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Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab

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Abstract

Objective

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 inflammatory bowel disease have attenuated serological responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

Design

Antibody responses in participants treated with infliximab were compared to 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 22nd September and 23rd December 2020.

Results

Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups. Seroprevalence was lower in infliximab- 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; odds ratio [OR] 0.66 [95% CI 0.51-0.87], p=0.0027) and immunomodulator use (OR 0.70 [95% CI 0.53-0.92], p=0.012) were independently associated with lower seropositivity. In patients with confirmed SARS-CoV-2 infection seroconversion was observed in fewer infliximab- than vedolizumab-treated patients (48% [39/81], vs 83% [30/36], p=0.00044) and the magnitude of anti-SARS-CoV2 reactivity was lower (median 0.8 COI [0.2-5.6] vs 37.0 [15.2-76.1], p<0.0001).

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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.

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Summary Box

1. What is already known about this subject?

- Anti-tumour necrosis factor (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

2. What are the new findings?

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

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

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- 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
- Impaired serological responses might lead to chronic nasopharyngeal colonisation which 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.

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Introduction

Induction of protective immunity following SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection and/or vaccination is critical to suppress transmission. By suppressing immune responses, biologic 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 inflammatory bowel disease (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 biologics 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 subject to the most restrictive public health measures.[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-CoV2 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, to 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]

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Objectives

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

i) seroprevalence of SARS-CoV-2.

ii) subsequent seroconversion in patients with infection confirmed by prior polymerase chain reaction (PCR) testing.

iii) magnitude of anti-SARS-Cov-2 reactivity.

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Methods

Patient and Settings

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 Supplementary Table S1)** between 22nd September 2020 and 23rd December 2020.

The eligibility criteria were:

i) age 5 years and over

ii) diagnosis of inflammatory bowel disease

iii) current treatment with infliximab or vedolizumab for 6 weeks or more, with a 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.

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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 (PHQ-8[19] and GAD-7[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 were 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 biologic 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 World Health Organisation (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 considered suspected/probable COVID-19 cases. We

omitted the gastrointestinal 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.

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 are 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 to 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- and inter-assay 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 seven 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 anti-drug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL respectively.

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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
- Odds ratio for SARS-CoV-2 seropositivity with immunomodulator use: 0.8
- Odds ratio 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 Inc (USA), 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. The Surrey Borders Research Ethics committee approved the study (REC reference: REC 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.

Statistics

Statistical analyses were undertaken in R 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. 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 interquartile range, 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, biologic medication, immunomodulator, and 5-aminosalicylate (5-ASA) 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- 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 two weeks prior to measurement of serology.

We conducted sensitivity analyses using propensity matching to account for significant differences in baseline variables between infliximab- 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 September 22nd 2020 and December 23rd 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 was 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- 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% - 4.8%). The proportion of patients with a positive anti-SARS-CoV-2 antibody test was lower in infliximab- 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, ulcerative colitis, 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 **(Table 2 and 3, See Supplementary Figure S1)**.

Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; odds ratio [OR] 0.66 [95% CI 0.51 - 0.87], p=0.0027) and immunomodulator use (OR 0.70 [95% CI 0.53 - 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 nonadherence 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 – 1.92], p=0.92). In our propensity matched analysis, we confirmed lower seroprevalence in infliximab- compared to vedolizumab-treated patients 3.9% (67/1704), vs 6.2% (105/1707) p=0.0037 **(See Supplementary Table S2)**.

Seroconversion in patients with confirmed SARS-CoV-2 infection

Sensitivity analyses in participants with confirmed SARS-CoV-2 infection demonstrated that fewer infliximab- than vedolizumab-treated patients had seroconverted (48% [39/81], vs 83% [30/36], p=0.00044). The magnitude of anti-SARS-Cov2 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 Supplementary 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-Cov2 reactivity (p=0.035; **See Supplementary 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-Cov2 antibody reactivity was observed four weeks after apositive PCR test in vedolizumab- (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**).

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 between infliximab- 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 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 pro-inflammatory actions of TNF include stimulation of B-cell immunoglobulin synthesis, induction of germinal centre formation, co-stimulation of antigen-activated T-cells and maturation of antigen presenting cells.[30–32]

Impaired serological responses to SARS-CoV-2 infection 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 which 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, ISRCTN33260034).[33]

Our study has other important findings. We have identified associations of SARS-CoV-2 seropositivity with non-white ancestry and nonadherence 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 multi-factorial and likely include multi-generational 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. Whilst direct comparisons to 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 7,000 consecutive patients within a narrow window mitigating against the potential for time during the pandemic course to be a significant co-variate. 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. Firstly, 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. Secondly, our patient reported data are subject to recall bias which may have underestimated the prevalence of possible COVID-19 symptoms. Thirdly, 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.

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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-CoV2 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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Figure Captions

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 = aminosalicylates, UC = ulcerative colitis, IBDU = inflammatory bowel disease unclassified.

Figure 2: Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic amongst participants who had a positive PCR to anti-SARS-CoV-2 at least two weeks prior to their serology sample. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.

Figure 3: Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic and time since prior positive PCR test. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.

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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, JRG, DC, SL, NC, JB, RC, NMC, ALH, PMI, KBK, CAL, JKL, JM, DPM, SJM, CDM, KVP, RCP, TR, RKR, CPS, PJS, JB, TJM, CWL, SS, 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, JRG, DC, SL, NC, TR, CWL, SS, NP, TA, SS 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.

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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 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.

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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Table 1: Baseline characteristics stratified by biologic

Variable		Infliximab	Vedolizumab	Overall	p
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
	Ulcerative colitis	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
Steroids 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

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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 Apr-Jul	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
GAD7		3.0 (0.0 - 7.0)	3.0 (0.0 - 7.0)	3.0 (0.0 - 7.0)	0.12

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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 (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

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

Variable		Seroprevalence	p
Biologic treatment	Infliximab	3.4% (161/4685)	<0.0001
	Vedolizumab	6.0% (134/2250)	
Biologic/ immunomodulator treatment	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
	Ulcerative colitis	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)	
Steroids 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)	

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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 Apr-Jul	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).

Abbreviations: IBD = inflammatory bowel disease, 5-ASA = aminosalicylates, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PRO2 = Patient Reported Outcome

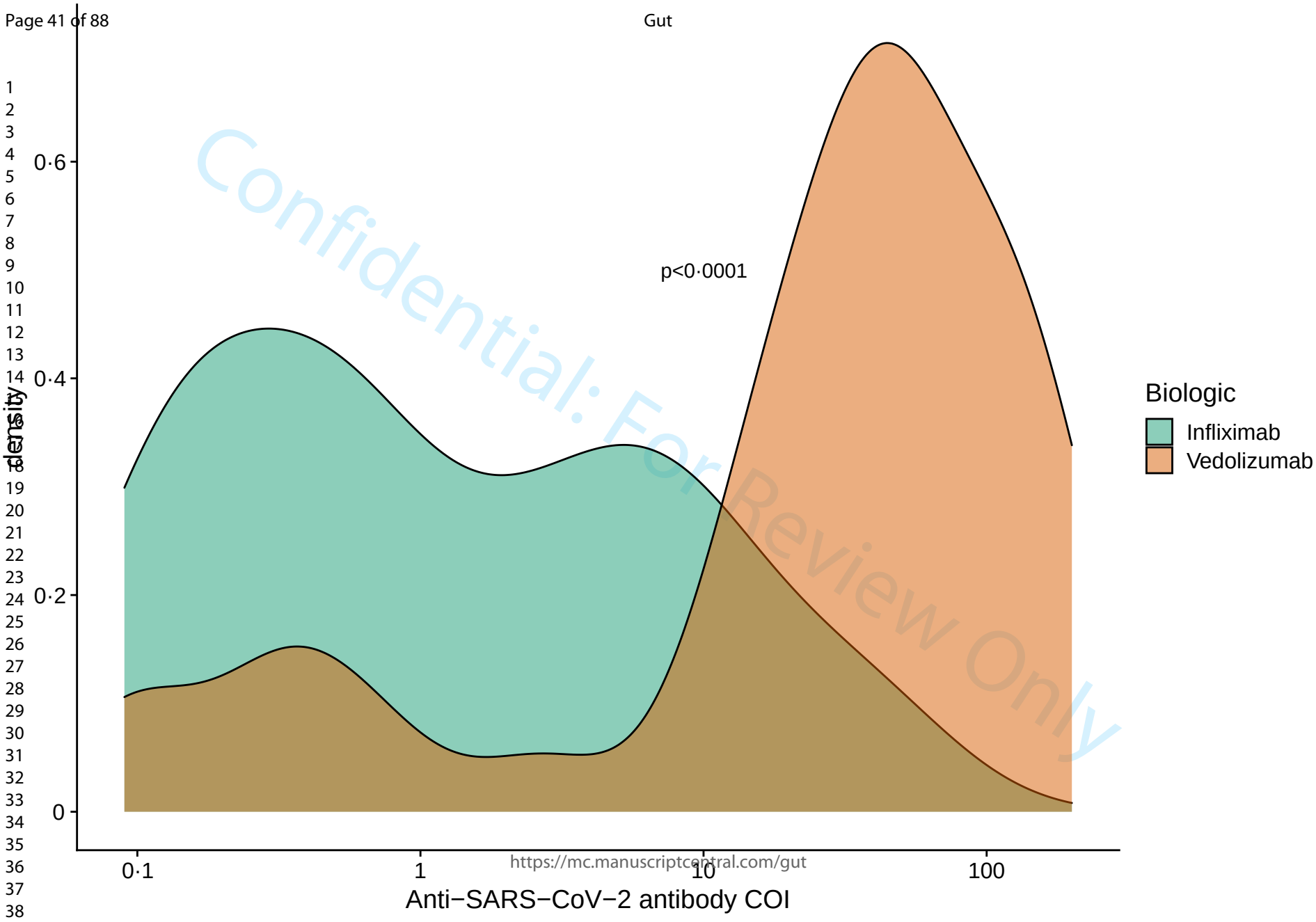
Table 3: Baseline characteristics, stratified by baseline anti-SARS-CoV-2 antibody status

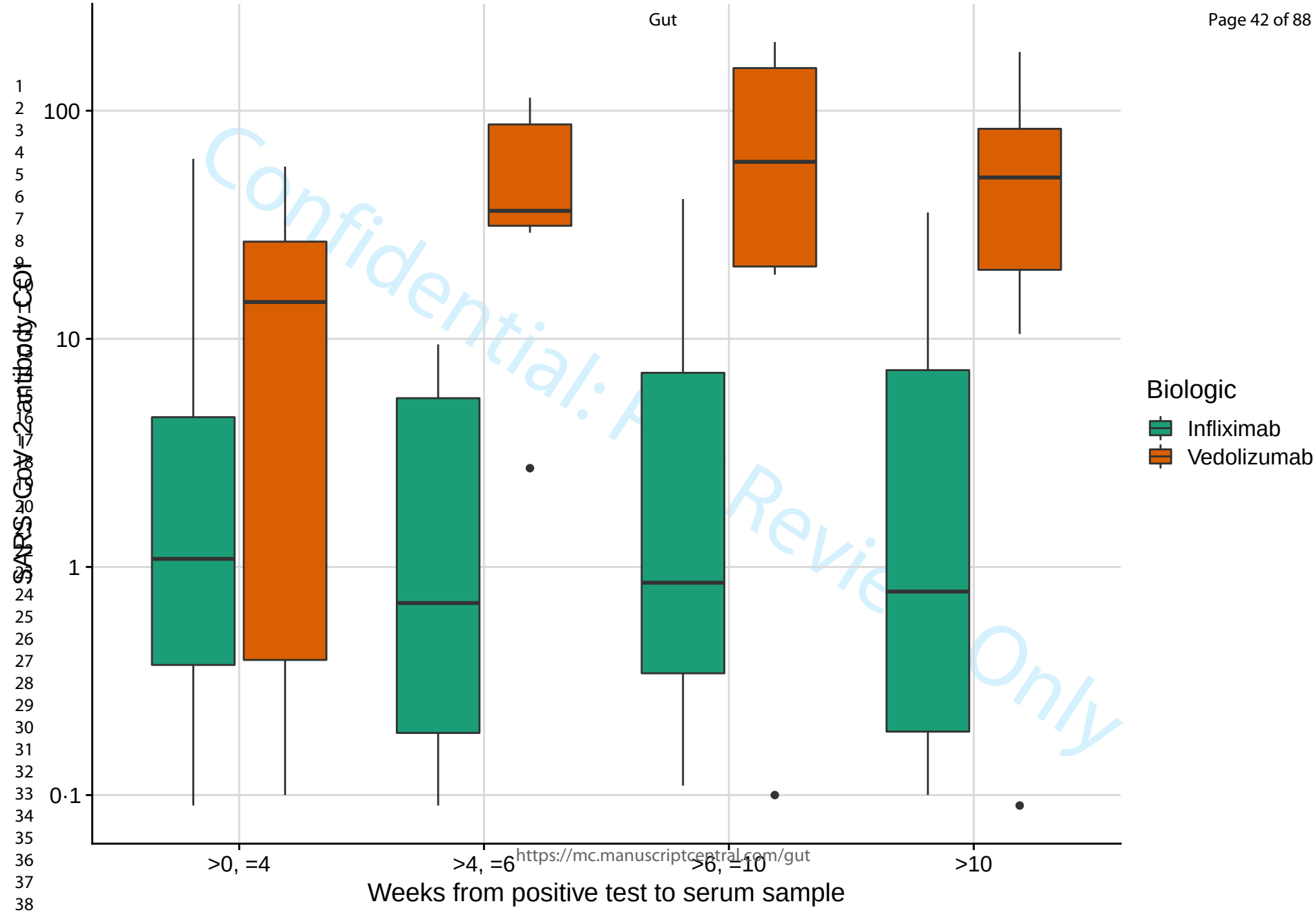
Variable	Positive	Negative	p
Age (years)	36.3 (26.9 - 50.6)	39.2 (28.7 - 53.3)	0.017
Duration of IBD (years)	7.0 (3.0 - 15.0)	8.0 (3.0 - 15.0)	0.25
Age at IBD diagnosis (years)	26.4 (19.8 - 36.4)	27.6 (19.8 - 40.0)	0.12
BMI	24.7 (21.7 - 28.1)	24.5 (21.7 - 28.3)	0.75
PHQ8	4.0 (1.0 - 8.0)	4.0 (1.0 - 9.0)	0.40
GAD7	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 (interquartile range).

Abbreviations: IBD = inflammatory bowel disease, BMI = body mass index, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, VAS = Visual Analogue Scale

Variable		N	Odds ratio	OR (95% CI)	p
Biologic	Vedolizumab	2245		Reference	
	Infliximab	4675		0·66 (0·51, 0·87)	0·0027
Immunomodulator		3059		0·70 (0·53, 0·92)	0·012
5−ASA		1825		0·99 (0·74, 1·32)	0·94
Steroid use at any point in 2020		1154		1·27 (0·93, 1·70)	0·12
Age > 70		387		0·56 (0·27, 1·06)	0·097
Region	South West	958		Reference	
	East Midlands	467		2·12 (1·01, 4·42)	0·044
	East of England	644		2·04 (1·03, 4·12)	0·043
	London	1188		3·35 (1·93, 6·20)	<0·0001
	North East	284		2·37 (1·06, 5·18)	0·031
	North West	630		3·92 (2·18, 7·44)	<0·0001
	Scotland	423		1·29 (0·54, 2·94)	0·55
	South East	654		2·52 (1·30, 5·03)	0·0069
	Wales	451		1·22 (0·51, 2·79)	0·64
	West Midlands	527		3·06 (1·63, 5·98)	0·00067
	Yorkshire and the Humber	694		3·10 (1·69, 5·94)	0·00038
Ethnicity	White	6116		Reference	
	Asian	479		1·97 (1·35, 2·81)	0·00031
	Mixed	154		1·86 (0·95, 3·36)	0·052
	Black	108		3·32 (1·75, 5·94)	0·00011
	Other	63		2·47 (0·98, 5·33)	0·034
Shielding Apr−Jul	Remained at home	2391		Reference	
	Exercise w/ own household	2699		1·09 (0·81, 1·47)	0·57
	Met others, social distancing	1694		1·33 (0·97, 1·83)	0·072
	No social distancing	136		2·83 (1·51, 5·01)	0·00062
Diagnosis	Crohn's disease	3941		Reference	
	UC/IBDU	2979		1·44 (1·09, 1·90)	0·011
Heart disease		210		0·98 (0·43, 1·97)	0·96
Diabetes		311		1·03 (0·57, 1·73)	0·93
Lung disease		963		0·83 (0·56, 1·18)	0·32
Cancer		50		0·70 (0·11, 2·36)	0·63
Income deprivation score		6920		5·36 (1·42, 19·55)	0·012





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

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Supplementary Table S1: Contributors to the CLARITY IBD study

Affiliation	First name	Surname
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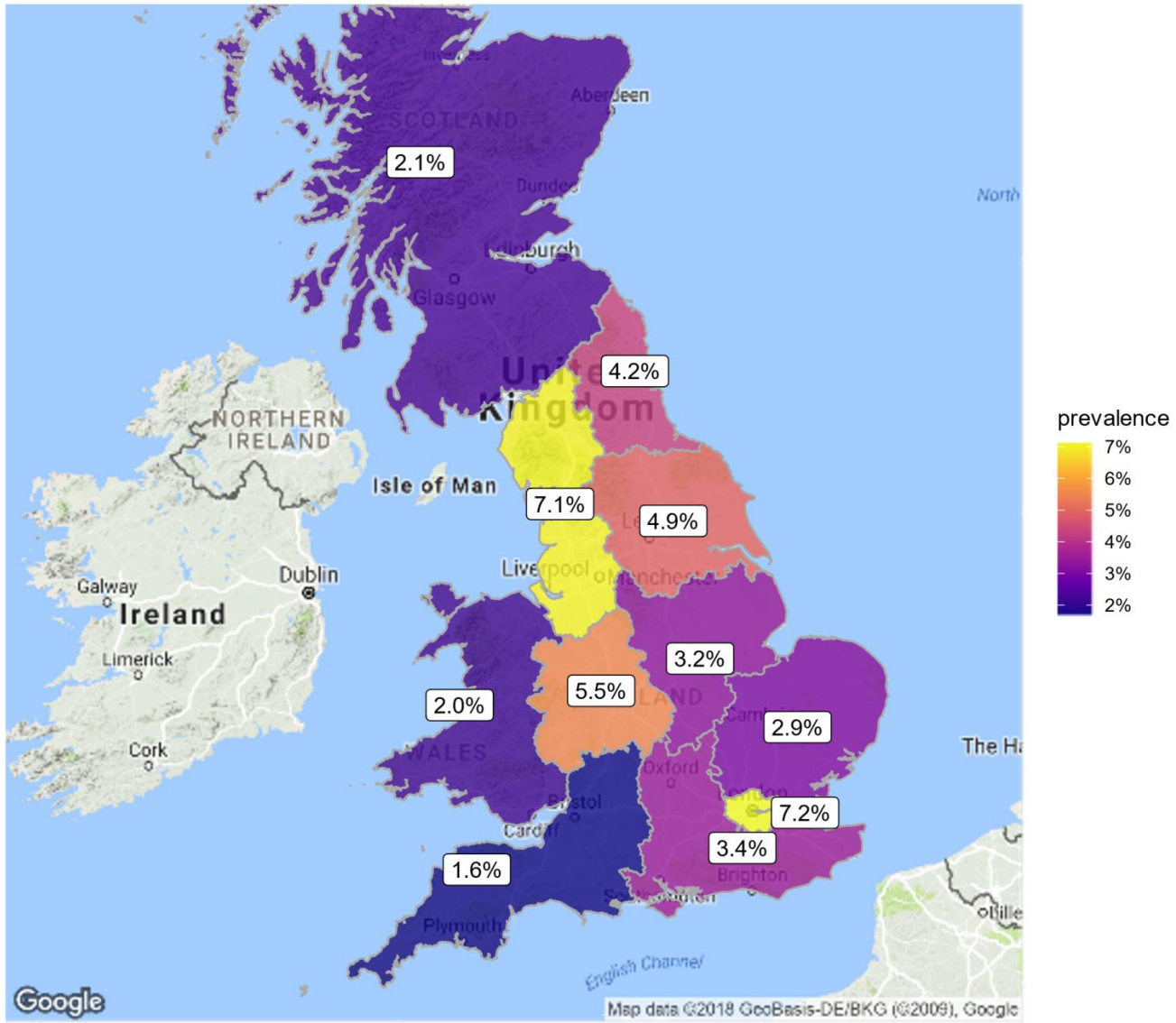
	Julia	Roberts

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 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

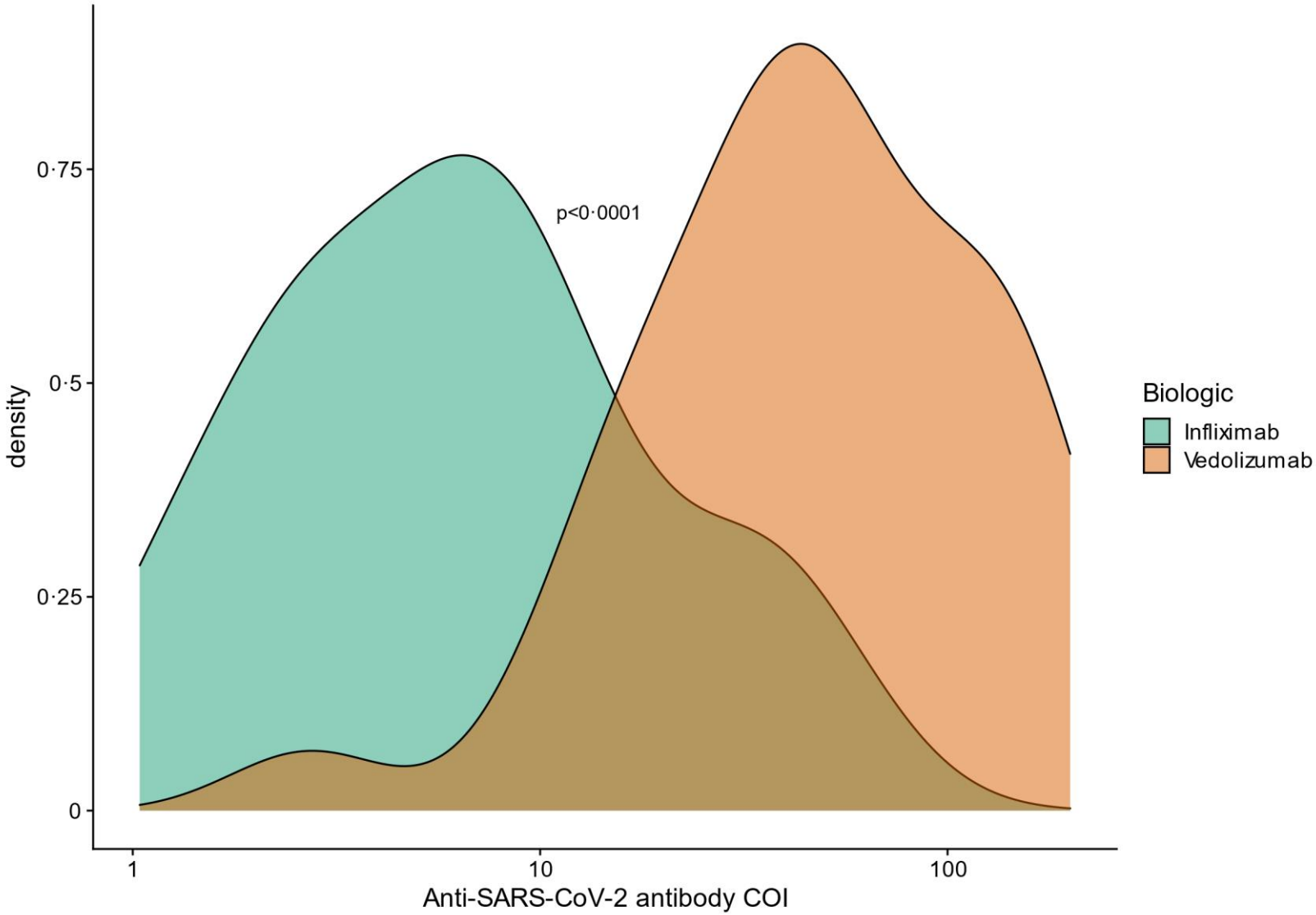
Variable		Positive	Negative	p
Positive serology to SARS-CoV-2	Positive	3·9% (67/1704)	6·2% (105/1707)	0·0037
	Negative	96·1% (1637/1704)	93·8% (1602/1707)	
Age (years)		41·7 (31·1 - 55·6)	41·4 (31·1 - 56·1)	0·91
Sex	Female	46·4% (791/1704)	50·2% (857/1707)	0·023
	Male	53·6% (913/1704)	49·7% (848/1707)	
	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

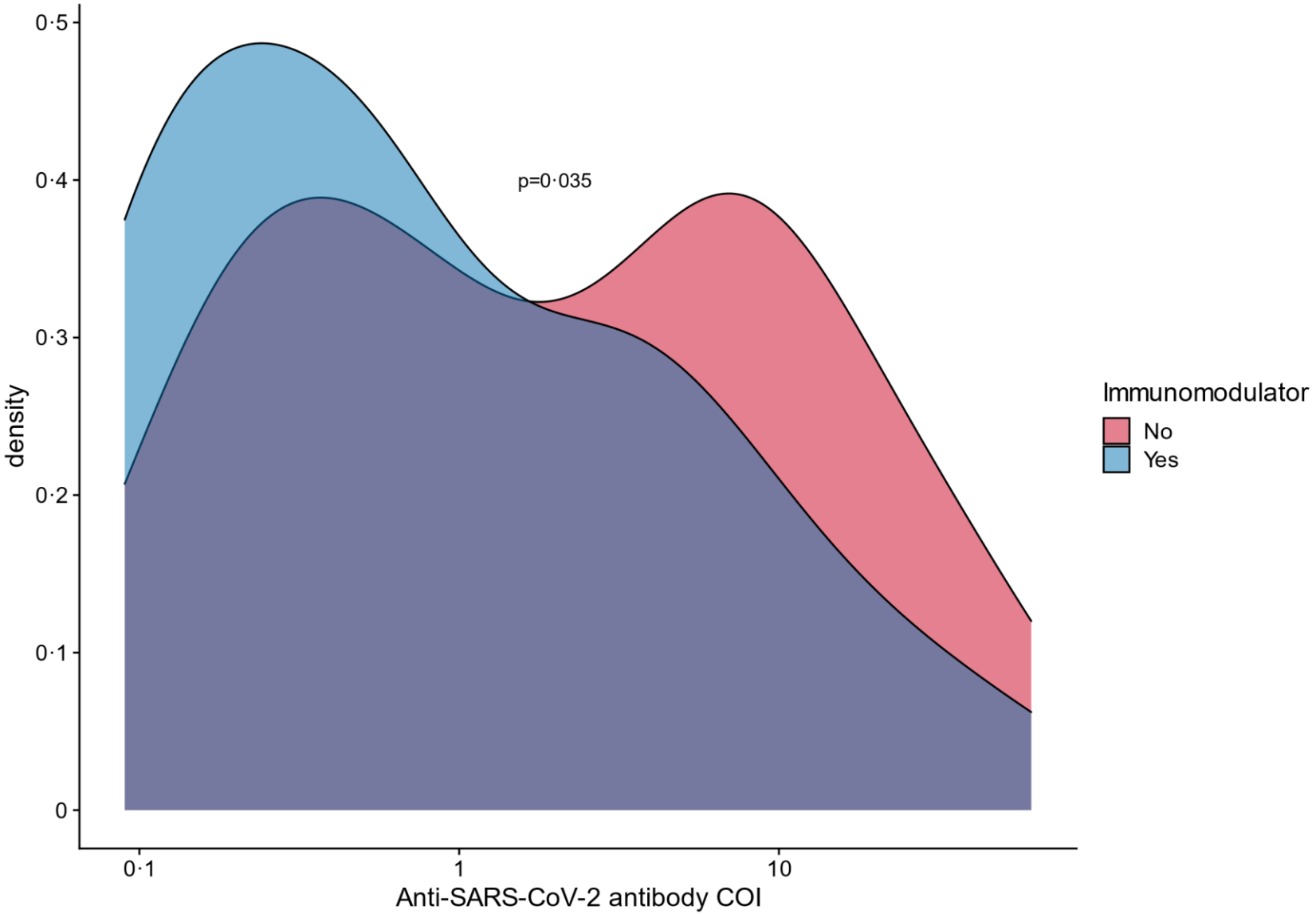
Supplementary Appendix for 'Anti-SARS-CoV2 antibody responses are impaired in patients with inflammatory bowel disease treated with infliximab'

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

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

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Running title	Infliximab impairs anti-SARS-CoV-2 antibody responses
Word count	2917~~847~~ excluding abstract and summary box

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Abstract

Objective

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 inflammatory bowel disease have attenuated serological responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

Design

Antibody responses in participants treated with infliximab were compared to 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~~patients were recruited from 92 UK hospitals between 22nd September and 23rd December 2020.

Results

Rates of symptomatic and proven SARS-CoV-2 infection were similar between groups. Seroprevalence was lower in infliximab- 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; odds ratio [OR] 0.66 [95% CI 0.51-0.87], p=0.0027) and immunomodulator use (OR 0.70 [95% CI 0.53-0.92], p=0.012) were independently associated with lower seropositivity. In patients with confirmed SARS-CoV-2 infection seroconversion was observed in fewer infliximab- than vedolizumab-treated patients (48% [39/81], vs 83% [30/36], p=0.00044) and the magnitude of anti-SARS-CoV2 reactivity was lower (median 0.8 COI [0.2-5.6] vs 37.0 [15.2-76.1], p<0.0001).

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Conclusions

Infliximab is associated with attenuated serological responses to SARS-CoV-2 that were further blunted by ~~concomitant~~ immunomodulators ~~use~~used as concomitant therapy. Impaired serological responses to SARS-CoV-2 infection ~~have~~ ~~may~~ 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.

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Summary Box

1. What is already known about this subject?

- Anti-tumour necrosis factor (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

2. What are the new findings?

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

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

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- 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
- Impaired serological responses might lead to chronic nasopharyngeal colonisation which 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.

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Introduction

Induction of protective immunity following SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection and/or vaccination is critical to suppress transmission. By suppressing immune responses, biologic 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 inflammatory bowel disease (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 biologics 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 subject to the most restrictive public health measures.[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-CoV2 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, to 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]

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Objectives

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

i) seroprevalence of SARS-CoV-2.

ii) subsequent seroconversion in patients with infection confirmed by prior polymerase chain reaction (PCR) testing.

iii) magnitude of anti-SARS-Cov-2 reactivity.

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Methods

Patient and Settings

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 Supplementary Table S1~~pp 2-7~~)** between 22nd September 2020 and 23rd December 2020.

The eligibility criteria were:

i) age 5 years and over

ii) diagnosis of inflammatory bowel disease

iii) current treatment with infliximab or vedolizumab for 6 weeks or more, with a 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 (PHQ-8[19] and GAD-7[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 were 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 biologic 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 World Health Organisation (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 considered suspected/probable COVID-19 cases. We

omitted the gastrointestinal 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.

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 are 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 to 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- and inter-assay 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 seven 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 anti-drug 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
- Odds ratio for SARS-CoV-2 seropositivity with immunomodulator use: 0.8
- Odds ratio 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 Inc (USA), 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. The Surrey Borders Research Ethics committee approved the study (REC reference: REC 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.

Statistics

Statistical analyses were undertaken in R 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. 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 interquartile range, 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, biologic medication, immunomodulator, and 5-aminosalicylate (5-ASA) 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- 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 two weeks prior to measurement of serology.

We conducted sensitivity analyses using propensity matching to account for significant differences in baseline variables between infliximab- 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 September 22nd 2020 and December 23rd 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 was 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- 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% - 4.8%). The proportion of patients with a positive anti-SARS-CoV-2 antibody test was lower in infliximab- 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, ulcerative colitis, 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 **(Table 2 and 3, See Supplementary Figure S1~~pp 9~~)**.

Multivariable logistic regression analyses confirmed that infliximab (vs vedolizumab; odds ratio [OR] 0.66 [95% CI 0.51 - 0.87], p=0.0027) and immunomodulator use (OR 0.70 [95% CI 0.53 - 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 nonadherence 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 – 1.92], p=0.92). In our propensity matched analysis, we confirmed lower seroprevalence in infliximab- compared to vedolizumab-treated patients 3.9% (67/1704), vs 6.2% (105/1707) p=0.0037 **(See Supplementary Table S2~~pp 8~~)**.

Seroconversion in patients with confirmed SARS-CoV-2 infection

Sensitivity analyses in participants with confirmed SARS-CoV-2 infection demonstrated that fewer infliximab- than vedolizumab-treated patients had seroconverted (48% [39/81], vs 83% [30/36], p=0.00044). The magnitude of anti-SARS-Cov2 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 **Supplementary Figure S2~~pp 10~~**).

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-Cov2 reactivity (p=0.035; See **Supplementary Figure S3~~pp 11~~**). 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-Cov2 antibody reactivity was observed four weeks after a ~~first~~ positive PCR test~~, compared to within four weeks,~~ in vedolizumab-~~treated patients~~ (47.2 COI [IQR 24.1 - 113.0] vs 14.5 COI [IQR 0.4 – 30.7], p=0.0079), ~~which ; this was~~ but not ~~seen in~~ 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**).

Discussion

We have shown that infliximab-treated patients have attenuated serological responses to SARS-CoV-2 infection with lower seroprevalence, seroconversion and antibody reactivity. ~~Despite similar rates of symptomatic and proven SARS-CoV-2 infection, the seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity were impaired in infliximab- compared with vedolizumab-treated patients.~~ Similar rates of symptomatic and proven SARS-CoV-2 infection between infliximab- 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 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 pro-inflammatory actions of TNF include stimulation of B-cell immunoglobulin synthesis, induction of germinal centre formation, co-stimulation of antigen-activated T-cells and maturation of antigen presenting cells.[30–32]

Impaired serological responses to SARS-CoV-2 infection 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 which 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, ISRCTN33260034).[33]

Our study has other important findings. We have identified associations of SARS-CoV-2 seropositivity with non-white ancestry and nonadherence 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 multi-factorial and likely include multi-generational 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. Whilst direct comparisons to 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 7,000 consecutive patients within a narrow window mitigating against the potential for time during the pandemic course to be a significant co-variate. 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. Firstly, 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. Secondly, our patient reported data are subject to recall bias which may have underestimated the prevalence of possible COVID-19 symptoms. Thirdly, 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 ~~results in substantial attenuation of~~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-CoV2 antibody responses were further attenuated in infliximab recipients concomitantly treated with immunomodulators, including thiopurines and methotrexate.

Impaired serological responses to SARS-CoV-2 infection ~~have~~ mightay 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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Figure Captions

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 = aminosalicylates, UC = ulcerative colitis, IBDU = inflammatory bowel disease unclassified.

Figure 2: Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic amongst participants who had a positive PCR to anti-SARS-CoV-2 at least two weeks prior to their serology sample. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.

Figure 3: Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biologic and time since prior positive PCR test. Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PCR = polymerase chain reaction, COI = Cut-Off Index.

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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, JRG, DC, SL, NC, JB, RC, NMC, ALH, PMI, KBK, CAL, JKL, JM, DPM, SJM, CDM, KVP, RCP, TR, RKR, CPS, PJS, JB, TJM, CWL, SS, 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, JRG, DC, SL, NC, TR, CWL, SS, NP, TA, SS 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.

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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 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.

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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584 **Table 1: Baseline characteristics stratified by biologic**

Variable		Infliximab	Vedolizumab	Overall	p
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
	Ulcerative colitis	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
Steroids 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

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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 Apr-Jul	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
GAD7		3.0 (0.0 - 7.0)	3.0 (0.0 - 7.0)	3.0 (0.0 - 7.0)	0.12

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

Variable		Seroprevalence	p
Biologic treatment	Infliximab	3.4% (161/4685)	<0.0001
	Vedolizumab	6.0% (134/2250)	
Biologic/ immunomodulator treatment	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
	Ulcerative colitis	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)	
Steroids 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)	

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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 Apr-Jul	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).

Abbreviations: IBD = inflammatory bowel disease, 5-ASA = aminosalicylates, COVID-19 = coronavirus, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, PRO2 = Patient Reported Outcome

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

Variable	Positive	Negative	p
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
GAD7	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 (interquartile range).

Abbreviations: IBD = inflammatory bowel disease, BMI = body mass index, PHQ8 = Patient Health Questionnaire depression scale, GAD7 = General Anxiety Disorder assessment, VAS = Visual Analogue Scale