COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP)

COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study

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Summary

Background The effects that therapies for inflammatory bowel disease (IBD) have on immune responses to SARS-CoV-2 vaccination are not yet fully known. Therefore, we sought to determine whether COVID-19 vaccine-induced antibody responses were altered in patients with IBD on commonly used immunosuppressive drugs.

Methods In this multicentre, prospective, case-control study (VIP), we recruited adults with IBD treated with one of six different immunosuppressive treatment regimens (thiopurines, infliximab, a thiopurine plus infliximab, ustekinumab, vedolizumab, or tofacitinib) and healthy control participants from nine centres in the UK. Eligible participants were aged 18 years or older and had received two doses of COVID-19 vaccines (either ChAdOx1 nCoV-19 [Oxford–AstraZeneca], BNT162b2 [Pfizer–BioNTech], or mRNA1273 [Moderna]) 6–12 weeks apart (according to scheduling adopted in the UK). We measured antibody responses 53–92 days after a second vaccine dose using the Roche Elecsys Anti-SARS-CoV-2 spike electrochemiluminescence immunoassay. The primary outcome was anti-SARS-CoV-2 spike protein antibody concentrations in participants without previous SARS-CoV-2 infection, adjusted by age and vaccine type, and was analysed by use of multivariable linear regression models. This study is registered in the ISRCTN Registry, ISRCTN13495664, and is ongoing.

Findings Between May 31 and Nov 24, 2021, we recruited 483 participants, including patients with IBD being treated with thiopurines (n=78), infliximab (n=63), a thiopurine plus infliximab (n=72), ustekinumab (n=57), vedolizumab (n=62), or tofacitinib (n=30), and 121 healthy controls. We included 370 participants without evidence of previous infection in our primary analysis. Geometric mean anti-SARS-CoV-2 spike protein antibody concentrations were significantly lower in patients treated with infliximab (156·8 U/mL [geometric SD 5·7]; p<0·0001), infliximab plus thiopurine (111·1 U/mL [5·7]; p<0·0001), or tofacitinib (429·5 U/mL [3·1]; p=0·0012) compared with controls (1578·3 U/mL [3·7]). There were no significant differences in antibody concentrations between patients treated with thiopurine monotherapy (1019·8 U/mL [4·3]; p=0·74), ustekinumab (582·4 U/mL [4·6]; p=0·11), or vedolizumab (954·0 U/mL [4·1]; p=0·50) and healthy controls. In multivariable modelling, lower anti-SARS-CoV-2 spike protein antibody concentrations were independently associated with infliximab (geometric mean ratio 0·12, 95% CI 0·08–0·17; p<0·0001) and tofacitinib (0·43, 0·23–0·81; p=0·0095), but not with ustekinumab (0·69, 0·41–1·19; p=0·18), thiopurines (0·89, 0·64–1·24; p=0·50), or vedolizumab (1·16, 0·74–1·83; p=0·51). mRNA vaccines (3·68, 2·80–4·84; p<0·0001; *vs* adenovirus vector vaccines) were independently associated with higher antibody concentrations and older age per decade (0·79, 0·72–0·87; p<0·0001) with lower antibody concentrations.

Interpretation For patients with IBD, the immunogenicity of COVID-19 vaccines varies according to immunosuppressive drug exposure, and is attenuated in recipients of infliximab, infliximab plus thiopurines, and tofacitinib. Scheduling of third primary, or booster, doses could be personalised on the basis of an individual's treatment, and patients taking anti-tumour necrosis factor and tofacitinib should be prioritised.

Funding Pfizer.

Introduction

Vaccination against SARS-CoV-2 has proved successful at stemming infections, hospitalisations, and deaths from COVID-19.[1] However, the efficacy of SARS-CoV-2 vaccines in patients treated with immunosuppressive therapies remains uncertain as these patients were excluded from initial vaccine trials. Inflammatory bowel disease (IBD) is an immune-mediated inflammatory disease with a prevalence of more than 0·3% in North America, Australia, New Zealand, and most European countries, and an

Research in context

Evidence before this study

We searched PubMed and Embase, without language restrictions, for studies published between Jan 1, 2000, and Dec 30, 2021, investigating humoral responses to vaccination in immunosuppressed individuals. We used the search terms ('vaccine' OR 'vaccination') AND ('immunosuppression' OR 'immunosuppressive' OR 'immunomodulator' OR 'thiopurine' OR 'azathioprine' OR 'biologic' OR 'tumour necrosis factor' OR 'infliximab' OR 'ustekinumab' OR 'anti-integrin' OR 'vedolizumab' OR 'JAK inhibitor' OR 'tofacitinib') AND ('antibody' OR 'humoral' OR 'immune response'). Previous studies of patients with inflammatory bowel disease (IBD) undergoing vaccination against infections other than SARS-CoV-2 (eg, influenza, pneumococcus, and viral hepatitides) show variable effects of different immunosuppressive therapies on vaccine immune responses. Anti-SARS-CoV-2 spike protein antibody concentrations and rates of seroconversion following vaccination with either BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) are lower in patients with IBD treated with infliximab than in patients with IBD treated with vedolizumab. There are currently scarce data on the effect of other commonly used IBD treatments, including thiopurine monotherapy, anti-IL-12 and anti-IL-23 therapy, and Janus kinase (JAK) inhibitor therapy, on vaccination response. Little is known about how patients with IBD respond to SARS-CoV-2 vaccination compared with non-immunosuppressed, healthy individuals.

Added value of this study

To our knowledge, this study is the first to systematically evaluate humoral immune responses to SARS-CoV-2 vaccination, both with mRNA and adenovirus vector vaccines, in patients receiving common immunosuppressives used in IBD. We show that, in addition to the significant attenuating effect of infliximab therapy, vaccine-induced anti-SARS-CoV-2 spike protein antibody responses were significantly reduced in patients treated with tofacitinib relative to healthy controls. No significant reductions in antibody responses were observed in patients treated with vedolizumab, ustekinumab, or thiopurine monotherapy compared with controls. Seroconversion was seen after two doses of vaccine in all participants in the thiopurine monotherapy, vedolizumab, tofacitinib, and healthy control groups. In the absence of previous infection, 10% of patients on infliximab monotherapy, 13% on thiopurine plus infliximab combination therapy, and 4% on ustekinumab did not generate protective antibody responses.

Implications of all the available evidence

In addition to patients with IBD who are treated with anti-tumour necrosis factor (TNF) therapies or anti-TNF plus immunomodulator combination therapies, patients who are treated with JAK inhibitors (eg, tofacitinib) have poorer antibody responses to COVID-19 vaccination than do healthy controls, which exposes them to a potential increased risk of SARS-CoV-2 infection. Reassuringly, no significant reductions in antibody responses were observed in patients treated with thiopurines, ustekinumab, or vedolizumab compared with controls. Third primary doses of COVID-19 vaccines should be urgently rolled out for patients with IBD who are receiving anti-TNF or JAK inhibitors.

accelerating incidence in countries that have recently industrialised.[2] Although immunosuppressive therapy is the cornerstone of IBD management, there are concerns that some of these treatments might impair the protective immune responses elicited to various vaccines. For example, the anti-tumour necrosis factor (TNF) drug infliximab is associated with reduced immunogenicity to hepatitis B, hepatitis A, pneumococcal, and influenza vaccination.[3–9] Furthermore, patients treated with anti-TNF drugs who are concomitantly prescribed immuno—modulators, such as thiopurines, have especially poor serological responses to influenza vaccination.[10,11] By contrast, the gut-specific anti-integrin drug vedolizumab does not affect response to hepatitis B vaccination,[12] and ustekinumab, which blocks the p40 subunit of IL-12 and IL-23, does not diminish antibody responses to pneumococcal and tetanus vaccines.[13] In patients with rheumatoid arthritis, the Janus kinase (JAK) inhibitor tofacitinib reduces the immunogenicity of pneumococcal vaccination, but responses to influenza vaccination are preserved.[14]

Data are now emerging on the impact of some immunosuppressive drugs on immune responses to SARS-CoV-2 vaccination. The CLARITY-IBD study has shown that antibody responses following infection with SARS-CoV-2 or a single dose of either the BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccines are impaired in patients treated with anti-TNF therapies compared with those treated with vedolizumab,[15–17] although how the responses of either group compare with the healthy, non-immunosuppressed population remains uncertain. Moreover, it is not yet known what effect other commonly used therapies in IBD, including thiopurines, anti-IL-12 and anti-IL-23 therapies, and JAK inhibitors, have on immune responses to SARS-CoV-2 vaccination, as existing small studies have inadequate power to discern the relative effects of different immunosuppressive regimens.[18–20] Therefore, we aimed to determine whether immunogenicity to SARS-CoV-2 vaccines is altered in patients receiving key immunosuppressive drug regimens commonly used in IBD.

Methods

Study design and participants

VIP is a multicentre, prospective, case-control study assessing the immunogenicity of SARS-CoV-2

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vaccination in patients with IBD being treated with one of six different immunosuppressive treatment regimens. Immunosuppressed patients with IBD and non-immunosuppressed healthy individuals were recruited at nine centres in the UK (Imperial College Healthcare National Health Service [NHS] Trust, London; Barts Health NHS Trust, London; London North West University Healthcare NHS Trust, London; Guy's and St Thomas' NHS Foundation Trust, London; King's College Hospital NHS Foundation Trust, London; St George's University Hospitals NHS Foundation Trust, London; Royal Devon and Exeter NHS Trust, Exeter; Western General Hospital, NHS Lothian, Edinburgh; and Cambridge University Hospitals NHS Foundation Trust, Cambridge). The protocol is available online.

For the **protocol** see https://www.vipstudy.uk

All participants were aged 18 years or older, able to give informed consent, and had received two doses of SARS-CoV-2 vaccines (ChAdOx1 nCoV-19, BNT162b2, or mRNA1273 [Moderna]) before enrolment. Participants were excluded at screening if they had received the second dose of a SARS-CoV-2 vaccine outside of the approved vaccine schedule being used in the UK, defined as fewer than 42 days or more than 91 days after the first dose (note that the vaccine manufacturers' dosing recommendations advise a 21-day interval between the first and second doses of the BNT162b2 vaccine and a 28-day interval for the ChAdOx1 nCoV-19 and mRNA1273 vaccines).[21] All participants were included after providing informed, written consent. The Wales Research Ethics Committee 5 approved the study (reference 21/WA/0105) in March, 2021.

Participants for the healthy control group were recruited from healthy volunteer databases (Healthy Volunteer Panel of the Imperial Clinical Research Facility, the National Institute for Health Research [NIHR] National Bioresource, and the Peninsula Research Bank) and from staff working at the medical and university centres involved in the study. Healthy controls were included if they did not have a diagnosis of IBD and were not currently being treated with systemic immunosuppressives for any other indication. Healthy controls were not excluded if they had other medical conditions.

For the **Healthy Volunteer Panel of the Imperial Clinical Research Facility** see www.imperial.crf.nihr.ac.uk

For the **National Institute for Health Research National Bioresource** see https://bioresource.nihr.ac.uk/

For the **Peninsula Research Bank** see https://exetercrfnihr.org/about/exeter-10000-prb/

Immunosuppressed patients with IBD were included if they had an established diagnosis of Crohn's disease, ulcerative colitis, or unclassified IBD using standard definitions of IBD, and were being treated with one of six immunosuppressive regimens (thiopurine monotherapy; infliximab monotherapy; infliximab and thiopurine combination therapy; ustekinumab monotherapy; vedolizumab monotherapy; or tofacitinib monotherapy) for at least 12 weeks at the time of their first dose of a SARS-CoV-2 vaccine. Patients were excluded if they were being treated with any other immunosuppressive therapies or treatment combinations, including methotrexate, adalimumab, and ciclosporin. Current treatment with systemic corticosteroids was not an exclusion criterion.

Procedures

Blood for laboratory analyses was collected from participants 53–92 days after the second vaccine dose. Laboratory analyses were done by RN and her team at the Academic Department of Blood Sciences at the Royal Devon and Exeter NHS Foundation Trust, Exeter, UK. To identify antibody responses specific to vaccination, we used the Roche Elecsys Anti-SARS-CoV-2 spike electrochemiluminescence immunoassay (Roche; Rotkreuz, Switzerland).[22] This double sandwich electrochemiluminescence immunoassay uses a recombinant protein of the receptor-binding domain (RBD) of the spike protein as an antigen for the identification of antibodies against SARS-CoV-2. Sample electrochemiluminescence signals are compared with an internal calibration curve and quantitative values are reported as units (U)/mL. In-house validation experiments have been described previously.[16] Seroconversion was defined at a threshold of 15 U/mL. Concentrations of anti-SARS-CoV-2 spike protein antibodies on the ElecSys assay of at least 15 U/mL are associated with neutralisation of 20% or more with a positive predictive value of 99·10% (95% CI 97·74–99·64). We have previously shown that an antibody concentration of 15 U/mL correlates with 20% neutralisation in a viral pseudo-neutralisation assay.[16] The rationale and data supporting this seroconversion threshold have been detailed previously.[16]

At entry to the VIP study, all participants were tested for previous SARS-CoV-2 infection by use of the Roche Elecsys anti-SARS-CoV-2 nucleocapsid immunoassay (Roche; Rotkreuz, Switzerland). A concentration of anti-SARS-CoV-2 nucleocapsid antibodies of 0·12 U/mL was defined as the threshold below which participants were deemed to have no evidence of previous infection. Participants who reported a previous PCR test confirming SARS-CoV-2 infection at any time before vaccination were deemed to have evidence of past infection irrespective of any antibody test result.

Either before the study visit or at the study visit, participants filled out electronic questionnaires detailing their demographics (eg, age, gender, ethnicity, comorbidities, height, weight, smoking status, corticosteroid use, and postcode), IBD disease activity (defined by patient-reported outcomes [assessed by PRO2 score]),[23,24] SARS-CoV-2 symptoms aligned to the ZOE COVID-19 Symptom Study (ie, symptoms, previous test results for SARS-CoV-2, and hospital admissions for COVID-19), and vaccine uptake (type and date of primary vaccination doses). Data were entered electronically and automatically into a purpose-designed REDCap database hosted at the Royal Devon and Exeter NHS Foundation Trust.[25] Participants without access to the internet or electronic devices completed their questionnaires on paper case record forms at the study visit for blood collection, which were subsequently entered into the database by local research teams.

Outcomes

The primary outcome was anti-SARS-CoV-2 spike protein RBD antibody concentrations—measured by use of the Elecsys assay 53–92 days after a second vaccine dose—in participants without previous SARS-CoV-2 infection, adjusted by age and vaccine type. Secondary outcomes were the proportions of participants in each study group with seroconversion, and anti-SARS-CoV-2 spike protein antibody concentrations and rates of seroconversion in participants with PCR or serological evidence of past SARS-CoV-2 infection versus those without.

Statistical analysis

A statistical analysis plan was designed by the study statistician (FF) and approved by the Study Management Group, and can be found online. At the time of study inception, there were no data available on the effect of different immunosuppressive therapies on humoral immune responses to SARS-CoV-2 vaccination in people with IBD compared with healthy people. Therefore, to inform power calculations, we modelled vaccination responses in patients with IBD on the basis of data from the CLARITY-IBD study, which investigated serological responses to SARS-CoV-2 infection and vaccination against SARS-CoV-2 in patients with IBD treated with infliximab or vedolizumab.[16] We made the assumption that the immune responses of the non-immunosuppressed control participants in our study would be similar to those of participants in the CLARITY-IBD study who were treated with vedolizumab (vedolizumab, an anti-integrin therapy, has a gut-specific mechanism of action that does not affect systemic immunity). In the CLARITY-IBD study, the mean (not adjusted by vaccine type) $\log_{10}$ concentration of anti-SARS-CoV-2 spike protein antibodies was 5·225 U/mL (SD 1·697) in participants on infliximab and 7·084 U/mL (1·704) in participants on vedolizumab. Assuming a similar difference in serological response, we calculated that 42 participants (21 in the infliximab monotherapy group and 21 in the control group) would be required to detect a similar difference of 1·859 U/mL between the infliximab monotherapy group and the healthy control group, with 90% power at a 0·05 significance level, accounting for a 10% dropout of participants due to evidence of previous SARS-CoV-2 infection at baseline. Pre-existing data to inform power calculations for the other immunosuppressive therapies were not available, although it was noted that, in the setting of pneumococcal vaccination, the response rate in thiopurine recipients was higher than in infliximab recipients.[4] We powered the study on the assumption that other immunosuppressive regimens would suppress antibody responses by 50% of the effect of infliximab, with a similar estimate for the SD. Thus, we estimated that 80 participants in each of the other drug regimen groups and 80 participants in the healthy control group would be needed to detect a difference of 0·93 U/mL with 90% power at a 0·05 significance level, accounting for a 10% dropout of participants due to evidence of previous SARS-CoV-2 infection at baseline.[16,17]

We included patients with missing clinical data in analyses for which they had data and have specified the denominator for each variable. No imputation of missing data was performed. Anti-SARS-CoV-2 spike protein antibody concentrations are reported as geometric means and SDs (geometric $SD[x]=e^{SD[\log x]}$). Other continuous data are reported as medians and IQRs, and discrete data are reported as numbers and percentages, unless otherwise stated.

For the primary outcome analysis, linear regression models of $\log_{10}$-transformed anti-SARS-CoV-2 spike protein antibody concentration, adjusted for age and vaccine type (adjustments made owing to the substantial effect of these variables on humoral responses to SARS-CoV-2 vaccination), were used to identify IBD treatment regimens associated with the concentration of anti-SARS-CoV-2 spike protein antibodies. We also used multivariable linear regression models to assess the association between immunosuppressive treatment regimens in IBD and COVID-19 vaccine-induced antibody responses, adjusting for a broader range of confounders. These confounders were identified using data from the CLARITY-IBD study; we included, a priori, IBD medication (for patients receiving thiopurine and infliximab combination therapy, each therapy was considered as an independent variable in our multivariable analysis of confounding), vaccine type (mRNA or adenovirus), age, IBD subtype, ethnicity, and smoking status.[16] We did not perform stepwise regression or adjust for multiple comparisons. Age was treated as a continuous variable in the analysis and its coefficient is expressed per decade. Results are presented after exponentiation, so that the coefficients of the model correspond to the geometric mean ratio (GMR) estimates associated with each binary covariate. We also report the proportions of patients who mounted protective immune responses (seroconversion) and the proportions of participants with anti-SARS-CoV-2 spike protein antibody concentrations greater than 2 geometric SDs below the geometric mean of healthy control participants. Concentrations of anti-SARS-CoV-2 spike protein antibodies were compared between participants with versus without evidence of previous infection (stratified by treatment group) by use of Mann–Whitney *U* tests, with two-tailed p values.

We conducted post-hoc diagnostics to test the statistical assumptions underlying the multivariable model and examined whether data skew impacted our results by conducting a post-hoc sensitivity analysis using a one-parameter Box Cox transformation with $\lambda=0{\cdot}15$ (based on optimising the log-likelihood of the model). Furthermore, because corticosteroid treatment might affect humoral responses to vaccination, we did a

For the **statistical analysis plan** see https://www.vipstudy.uk/info

post-hoc sensitivity analysis excluding participants who reported corticosteroid use from the multivariable model. We did another post-hoc sensitivity analysis in which we included corticosteroid use, body-mass index (BMI), and gender as additional independent variables in the multivariable model.

	Thiopurine (n=64)	Thiopurine plus infliximab (n=56)	Infliximab (n=49)	Ustekinumab (n=49)	Vedolizumab (n=50)	Tofacitinib (n=19)	Healthy controls (n=88)	p value
Age, years	45·1 (30·8–54·2)	36·0 (29·8–46·5)	41·4 (31·8–55·0)	42·7 (33·9–52·1)	44·4 (35·2–59·5)	47·0 (35·3–54·5)	33·9 (28·0–45·7)	0·0011
Gender								
Female	36/63 (57%)	28/56 (50%)	22/49 (45%)	23/48 (48%)	11/48 (23%)	5/19 (26%)	56/88 (64%)	0·0005
Male	27/63 (43%)	28/56 (50%)	27/49 (55%)	25/48 (52%)	37/48 (77%)	14/19 (74%)	30/88 (34%)	..
Other	0/63	0/56	0/49	0/48	0/48	0/19	1/88 (1%)	..
Prefer not to say	0/63	0/56	0/49	0/48	0/48	0/19	1/88 (1%)	..
Ethnicity								
White	52/63 (83%)	45/56 (80%)	35/49 (71%)	41/48 (85%)	36/48 (75%)	17/19 (89%)	69/88 (78%)	0·51
Non-White	11/63 (17%)	11/56 (20%)	14/49 (29%)	7/48 (15%)	12/48 (25%)	2/19 (11%)	19/88 (22%)	..
Asian	3/63 (5%)	10/56 (18%)	7/49 (14%)	6/48 (13%)	9/48 (19%)	2/19 (11%)	12/88 (14%)	..
Mixed	2/63 (3%)	1/56 (2%)	4/49 (8%)	1/48 (2%)	1/48 (2%)	0/19	3/88 (3%)	..
Black	2/63 (3%)	0/56	1/49 (2%)	0/48	1/48 (2%)	0/19	3/88 (3%)	..
Other	4/63 (6%)	0/56	2/49 (4%)	0/48	1/48 (2%)	0/19	1/88 (1%)	..
Diagnosis								
Crohn's disease	27/64 (42%)	34/56 (61%)	35/49 (71%)	47/49 (96%)	18/50 (36%)	1/19 (5%)	0/0	0·0005
Ulcerative colitis	35/64 (55%)	19/56 (34%)	13/49 (27%)	1/49 (2%)	32/50 (64%)	18/19 (95%)	0/0	..
Unclassified inflammatory bowel disease	2/64 (3%)	3/56 (5%)	1/49 (2%)	1/49 (2%)	0/50	0/19	0/0	..
Body-mass index, kg/m²	24·2 (22·6–27·0)	24·3 (21·3–27·2)	25·5 (23·5–29·5)	24·2 (22·4–28·3)	25·1 (22·2–27·7)	25·7 (23·5–28·4)	22·5 (20·9–25·1)	0·0001
Comorbidities								
Heart disease	1/63 (2%)	1/56 (2%)	2/49 (4%)	0/48	1/48 (2%)	0/19	0/88	0·42
Diabetes	3/63 (5%)	0/56	2/49 (4%)	3/48 (6%)	3/48 (6%)	0/19	1/88 (1%)	0·24
Lung disease	7/63 (11%)	9/56 (16%)	5/49 (10%)	5/48 (10%)	3/48 (6%)	3/19 (16%)	4/87 (5%)	0·28
Kidney disease	1/63 (2%)	0/56	2/49 (4%)	0/48	1/48 (2%)	0/19	0/88	0·25
Cancer	1/63 (2%)	0/56	1/49 (2%)	0/48	0/48	0/19	0/88	0·56
Smoker								
Yes	2/63 (3%)	4/56 (7%)	4/49 (8%)	5/48 (10%)	5/48 (10%)	0/19	4/88 (5%)	0·24
Not currently	21/63 (33%)	14/56 (25%)	16/49 (33%)	14/48 (29%)	14/48 (29%)	10/19 (53%)	18/88 (20%)	..
Never	40/63 (63%)	38/56 (68%)	29/49 (59%)	29/48 (60%)	29/48 (60%)	9/19 (47%)	66/88 (75%)	..
Vaccine*								
BNT162b2 (Pfizer–BioNTech)	25/63 (40%)	23/56 (41%)	25/49 (51%)	14/48 (29%)	18/48 (38%)	7/19 (37%)	50/88 (57%)	0·0090
ChAdOx1 nCoV-19 (Oxford–AstraZeneca)	38/63 (60%)	33/56 (59%)	24/49 (49%)	34/48 (71%)	30/48 (63%)	12/19 (63%)	32/88 (36%)	..
mRNA-1273 (Moderna)	0/63	0/56	0/49	0/48	0/48	0/19	5/88 (6%)	..
Unsure	0/63	0/56	0/49	0/48	0/48	0/19	1/88 (1%)	..
Prednisolone	1/63 (2%)	4/56 (7%)	5/49 (10%)	3/47 (6%)	4/48 (8%)	2/19 (11%)	0/0	0·35
Active disease (PRO2)	4/63 (6%)	2/53 (4%)	1/49 (2%)	4/44 (9%)	8/45 (18%)	2/19 (11%)	0/0	0·066
Days since second vaccine dose	78·0 (63·5–86·0)	83·5 (62·8–88·2)	73·0 (61·0–87·0)	80·0 (65·5–87·0)	80·5 (64·0–87·0)	80·0 (63·5–89·5)	80·0 (78·0–87·0)	0·25

Data are median (IQR) or n/N (%), unless otherwise specified. Previous infection was defined by a concentration of anti-SARS-CoV-2 nucleocapsid antibodies of 0·12 U/mL or more or a self-reported previous PCR test confirming SARS-CoV-2 infection. *All participants received two homologous doses of vaccine. No vaccine mixing occurred between the first and second vaccine doses.

Table: **Characteristics of VIP study participants without evidence of previous infection (n=375)**

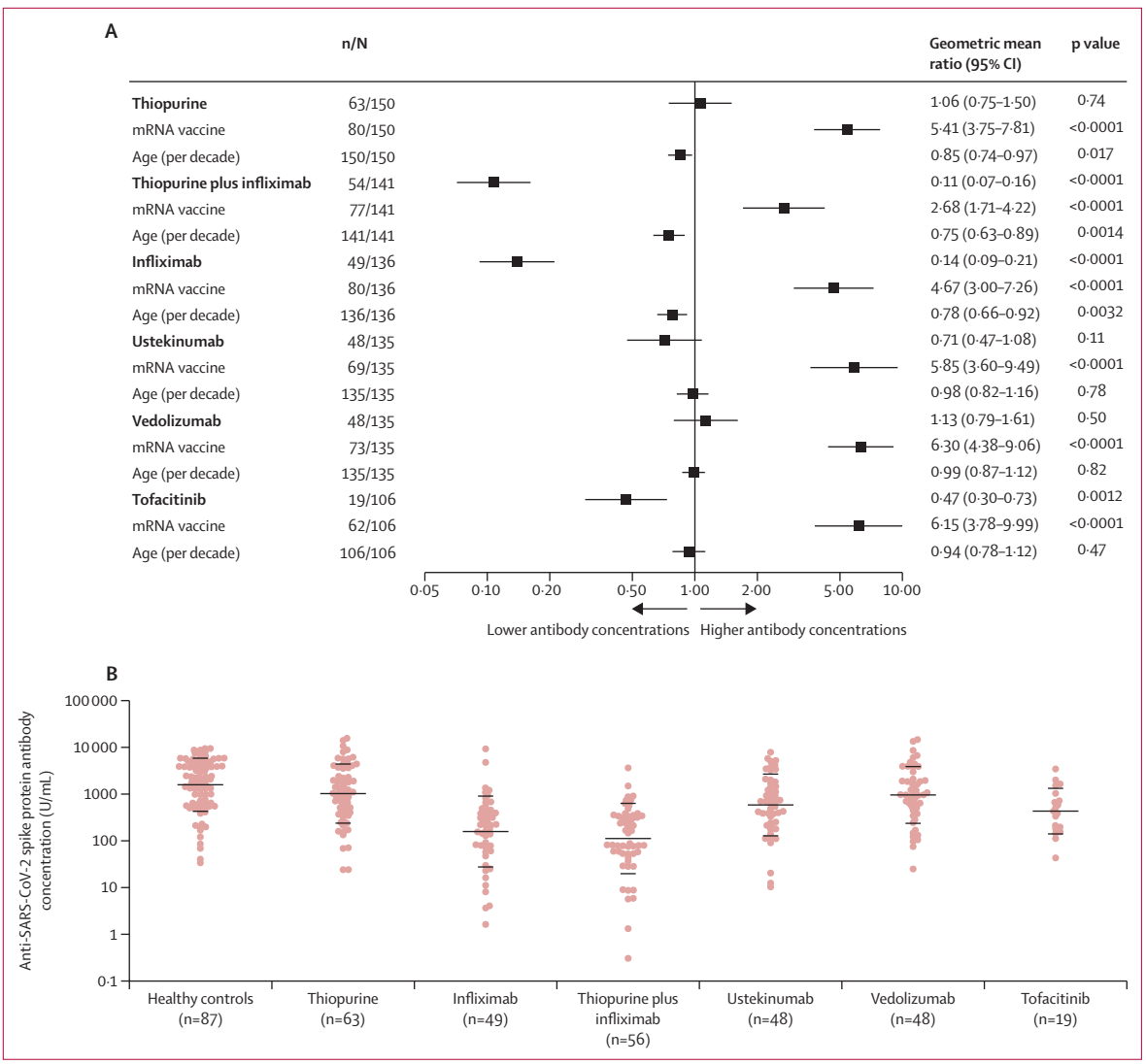

Figure 1: **Anti-SARS-CoV-2 spike protein antibody concentrations in people without evidence of previous infection**
(A) Multivariable model, adjusted for vaccine type and age, showing the exponentiated coefficients of linear regression models of log_{10}-transformed concentrations of anti-SARS-CoV-2 spike protein antibodies stratified by study treatment group. Results are for individuals without evidence of previous infection. The values shown represent the geometric mean ratios of antibody concentrations associated with each variable. (B) Anti-SARS-CoV-2 spike protein antibody concentration stratified by study treatment group. The longer black bar represents the geometric mean and the shorter black bars represent 1 geometric SD either side of the geometric mean.

Statistical analyses were done in R, version 4.0.4. Figures were created in R, version 4.0.4, and Graphpad Prism, version 9.0.0. We obtained p values using Fisher's exact tests for categorical variables and Kruskal–Wallis tests for continuous variables. All tests were two-tailed and p values of less than 0·05 were considered significant. This study is registered in the ISRCTN Registry, ISRCTN13495664.

Role of the funding source

VIP is an investigator-led, UK NIHR COVID-19 study. Financial support was provided as a research grant by Pfizer. Pfizer had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor was Imperial College London.

Results

Between May 31 and Nov 24, 2021, 483 participants were recruited to the VIP study from nine UK hospitals, comprising 78 treated with a thiopurine, 63 treated with infliximab, 72 treated with a thiopurine plus infliximab, 57 treated with ustekinumab, 62 treated with vedolizumab, 30 treated with tofacitinib, and 121 healthy controls. There were 108 participants with evidence of previous SARS-CoV-2 infection and 375 participants without evidence of previous infection. Participant

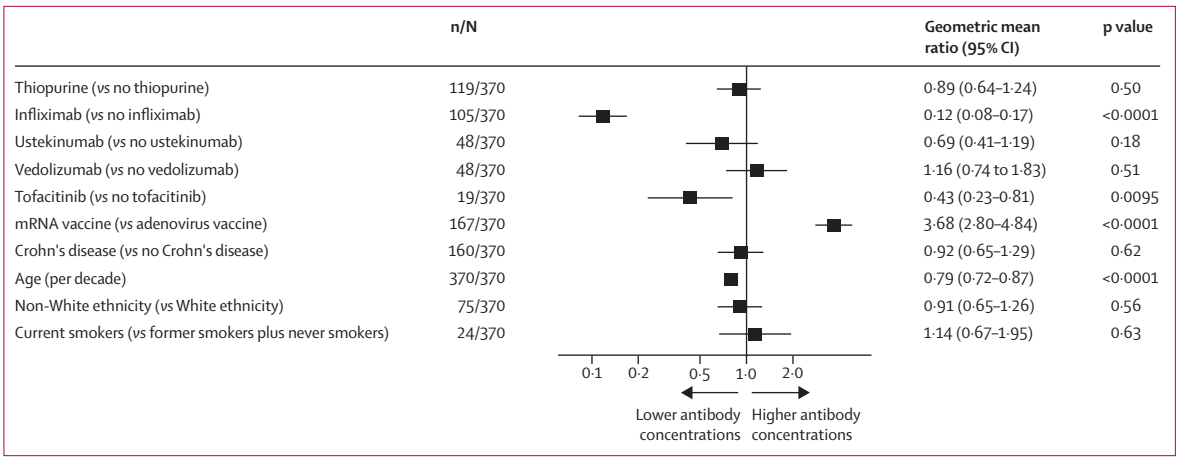

Figure 2: **Multivariable model showing exponentiated coefficients of linear regression models of log_{10}-transformed concentrations of anti-SARS-CoV-2 spike protein antibodies, adjusting for known confounders**

Results are for individuals without evidence of previous infection. The values shown represent the geometric mean ratios of antibody concentrations associated with each variable. Age was treated as a continuous variable in the analysis and its coefficient is expressed per decade.

characteristics (excluding those with evidence of previous SARS-CoV-2 infection) are shown in the table and characteristics for the entire study population (including participants with evidence of previous SARS-CoV-2 infection) are shown in the appendix (pp 1–5).

See Online for appendix

For the primary analysis, we included 370 participants without evidence of previous infection (five participants had missing data for either age or vaccine type and therefore could not be included in the primary analysis). Geometric mean anti-SARS-CoV-2 spike protein antibody concentrations were significantly lower in patients treated with infliximab (156·8 U/mL [geometric SD 5·7]; p<0·0001), thiopurine plus infliximab (111·1 U/mL [5·7]; p<0·0001), or tofacitinib (429·5 U/mL [3·1]; p=0·0012) compared with controls (1578·3 U/mL [3·7]; figure 1A, B). No significant differences in anti-SARS-CoV-2 spike protein antibody concentrations were found between patients treated with thiopurine monotherapy (1019·8 U/mL [4·3]; p=0·74), ustekinumab (582·4 U/mL [4·6]; p=0·11), or vedolizumab (954·0 U/mL [4·1]; p=0·50) and healthy controls (figure 1A, B). Anti-SARS-CoV-2 spike protein antibody concentrations for each vaccine type (mRNA and adenovirus vector) stratified by study group are shown in the appendix (pp 6–8).

In multivariable modelling including 370 participants without evidence of previous infection, lower anti-SARS-CoV-2 spike protein antibody concentrations were independently associated with infliximab (GMR 0·12 [95% CI 0·08–0·17]) and tofacitinib (GMR 0·43 [0·23–0·81]) use, but not with ustekinumab (GMR 0·69 [0·41–1·19]), thiopurine (GMR 0·89 [0·64–1·24]), or vedolizumab (GMR 1·16 [0·74–1·83]) use (*vs* healthy controls; figure 2). mRNA vaccines (GMR 3·68 [95% CI 2·80–4·84]; *vs* adenovirus vector vaccines) were independently associated with higher antibody concentrations, and older age per decade (GMR 0·79 [0·72–0·87]) was independently associated with lower antibody concentrations (figure 2). IBD subtype, ethnicity, and smoking status were not associated with anti-SARS-CoV-2 spike protein antibody concentrations (figure 2). After performing post-hoc diagnostics to test the statistical assumptions underlying the multivariable model, which showed that the data did not quite fit a log_{10} normal distribution (appendix p 9), we further ensured that data skew did not affect our results by conducting a post-hoc sensitivity analysis using a one-parameter Box Cox transformation (appendix p 10) with λ=0·15 (based on optimising the log-likelihood of the model), which showed no significant effect on the multivariable linear regression model (appendix p 11).

A small number of patients with IBD were receiving systemic corticosteroids at the time of vaccination (n=19). Because corticosteroids might additionally affect humoral responses to vaccination, we did a post-hoc sensitivity analysis on the multivariable model, excluding participants who reported corticosteroid use (appendix p 12). After we excluded corticosteroid recipients, the variables that were independently associated with significant changes in GMR estimates of anti-SARS-CoV-2 spike protein antibody concentration (infliximab, tofacitinib, mRNA vaccine, and age) in the main analysis remained significant, and the variables that were not associated with antibody concentration in the main analysis remained non-significant (appendix p 12). We did a further post-hoc sensitivity analysis on the multivariable model, including corticosteroid use, BMI, and gender as additional independent variables (appendix p 13). Corticosteroid use, BMI, and gender were not associated with significant changes in GMR estimates of anti-SARS-CoV-2 spike protein antibody concentration (appendix p 13).

We further compared anti-SARS-CoV-2 spike protein antibody responses, stratified by IBD therapy, in the 108 participants with evidence of previous infection with

the 370 participants without evidence of previous infection. Among healthy controls and patients with IBD in all treatment groups, people with evidence of previous natural infection had significantly stronger anti-SARS-CoV-2 spike protein antibody responses following vaccination than did those without evidence of previous infection (appendix p 14).

Among the 375 participants included in our analysis without evidence of previous SARS-CoV-2 infection, all participants in the thiopurine monotherapy, vedolizumab, tofacitinib, and control groups had seroconverted (concentrations of anti-SARS-CoV-2 spike protein antibodies of at least 15 U/mL; figure 3A). However, five (10%) of 49 patients on infliximab monotherapy, seven (13%) of 56 patients on thiopurine plus infliximab, and two (4%) of 49 patients on ustekinumab did not generate antibody concentrations of 15 U/mL or more (figure 3A). The proportions of individuals who generated antibody concentrations of greater than 2 geometric SDs below the geometric mean of the healthy control population were highest in the infliximab monotherapy, thiopurine plus infliximab, and tofacitinib groups (figure 3B). All 108 participants with evidence of previous SARS-CoV-2 infection seroconverted (appendix p 14).

Discussion

This study provides new insights into the effect of different commonly used immunosuppressive drugs on COVID-19 vaccine-induced humoral responses. The key findings are that patients with IBD being treated with infliximab or tofacitinib had lower anti-SARS-CoV-2 spike protein antibody concentrations after two doses of vaccine than did healthy controls. Reassuringly, no significant reductions in antibody responses were observed in patients with IBD being treated with thiopurines, ustekinumab, or vedolizumab relative to control participants. The magnitude of reduction in antibody response was especially striking in patients treated with infliximab patients, with a 10-times reduction in antibody concentration compared with control participants. Other studies measuring humoral responses following two doses of COVID-19 vaccines have corroborated our findings in patients receiving anti-TNF therapy (eg, infliximab), although, in general, these studies have reported a more modest reduction in anti-SARS-CoV-2 spike protein antibody concentrations.[19,20,26] However, there are important differences between those studies and our study. Most previous studies have reported serological responses elicited exclusively by mRNA COVID-19 vaccines. In our study, serological responses were more than 3-times higher following vaccination with mRNA versus adenovirus vector vaccines and were consistently higher for mRNA versus adenovirus vaccines irrespective of IBD medication prescribed. The other studies also do not include healthy controls without IBD as a comparator group, have used different antibody assays, and have evaluated the manufacturer-recommended standard vaccine dosing schedules. These studies also looked at serological responses at slightly earlier timepoints post-vaccination than we did, when responses are likely to be at their highest.

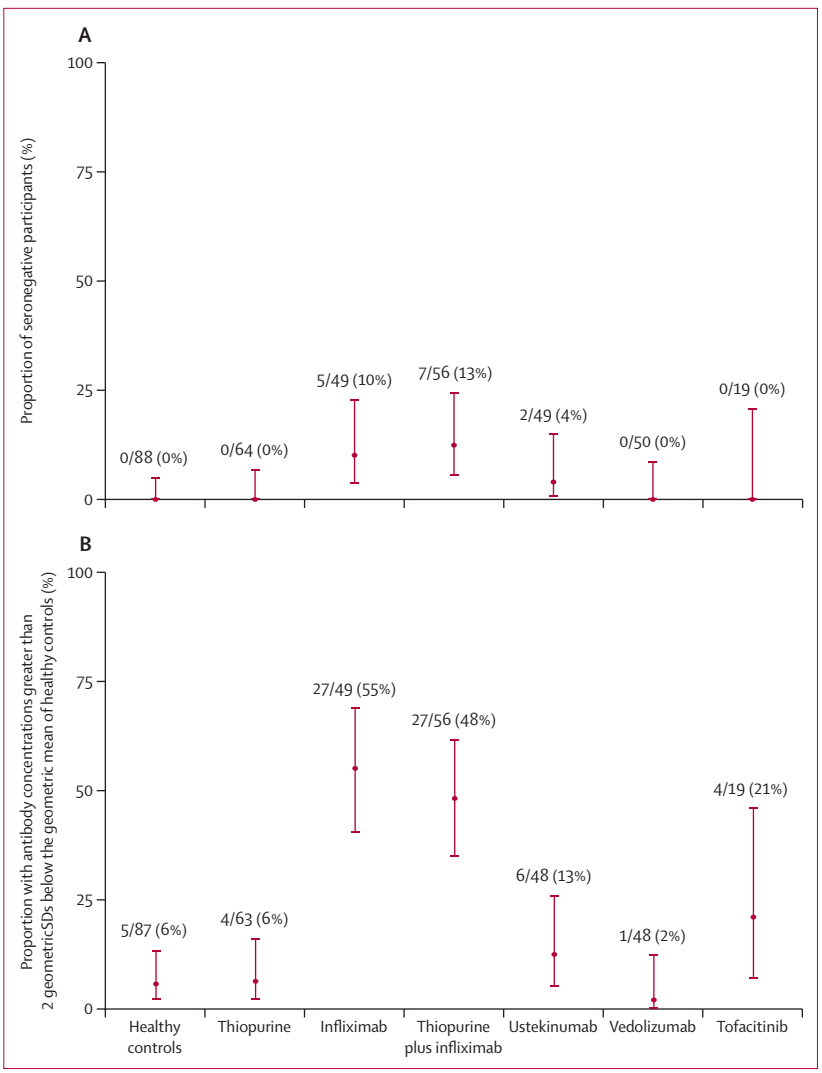

Figure 3: **Seroconversion after vaccination in people without evidence of previous SARS-CoV-2 infection**
(A) Proportion of participants who were seronegative, defined by an anti-SARS-CoV-2 spike protein antibody concentration of less than 15 U/mL. The circles represent the proportion estimates and the error bars represent 95% CIs on either side. (B) Proportion of participants with anti-SARS-CoV-2 spike protein antibody concentrations greater than 2 geometric SDs below the geometric mean of healthy control participants. The circles represent the proportion estimates and the error bars represent 95% CIs on either side.

Within 92 days of having two doses of a COVID-19 vaccine, 55% of patients on infliximab monotherapy and 48% of patients on thiopurine and infliximab combination therapy had antibody concentrations greater than 2 geometric SDs below the geometric mean of control participants; 10% and 13%, respectively, did not mount antibody responses at concentrations of 15 U/mL or more, which correlate with viral neutralisation in functional assays.[16] Given that antibody concentrations wane with time, even in healthy

populations,[27] these results raise serious concerns about whether durable, protective antibody responses will be maintained in patients with IBD on these treatments, especially when the initial magnitude of the response is so substantially diminished. Similar concerns about durability might be expected in patients treated with tofacitinib, in whom post-vaccination antibody concentrations were also significantly diminished relative to healthy controls (geometric mean concentration 430 U/mL *vs* 1578 U/mL). These concerns might be especially pertinent with the emergence of more transmissible SARS-CoV-2 variants, such as the omicron (B.1.1.529) variant, for which higher antibody concentrations might be needed to confer protection.

As expected, increasing age was significantly associated with diminished antibody responses, which is consistent with other reports[28] and in keeping with the acknowledged effect of immunosenescence on humoral immunity.[29] In multivariable modelling, mRNA vaccines (*vs* adenovirus vaccines) were independently associated with significantly higher antibody concentrations across all study groups, including patients on drug regimens associated with the most impaired serological responses. Notably, serological responses were significantly higher in participants across all treatment groups and the control group if they were previously exposed to natural COVID-19 infection. These data support the rationale for providing third doses, or booster doses, to patients with IBD.

Several limitations of this study should be acknowledged. First, humoral immune responses were measured at a single timepoint and we are not able to comment on the durability of antibodies with time following two doses of COVID-19 vaccines. Data are not yet available on the effect of third vaccine doses. Second, although we have accounted for several potential confounding factors in our multivariable models that have been associated with humoral responses to vaccination in other studies (eg, age, vaccine type, IBD subtype, smoking status, and ethnicity), we cannot exclude the possibility that our results are affected by other unmeasured confounding factors. For example, data were not available on dose or dosing schedule for the different IBD therapies. Although we performed sensitivity analyses showing that corticosteroids did not have a large impact on our findings, the small number of corticosteroid recipients in our study prevents us from drawing firm conclusions about the effect of corticosteroids on vaccine-induced antibody responses. Third, the power calculations for this study of vaccines that have not been previously trialled in patients with IBD relied on several assumptions. Fourth, after excluding participants with evidence of previous infection from the primary analysis, the size of the tofacitinib group was modest, which limited the certainty with which conclusions could be drawn for some outcomes. Fifth, although we used multivariable modelling to identify whether individual IBD therapies were independently associated with vaccine-induced anti-SARS-CoV-2 spike protein antibody concentration, adjustment for multiple comparisons was not done in the primary analysis. Sixth, the data regarding ustekinumab also require cautious interpretation. Although the reduction in antibody concentrations observed in patients receiving ustekinumab was not statistically significant, our study was not powered to detect modest reductions in antibody response. Accordingly, this study cannot reliably exclude a minor inhibitory effect for ustekinumab on SARS-CoV-2 vaccine-induced antibody responses. Although our data are far more convincing for thiopurines and vedolizumab not having an inhibitory effect on serological response, the study size precludes us from being absolutely certain that marginal reductions in antibody concentrations are not present in patients treated with these drugs. In any case, it is debatable whether very minor reductions in antibody responses are likely to be clinically relevant for protection. Finally, another potential limitation of this study is that we looked at humoral immunity, but not cell-mediated immunity. There has been some work on T-cell responses after SARS-CoV-2 vaccination in immunocompromised patients with IBD,[26,30] but the extent to which such responses correlate with humoral immunity across the spectrum of immunosuppressive therapies used in IBD is yet to be fully elucidated. A key priority of future work will be to probe the effect of COVID-19 vaccines on antigen-specific T-cell responses in the VIP cohort. There is also a pressing need to understand how the magnitude of vaccine-induced humoral and cell-mediated immune responses correlate with protective immunity.

Our data have important implications for global public health policy decision making. Some countries have already embarked on third primary doses and booster programmes, and a framework for informing the prioritisation of people requiring repeated dosing is urgently needed. Our results raise the question of whether there could be a role for clinical testing of humoral immunity to guide prioritisation of future vaccine doses, particularly in resource-limited settings. Our findings support a personalised approach to scheduling of vaccine dosing and, given the poor vaccine-induced serological responses observed in patients with IBD being treated with infliximab or tofacitinib, these individuals should be fast-tracked to early repeat vaccine dosing. The increased magnitude of response elicited by mRNA versus adenovirus vaccines indicates that strategies using full-dose mRNA vaccines might be favoured in these patient groups.

Contributors

JLA, NAK, CB, JRG, CWL, TA, and NP participated in the conception and design of this study. CB was the project manager and coordinated patient recruitment. RN coordinated all biochemical analyses and central laboratory aspects of the project. JLA, NAK, HI, SA, AS, RCS, ZL, CB, ADM, GRJ, LC, FF, SS, PMI, LCH, HRTW, AJK, MP, KK, KVP, JPT, DMA, RJB, ALH, CWL, JRG, TA, SB, and RL, and NP were involved in the acquisition, analysis, or interpretation of data. Drafting of the

manuscript was done by JLA, NAK, and NP. JLA, CWL, TA, and NP obtained funding for the study. All authors contributed to the critical review and final approval of the manuscript. JLA, NAK, NP, and TA accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JLA reports sponsorship from Vifor Pharma for accommodation and travel to the British Society of Gastroenterology annual meeting 2019, outside the submitted work. NAK reports grants from AbbVie, Biogen, Celgene, Celtrion, Galapagos, MSD, Napp, Pfizer, Pharmacosmos, Roche, and Takeda; consulting fees from Amgen, Bristol Myers Squibb, Falk, Janssen, Mylan, Pharmacosmos, Galapagos, Takeda, and Tillotts; personal fees from Allergan, Celltrion, Falk, Ferring, Janssen, Pharmacosmos, Takeda, Tilllotts, and Galapagos; and support for attending meetings from AbbVie, Falk, and Janssen, outside the submitted work. AS has received travel expense support from Janssen. SS reports grants from Takeda, AbbVie, Tillots Pharma, Janssen, Pfizer, and Biogen, and personal fees from Takeda, AbbVie, Janssen, Pharmacocosmos, Biogen, Pfizer, Tillots Pharma, and Falk Pharma, outside the submitted work. ALH reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, AZ, Atlantic, Bristol Myers Squibb, Celltrion, Falk, Galapogos, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire, and Takeda; participation on the Global Steering Committee for Genentech; support for attending meetings from AbbVie, Takeda, and Janssen; and participation on a data safety monitoring board or advisory board for AbbVie, AZ, Atlantic, Bristol Myers Squibb, Galapogos, Janssen, Pfizer, and Takeda. PMI reports grants from Celltrion, Takeda, MSD, Pfizer, and Galapagos, and personal fees from Celltrion, Takeda, Pfizer, Galapagos, Gilead, AbbVie, Janssen, Bristol Myers Squibb, Lilly, and Arena, outside the submitted work. MP receives unrestricted educational grants from Pfizer for genetic analyses to support the IBD BioResource and speaker fees from Janssen. GRJ has received grants from the Wellcome Trust and ECCO; speaker fees from Takeda, Ferring, and Janssen; and support for attending meetings or travel from Ferring. KK reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen and Ferring; support for attending meetings or travel from Janssen and Takeda; and participation on a data safety monitoring board or advisory board for Janssen and PredictImmune. KVP reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, DrFalk, Janssen, PreddictImmune, and Takeda; support for attending meetings or travel from AbbVie, Ferring, Janssen, and Tillots; and participation on a data safety monitoring board or advisory board for AbbVie, Galapagos, and Janssen. AJK reports consulting fees from Janssen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer and Takeda; support for attending meetings or travel from Janssen, Tillots, and Norgine; and participation on a data safety monitoring board or advisory board for AbbVie. LCH reports support for attending meetings or travel from AbbVie. CWL reports a Future Leaders Fellow award from UK Research and Innovation; personal consulting fees from Galapagos, AbbVie, Takeda, Pfizer, Janssen, and Iterative Scopes; institutional consulting fees from Trellus Health; personal fees from Galapagos, AbbVie, Takeda, Pfizer, Janssen, GSK, Gilead, Fresnius Kabi, Ferring, and Dr Falk; and support for attending meetings from Galapagos, AbbVie, Takeda, Pfizer, Janssen, GSK, Gilead, Fresnius Kabi, Ferring, and Dr Falk. RJB and DMA are members of the Global T cell Expert Consortium and have consulted for Oxford Immunotec outside the submitted work. JRG reports grants from F Hoffmann-La Roche, Biogen, Celltrion Healthcare, and Galapagos, and non-financial support from Immundiagnostik, during the conduct of the study. TA reports grant funding from Pfizer to his institution to deliver this study; grants from Celltrion, Roche, Takeda, Biogen, and Galapagos; and honoraria for lectures from Takeda and Roche, outside the submitted work. NP is the principal investigator on the research grant from Pfizer that helped to fund the VIP study; has received research grants from Bristol Myers Squibb outside the submitted work; reports personal fees from Takeda, Janssen, Pfizer, Bristol Myers Squibb, AbbVie, Roche, Lilly, Allergan, and Celgene, outside the submitted work; and has served as a speaker or advisory board member for AbbVie, Allergan, Bristol Myers Squibb, Celgene, Falk, Ferring, Janssen, Pfizer, Tillotts, Takeda, and Vifor Pharma. All other authors declare no competing interests.

Data sharing

The study protocol, including the statistical analysis plan, is available at www.vipstudy.uk. Individual de-identified participant 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 nicholas.powell@ic.ac.uk. To gain access, data requestors will need to sign a data access agreement.

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