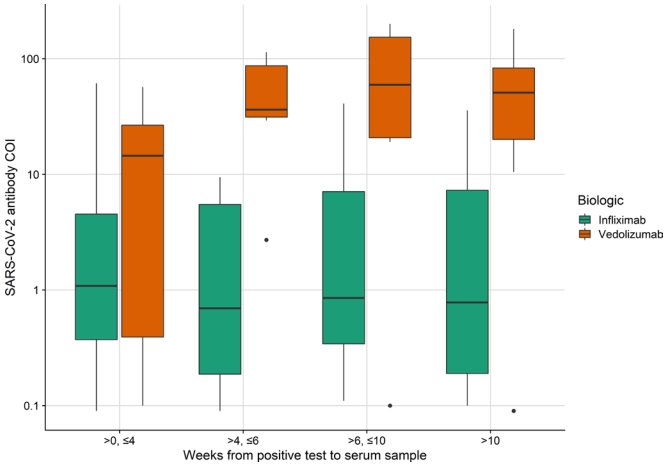

Figure 3 Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy and time since prior positive PCR test. COI, cut-off index.

detectable anti-SARS-CoV-2 antibodies after a median of 5.4 weeks following PCR confirmed infection.

Infliximab may directly impede the immune mechanisms responsible for generating antibody responses. This is biologically plausible, since the proinflammatory actions of TNF include stimulation of B cell immunoglobulin synthesis, induction of germinal centre formation, costimulation of antigen-activated T cells and maturation of antigen presenting cells.[30–32]

Impaired serological responses to SARS-CoV-2 infection might have important implications for global public health policy and individual anti-TNF treated patients. From a public health perspective, impaired serological responses might lead to chronic nasopharyngeal colonisation that may act as a reservoir to drive persistent transmission and the evolution of new SARS-CoV-2 variants.[2] Virus surveillance will define if persistent infection and viral evolution occurs in this patient group.[3]

For the individual anti-TNF treated patient, lower rates of seroconversion and reduced anti-SARS-CoV-2 antibody reactivity levels may ultimately increase their susceptibility to recurrent COVID-19.

Accepting that vaccination is critical to suppress transmission, serology testing should be considered to detect suboptimal vaccine responses to inform the need for the most restrictive social distancing measures to protect patients and public health. If attenuated serological responses following vaccination are observed, then modified vaccination schedules given in combination might need to be considered in these patients.

Any negative impact on seroconversion following infection or vaccination needs to be balanced against theoretical benefits for the individual patient of reducing the excessive cytokine production that characterises severe COVID-19 disease. Indeed, this is the rationale behind the proposals for trials of anti-TNF therapy in severe COVID-19 (ISRCTN40580903 and ISRCTN33260034).[33]

Our study has other important findings. We have identified associations of SARS-CoV-2 seropositivity with non-white ancestry and non-adherence to social distancing guidance. These findings are consistent with observations reported in general non-immunosuppressed populations.[28] The mechanisms underlying these associations are complex and multifactorial and likely include multigenerational living, at-risk employment, inability to work from home, socioeconomic deprivation and religious congregation.

The region-specific seroprevalence rates for vedolizumab-treated patients are consistent with those reported in the general UK population. While direct comparisons with other datasets are limited, confounded in part by differences in the time of testing during the pandemic and the diagnostic accuracies of the anti-SARS-CoV-2 assays used, this adds to the evidence that patients with IBD are at a similar risk of SARS-CoV-2 infection as the general population.[34]

The main strength of this study was our recruitment of over 7000 consecutive patients within a narrow window mitigating against the potential for time during the pandemic course to be a significant covariate. Other strengths include comprehensive electronic collection of patient-reported outcomes, linkage with SARS-CoV-2 public health testing data, case ascertainment aligned with the WHO criteria, inclusion of social distancing behaviours and the use of a sensitive and specific serological assay.[35]

Limitations

We acknowledge, however, the following limitations. First, it is not known whether attenuated immune responses in infliximab-treated patients translates into increased risk of infection. Moreover, we only assessed humoral responses to infection, and it is likely that protective immunity additionally requires induction of memory T cell responses. Second, our patient-reported data are subject to recall bias that may have underestimated the prevalence of possible COVID-19 symptoms. Third, the only anti-TNF drug investigated in this study was infliximab. However, we suspect that our key findings apply to other anti-TNF monoclonal antibodies used to treat IMIDs, including adalimumab, certolizumab and golimumab.

CONCLUSIONS

In summary, infliximab therapy is associated with attenuated serological responses to SARS-CoV-2 infection. Poor antibody responses in infliximab-treated patients were observed despite similar rates of symptomatic and proven SARS-CoV-2 infection as vedolizumab-treated patients. Anti-SARS-CoV-2 antibody responses were further attenuated in infliximab recipients concomitantly treated with immunomodulators, including thiopurines and methotrexate.

Impaired serological responses to SARS-CoV-2 infection might have important implications for global public health policy and millions of anti-TNF treated patients. Serological testing and virus surveillance should be considered to detect suboptimal vaccine responses, persistent infection and viral evolution to inform public health policy.

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Patient and public involvement statement We conducted an electronic survey to gauge the opinion of patients with IBD on the patient questionnaires to

be delivered as part of the CLARITY IBD study. We surveyed 250 patients across 74 hospitals. All our proposed questions for study inclusion were rated as important or very important by at least 83% of participants. The Exeter IBD Patient Panel refined the questions included in the study questionnaire, reviewed the study protocol, supported the writing of the patient information sheet, and participated in testing of electronic consent form and patient questionnaire. A member of the Exeter IBD Patient Panel sits on the study management committee, ensuring patient involvement in all aspects of study delivery, data analysis and dissemination of findings.

Patient consent for publication Not required.

Ethics approval The Surrey Borders Research Ethics committee approved the study (REC reference: REC 20/HRA/3114) in September 2020.

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Data availability statement Data are available on reasonable request. The study protocol including the statistical analysis plan is available at www.clarityibd.org. Individual participant deidentified data that underlie the results reported in this article will be available immediately after publication for a period of 5 years. The data will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be directed to tariq.ahmad1@nhs.net; to gain access, data requestors will need to sign a data access agreement.

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Title	**Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines**
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Research in context

Evidence before this study

Faced with further surges of SARS-CoV-2 infection, a growing number of countries, including the UK, have opted to delay second vaccine doses for all people. This strategy trades maximal effectiveness against a lower level of protective immunity across more of the at-risk population.

We have previously shown that seroprevalence, seroconversion in PCR-confirmed cases, and the magnitude of anti-SARS-CoV-2 antibodies following SARS-CoV-2 infection are reduced in infliximab- compared with vedolizumab-treated patients. Whether single-doses of vaccines are effective in patients treated with anti-TNF therapies is unknown.

We searched PubMed from 25 November 2019 to 23 March 2021 with the terms “anti-tumour necrosis factor” or “anti-integrin” or “infliximab” or “adalimumab” or “vedolizumab” or “biological therapy” or “biologic therapy” AND “SARS-CoV-2" or “coronavirus” or “COVID-19” or AND “seroprevalence” or “seroconversion” or “antibody” or “antibody response” or “magnitude” or “immunogenicity” AND “vaccine” or “vaccination” or “immunisation” or “immunization” or “ChAdOx1 nCoV-19" or “BNT162b2” or “mRNA-1273”, without restriction on language.

Serological responses to SARS-CoV-2 vaccines have been reported in registration trials and small observational cohorts of healthy volunteers. Two small studies, including one unpublished preprint, found that COVID-19 vaccine immunogenicity rates were lower in transplant recipients and patients with malignancy receiving immunosuppressive therapy, and fewer patients treated with potent immunosuppressants seroconverted than healthy controls. No studies have assessed the effect of anti-TNF therapy on immunogenicity following SARS-CoV-2 vaccination.

Added value of this study

To test if anti-TNF drugs attenuate serological responses to primary SARS-CoV-2 vaccines, we analysed anti-SARS-CoV-2 spike (S) antibody concentrations and seroconversion rates in 1293 patients with inflammatory bowel disease who received primary vaccinations with either the ChAdOx1 nCoV-19 or BNT162b2 vaccines. 865 were treated with the anti-TNF drug infliximab and outcomes were compared to a reference cohort of 428 patients treated with vedolizumab, a gut selective anti-integrin α4β7 monoclonal antibody that is not associated with impaired systemic immune responses.

Anti-SARS-CoV-2 antibody levels and rates of seroconversion were lower following primary vaccination with both the BNT162b2 and ChAdOx1 nCoV-19 vaccines in patients with IBD treated with infliximab compared to vedolizumab. Older age, immunomodulator use, Crohn's disease (versus ulcerative colitis or inflammatory bowel disease unclassified), and current smoking were associated with lower anti-SARS-CoV-2 antibody concentrations, irrespective of vaccine type. Non-white ethnicity was associated with higher anti-SARS-CoV-2 (S) antibody concentrations following primary vaccination with both vaccines. Antibody concentrations and seroconversion rates were higher in patients with past SARS-CoV-2 infection prior to a single-dose of either vaccine, and after 2 doses of the BNT162b2 vaccine.

Implications of the available evidence

Our findings have important implications for patients treated with anti-TNF therapy, particularly for those also treated with an immunomodulator. Poor antibody responses to a single-dose of vaccine exposes these patients to a potential increased risk of SARS-CoV-2 infection. However, higher rates of seroconversion in patients with two exposures to SARS-CoV-2 antigen, even in the presence of TNF blockade, suggest that all patients receiving these drugs should be prioritized for optimally

timed second doses. Until patients receive a second vaccine dose, they should consider that they are not protected from SARS-CoV-2 infection and continue to practice enhanced physical distancing and shielding if appropriate. Even after two antigen exposures, a small subset of patients failed to mount an antibody response. Antibody testing and adapted vaccine schedules should be considered to protect these at-risk patients.

Abstract

Background

Delayed second-dose SARS-CoV-2 vaccination trades maximal effectiveness for a lower level of immunity across more of the population. We investigated whether patients with inflammatory bowel disease treated with infliximab have attenuated serological responses to a single-dose of a SARS-CoV-2 vaccine.

Methods

Antibody responses and seroconversion rates in infliximab-treated patients (n=865) were compared to a cohort treated with vedolizumab (n=428), a gut-selective anti-integrin α4β7 monoclonal antibody. Our primary outcome was anti-SARS-CoV-2 spike (S) antibody concentrations 3-10 weeks after vaccination in patients without evidence of prior infection. Secondary outcomes were seroconversion rates, and antibody responses following past infection or a second dose of the BNT162b2 vaccine.

Findings

Geometric mean [SD] anti-SARS-CoV-2 antibody concentrations were lower in patients treated with infliximab than vedolizumab, following BNT162b2 (6·0 U/mL [5·9] vs 28·8 U/mL [5·4] P<0·0001) and ChAdOx1 nCoV-19 (4·7 U/mL [4·9]) vs 13·8 U/mL [5·9] P<0·0001) vaccines. In our multivariable models, antibody concentrations were lower in infliximab- compared to vedolizumab-treated patients who received the BNT162b2 (fold change [FC] 0·29 [95% CI 0·21, 0·40], p<0·0001) and ChAdOx1 nCoV-19 (FC 0·39 [95% CI 0·30, 0·51], p<0·0001) vaccines. In both models, age ≥ 60 years, immunomodulator use, Crohn's disease, and smoking were associated with lower, whilst non-white ethnicity was associated with higher, anti-SARS-CoV-2 antibody concentrations. Seroconversion rates after a single-dose of either vaccine were higher in patients with prior SARS-CoV-2 infection and after two doses of BNT162b2 vaccine.

76 *Interpretation*

77 Infliximab is associated with attenuated immunogenicity to a single-dose of the BNT162b2 and
78 ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. Vaccination after SARS-CoV-2 infection, or a second dose of
79 vaccine, led to seroconversion in most patients. Delayed second dosing should be avoided in
80 patients treated with infliximab.

81

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Introduction

Limited SARS-CoV-2 vaccine supplies and pressure on critical care services have forced governments to prioritise primary vaccination to vulnerable groups. In the United Kingdom, second vaccine doses have also been delayed, trading maximal effectiveness for a lower level of protective immunity across a greater proportion of the most at-risk population.[1] Consequently, more than half of the adult population have received a single-dose of either the RNA vaccine, BNT162b2 (Pfizer/BioNTech) or the adenovirus-vector vaccine, ChAdOx1 nCoV-19 (Oxford/AstraZeneca). Faced with further surges of SARS-CoV-2 infection, a growing number of other countries have also opted to delay second vaccine doses.[2,3]

The inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis (UC) are chronic immune-mediated inflammatory diseases (IMIDs) that affect about 1% of the UK population.[4,5] Treatment typically requires immunosuppression with immunomodulators (azathioprine, mercaptopurine, and methotrexate) and/or biological therapies that target disease relevant cytokines or the immune cells that produce them. Anti-tumour necrosis factor (TNF) drugs, such as infliximab and adalimumab, are the most frequently prescribed biopharmaceuticals used in the treatment of IMIDs. These drugs impair immunogenicity following pneumococcal,[6] influenza,[7] and hepatitis B[8] vaccinations and increase the risk of serious infection, most notably with respiratory pathogens.[9] Conversely, vedolizumab, a gut-selective anti-integrin α4β7 monoclonal antibody is not associated with increased susceptibility to systemic infection or attenuated serological responses to vaccination.[10]

We have recently reported that seroprevalence, seroconversion in PCR-confirmed cases, and the magnitude of anti-SARS-CoV-2 antibodies following SARS-CoV-2 infection are reduced in infliximab- compared with vedolizumab-treated patients.[11] We hypothesised that, following at least a single-dose with BNT162b2 or ChAdOx1 nCoV-19 vaccine, serological responses would be similarly

impaired in patients treated with infliximab compared to vedolizumab arguing against delaying second doses in these patients.

We aimed to define, in patients with IBD who had received a COVID-19 vaccination, whether biologic class and concomitant use of an immunomodulator impact:

i) anti-SARS-CoV-2 spike (S) antibody levels
ii) rates of seroconversion
iii) antibody responses in patients who had previously been infected with SARS-CoV-2 or who had two doses of vaccine

Methods

Study design and participants

impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY (CLARITY) IBD is a UK wide, multicentre, prospective observational cohort study investigating the impact of infliximab and vedolizumab and/or concomitant immunomodulators (azathioprine, mercaptopurine, and methotrexate) on SARS-CoV-2 acquisition, illness, and immunity in patients with IBD.

Study methods have been described in detail previously.[11] In brief, consecutive patients were recruited at the time of attendance at infusion units from 92 National Health Service (NHS) hospitals across the UK between 22nd September 2020 and 23rd December 2020 (Supplementary pp 2 - 17). The eligibility criteria were age 5 years and over, a diagnosis of IBD, and current treatment with infliximab or vedolizumab for 6 weeks or more, with at least one dose of drug received in the previous 16 weeks. Patients were excluded if they had participated in a SARS-CoV-2 vaccine trial.

Follow-up visits were timed to coincide with biologic infusions and occurred approximately eight-weekly. Here, we report vaccine-induced antibody responses at first study visit after primary vaccination, and where possible, after two doses. Participants were eligible for inclusion in our vaccine immunogenicity analysis if they had had a SARS-CoV-2 antibody test within the first ten weeks after their primary vaccination with any of the available SARS-CoV-2 vaccines.

The Surrey Borders Research Ethics committee approved the study (REC reference: 20/HRA/3114) in September 2020. Patients were included after providing informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The protocol is available online at https//www.clarityibd.org. The study was registered with the ISRCTN registry, ISRCTN45176516.

Procedures

Variables recorded by participants were demographics (age, sex, ethnicity, comorbidities, height and weight, smoking status, and postcode), IBD disease activity (PRO2), SARS-CoV-2 symptoms aligned to the COVID-19 symptoms study (symptoms, previous testing, and hospital admissions for COVID-19), and vaccine uptake (type and date of primary vaccination). Study sites completed data relating to IBD history (age at diagnosis, disease duration, and phenotype according to the Montreal classifications, previous surgeries, and duration of current biologic and immunomodulator therapy).[11] We linked our data by NHS number or Community Health Index to Public Health England, Scotland, and Wales who archive dates and results of all SARS-CoV-2 PCR tests undertaken. Data were entered electronically into a purpose-designed REDCap database hosted at the Royal Devon and Exeter NHS Foundation Trust.[12] 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.

Laboratory analyses were performed at the Academic Department of Blood Sciences at the Royal Devon and Exeter NHS Foundation Trust. To determine antibody responses specific to vaccination we used the Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay[13] alongside the nucleocapsid (N) immunoassay.[14] This double sandwich electrochemiluminescence immunoassay uses a recombinant protein of the receptor binding domain on the spike protein as an antigen for the determination of antibodies against SARS-CoV-2. Sample electrochemiluminescence signals are compared to an internal calibration curve and quantitative values are reported as units (U)/mL.

In-house assay validation experiments demonstrated:

i) The intra-assay and inter-assay coefficient of variation were 1·3% and 5·6%, respectively

ii) Anti-SARS-CoV-2 (S) antibodies were stable in uncentrifuged blood and serum at ambient temperature for up to seven days permitting postal transport

iii) No effect was observed on recovery of anti-SARS-CoV-2 (S) antibodies following four freeze/thaw cycles

iv) No analytical interference was observed for the detection of anti-SARS-CoV-2 (S) with infliximab or vedolizumab up to 10,000 mg/L and 60,000 mg/L, respectively, or with anti-drug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL, respectively (data not shown).

At entry to CLARITY IBD and at follow-up visits, all patients were tested for previous SARS-CoV-2 infection using the Roche Elecsys anti-SARS-CoV-2 (N) immunoassay. Because antibody responses are impaired following PCR-confirmed natural infection we set a threshold of 0·25 times the cut-off index (COI) at or above which patients were deemed to have had prior infection.[11] We defined a second threshold of 0·12 times the COI, below which patients were deemed to have no evidence of prior infection. Patients with a PCR test confirming SARS-CoV-2 infection at any time prior to vaccination were deemed to have evidence of past infection irrespective of any antibody test result.

Outcomes

Our primary outcome was anti-SARS-CoV-2 anti-spike (S) protein receptor-binding protein antibodies three to ten weeks after primary vaccination.

Secondary outcomes were:

(i) proportion of participants with seroconversion, defined by a threshold which has been associated with pseudoneutralisation in vitro.

(ii) antibody concentrations and seroconversion in patients with PCR or serological evidence of past SARS-CoV-2 infection at, or prior, to the post-vaccination serum sample.

(iii) antibody concentrations and seroconversion after two doses of vaccine.

187

188 *Statistical Analysis*

189 The sample size for CLARITY IBD was based on the number of participants required to demonstrate a
190 difference in the impact of infliximab and vedolizumab on seroprevalence and seroconversion
191 following SARS-CoV-2 infection, with an estimated background seroprevalence of 0·05. We
192 calculated that a sample of 6970 patients would provide 80% power to detect differences in the
193 seroprevalence of anti-SARS-CoV-2 antibodies in infliximab- compared with vedolizumab-treated
194 patients, whilst controlling for immunomodulator status at the 0·05 significance level. We stored and
195 then analysed all serum samples as soon as the Roche Elecsys anti-SARS-CoV-2 (S) immunoassay was
196 established in our laboratory.

197 Statistical analyses were undertaken in R 4·0·4 (R Foundation for Statistical Computing, Vienna,
198 Austria). All tests were two tailed and p-values <0·05 were considered significant. We included
199 patients with missing clinical data in analyses for which they had data and have specified the
200 denominator for each variable. Anti-S antibody concentrations are reported as geometric means and
201 standard deviations. Other continuous data are reported as median and interquartile range, and
202 discrete data as numbers and percentages, unless otherwise stated.

203 Univariable analyses, using t-tests of log-transformed anti-SARS-CoV-2 (S) antibody concentration
204 and Spearman's rank correlation coefficients, were used to identify demographic, disease, vaccine,
205 and treatment-related factors associated with the concentration of anti-SARS-CoV-2 (S) antibodies.
206 To test our primary outcome, we used multivariable linear regression models to identify factors
207 independently associated with log anti-SARS-CoV-2 (S) levels. A priori, we included age, ethnicity,
208 biologic medication, and immunomodulator use. No stepwise regression was performed. Results are
209 presented after exponentiation, so that the coefficients of the model correspond to the fold change
210 associated with each binary covariate. For age, a cut-off was chosen based on graphical inspection of

the relationship between age and anti-SARS-CoV-2 (S) antibody concentrations. We also report the proportions of patients who seroconverted following vaccination. Seroconversion was defined by an optimized cut-off of 15 U/mL, with a positive predictive value of 99·1%, based on the correlation between receptor-binding domain antibodies and the cPass SARS-CoV-2 surrogate virus neutralisation test (internal data, Roche Diagnostics GmbH, Germany).[15,16] We conducted sensitivity analyses to compare antibody responses stratified by participants with serological or PCR evidence of SARS-CoV-2 infection at any time prior to vaccination and in those who had received 2 doses of vaccine.

Role of the funding source

CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public health study, funded by the Royal Devon and Exeter NHS Foundation Trust, Hull University Teaching Hospital NHS Trust, and by unrestricted educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH (Switzerland), Celltrion Healthcare (South Korea) and Galapagos NV (Belgium). None of our funding bodies had any role in study design, data collection or analysis, writing, or decision to submit for publication.

Results

Between September 22nd 2020 and December 23rd 2020, 7226 patients were recruited to the CLARITY study from 92 UK hospitals.[11] For the primary immunogenicity analyses we included 865 infliximab- and 428 vedolizumab-treated participants without evidence of prior SARS-CoV-2 infection, who had received uninterrupted biologic therapy since recruitment and had an antibody test between 21 and 70 days after primary vaccination. Participant characteristics are shown in Table 1.

Anti-SARS-CoV-2 (S) antibody level following primary COVID-19 vaccine

Geometric mean [geometric SD] anti-SARS-CoV-2 (S) antibody concentrations were lower in patients treated with infliximab than vedolizumab, following both the BNT162b2 (6·0 U/mL [5·9] vs 28·8 U/mL [5·4] P<0·0001) and ChAdOx1 nCoV-19 (4·7 U/mL [4·9] vs 13·8 U/mL [5·9] P<0·0001) vaccines (Figure 1). Amongst infliximab-treated patients, the geometric mean [geometric SD] anti-SARS-CoV-2 (S) antibody concentrations were also lower in patients treated with a concomitant immunomodulator. Additional univariable analyses are shown in Table 2.

In our multivariable models, anti-SARS-CoV-2 antibody concentrations were lower in infliximab- compared with vedolizumab-treated patients in participants who received the BNT162b2 (fold change [FC] 0·29 [95% CI 0·21, 0·40], p<0·0001) and ChAdOx1 nCoV-19 [FC] 0·39 [95% CI 0·30, 0·51], p<0·0001) vaccines. Age ≥ 60 years, immunomodulator use, and current smoking were also independently associated with lower anti-SARS-CoV-2 antibody concentrations in participants who received either vaccine. Conversely, non-white ethnicity was associated with higher antibody concentrations following both vaccines (figure 2).

The 15-day rolling geometric mean of anti-SARS-CoV-2 antibody concentrations are shown in Figure 3. Three weeks after vaccination, we observed lower anti-SARS-CoV-2 (S) antibody concentrations in infliximab- compared to vedolizumab-treated patients following both vaccines. Sustained serological responses were observed in the vedolizumab- but not infliximab-treated patients.

Seroconversion following primary COVID-19 vaccination

The lowest rates of seroconversion were observed in participants treated with infliximab in combination with an immunomodulator with both the BNT162b2 (34.2%; 97/284) or ChAdOx1 nCoV-19 (27·4%; 93/340) vaccines. Highest rates of seroconversion were seen in patients treated with vedolizumab monotherapy who received the BNT162b2 (77·2%;142/184) or ChAdOx1 nCoV-19 (61·3%; 117/191) vaccines (Figure 4).

Antibody responses following prior SARS-CoV-2 infection and two COVID-19 vaccine doses

Amongst participants with SARS-CoV-2 infection prior to vaccination, geometric mean [SD] anti-SARS-CoV-2 (S) antibody concentrations were lower in infliximab- compared with vedolizumab-treated patients in those who received a single-dose of BNT162b2 (191 U/mL [12·5] vs 1865 U/mL [8·0] P<0·0001) and ChAdOx1 nCoV-19 (185 U/mL [9·3] vs 752 [12·5] P=0·046) vaccines. In both infliximab- and vedolizumab-treated patients, antibody concentrations following vaccination were higher than those observed in patients without prior infection (Figure 5). Overall, across both vaccines, 82% (76/93) patients treated with infliximab and 97% (33/34) patients treated with vedolizumab seroconverted (p=0·041).

Antibody responses were assessed in 27 patients following two doses of the BNT162b2 vaccine without serological evidence of prior infection (Figure 5). In both infliximab- and vedolizumab-treated patients, antibody levels and seroconversion rates were higher after two doses than after a primary vaccine without prior infection (geometric means infliximab 158 U/mL [7·0] vs 6·0 U/mL [5·9], p<0·0001; vedolizumab 562 U/mL [11·5] vs 28·8 U/mL [5·4], p = 0·018). After second-vaccine doses 85% (17/20) infliximab- and 86% (6/7) vedolizumab-treated patients seroconverted (p=0·68).

Discussion

Key results

We have shown that anti-SARS-CoV-2 spike antibody levels and rates of seroconversion are lower following vaccination with a single-dose of either BNT162b2 or ChAdOx1 nCoV-19 vaccines in patients with IBD treated with infliximab than vedolizumab. Combination therapy with an immunomodulator further attenuated immunogenicity to both vaccines in infliximab-treated patients. Reassuringly, however, a second exposure to antigen, either by vaccination after infection, or a second dose of vaccine led to seroconversion in most patients.

Direct comparisons between our data and the antibody responses reported in the vaccine registration trials are limited by differences in the assays used to define immunogenicity and the adoption of different thresholds to define seroconversion. No adequately powered studies have reported the effect of anti-TNF drugs on vaccine responses.[17] Our findings are similar, however, to recent reports of the immunogenicity of the BNT162b2 and mRNA-1273 vaccines in transplant recipients and in patients with malignancy treated with anti-metabolite immunosuppression, conventional chemotherapy or immune checkpoint inhibitors.[18,19] The authors showed fewer patients treated with potent immunosuppressants seroconverted than healthy controls. Importantly, as we have also shown here, second vaccine doses led to seroconversion in the cancer cohort. However, even after two antigen exposures, a small subset of patients (18% [20/113] infliximab-treated patients and 5% [2/41] vedolizumab-treated patients) in our study failed to mount an antibody response. To identify this group, and because the sustainability of antibody responses overall is unknown, serial measurement of antibody responses are indicated.

Urgent research is needed to understand the factors linked to non-response and how to potentiate long-term immunogenicity in this group. Strategies to be tested include the manipulation of timing

of second vaccinations of second vaccinations, booster doses, the use of adjuvants and/or switching between vaccines with different mechanisms of action. Moreover, from the public health standpoint, recent case reports have shown that potent immunosuppression leads to chronic nasopharyngeal carriage and evolution of new SARS-CoV-2 variants.[20,21] Whether this occurs in patients treated with anti-TNF therapy with impaired antibody response is an important conceptual concern.

Our data has other important findings relating to SARS-CoV-2 vaccine responses. We have demonstrated that antibody responses to SARS-CoV-2 vaccines are reduced in older individuals and current smokers. Smoking has also been associated with lower antibody responses to hepatitis B vaccination and faster decay of antibodies after vaccination with live attenuated and trivalent influenza vaccines.[22,23] We have also demonstrated higher antibody responses to both the BNT162b2 and ChAdOx1 nCoV-19 vaccines in non-white participants. This might be explained by differences in genetics,[24] gut microbiota,[25] nutrition,[26] and priming of the immune system by prior exposure to SARS-CoV-2 not detected by our pre-vaccination antibody test. Lower antibody concentrations were also observed in patients with Crohn's disease when compared to patients with ulcerative colitis or IBD-unclassified. Despite evidence of defective mucosal immunity, previous vaccine studies involving patients with Crohn's disease or ulcerative colitis have not shown attenuated antibody responses to vaccination in the absence of concomitant immunomodulator or biologic therapy.[6,7]

The cytokine TNF shapes multiple aspects of host immune responses, including T-cell dependent antibody production. Genetic ablation of TNF results in disruption of B-cell follicles in germinal centres with defective induction of antigen-induced antibody production.[27,28] These biological properties may in part explain why TNF blockade is clinically beneficial in IMIDs, but also explain the increased risk of serious and opportunistic infections and impaired response to other vaccines.

Whilst our data are biologically plausible, we acknowledge the following limitations of our study. We have used an electrochemiluminescence immunoassay to measure antibody concentrations rather than using a neutralising assay. Although neutralisation assays are considered more biologically relevant, it is now established that anti receptor-binding domain antibodies, which target the spike protein component that engages host cells through ligation of angiotensin-converting enzyme 2, closely correlate with neutralisation assays.[29,30] Second, we only assessed humoral responses to infection, and it is likely that protective immunity additionally requires induction of memory T cell responses. Finally, we investigated one anti-TNF drug, infliximab, only. However, we suspect that our key findings will apply to other anti-TNF biologics used to treat IMIDs, including adalimumab, certolizumab, golimumab, and etanercept. Further observational data will be required to elucidate the impact of other classes of therapies for IMIDs on SARS-CoV-2 vaccine immunogenicity.

Our findings have important implications for patients treated with anti-TNF drugs particularly those also treated with an immunomodulator. Poor antibody responses to a single-dose of vaccine unnecessarily exposes infliximab-treated patients to SARS-CoV-2 infection. However, because we observed higher rates of seroconversion in patients with two exposures to SARS-CoV-2 antigen, even in the presence of TNF blockade, these patients should be prioritised for optimally timed second doses. Until patients receive a second dose of vaccine they should consider that they are not protected from SARS-CoV-2 infection and continue to practice enhanced physical distancing and shielding if appropriate.

Conclusion

Infliximab is associated with attenuated immunogenicity to a single-dose of the BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with inflammatory bowel disease. Immunomodulators further blunted immunogenicity rates to both vaccines. Reassuringly,

vaccination after infection, or a second dose of vaccine led to seroconversion in most patients. Delayed second dosing should be avoided in patients treated with infliximab.

Table 1: Baseline characteristics of participants who had anti-SARS-CoV-2 spike antibodies measured 3 to 10 weeks following primary vaccination against SARS-CoV-2

Variable		Infliximab	Vedolizumab	Overall	p
Vaccine	BNT162b2	44·7% (387/865)	47·2% (202/428)	45·6% (589/1293)	0·41
	ChAdOx1 nCoV-19	55·3% (478/865)	52·8% (226/428)	54·4% (704/1293)	
Age (years)		41·4 (31·5 - 54·8)	49·6 (37·1 - 63·8)	43·8 (32·8 - 57·6)	<0·0001
Sex	Female	50·3% (434/863)	47·1% (200/425)	49·2% (634/1288)	0·19
	Male	49·7% (429/863)	52·7% (224/425)	50·7% (653/1288)	
	Intersex	0·0% (0/863)	0·0% (0/425)	0·0% (0/1288)	
	Prefer not to say	0·0% (0/863)	0·2% (1/425)	0·1% (1/1288)	
Ethnicity	White	91·8% (791/862)	89·9% (381/424)	91·1% (1172/1286)	0·62
	Asian	5·3% (46/862)	7·5% (32/424)	6·1% (78/1286)	
	Mixed	1·9% (16/862)	1·9% (8/424)	1·9% (24/1286)	
	Black	0·7% (6/862)	0·5% (2/424)	0·6% (8/1286)	
	Other	0·3% (3/862)	0·2% (1/424)	0·3% (4/1286)	
Diagnosis	Crohn's disease	65·4% (566/865)	40·7% (174/428)	57·2% (740/1293)	0·00050
	Ulcerative colitis or IBD-unclassified	34·6% (299/865)	59·3% (254/428)	42.8% (553/1293)	
Duration of IBD (years)		8·0 (4·0 - 16·0)	10·0 (5·0 - 17·8)	9·0 (4·0 - 16·0)	0·0040
Age at IBD diagnosis (years)		28·8 (21·6 - 41·8)	34·0 (23·3 - 47·6)	30·3 (21·9 - 43·7)	<0·0001
Immunomodulator		61·6% (533/865)	22·0% (94/427)	48·5% (627/1292)	<0·0001
5-ASA		23·0% (199/865)	31·6% (135/427)	25·9% (334/1292)	0·0012
Steroids		3·0% (26/865)	8·4% (36/427)	4·8% (62/1292)	<0·0001
BMI (kg/m^2)		25·9 (22·8 - 30·6)	26·1 (23·1 - 30·1)	26·0 (22·9 - 30·4)	0·75
Heart disease		3·6% (31/865)	6·5% (28/428)	4·6% (59/1293)	0·023
Diabetes		3·8% (33/865)	7·5% (32/428)	5·0% (65/1293)	0·0065
Lung disease		13·5% (117/865)	18·2% (78/428)	15·1% (195/1293)	0·032
Kidney disease		1·2% (10/865)	2·1% (9/428)	1·5% (19/1293)	0·22
Cancer		0·5% (4/865)	2·1% (9/428)	1·0% (13/1293)	0·013
Smoker	Yes	9·7% (84/862)	5·4% (23/425)	8·3% (107/1287)	0·0010
	Not currently	32·0% (276/862)	41·6% (177/425)	35·2% (453/1287)	
	Never	58·2% (502/862)	52·9% (225/425)	56·5% (727/1287)	
Exposure to documented cases of COVID-19		9·4% (81/862)	8·7% (37/425)	9·2% (118/1287)	0·76
Income deprivation score		0·086 (0·052 - 0·151)	0·084 (0·054 - 0·141)	0·086 (0·052 - 0·147)	0·94
Active disease (PRO2)		4·9% (41/831)	11·4% (46/405)	7·0% (87/1236)	<0·0001

Abbreviations: IBD = inflammatory bowel disease; 5-ASA = 5-aminosalicylic acid; BMI = Body Mass Index; PRO2 = IBD disease activity. Values presented are median (interquartile range) or percentage (numerator/denominator). P values represent the results of a Mann Whitney U, Kruskal Wallis or Fisher's exact test.

Table 2: Univariable associations with anti-SARS-CoV-2 spike antibodies, stratified by vaccine type

Variable		BNT162b2		ChAdOx1 nCoV-19	
		Value	p	Value	p
Biologic treatment	Infliximab	6·0 (5·9)	<0·0001	4·7 (4·9)	<0·0001
	Vedolizumab	28·8 (5·4)		13·8 (5·9)	
Immunomodulator in infliximab-treated participants	No	9·7 (4·7)	<0·0001	5·7 (5·1)	0·045
	Yes	4·4 (6·3)		4·2 (4·7)	
Immunomodulator in vedolizumab-treated participants	No	32·4 (5·2)	0·052	15·6 (6·0)	0·082
	Yes	16·7 (6·3)		10·0 (5·5)	
Age (years)		rho = -0·22	<0·0001	rho = -0·15	<0·0001
Sex	Female	9·4 (7·0)	0·092	6·6 (5·5)	0·83
	Male	10·9 (6·3)		6·8 (5·7)	
Ethnicity	White	9·4 (6·6)	0·037	6·2 (5·6)	0·0051
	Asian	20·9 (7·3)		16·1 (5·2)	
	Mixed	25·7 (6·7)		13·7 (5·3)	
	Black	12·5 (1·6)		19·4 (2·2)	
	Other	22·9 (3·7)		5·7 (3·1)	
Diagnosis	Crohn's disease	7·3 (6·4)	<0·0001	5·6 (5·6)	0·0014
	Ulcerative colitis or IBD-unclassified	15·6 (6·5)		8·5 (5·5)	
Duration of IBD (years)		rho = -0·16	<0·0001	rho = -0·12	0·0013
Age at IBD diagnosis (years)		rho = -0·13	0·0021	rho = -0·04	0·25
5-ASA	No	9·8 (6·6)	0·40	6·7 (5·5)	0·93
	Yes	11·5 (7·1)		6·6 (5·9)	
Steroids	No	10·2 (6·7)	0·90	6·8 (5·5)	0·12
	Yes	10·7 (7·3)		4·1 (6·7)	
BMI (kg/m^2)		rho = -0·08	0·068	rho = -0·01	0·81
Heart disease	No	10·3 (6·7)	0·65	6·9 (5·6)	0·010
	Yes	8·7 (7·0)		2·8 (5·2)	
Diabetes	No	10·7 (6·7)	0·0028	6·8 (5·6)	0·066
	Yes	4·1 (4·6)		4·0 (5·2)	
Lung disease	No	10·1 (6·9)	0·70	6·9 (5·5)	0·31
	Yes	10·9 (5·7)		5·7 (6·1)	
Kidney disease	No	10·2 (6·6)	0·60	6·7 (5·5)	0·66
	Yes	15·6 (10·4)		4·7 (12·4)	
Cancer	No	10·4 (6·6)	0·13	6·7 (5·6)	0·069
	Yes	2·0 (9·2)		2·3 (3·6)	
Smoking	Yes	4·7 (7·1)	0·0077	3·4 (4·8)	0·00077
	Not currently	9·4 (6·6)		6·1 (5·4)	
	Never	11·8 (6·5)		8·0 (5·7)	
Exposure to documented cases of COVID-19	No	10·3 (6·7)	0·87	6·6 (5·5)	0·53
	Yes	9·8 (6·8)		7·8 (6·1)	
Income deprivation score		rho = 0·01	0·75	rho = 0·02	0·65
Active disease (PRO2)	No	10·1 (6·5)	0·32	6·6 (5·4)	0·51
	Yes	14·0 (7·6)		8·1 (7·0)	

Abbreviations: IBD = inflammatory bowel disease; 5-ASA = 5-aminosalicylic acid; VAS = visual analogue scale. Values presented are geometric mean antibody concentration (geometric standard deviation) or Spearman's rho. P values represent the results of an unpaired t test or test of Spearman's rho.

Figure Captions

Figure 1: Anti-SARS-CoV-2 spike antibody concentration stratified by biologic therapy (infliximab vs vedolizumab) and type of vaccine. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric standard deviation either side of the geometric mean. The threshold shown of 15 U/mL is the one used to determine seroconversion.

Figure 2: Exponentiated coefficients of linear regression models of log(anti-SARS-CoV-2 spike antibody concentration). The resultant values represent the fold change of antibody concentration associated with each variable. Each vaccine was modelled separately, and then a further model was created using all of the available data.

Figure 3: Rolling geometric mean antibody concentration over time stratified by biologic therapy (infliximab vs vedolizumab) and vaccine. Geometric means are calculated using a rolling 15 day window (i.e. 7 days either side of the day indicated). The shaded areas represent the 95% confidence intervals of the geometric means. Overall, data from 2126 participants (1427 on infliximab and 699 on vedolizumab) are included in this graph between 1 and 63 days post vaccination.

Figure 4: Percentages of participants with seroconversion defined by an anti-SARS-CoV-2 spike antibody concentration ≥ 15 U/mL, stratified by vaccine, biologic and immunomodulator use. Error bars represent the 95% confidence interval of the percentages. **Abbreviations**: IMM = immunomodulator

Figure 5: Anti-SARS-CoV-2 spike antibody concentration stratified by biologic therapy (infliximab vs vedolizumab), prior infection, number of doses and type of vaccine. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric standard deviation either side of the geometric mean. The threshold shown of 15 U/mL is the one used to determine seroconversion.

Contributions

NAK, JRG, CB, SS, NP, TA participated in the conception and design of this study. CB was the project manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analyses and central laboratory aspects of the project. NAK, SL, JRG, NC, BH, DC, JRF, AF, PMI, NK, KBK, CAL, JM, SJM, RCGP, TR, PJS, AMV, TJM, SS, CWL, NP, TA were involved in the acquisition, analysis, or interpretation of data. Data analysis was done by NAK. Drafting of the manuscript was done by NAK, SL, JRG, NC, RN, DC, RCGP, SS, CWL, NP, TA. SS, NP and TA obtained the funding for the study. All the authors contributed to the critical review and final approval of the manuscript. NAK and TA have verified the underlying data.

Declarations of interest

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456

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Patient involvement

We conducted an electronic survey to gauge the opinion of patients with IBD on the patient questionnaires to be delivered as part of the CLARITY IBD study. We surveyed 250 patients across 74 hospitals. All our proposed questions for study inclusion were rated as important or very important by at least 83% of participants. The Exeter IBD Patient Panel refined the questions included in the study questionnaire, reviewed the study protocol, supported the writing of the patient information sheets, and participated in testing of the electronic consent form and patient questionnaire. A member of the Exeter IBD Patient Panel sits on the study management committee, ensuring patient involvement in all aspects of study delivery, data analysis and dissemination of findings.

Data sharing

The study protocol including the statistical analysis plan is available at www.clarityibd.org. Individual participant de-identified data that underlie the results reported in this article will be available immediately after publication for a period of 5 years. The data will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be directed to tariq.ahmad1@nhs.net. To gain access data requestors will need to sign a data access agreement.

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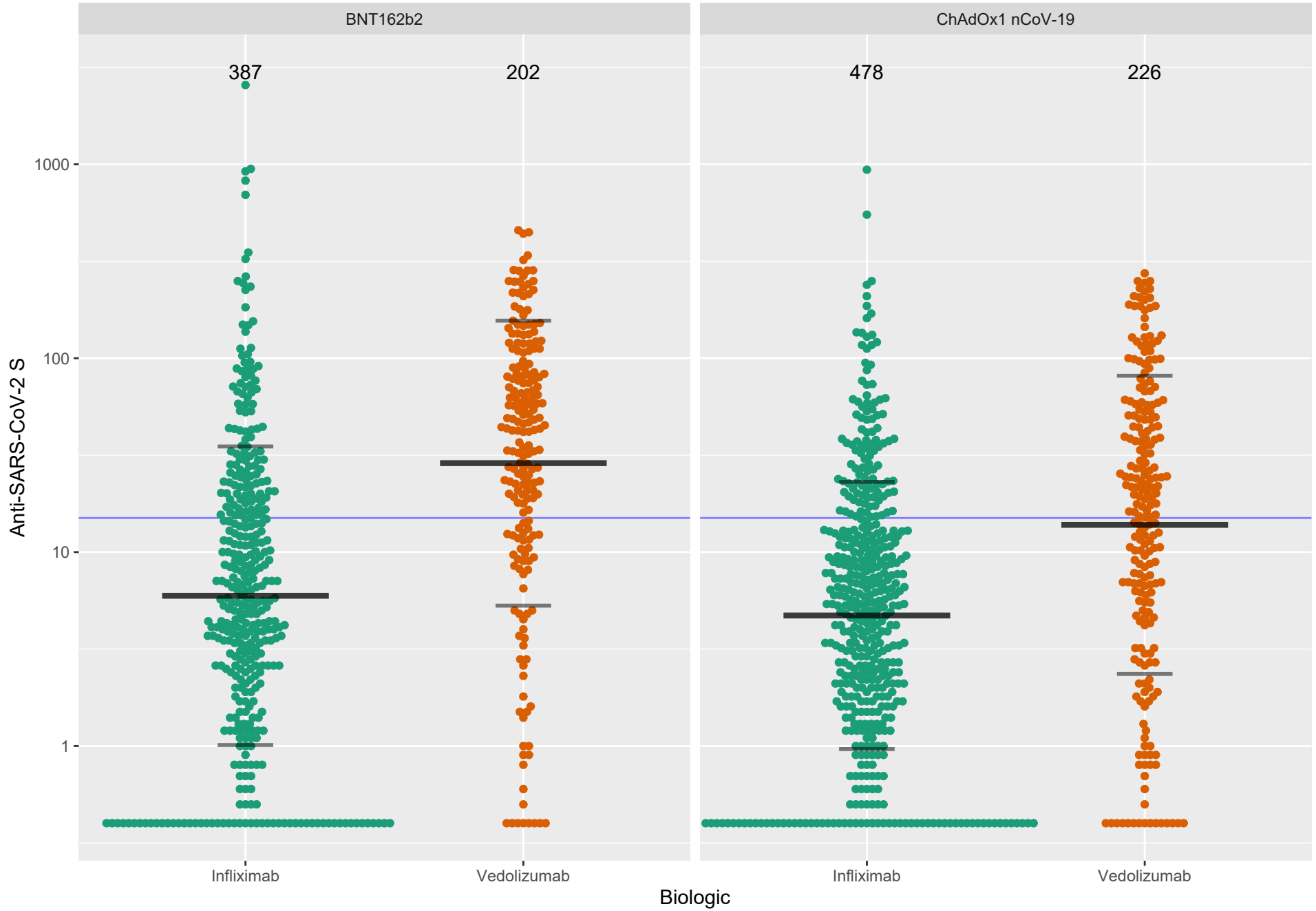

BNT162b2
ChAdOx1 nCoV-19
387
202
478
226
1000
100
10
1
Anti-SARS-CoV-2 S
Infliximab
Vedolizumab
Infliximab
Vedolizumab
Biologic

BNT162b2

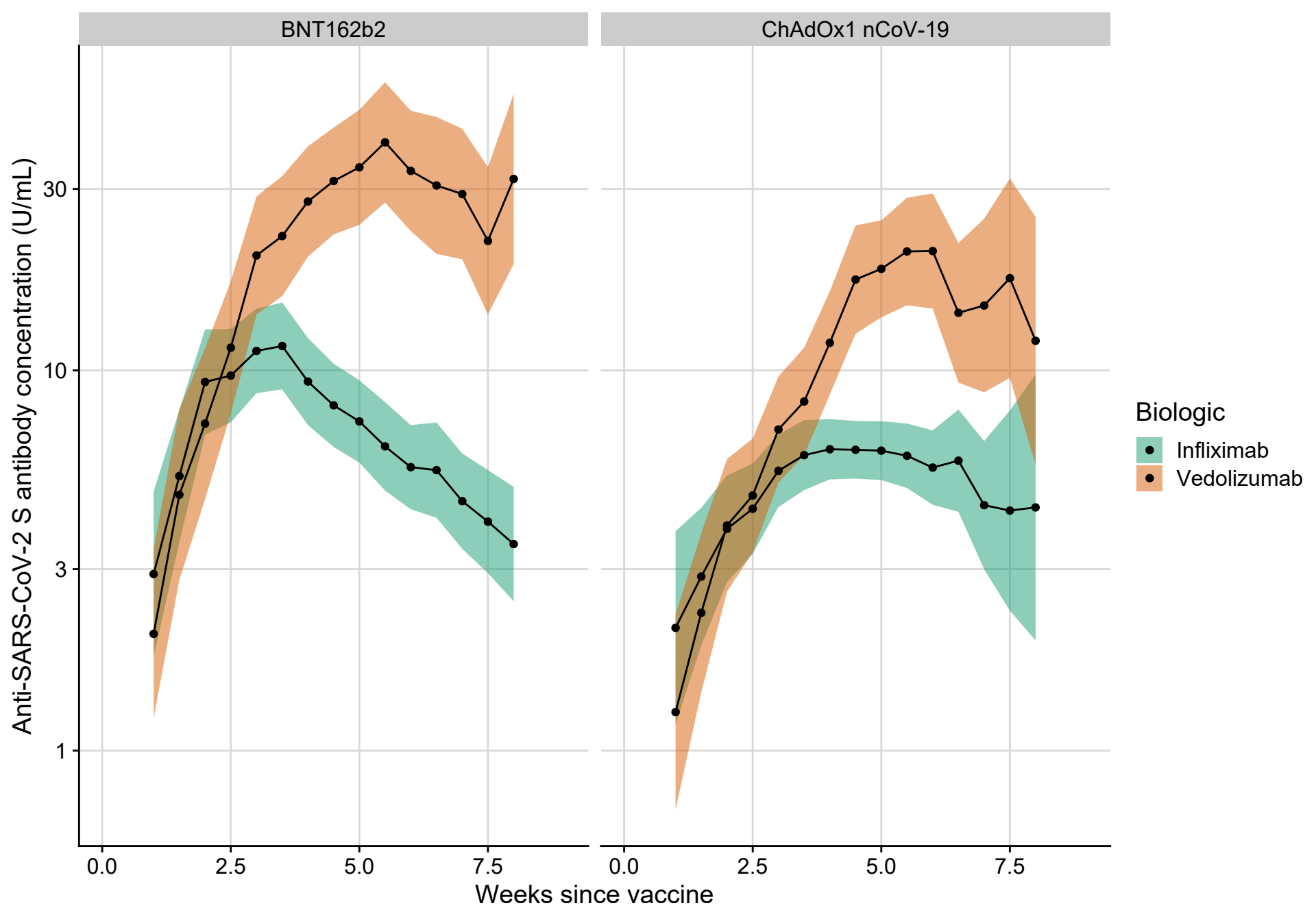
Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	386/587	0·29 (0·21, 0·40)	<0·0001
Immunomodulator	269/587	0·41 (0·31, 0·55)	<0·0001
Crohn's disease (vs UC or IBDU)	327/587	0·75 (0·57, 1·00)	0·046
Age ≥ 60	113/587	0·34 (0·24, 0·47)	<0·0001
Non-white ethnicity	61/587	1·81 (1·16, 2·81)	0·0085
Current smoker	44/587	0·52 (0·31, 0·86)	0·011

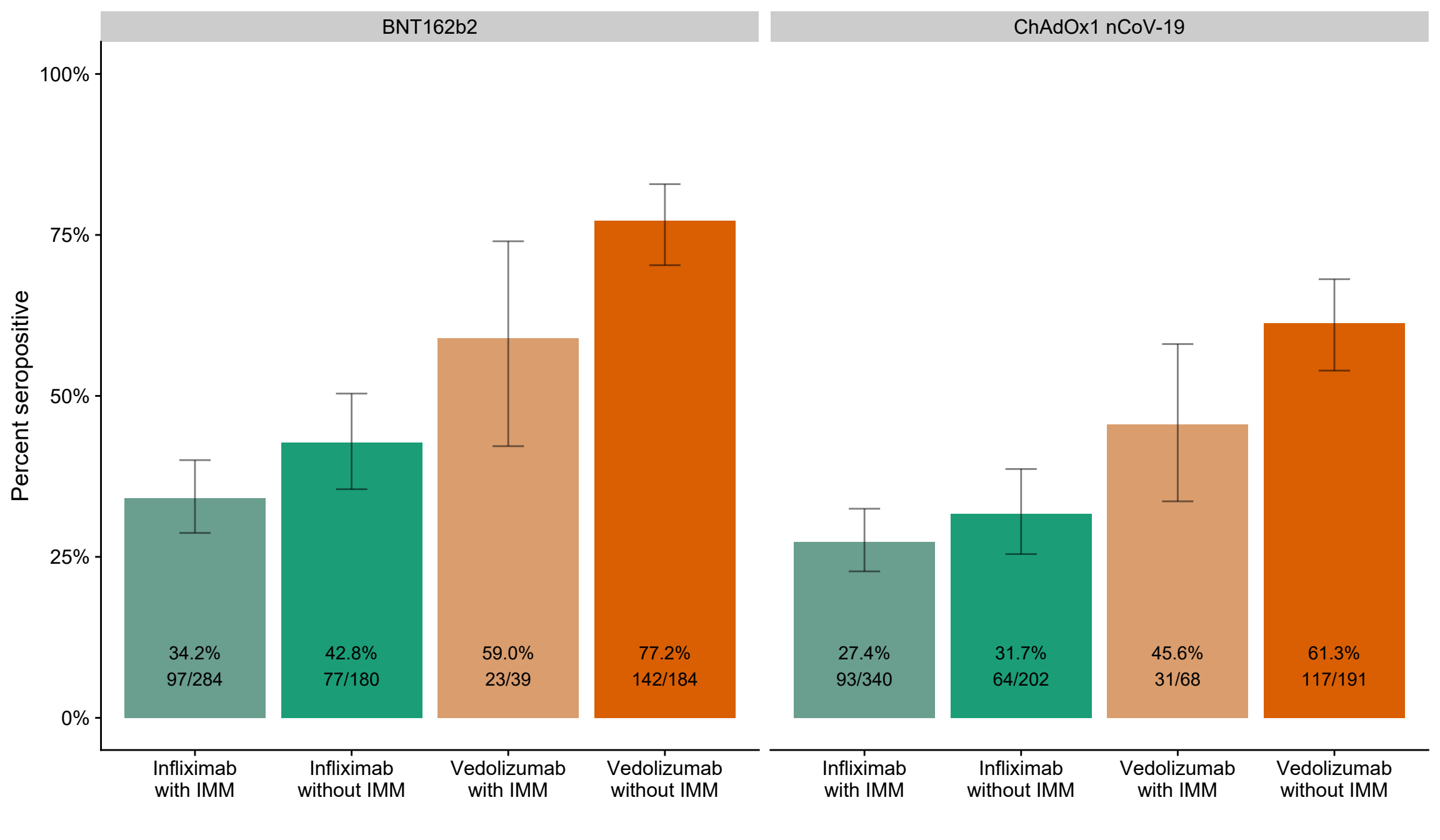
ChAdOx1 nCoV-19

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	475/697	0·39 (0·30, 0·51)	<0·0001
Immunomodulator	355/697	0·65 (0·50, 0·84)	0·00085
Crohn's disease (vs UC or IBDU)	409/697	0·85 (0·66, 1·09)	0·20
Age ≥ 60	162/697	0·48 (0·36, 0·65)	<0·0001
Non-white ethnicity	55/697	2·04 (1·31, 3·17)	0·0017
Current smoker	63/697	0·55 (0·36, 0·84)	0·0059

All

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	861/1284	0·34 (0·27, 0·41)	<0·0001
Immunomodulator	624/1284	0·51 (0·42, 0·62)	<0·0001
Crohn's disease (vs UC or IBDU)	736/1284	0·79 (0·66, 0·96)	0·015
Age ≥ 60	275/1284	0·40 (0·32, 0·50)	<0·0001
Non-white ethnicity	116/1284	1·95 (1·43, 2·67)	<0·0001
Current smoker	107/1284	0·53 (0·39, 0·74)	0·00016


BNT162b2
ChAdOx1 nCoV-19
Anti-SARS-CoV-2 S antibody concentration (U/mL)
30
10
3
1
0.0
2.5
5.0
7.5
Weeks since vaccine
Biologic
Infliximab
Vedolizumab


BNT162b2
ChAdOx1 nCoV-19
Percent seropositive
100%
75%
50%
25%
0%
34.2%
97/284
42.8%
77/180
59.0%
23/39
77.2%
142/184
27.4%
93/340
31.7%
64/202
45.6%
31/68
61.3%
117/191
Infliximab with IMM
Infliximab without IMM
Vedolizumab with IMM
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Infliximab with IMM
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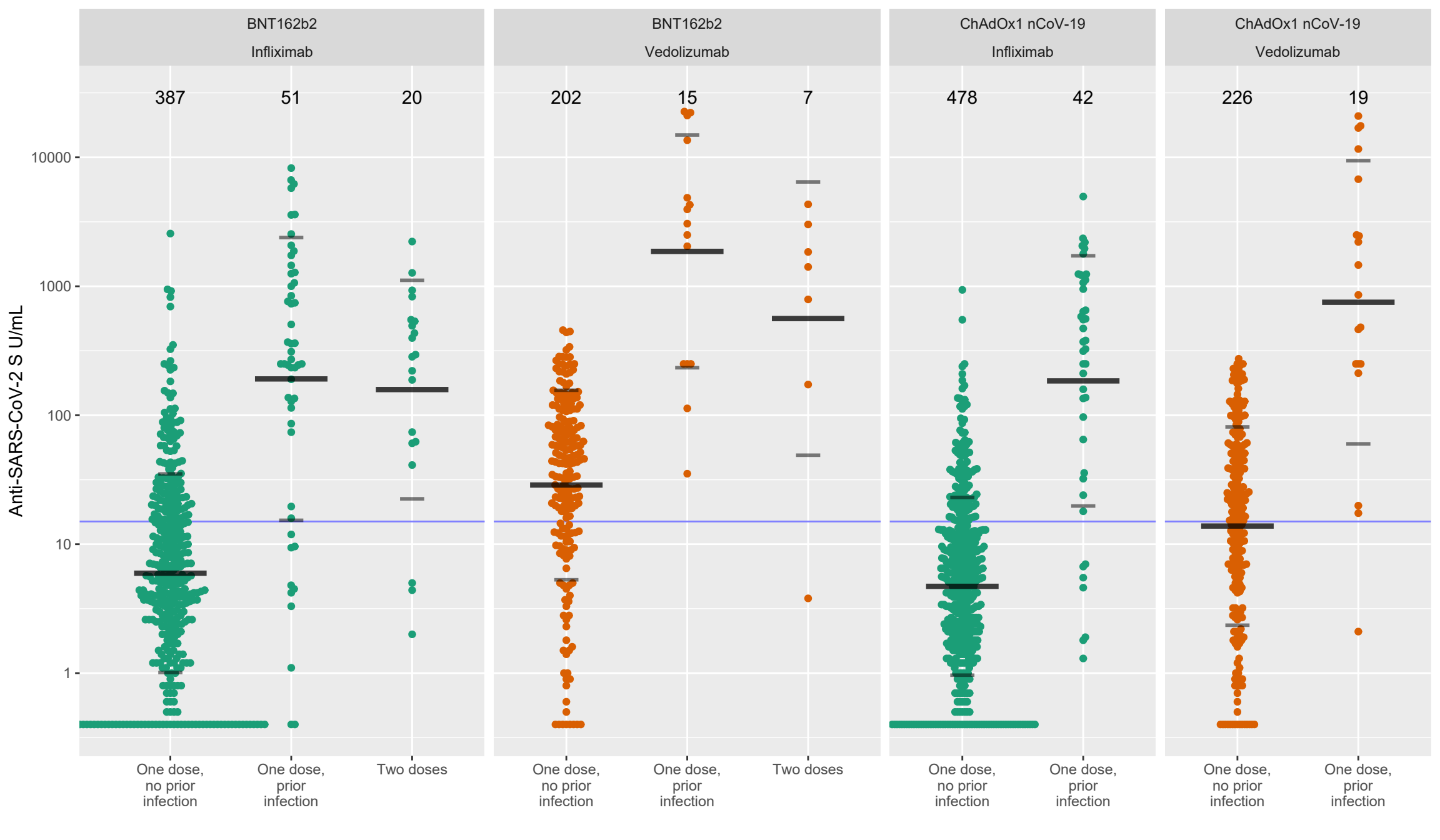
Vedolizumab with IMM
Vedolizumab without IMM


BNT162b2
Infliximab
BNT162b2
Vedolizumab
ChAdOx1 nCoV-19
Infliximab
ChAdOx1 nCoV-19
Vedolizumab
387
51
20
202
15
7
478
42
226
19
Anti-SARS-CoV-2 S U/mL
10000
1000
100
10
1
One dose, no prior infection
One dose, prior infection
Two doses