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| **Title** | **Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab** |
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| **Key words** | SARS-CoV-2, immune-mediated inflammatory diseases, inflammatory bowel disease, anti-TNF therapy, vedolizumab, immunosuppressant, CLARITY |
| **Running title** | Infliximab impairs anti-SARS-CoV-2 antibody responses |
| **Word count** | 2917 excluding abstract and summary box |

# 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).

## 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.

# 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

1. 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.

1. 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 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.

# 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 hepatitis9 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

# Objectives

We aimed to define, in patients with IBD, whether biologic 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 polymerase chain reaction (PCR) testing.
3. magnitude of anti-SARS-Cov-2 reactivity.

# 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 **(Supplementary pp 2-7)** between 22nd September 2020 and 23rd December 2020.

The eligibility criteria were:

1. age 5 years and over
2. diagnosis of inflammatory bowel disease
3. 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-819 and GAD-720), SARS-CoV-2 outcomes aligned to the COVID-19 symptoms study21 (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 201926 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 outcomes28 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, Supplementary 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 **(Supplementary 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; **Supplementary Figure 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; **Supplementary Figure 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 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.

# 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.

# 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.

# 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.

# Declarations of interest

Dr. Kennedy reports grants from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support from Immundiagnostik, during the conduct of the study; grants and non-financial support from AbbVie, grants and personal fees from Celltrion, personal fees and non-financial support from Janssen, personal fees from Takeda, personal fees and non-financial support from Dr Falk, outside the submitted work. Dr. Goodhand reports grants from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support from Immundiagnostik, during the conduct of the study. Dr. Chee reports non-financial support from Ferring, personal fees and non-financial support from Pfizer, outside the submitted work. Dr. Lin reports non-financial support from Pfizer, non-financial support from Ferring, outside the submitted work. Dr. Cooney reports personal fees from Takeda, outside the submitted work. Dr. Croft reports trial funding, advisory board and speaker fees paid to his institution from AbbVie, Eli Lilly, Takeda, Shire, Pfizer and Janssen. Dr. Hart reports personal fees from Abbvie, personal fees from Allergan, personal fees from BMS, personal fees from Celltrion, personal fees from Falk, personal fees from GSK, personal fees from Takeda, personal fees from Pfizer, personal fees from Janssen, personal fees from Galapogos, personal fees from Astra Zeneca, outside the submitted work. Dr. Irving reports grants and personal fees from Takeda, grants from MSD, grants and personal fees from Pfizer, personal fees from Galapagos, personal fees from Gilead, personal fees from Abbvie, personal fees from Janssen, personal fees from Boehringer Ingelheim, personal fees from Topivert, personal fees from VH2, personal fees from Celgene, personal fees from Arena, personal fees from Samsung Bioepis, personal fees from Sandoz, personal fees from Procise, personal fees from Prometheus, outside the submitted work. Dr. Kok reports personal fees from Janssen, personal fees from Takeda, personal fees from PredictImmune, personal fees from Amgen, outside the submitted work. Dr. Lamb reports grants from Genentech, grants and personal fees from Janssen, grants and personal fees from Takeda, grants from AbbVie, personal fees from Ferring, grants from Eli Lilly, grants from Pfizer, grants from Roche, grants from UCB Biopharma, grants from Sanofi Aventis, grants from Biogen IDEC, grants from Orion OYJ, personal fees from Dr Falk Pharma, grants from AstraZeneca, outside the submitted work. Dr. Limdi reports personal fees from MSD, personal fees from Janssen, grants and personal fees from Takeda, grants and personal fees from Galapagos, personal fees from Tillotts, outside the submitted work. Dr. Macdonald reports grants and personal fees from Takeda Pharmaceuticals, grants and personal fees from Biogen, personal fees and non-financial support from AbbVie, personal fees from Grifols, personal fees from Sandoz, personal fees from Celltrion, personal fees and non-financial support from Janssen, personal fees from Vifor Pharmaceuticals, personal fees from Predictimmune, personal fees from Bristol Myers Squibb, non-financial support from Ferring Pharmaceuticals, outside the submitted work. Dr. McGovern reports grants from the Leona M. and Harry B. Helmsley Charitable Trust, during the conduct of the study; personal fees from Takeda Pharmaceuticals, personal fees from Pfizer, personal fees from Bridge Biotherapeutics, personal fees from Palatin Technologies, personal fees from Boehringer-Ingelheim, personal fees and other from Prometheus Biosciences, personal fees from Gilead, outside the submitted work. Dr. Patel reports personal fees and non-financial support from Takeda, personal fees and non-financial support from Janssen, personal fees and non-financial support from Abbvie, personal fees from DrFalk, non-financial support from Ferring, outside the submitted work. Dr. Pollok reports acting as consultant, advisory board member, speaker or recipient of educational grant from Dr Falk, Ferring, Janssen, Pharmacosmos and Takeda. Dr. Raine reports grants and personal fees from Abbvie, personal fees from BMS, personal fees from Celgene, personal fees from Ferring, personal fees from Gilead, personal fees from GSK, personal fees from LabGenius, personal fees from Janssen, personal fees from Mylan, personal fees from MSD, personal fees from Novartis, personal fees from Pfizer, personal fees from Sandoz, personal fees from Takeda, personal fees from Galapagos, personal fees from Arena, outside the submitted work. Dr. Russell reports grants from NHS Research Scotland Senior Research Fellowship, personal fees from Nestlé, personal fees from AbbVie, personal fees from Dr Falk, personal fees from Takeda, personal fees from Napp, personal fees from Mead Johnson, personal fees from Nutricia, personal fees from 4D Pharma, outside the submitted work. Dr. Selinger reports grants and personal fees from AbbVie, grants and personal fees from Janssen, grants and personal fees from Takeda, personal fees from Dr Falk, personal fees from Pfizer, personal fees from Galapagos, personal fees from Arena, personal fees from Fresenius Kabi, outside the submitted work. Dr Philip J Smith reports speaker fees and advisory board sponsorship from Janssen, Celltrion and Takeda outside the submitted work. Dr. Lees 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. Dr. Sebastian 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. Dr. Powell reports personal fees from Takeda, personal fees from Janssen, personal fees from Pfizer, personal fees from Bristol-Myers Squibb, personal fees from Abbvie, personal fees from Roche, personal fees from Lilly, personal fees from Allergan, personal fees from Celgene, outside the submitted work; and Dr Powell has served as a speaker/advisory board member for Abbvie, Allergan, Bristol Myers Squibb, Celgene, Falk, Ferring, Janssen, Pfizer, Tillotts, Takeda and Vifor Pharma. Dr. Ahmad reports grants and non-financial support from F. Hoffmann-La Roche AG, grants from Biogen Inc, grants from Celltrion Healthcare, grants from Galapagos NV, non-financial support from Immundiagnostik, during the conduct of the study; personal fees from Biogen inc, grants and personal fees from Celltrion Healthcare, personal fees and non-financial support from Immundiagnostik, personal fees from Takeda, personal fees from ARENA, personal fees from Gilead, personal fees from Adcock Ingram Healthcare, personal fees from Pfizer, personal fees from Genentech, non-financial support from Tillotts , outside the submitted work. The following authors have nothing to declare: Claire Bewshea, Rachel Nice, Neil Chanchlani, Jeffrey Butterworth, Shameer J Mehta, Charles D Murray, Jack Bowden, Timothy J McDonald.

# Acknowledgements

CLARITY IBD is a UK National Institute for Health Research (NIHR) Urgent Public Health Study. The NIHR Clinical Research Network supported study set-up, site identification, and delivery of this study. This was facilitated by Professor Mark Hull, the National speciality lead for Gastroenterology. We acknowledge the contribution of our Patient Advisory Group who helped shape the trial design around patient priorities. Our partners, Crohn’s and Colitis UK (CCUK), continue to support this group and participate in Study Management Team meetings. Laboratory tests were undertaken by the Exeter Blood Sciences Laboratory at the Royal Devon and Exeter NHS Foundation Trust. The Exeter NIHR Clinical Research Facility coordinated sample storage and management. Tariq Malik and James Thomas from Public Health England, Guy Stevens, Katie Donelon, Elen de Lacy from Public Health Wales and Johanna Bruce from Public Health Scotland supported linkage of central SARS-CoV-2 PCR test results with study data. Roche Diagnostics Limited provided the Elecsys Anti-SARS-CoV-2 immunoassay for the study. SL is supported by a Wellcome GW4-CAT fellowship. NC acknowledges support from CCUK. CAL acknowledges support from the NIHR Newcastle Biomedical Research Centre and the support of the Programmed Investigation Unit at Royal Victoria Infirmary, Newcastle upon Tyne. TR acknowledges support with recruitment from the NIHR Cambridge BRC. RKR is supported by an NHS Research Scotland Senior Research Fellowship. NP is supported by the NIHR Imperial Biomedical Research Center (BRC). We acknowledge the study co-ordinators of the Exeter Inflammatory Bowel Disease Research Group: Marian Parkinson and Helen Gardner-Thorpe for their ongoing administrative support to the study. The sponsor of the study was the Royal Devon and Exeter NHS Foundation Trust.

# 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](http://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 |
| 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 |
| 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) | |
| 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