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).

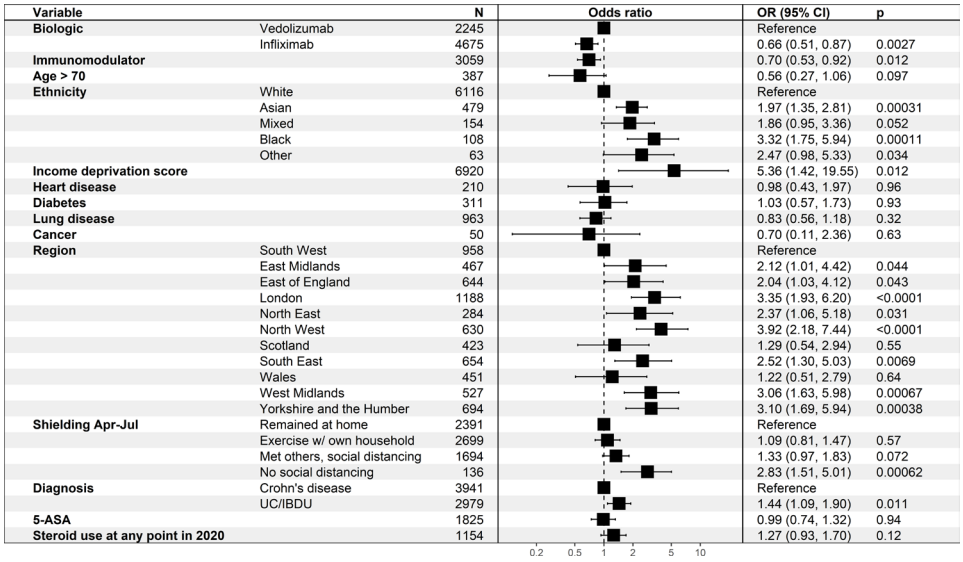

Figure 1 Forest plot showing the coefficients from a multivariable logistic regression model of associations with a positive anti-SARS-CoV-2 antibody. abbreviations: 5-ASA, 5-aminosalicylates; IBDU, IBD unclassified.

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

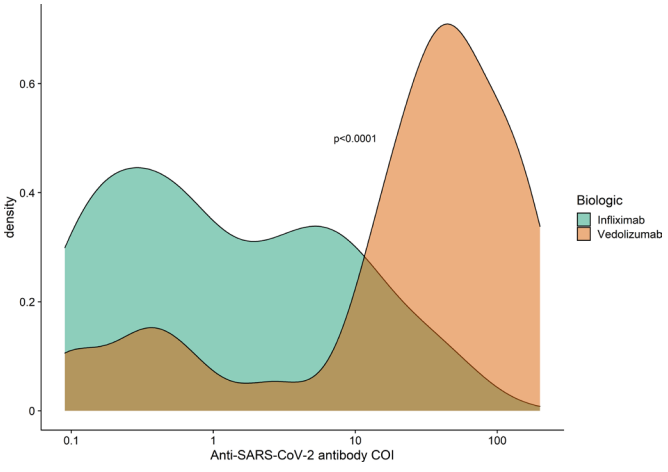

Figure 2 Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy among participants who had a positive PCR to anti-SARS-CoV-2 at least 2 weeks prior to their serology sample. COI, cut-off index.

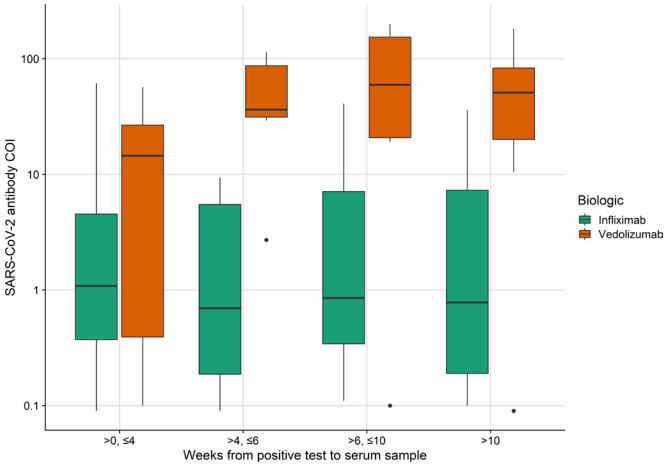

Figure 3 Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy and time since prior positive PCR test. COI, cut-off index.

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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CWL reports personal fees from Abbvie, personal fees from Janssen, personal fees from Pfizer, personal fees from Takeda, grants from Gilead, personal fees from Gilead, personal fees from Galapagos, personal fees from Iterative Scopes, personal fees from Trellus Health, personal fees from Celltion, personal fees from Ferring, personal fees from BMS, during the conduct of the study. SS reports grants from Takeda, Abbvie, AMGEN, Tillots Pharma, personal fees from Jaansen, Takeda, Galapagos, Celltrion, Falk Pharma, Tillots pharma, Cellgene, Pfizer, Phamrmacocosmos, outside the submitted work. 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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.

Provenance and peer review Not commissioned; externally peer reviewed.

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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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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West Hertfordshire Hospitals NHS Trust	Rakesh	Chaudhary
	Melanie	Claridge
	Chiara	Ellis
	Cheryl	Kemp
	Ogwa	Tobi
West Middlesex University Hospital	Emma	Johnston
	Metod	Oblak
	Richard	Appleby
West Suffolk NHS Foundation Trust	Marium	Asghar
Western General Hospital	Charlie	Lees
	Debbie	Alexander
	Kate	Covil
	Lauranne	Derikx

Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

	Sryros	Siakavellas
	Helen	Baxter
	Scott	Robertson
Withybush General Hospital	Kerrie	Johns
	Rachel	Hughes
	Janet	Phipps
	Abigail	Taylor
Yeovil District Hospital NHS Foundation Trust	Katie	Smith
	Linda	Howard
	Dianne	Wood
York Teaching Hospital NHS Foundation Trust	Ajay	Muddu
	Laura	Barman
	Janine	Mallinson
Ysbyty Gwynedd	Iona	Thomas
	Kelly	Andrews
	Caroline	Mulvaney Jones
	Julia	Roberts

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Supplementary Table S2: Baseline characteristics stratified by baseline characteristics after propensity matching by inflammatory bowel disease (IBD) subtype, immunomodulator use, cancer, age, active IBD and comorbidities

Variable		Positive	Negative	p
Positive serology to SARS-CoV-2	Positive	3.9% (67/1704)	6.2% (105/1707)	0.0037
	Negative	96.1% (1637/1704)	93.8% (1602/1707)	
Age (years)		41.7 (31.1 - 55.6)	41.4 (31.1 - 56.1)	0.91
Sex	Female	46.4% (791/1704)	50.2% (857/1707)	0.023
	Male	53.6% (913/1704)	49.7% (848/1707)	
	Intersex	0.0% (0/1704)	0.1% (1/1707)	
	Prefer not to say	0.0% (0/1704)	0.1% (1/1707)	
Ethnicity	White	88.6% (1510/1704)	88.1% (1504/1707)	0.99
	Asian	7.1% (121/1704)	7.4% (127/1707)	
	Mixed	2.3% (40/1704)	2.3% (39/1707)	
	Black	1.2% (21/1704)	1.3% (23/1707)	
	Other	0.7% (12/1704)	0.8% (14/1707)	
Diagnosis	Crohn's disease	43.4% (739/1704)	43.4% (740/1707)	1.0
	Ulcerative colitis	53.2% (907/1704)	53.3% (909/1707)	
	IBD-unclassified	3.4% (58/1704)	3.4% (58/1707)	
Duration of IBD (years)		8.0 (3.0 - 15.0)	9.0 (4.0 - 16.0)	0.0010
Age at IBD diagnosis (years)		29.8 (21.5 - 42.8)	29.0 (20.8 - 41.8)	0.29
Immunomodulators at recruitment		23.4% (399/1704)	23.5% (401/1707)	0.97
5-ASA at recruitment		32.4% (552/1704)	33.4% (570/1707)	0.54
Steroids in 2020		19.5% (333/1704)	21.7% (370/1707)	0.13
BMI		25.2 (22.1 - 28.6)	24.8 (21.9 - 28.4)	0.52
Heart disease		3.6% (61/1704)	3.3% (57/1707)	0.71
Diabetes		5.3% (91/1704)	5.7% (97/1707)	0.71
Lung disease		16.0% (272/1704)	16.0% (273/1707)	1.0
Kidney disease		1.2% (20/1704)	1.8% (30/1707)	0.20
Cancer		0.5% (8/1704)	0.5% (8/1707)	1.0
Smoker	Yes	11.5% (196/1704)	10.3% (175/1707)	0.48
	Not currently	32.2% (549/1704)	32.3% (551/1707)	
	Never	56.3% (959/1704)	57.5% (981/1707)	
Meets clinical criteria for suspected or probable COVID-19		9.4% (161/1704)	9.0% (154/1707)	0.68
Tested with PCR for SARS-CoV-2		37.9% (645/1704)	38.4% (656/1707)	0.75
Positive PCR for SARS-CoV-2		5.6% (37/645)	4.8% (31/656)	0.46
Positive PCR for SARS-CoV-2 at least 2 weeks prior to serum sample		5.6% (33/586)	4.8% (29/610)	0.52
Hospitalised for confirmed COVID-19		0.4% (6/1704)	0.2% (4/1707)	0.55
Shielding behaviour Apr-Jul	I remained in my house or garden	32.3% (550/1704)	34.2% (583/1706)	0.20
	I only left the house for exercise on my own or with members of my household	38.8% (661/1704)	40.2% (686/1706)	
	I encountered people from outside of my household but *maintained social distancing*	26.6% (454/1704)	23.6% (403/1706)	
	I encountered people from outside of my household but *did not maintain social distancing*	2.3% (39/1704)	2.0% (34/1706)	
Exposure to documented cases of COVID-19		11.5% (196/1703)	11.0% (188/1707)	0.66
PHQ8		4.0 (1.0 - 9.0)	5.0 (1.0 - 9.0)	0.035
GAD7		3.0 (0.0 - 7.0)	3.0 (0.0 - 7.0)	0.17
Income deprivation score		0.1 (0.1 - 0.2)	0.1 (0.1 - 0.2)	0.049
Active disease (PRO2)		10.9% (185/1704)	10.4% (178/1707)	0.70
IBD Control 8		13.0 (9.0 - 16.0)	13.0 (9.0 - 16.0)	0.40
IBD Control VAS		79.0 (63.8 - 92.0)	79.0 (62.0 - 92.0)	0.21

Values shown are medians (interquartile range) and percentages (proportions) as appropriate.

Abbreviations: IBD = inflammatory bowel disease, 5-ASA = aminosalicylates, BMI = Body Mass Index, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, PRO2 = Patient Reported Outcome, VAS = Visual Analogue Scale

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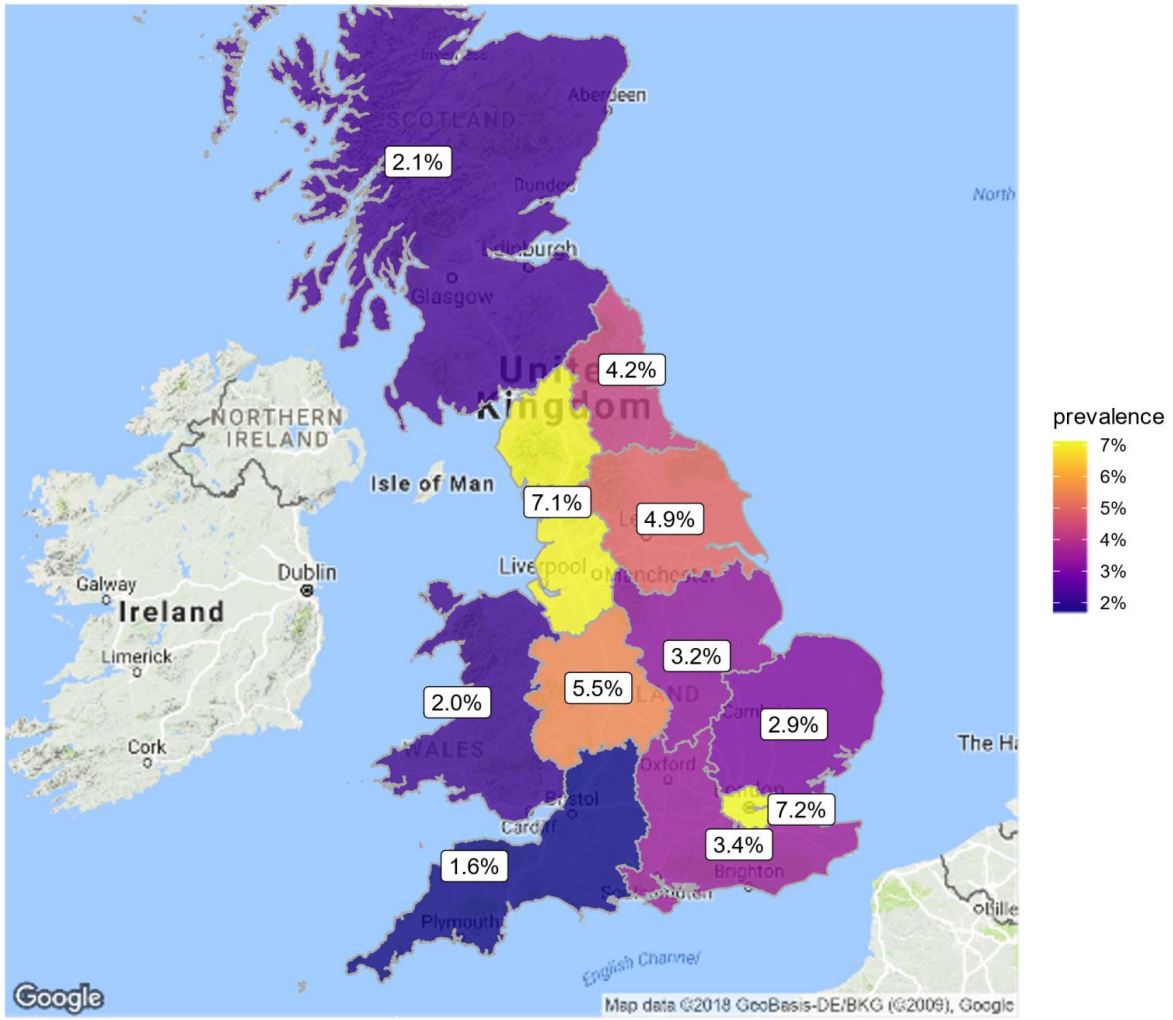
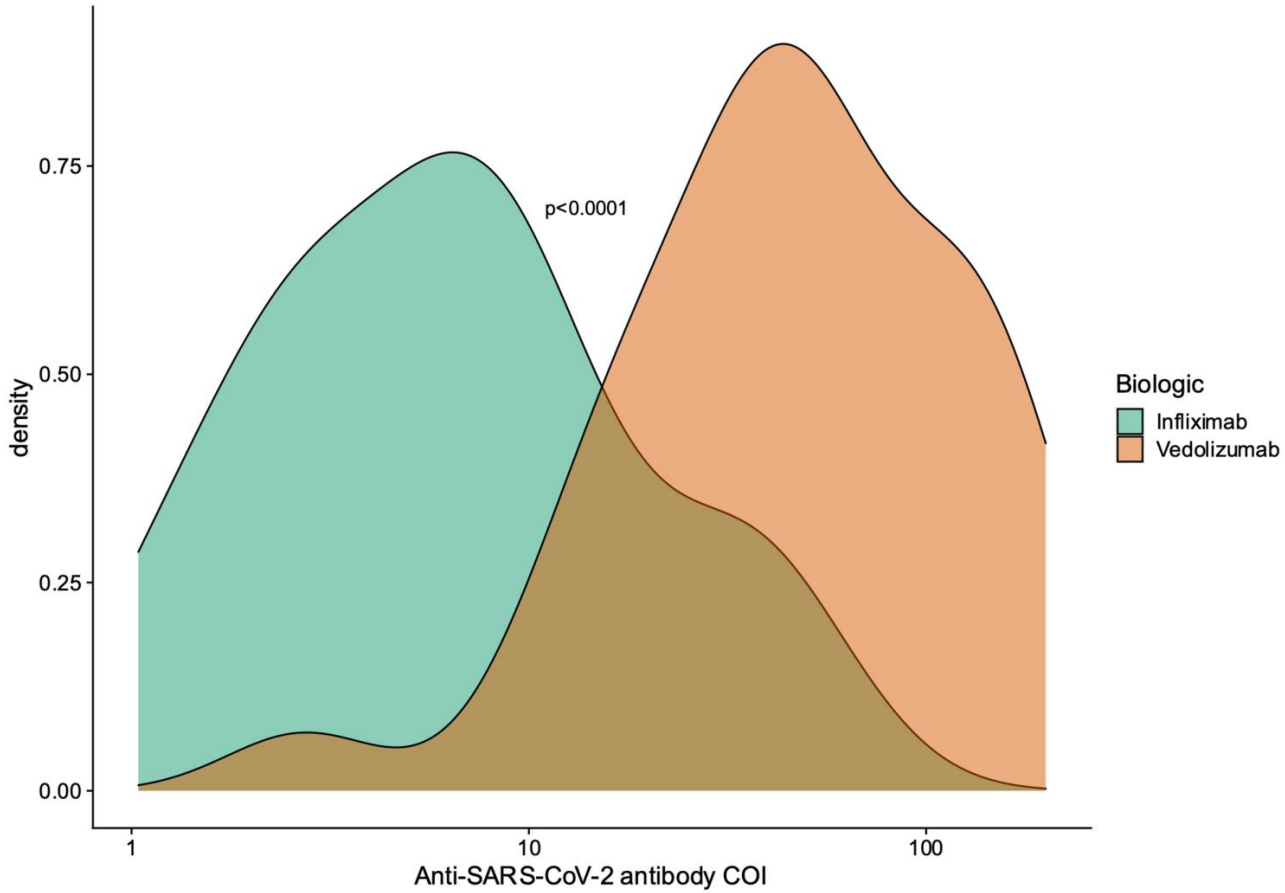
Supplementary Figure S1: Regional seroprevalence of SARS-CoV-2 by NUTS1 region



Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, NUTS = Nomenclature of territorial units for statistic

Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

Supplementary Figure S2: Magnitude of antibody reactivity to SARS-CoV-2 in participants who had a positive PCR to SARS-CoV-2 at least two weeks earlier and positive anti-SARS-CoV-2 serology (≥1 COI), stratified by choice of biologic



Abbreviations: PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COI = Cut-Off Index

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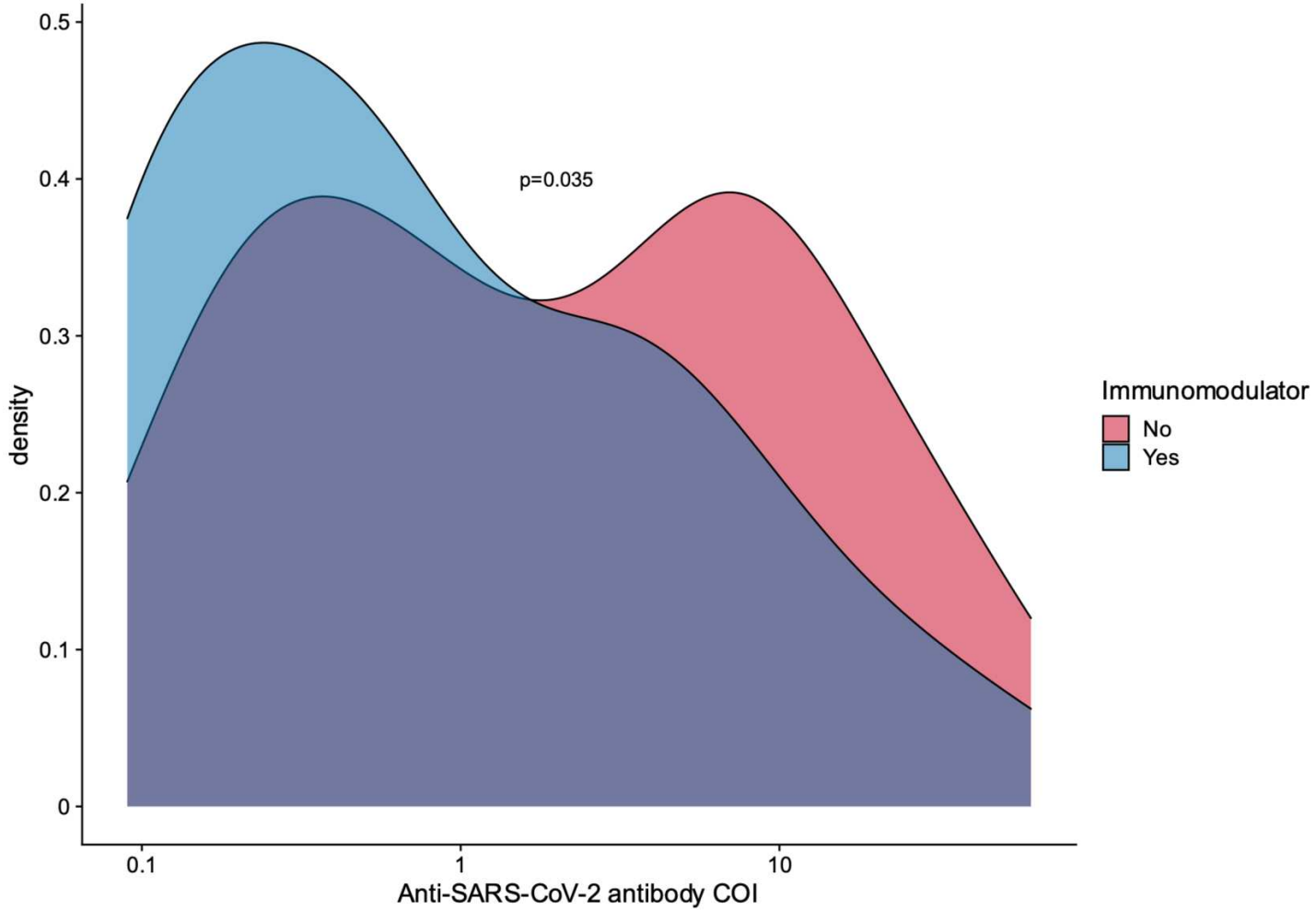
Supplementary Figure S3: Magnitude of antibody reactivity to SARS-CoV-2 in participants treated with infliximab who had a positive PCR to SARS-CoV-2 at least two weeks earlier, stratified by immunomodulator use



Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COI = Cut-Off Index; PCR = polymerase chain reaction