1   Title: Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in

2   infliximab- and vedolizumab-treated patients

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55   **Abstract**

56   We report SARS-CoV-2 vaccine-induced immunity and risk of breakthrough infections in

57   patients with inflammatory bowel disease treated with infliximab, a commonly used anti-TNF

58   drug and those treated with vedolizumab, a gut-specific antibody targeting integrin a4b7 that does

59   not impact systemic immunity. In infliximab-treated patients, the magnitude of anti-SARS-CoV2

60   antibodies was reduced 4-6-fold. One fifth of both infliximab- and vedolizumab-treated patients did

61   not mount a T cell response. Antibody half-life was shorter in infliximab-treated patients.

62   Breakthrough SARS-CoV-2 infections occurred more frequently in infliximab-treated patients and the

63   risk was predicted by the level of antibody response after second vaccine dose. Overall, recipients of

64   two doses of the BNT162b2 vaccine had higher anti-SARS-CoV-2 antibody concentrations,

65   higher seroconversion rates, shorter antibody half-life and less breakthrough infections compared

66   to ChAdOx1 nCoV-19 vaccine recipients. Irrespective of biologic treatment, higher, more sustained

67   antibody levels were observed in patients with a history of SARS-CoV-2 infection prior to

68   vaccination. Patients treated with anti-TNF therapy should be offered third vaccine doses.

69

70 **Introduction**

71 Vaccination programmes have reduced SARS-CoV-2 transmission, hospitalisation and deaths[1].

72 Patients treated with immunosuppressive drugs were excluded from the original trials for COVID-19

73 vaccines[2,3]. Consequently, data relating to the magnitude and durability of immune responses and

74 subsequent vaccine effectiveness in this population are limited[4].

75

76 Drugs targeting tumor necrosis factor (TNF), such as infliximab, are the most frequently prescribed

77 biological therapies used in the treatment of immune-mediated inflammatory disorders (IMIDs).

78 Observational studies indicate that most patients with inflammatory bowel disease (IBD), an

79 archetypal IMID, mount serological responses following SARS-CoV-2 vaccines, although most were

80 underpowered to discern the impact of specific drugs, including immunomodulators (azathioprine,

81 mercaptopurine, and methotrexate) and/or biologic therapies[5–8]. We reported that antibody

82 responses following SARS-CoV-2 infection[9,10] or a single-dose of either the BNT162b2 or ChAdOx1

83 nCoV-19 SARS-CoV-2 vaccines were impaired in anti-TNF treated patients when compared to

84 vedolizumab treated patients[11]. Vedolizumab, is a gut-selective anti-integrin α4β7 monoclonal

85 antibody that, unlike anti-TNF drugs is not associated with increased susceptibility to systemic

86 infection or attenuated serological responses to vaccination[12].

87

88 Here we compare immune responses between infliximab- and vedolizumab-treated patients with

89 IBD who received two doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccines. We hypothesised that,

90 irrespective of the type of vaccine, antibody and T cell responses would be attenuated and less

91 durable with an associated increased risk of breakthrough SARS-CoV-2 infections in patients treated

92 with infliximab.

93

5

Results

Patient characteristics

Between September 22nd 2020 and December 23rd 2020, 7,226 patients were recruited to the

CLARITY study from 92 UK hospitals[10]. In this analysis we included 2,264 infliximab- and 1,024

vedolizumab-treated participants without a history of prior SARS-CoV-2 infection, who had received

uninterrupted biologic therapy since recruitment and had an antibody test between 14 and 70 days

after a second-dose of the either the BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines.

Participant characteristics are shown in Table 1.

Additional analyses are presented for a subset of 211 infliximab- and 71 vedolizumab-treated

patients included in our T cell experiments (Supplementary Table 2), and a further 525 infliximab-

and 224 vedolizumab-treated participants who had a history of SARS-CoV-2 infection before

vaccination (Supplementary Table 3).

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

Overall, the geometric mean [geometric SD] of anti-S RBD antibody concentration was higher in

recipients of two doses of the BNT162b2 than ChAdOx1 nCoV-19 vaccines (1080.2 U/mL [7.6] vs

289.9 U/mL[5.2], $p < 0.0001$). Anti-S RBD antibody concentrations were lower in patients treated

with infliximab than in those treated with vedolizumab, following a second dose of BNT162b2 (565.1

U/mL [6.2] vs 4527.6 U/mL [5.4], $p < 0.0001$) and ChAdOx1 nCoV-19 (184.5 U/mL [5.0] vs 786.2 U/mL

[3.5], $p < 0.0001$) vaccines (Fig. 1).

Crude sensitivity analyses, excluding patients treated with a concomitant immunomodulator,

confirmed lower anti-S RBD antibody concentrations in patients treated with infliximab alone versus

118   vedolizumab alone (BNT162b2 816.5 U/mL [4.9] vs 4616.3U/mL [6.0], p <0.0001, ChAdOx1 nCoV-19

119   181.4 U/mL [4.4] vs 774.9 U/mL [3.6], p <0.0001).

120   After propensity matching for immunomodulator use and the other factors associated with choice of

121   biologic, we confirmed lower anti-S RBD antibody concentrations in infliximab- compared to

122   vedolizumab-treated patients (BNT162b2 587.9 U/mL [6.1] vs 4657.5U/mL [4.7], p <0.0001,

123   ChAdOx1 nCoV-19 191.1 U/mL [4.7] vs 778.6 U/mL [3.7], p <0.0001) (Supplementary Table 4).

124

125   Multivariable linear regression analyses in patients without prior SARS-CoV-2 infection confirmed

126   that antibody concentrations were reduced four and six-fold in infliximab- compared with

127   vedolizumab- treated participants who received the BNT162b2 (fold change [FC] 0.15 [95% CI 0.12,

128   0.19], p<0.0001) and ChAdOx1 nCoV-19 ([FC] 0.24 [95% CI 0.20, 0.28], p<0.0001) vaccines (Fig. 2a

129   and Fig. 2b respectively). Age ≥60 years and Crohn's disease were also independently associated

130   with lower anti-S RBD antibody concentrations in vaccinated participants. Thiopurine or

131   methotrexate use was independently associated with lower anti-S RBD antibody concentrations in

132   participants who received the BNT162b2, but not the ChAdOx1 nCoV-19 vaccine. Current smoking,

133   non-white ethnicity and steroid use were associated with lower anti-S RBD antibody concentrations

134   in participants who received the ChAdOx1 nCoV-19 but not the BNT162b2 vaccine. To assess the

135   effect of vaccine type on antibody responses, we combined our response data in a model that

136   included vaccine type in addition to the significant factors above. Vaccination with the BNT162b2

137   vaccine compared to the ChAdOx1 nCoV-19 was independently associated with a 3.7 fold [95% CI

138   3.28 – 4.12] higher anti-S RBD antibody concentration (p < 0.0001) (Fig. 2c).

139

140   Seroconversion rates after the first vaccine dose were lower in infliximab- compared to

141   vedolizumab-treated participants (Fig. 1). However, administration of a second vaccine dose resulted

142   in a >100-fold and >25 fold increase in antibody concentrations in recipients of the BNT162b2 and

143   ChAdOx1 nCoV-19 vaccines, respectively (Fig. 1). Overall, more infliximab- than vedolizumab-treated

7

144   patients failed to seroconvert after their second vaccine dose (5.9% vs 1.3%, p < 0.0001).

145   Seroconversion rates stratified by biologic therapy and vaccine type are reported in Supplementary

146   Fig 1.

147

148   ***Anti-spike T cell responses following two doses of BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2***

149   ***vaccines***

150   There were no significant differences in the magnitude of anti-spike T cell responses observed in

151   infliximab- compared with vedolizumab-treated patients after one or two doses of either vaccine

152   (Fig. 3a). The proportion of patients failing to mount detectable T cell responses were similar in both

153   groups (infliximab 19.6% vs. vedolizumab 19.2%). For recipients of one and two doses of BNT162b2

154   vaccine there was a modest positive correlation between T cell responses and antibody

155   concentration. This association was not observed in recipients following either dose of the ChAdOx1

156   nCoV-19 vaccine (Fig. 3b). When T cell responses were ranked by magnitude of antibody responses,

157   most patients who did not mount an antibody response after the first vaccine dose (indicated by the

158   dark grey bar) had a detectable T cell response (Fig. 4). In addition to the uncoupling of the T cell and

159   antibody responses demonstrated, this analysis emphasised that about one fifth of participants

160   made no T cell responses irrespective of vaccine used (indicated by the light grey bars). Moreover,

161   a minority of individuals (3/67) 4.5% for BNT162b2 and (1/56) 1.8% for ChAdOx1 nCoV-19 vaccines

162   carry neither detectable antibody nor T cell responses after two doses of vaccine (Fig. 3b, Fig. 4).

163

164   ***Durability of antibody responses following two doses of BNT162b2 and ChAdOx1 nCoV-19 SARS-***

165   ***CoV-2 vaccines***

166   The estimated half-life of anti-S RBD antibodies was shorter in participants receiving the BNT162b2

167   compared to the ChAdOx1 nCoV-19 vaccines (4.6 weeks [95% CI 4.44 – 4.74] vs 5.9 weeks [95% CI

168   5.88 – 6.29], p value < 0.0001). When stratified by biologic, half-life estimates were shorter in

169   infliximab- than vedolizumab-treated patients following two-doses of BNT162b2 (4.0 weeks [95% CI

170   3.8 – 4.1] vs 7.2 weeks [95% CI 6.8 – 7.6]) and ChAdOx1 nCoV-19 (5.3 weeks [95% CI 5.1 – 5.5] vs 9.3

171   weeks [95% CI 8.5 – 10.2], p value < 0.0001) (Supplementary Fig. 2 and Supplementary Table 5).

172   Overall, following two doses of either vaccine, anti-S RBD antibodies showed minimal decay to last

173   follow-up in patients treated with vedolizumab (Fig. 5) and were similar to those observed in

174   participants in the Virus Watch community cohort (Supplementary Fig. 4). However, in infliximab-

175   treated participants the geometric mean concentrations dropped to the seroconversion threshold by

176   about 25 weeks after the second dose irrespective of vaccine administered (Fig. 5). Infliximab

177   compared to vedolizumab treatment, current smoking and white ethnicity were associated with a

178   faster fall in anti-S RBD antibody concentration below the seroconversion threshold.

179   (Supplementary Fig. 5, 6).

180

181   ***Breakthrough SARS-CoV-2 infections following two doses of vaccine***

182
183   267/5123 participants without PCR-positive or serological evidence of prior SARS-CoV-2 infection

184   had a first positive SARS-CoV-2 PCR test two or more weeks after the second vaccine dose. Overall,

185   89.2% patients were symptomatic: the most commonly reported symptoms were fatigue (73.7%),

186   anosmia/ageusia (71.4%), fever (57.1%), cough (54.9%), myalgia (45.9%), hoarse voice (30.8%),

187   confusion (27.8%) and chest pains (23.3%). 1.2% (3/251) of participants with PCR confirmed

188   infection were hospitalised because of COVID-19.

189

190   Breakthrough SARS-CoV-2 infections were more frequent (5.8% (201/3441) vs 3.9% (66/1682), p =

191   0.0039) and the time to breakthrough shorter in patients treated with infliximab than vedolizumab

192   (p = 0.0027) (Fig. 6b). In contrast biologic class did not impact on time to PCR confirmed infection

193   prior to vaccination (p = 0.63) (Fig. 6a). In a model that included biologic and vaccine type, shorter

194   time to breakthrough infection was associated with infliximab (Hazard Ratio (HR) 1.52 [95% CI 1.15 –

9

195   2.01], p = 0.003) and having received the ChAdOx1 nCoV-19 (HR 1.49 [95% CI 1.15 – 1.92], p =

196   0.0023) vaccine. Geometric mean [geometric SD] anti-S RBD antibody concentrations measured 2 to

197   10 weeks after a second vaccine dose were significantly lower in participants who subsequently had

198   a PCR confirmed breakthrough SARS-CoV-2 infection: for every 10-fold rise in anti-S RBD antibody

199   level we observed a 0.8-fold reduction in odds of breakthrough infection ([95% CI 0.70 – 0.99], p =

200   0.03).

201

202   *Antibody responses in patients with prior SARS-CoV-2 infection*

203   Amongst patients with a history of SARS-CoV-2 infection before vaccination, geometric mean [SD]

204   anti-S RBD antibody concentrations were lower in infliximab- compared with vedolizumab-treated

205   patients after a second dose of BNT162b2 (1330.0 U/mL [5.3] vs 7169.5 U/mL [4.6], p <0.0001) and

206   ChAdOx1 nCoV-19 (401.2 U/mL [5.5] vs 2077.3 [4.6] p <0.0001) vaccines. In all patients, antibody

207   concentrations following vaccination were higher in patients without a history of SARS-CoV-2

208   infection (Fig. 1). Irrespective of vaccine or biologic type, minimal decay of anti-S RBD antibodies

209   were observed up to a follow-up of 21 weeks.

210   **Discussion**

211   We have shown that in infliximab-treated patients, anti-SARS-CoV-2 spike antibody responses are

212   attenuated following two doses of the BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. One

213   fifth of both infliximab- and vedolizumab-treated patients did not mount a T cell response and a

214   small subset of patients had neither antibody nor T cell responses. Antibody half-lives were shorter

215   in infliximab treated patients. Breakthrough SARS-CoV-2 infections were more common and

216   occurred earlier in infliximab-treated patients who received the ChAdOx1 nCoV-19 vaccine. The risk

217   of breakthrough infection was predicted by lower antibody levels after the second dose of vaccine.

218   Irrespective of biologic treatment, higher and more sustained antibody levels, were observed in

219   patients with a history of SARS-CoV-2 infection.

220

221   Sustained antibody responses observed in vaccinated patients with a history of prior SARS-CoV-2

222   infection indicates that third antigen exposure enhances the serological response. This supports the

223   rationale for prioritising a third dose of vaccine to clinically vulnerable patient populations[13–16], who

224   otherwise may face further periods of social distancing or hospitalisation following infection. Whilst

225   drawing direct comparisons between IBD patients and patients treated with more potent

226   chemotherapies is limited by the degree to which patients are immunosuppressed, data from solid

227   organ transplant recipients shows that a third dose of vaccine also leads to sustained immune

228   responses[17].

229
230   Irrespective of biologic or immunosuppressant use, and in keeping with the original trials[2,18], the

231   highest antibody responses were seen in recipients of the BNT162b2 vaccine. Like in the general

232   population these responses waned more quickly than in the recipients of the ChAdOx1 nCoV-19

233   vaccine[19]. Unlike the general population[20], but similar to renal transplant recipients[4], we did not

234   observe differences in T cell ELISpot responses between recipients of the BNT162b2 and ChAdOx1

235   nCoV-19 vaccines. The differences observed in breakthrough infection by vaccine type reported here

236   are consistent with the differences in efficacy reported in the respective clinical trials[2,3,21]. The

237   higher peak antibody levels and the lower rate of SARS-CoV-2 breakthrough infections suggest that

238   the BNT162b2 rather than the ChAdOx1 nCoV-19 vaccine should be used for primary vaccination in

239   infliximab-treated patients and although untested supports the use of BNT162b2 for third doses in

240   all patients treated with an anti-TNF regardless of the primary vaccine type.

241

242   All patients treated with anti-TNF therapy should receive a third primary dose of SARS-CoV-2

243   vaccine and our data support recent recommendations that this should occur about 4-8 weeks after

244   the second dose[13,14,16] during periods of high transmission in the population. Our data demonstrate

245   that patients treated with vedolizumab and infliximab-treated patients with prior SARS-CoV-2

246   infection have sustained antibody levels beyond 6 months.

247

248   When starting a biologic, it would be reasonable to consider differences in SARS-CoV-2 vaccine

249   response as one of the factors when determining which drug to use. For patients who need to start

250   anti-TNF therapy, the benefits of combination immunomodulator therapy should be weighed against

251   the risk of attenuated vaccine response and whenever feasible, patients should first receive a SARS-

252   CoV-2 vaccine dose. Further research to determine whether timing third vaccine doses towards the

253   end of anti-TNF treatment cycles when drug levels are lowest leads to greater immunogenicity[9] is

254   needed. Other strategies including the temporary discontinuation of immunomodulators[22], the use

255   of heterologous vaccines[23] and adjuvants including the influenza vaccines (ComFluCOV)[24] need to be

256   studied in immunosuppressed patient groups.

257

258   The biology underpinning loss of durable antibody responses and uncoupling of the B cell and T cell

259   responses merit further research. TNF is a pleiotropic cytokine and its activities include maturation

260   of antigen presenting cells, modulation of T cell responses and stimulation of immunoglobulin

261   synthesis[25–27]. TNF neutralization, or genetic ablation, results in substantial loss of B-cells in primary

262   follicles in germinal centres, reduced numbers of memory B-cells in the periphery but preserved

263   numbers of T cells[25]. Uncoupling of humoral and T cell immunity to SARS-CoV-2 has been observed

264   in healthy individuals[28], and although the relative contributions of memory B cell and T cell

265   responses have yet to be fully defined in SARS-CoV-2 immunity, the preservation of T cell immunity

266   reported here should provide some reassurance for anti-TNF treated patients. However, it is

267   noteworthy that one fifth made no anti-spike T cell response following two doses of either vaccine.

268   Chronic TNF exposure, a feature of many IMIDs, can render T cells anergic and can be reversed by

269   anti-TNF treatment[29]. This may in part explain why the magnitude of T cell responses observed in

270   anti-TNF-treated patients in this study did not differ significantly from patients treated with

271   vedolizumab.

272   *Limitations*

273   Although our data show major differences in the magnitude and durability of antibody responses,

274   we have not assessed the impact of biologic therapy on specific immunoglobulin classes, antibody

275   neutralisation or mucosal immune responses, which may be impaired, in particular, with anti-a4b7

276   therapy[30,31]. However, previous studies have demonstrated that anti-RBD antibody levels such as the

277   ones measured in this study, strongly correlate with Wuhan Hu-1 live virus neutralization assays[32]

278   and we have demonstrated here that early antibody responses to vaccination correlates with the

279   subsequent risk of breakthrough infection in immunosuppressed patients.

280

281   **Conclusions**

282   Infliximab was associated with attenuated, less durable vaccine induced anti-SARS-CoV-2 spike

283   antibody responses and a 50% increase in subsequent breakthrough SARS-CoV-2 infection. Patients

284   treated with anti-TNF therapy should be prioritised for third vaccine doses.

285

286   **Methods**

287   *Patient and settings*

288   impaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY (CLARITY) IBD is a UK wide,

289   multicentre, prospective observational cohort study investigating the impact of infliximab and

290   vedolizumab and/or concomitant immunomodulators (azathioprine, mercaptopurine, and

291   methotrexate) on SARS-CoV-2 acquisition, illness, and immunity in patients with IBD.

292   Study methods have been previously described[10,11]. Consecutive patients were recruited at the time

293   of attendance at infusion units between 22nd September 2020 and 23rd December 2020

294   (Supplementary Table 1). Patients aged 5 years and over, with a diagnosis of IBD, treated

13

295   with infliximab or vedolizumab were eligible for inclusion. Follow-up visits coincided with biologic

296   infusions and occurred eight-weekly. Here, we report vaccine-induced antibody responses after a

297   second-dose of either the BNT162b2 or ChAdOx1 nCoV-19 vaccines. Participants were eligible

298   for our primary immunogenicity analysis, if they had had an anti-S RBD antibody test between 14

299   and 70 days after a second-dose vaccine, defined as a second dose of any of the licenced COVID-

300   19 vaccines, 10-14 weeks after the first dose. Anti-S RBD antibody levels were compared with

301   samples from 605 fully vaccinated adult participants from the Virus Watch study, a household

302   community cohort of 10,000 individuals representative of the UK population of England and Wales

303   recruited between 1 June 2020 to 31 August 2021[19]. Peripheral blood mononuclear cells (PBMC) for

304   T cell experiments were collected from patients 4 to 6 weeks after the first and second dose of

305   vaccine at the time of biologic infusions, at selected sites which could facilitate PBMC extraction

306   within 12 hours of venepuncture.

307   ***Outcome measures***

308   Our primary outcome was anti-S RBD antibodies 2 to 10 weeks after second dose of the BNT162b2

309   or ChAdOx1 nCoV-19 vaccines.

310   Secondary outcomes were:

311   (i)the proportion of participants who seroconverted

312   (ii) anti-spike T cell responses in patients following the first and second dose of vaccines

313   (iii) the durability of vaccine responses

314   (iv) risk of breakthrough infections two or more weeks after two doses of vaccine

315   (v) antibody concentrations and seroconversion rates in patients with PCR or serological

316   evidence of past SARS-CoV-2 infection at, or prior, to the post-vaccination serum sample

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14

318   *Variables*

319   Variables recorded by participants were demographics (age, sex, ethnicity, comorbidities, height and

320   weight, smoking status, and postcode), IBD disease activity (PRO2), SARS-CoV-2 symptoms aligned to

321   the COVID-19 symptoms study (symptoms, previous testing, and hospital admissions for COVID-19),

322   and vaccine uptake (type and date of primary vaccination). Study sites completed data relating to

323   IBD history (age at diagnosis, disease duration, and phenotype according to the Montreal

324   classifications, previous surgeries, and duration of current biologic and immunomodulator

325   therapy)[10]. We linked our data by NHS number or Community Health Index to Public Health England,

326   Scotland, and Wales who archive dates and results of all SARS-CoV-2 PCR tests undertaken and

327   vaccines administered. Data were entered electronically into a purpose-designed REDCap database

328   hosted at the Royal Devon and Exeter NHS Foundation Trust[33]. Participants without access to the

329   internet or electronic device completed their questionnaires on paper case record forms that were

330   subsequently entered by local research teams.

331

332   *Laboratory methods*

333   To determine antibody responses specific to vaccination we used the Roche Elecsys Anti-SARS-CoV-2

334   spike (S) immunoassay[34] alongside the nucleocapsid (N) immunoassay[35]. This double sandwich

335   electrochemiluminescence immunoassay uses a recombinant protein of the receptor binding

336   domain on the spike protein as an antigen for the determination of antibodies against SARS-CoV-2.

337   Sample electrochemiluminescence signals are compared to an internal calibration curve and

338   quantitative values are reported as units (U)/mL. In-house assay validation experiments were

339   previously reported and included in the Supplementary methods[10,11]. Seroconversion was defined at

340   a threshold of 15 U/mL. ElecSys Anti-SARS-CoV-2 spike (S) RBD concentrations of greater than or

341   equal to 15 U/ml are associated with neutralization of ≥20% with a positive predictive value of 99.10

342   % (95% CI: 97.74-99.64)[11].

15

343   At entry to CLARITY IBD and at follow-up visits, all patients were tested for previous SARS-CoV-2

344   infection using the Roche Elecsys anti-SARS-CoV-2 (N) immunoassay. We have previously reported

345   that anti-N antibody responses following SARS-CoV-2 natural infection are impaired in patients

346   treated with infliximab or vedolizumab[11]. As such, a threshold 0.12 times above the cut-off index

347   was set, using receiver operator characteristic curve and area under the curve analysis of anti-N

348   antibody results from participants two weeks following a PCR-confirmed infection to maximise

349   specificity, beyond which patients were deemed to have had prior SARS-CoV-2 infection

350   (Supplementary Figure 7). Patients with a PCR test confirming SARS-CoV-2 infection at any time prior

351   to vaccination were deemed to have evidence of past infection irrespective of any antibody test

352   result. Breakthrough infections were defined by a positive SARS-CoV-2 PCR test 2 or more weeks

353   after the second vaccine dose.

354   **Peripheral blood mononuclear cell isolation**

355   Whole blood was collected in lithium heparin tubes and PBMCs were isolated by density-gradient

356   centrifugation using Lymphoprep™ (Stem Cell Technologies) layered on to SepMate™ (Stem Cell

357   Technologies) tubes. PBMC isolation was performed within 12 hours of venepuncture. Purified

358   PBMCs were cryopreserved in 10% DMSO/50% FBS and stored in liquid nitrogen pending batch

359   analysis.

360   **Spike-peptide specific T cell responses**

361   IFNg T cell ELISpot assays were performed using pre-coated plates (Mabtech 3420-2APT) and using

362   the protocol described previously[28,32]. Two-hundred thousand cells were seeded per well and cells

363   were stimulated with a peptide pool, containing 18 peptides derived from SARS-CoV-2 spike

364   protein[36] at a concentration of 10 μg/ml/peptide; the peptide pool utilises a mapped epitope pool

365   (MEP) or 12-20mer peptides, mapped as eliciting high-prevalence CD4 responses covering diverse

366   HLA-II haplotypes[28,32]. Use of this spike MEP in otherwise healthy SARS-CoV-2 seropositive

16

367   individuals elicits a T cell response in 83% of individuals at 16 – 18 weeks after natural SARS-CoV-2

368   infection and 91% of healthy individuals 2-3 weeks after two dose vaccination with seronegative

369   individuals showing a level of response indistinguishable from pre-pandemic controls[28,32].Plates were

370   cultured for 18-20 hours before development and data collected using an AID classic ELISpot plate

371   reader (Autoimmun Diagnostika GMBH). Results are expressed as difference in (delta) spot forming

372   cells (SFC) per 10^6 PBMC between peptide stimulation and a media only control. A response below 2

373   standard deviations of the media only control wells was deemed to be a null response. Data was

374   excluded if response to the positive control anti-CD3 stimulation was <200 SFC per 10^6 PBMCs.

375   *Sample size*

376   The sample size for CLARITY IBD was based on the number of participants required to demonstrate a

377   difference in the impact of infliximab and vedolizumab on seroprevalence and seroconversion

378   following SARS-CoV-2 infection, with an estimated background seroprevalence of 0.05. We

379   calculated that a sample of 6970 patients would provide 80% power to detect differences in the

380   seroprevalence of SARS-CoV-2 antibodies in infliximab- compared with vedolizumab-treated

381   patients, whilst controlling for immunomodulator status at the 0.05 significance level.

382   **Statistical analyses**

383   Analyses were undertaken using R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). All

384   tests were two tailed and p-values reported without correction for multiple testing. P-values <0.05

385   were considered significant. We included patients with missing clinical data in analyses for which

386   they had data and have specified the denominator for each variable. Anti-S RBD antibody

387   concentrations are reported as geometric means and standard deviations. Other continuous data

388   are reported as median and interquartile range, and discrete data as numbers and percentages,

389   unless otherwise stated.

390   Univariable analyses, using Spearman's rank correlation coefficients, and t-tests of log-transformed

391   anti-S RBD antibody concentration were used to identify demographic, disease, vaccine, and

17

392   treatment-related factors associated with the concentration of anti-S RBD antibodies across the

393   cohort. Crude sensitivity analyses excluding patients treated without a concomitant

394   immunomodulator were undertaken to control for the effect of immunomodulator use on anti-S

395   RBD antibody concentrations. Propensity matching was used to account for the other significant

396   differences in baseline variables between infliximab- and vedolizumab-treated patients using the

397   MatchIt package[37]. A priori, patients were matched exactly on diagnosis, immunomodulator use, and

398   then using optimal matching, on age, number of comorbidities, ethnicity, and presence of active

399   disease. Multivariable linear regression models were used to identify factors independently

400   associated with log anti-S RBD concentration. A priori, we included age, ethnicity, biological

401   medication and immunomodulator use. Results are presented after exponentiation, so that the

402   coefficients of the model correspond to the fold change (FC) associated with each binary covariate.

403   For age, a cut-off was chosen based on graphical inspection of the relationship between age and

404   anti-S RBD antibody concentrations.

405   Mann-Whitney U test was used to compare the magnitude of T cell response (SFC/10^6 PBMCs)

406   stratified by treatment and vaccine received, and Spearman's rank correlation coefficient was

407   calculated to determine correlation between antibody and T cell responses.

408   Anti-S RBD antibody half-lives were estimated using an exponential model of decay. Linear mixed

409   models were fit using the lme4 and lmerTest package, with biologic treatment and vaccine type as

410   fixed effects and each subject as a random effect. Each of these effects were estimated

411   independently for gradient and intercept. 95% confidence intervals of fixed effects were calculated

412   using likelihood ratios. P values for comparison of half-lives were estimated from the full linear

413   mixed effects model that incorporated vaccine, biologic drug and prior SARS-CoV-2 infection status.

414   We visualized durability of antibody responses by calculating 15-day rolling geometric mean anti-S

415   RBD antibody concentrations. For this analysis we included participants who had an antibody test

416   carried out between 1 and 70 days after second vaccine dose. Cox proportional hazard regression

18

417   models were used to identify demographic, disease and treatment-related factors associated with

418   the time to fall in anti-S RBD antibody concentration below the seroconversion threshold.

419   Kaplan-Meier curves and cox proportional hazard regression model was used to identify treatment-

420   related factors associated with time to breakthrough infection. Linear regression model of log-

421   transformed geometric mean anti-S RBD antibody concentration was used to determine the risk of

422   breakthrough infections.

423   Where appropriate the same analyses were used to compare antibody responses in participants

424   with PCR evidence of SARS-CoV-2 infection at any time prior to vaccination.

425

426   ***Ethical consideration and role of funders***

427   CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public

428   health study, funded by the Royal Devon and Exeter NHS Foundation Trust, NIHR Imperial

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430   educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH (Switzerland),

431   Celltrion Healthcare (South Korea), Takeda (UK), and Galapagos NV (Belgium). None of our funding

432   bodies had any role in study design, data collection or analysis, writing, or decision to submit for

433   publication. Patients were included after providing informed, written consent. The sponsor was the

434   Royal Devon and Exeter NHS Foundation Trust. The Surrey Borders Research Ethics committee

435   approved the study (REC reference: REC 20/HRA/3114) in September 2020. The protocol is available

436   online at https//www.clarityibd.org. The study was registered with the ISRCTN registry

437   (ISRCTN45176516).

438   **Data availability**

439   The study protocol including the statistical analysis plan is available at www.clarityibd.org. Individual

440   participant de-identified data that underlie the results reported in this article will be available

441   immediately after publication for a period of 5 years. The data will be made available to

442   investigators whose proposed use of the data has been approved by an independent review

443   committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be

444   directed to tariq.ahmad1@nhs.net. To gain access data requestors will need to sign a data access

445   agreement.

446   **Code availability**
447   Code used for data analysis will be available upon request directed to nick.kennedy1@nhs.net.
448

449

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554

589   **Author Contributions**

590   NAK, JRG, CB, SS, NP, TA participated in the conception and design of this study. CB was the project

591   manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analyses and

592   central laboratory aspects of the project. SL, NAK, AS, DMS, CJR, RCS, SHK, FPP, KML, DKB, NC,

593   DC, CB, MJ, SS, JLA, LC, JCL, CDM, ALH, PMI, GRJ, KBK, CAL, CWL, DMA, RJB, JRG, NP, TA were

594   involved in the acquisition, analysis, or interpretation of data. DMS, CJR, KML, DKB, and FFP

595   performed, analysed and interpreted T cell experiments. T cell experiments

596   were supervised, designed, analysed and interpreted by RJB and DMA. Data analysis was done by

597   NAK, DMS and RJB. Drafting of the manuscript was done by SL, NAK, NC, SS, CWL, DMA, RJB, JRG,

598   NP, TA. NP and TA obtained the funding for the study. All the authors contributed to the critical

599   review and final approval of the manuscript. NAK, NP and TA have verified the underlying data.

600

27

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654   Laura Constable, Charles D Murray, Timothy J McDonald.

655

656 **Table**

Variable	Level	Vedolizumab	Infliximab	Overall	p
Vaccine	BNT162b2	40.0% (410/1024)	40.1% (907/2264)	40.1% (1317/3288)	1.0
	ChAdOx1 nCoV-19	60.0% (614/1024)	59.9% (1357/2264)	59.9% (1971/3288)	
Age (years)		48.0 (35.1 - 61.5)	40.2 (30.0 - 53.1)	42.0 (31.3 - 55.7)	<0.0001
Sex	Female	48.0% (490/1021)	45.9% (1038/2260)	46.6% (1528/3281)	0.16
	Male	51.8% (529/1021)	54.0% (1221/2260)	53.3% (1750/3281)	
	Intersex	0.0% (0/1021)	0.0% (0/2260)	0.0% (0/3281)	
	Prefer not to say	0.2% (2/1021)	0.0% (1/2260)	0.1% (3/3281)	
Ethnicity	White	89.9% (917/1020)	92.6% (2091/2259)	91.7% (3008/3279)	0.029
	Asian	6.5% (66/1020)	4.6% (103/2259)	5.2% (169/3279)	
	Mixed	2.5% (25/1020)	1.4% (32/2259)	1.7% (57/3279)	
	Black	0.5% (5/1020)	0.8% (18/2259)	0.7% (23/3279)	
	Other	0.7% (7/1020)	0.7% (15/2259)	0.7% (22/3279)	
Diagnosis	Crohn's disease	36.9% (378/1024)	67.2% (1521/2264)	57.8% (1899/3288)	<0.0001
	UC/IBDU	63.1% (646/1024)	32.8% (743/2264)	42.2% (1389/3288)	
Duration of IBD (years)		9.0 (5.0 - 17.0)	8.0 (3.0 - 16.0)	8.5 (4.0 - 16.0)	0.00015
Age at IBD diagnosis (years)		33.5 (22.8 - 47.2)	27.6 (20.2 - 39.5)	29.2 (20.8 - 42.1)	<0.0001
Immunomodulators at vaccine		20.5% (207/1009)	57.7% (1295/2244)	46.2% (1502/3253)	<0.0001
5-ASA		33.8% (341/1009)	20.6% (463/2244)	24.7% (804/3253)	<0.0001
Steroids		5.9% (60/1009)	2.8% (62/2244)	3.8% (122/3253)	<0.0001
BMI		25.9 (23.0 - 29.8)	25.9 (22.8 - 30.1)	25.9 (22.9 - 30.0)	0.81
Heart disease		4.8% (49/1020)	2.6% (59/2256)	3.3% (108/3276)	0.0020
Diabetes		7.6% (78/1020)	3.6% (82/2256)	4.9% (160/3276)	<0.0001
Lung disease		16.5% (168/1020)	13.1% (295/2256)	14.1% (463/3276)	0.011
Kidney disease		1.8% (18/1020)	0.8% (17/2256)	1.1% (35/3276)	0.015
Cancer		1.6% (16/1020)	0.3% (6/2256)	0.7% (22/3276)	<0.0001
Smoker	Yes	8.1% (83/1020)	10.8% (244/2256)	10.0% (327/3276)	0.00050
	Not currently	37.6% (384/1020)	30.2% (682/2256)	32.5% (1066/3276)	
	Never	54.2% (553/1020)	59.0% (1330/2256)	57.5% (1883/3276)	
Exposure to documented cases of COVID-19		7.8% (80/1020)	8.6% (194/2256)	8.4% (274/3276)	0.50
Income deprivation score		0.089 (0.055 - 0.146)	0.091 (0.052 - 0.153)	0.090 (0.053 - 0.151)	0.86
Active disease (PRO2)		10.5% (100/956)	5.1% (109/2132)	6.8% (209/3088)	<0.0001
Time between vaccine doses (weeks)		10.9 (9.7 - 11.1)	11.0 (10.0 - 11.3)	10.9 (10.0 - 11.3)	0.0042
Time from second dose to serum sample (weeks)		5.7 (3.7 - 7.7)	5.7 (3.7 - 7.7)	5.7 (3.7 - 7.7)	0.74

657

658 **Table 1: Baseline characteristics of participants who had anti-S RBD antibodies measured 2 to 10**

659 **weeks following 2 doses of COVID-19 vaccine**

660   Abbreviations: IBD = inflammatory bowel disease; 5-ASA = 5-aminosalicylic acid; BMI = Body Mass

661   Index; PRO2 = IBD disease activity. Values presented are median (interquartile range) or percentage

662   (numerator/denominator). P values represent the results of a Mann Whitney U, Kruskal Wallis or

663   Fisher's exact test.
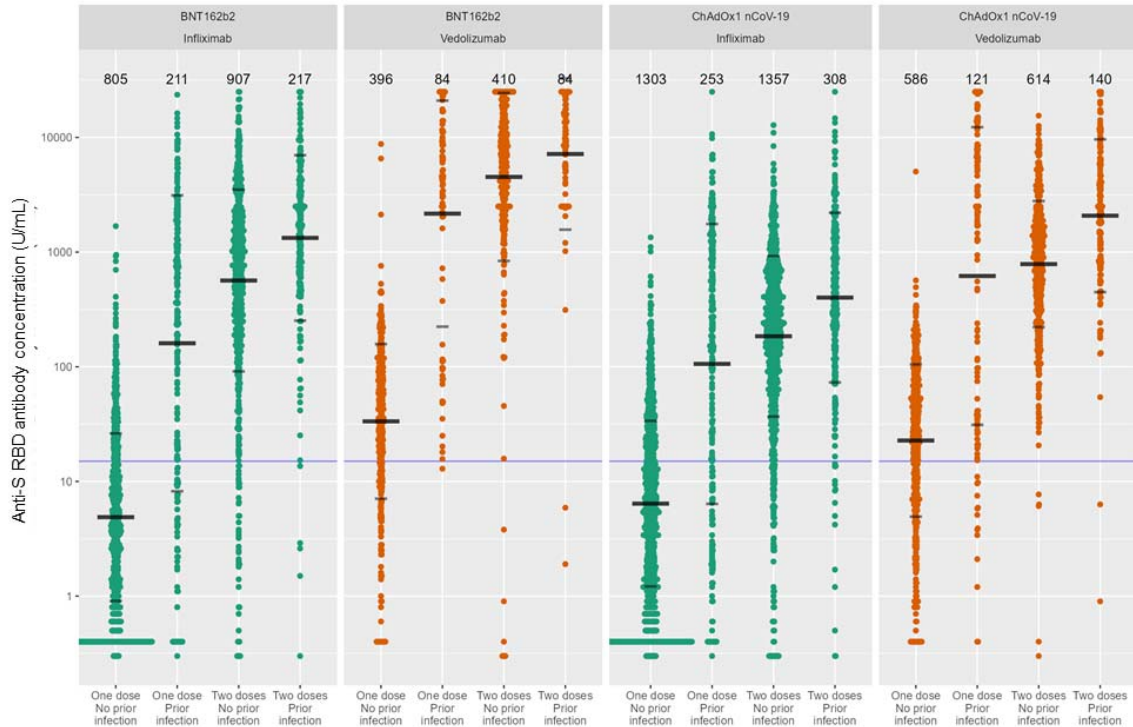
664

665   **Figure 1: Anti-S RBD antibody concentration stratified by biologic therapy (infliximab**

666   **vs vedolizumab), type of vaccine, vaccine dose and history of prior SARS-CoV-2 infection.** The

667   wider bar represents the geometric mean, while the narrower bars are drawn one geometric

668   standard deviation either side of the geometric mean. Based on published data using neutralization

669   assays threshold shown of 15 U/mL was used to determine seroconversion[11]. The biologic treatment

670   infliximab is shown in green and vedolizumab in orange. The number of individuals tested for each

671   group are shown in black at the top of each panel.

31

a   BNT162b2

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	899/1303	0.15 (0.12, 0.19)	<0.0001
Thiopurine	545/1303	0.64 (0.52, 0.79)	<0.0001
Methotrexate	67/1303	0.26 (0.17, 0.41)	<0.0001
Steroids	62/1303	0.70 (0.45, 1.10)	0.12
Crohn's disease (vs UC or IBDU)	719/1303	0.79 (0.64, 0.96)	0.018
Age ≥ 60	246/1303	0.55 (0.43, 0.70)	<0.0001
Non-white ethnicity	134/1303	1.27 (0.92, 1.74)	0.14
Current smoker	118/1303	0.93 (0.67, 1.30)	0.67

b   ChAdOx1 nCoV-19

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	1340/1941	0.24 (0.20, 0.28)	<0.0001
Thiopurine	778/1941	1.03 (0.89, 1.19)	0.69
Methotrexate	109/1941	0.94 (0.70, 1.26)	0.66
Steroids	59/1941	0.66 (0.45, 0.98)	0.038
Crohn's disease (vs UC or IBDU)	1162/1941	0.81 (0.70, 0.93)	0.0037
Age ≥ 60	344/1941	0.66 (0.55, 0.79)	<0.0001
Non-white ethnicity	140/1941	1.32 (1.02, 1.71)	0.033
Current smoker	206/1941	0.71 (0.57, 0.88)	0.0018

c   All

Variable	N	Fold change (95% CI)	p
Infliximab (vs vedolizumab)	2239/3244	0.20 (0.17, 0.23)	<0.0001
BNT162b2 vaccine	1303/3244	3.68 (3.28, 4.12)	<0.0001
Thiopurine	1323/3244	0.85 (0.75, 0.96)	0.0073
Methotrexate	176/3244	0.57 (0.44, 0.74)	<0.0001
Steroids	121/3244	0.69 (0.51, 0.92)	0.013
Crohn's disease (vs UC or IBDU)	1881/3244	0.80 (0.71, 0.90)	0.00019
Age ≥ 60	590/3244	0.62 (0.54, 0.72)	<0.0001
Non-white ethnicity	274/3244	1.33 (1.09, 1.63)	0.0053
Current smoker	324/3244	0.79 (0.66, 0.95)	0.014

Figure 2: Exponentiated coefficients of linear regression models of log anti-S RBD antibody concentration

Exponentiated coefficients of linear regression model of log anti-S RBD antibody concentration in participants who received **a.** BNT162b2 vaccine. **b.** ChAdOx1 nCoV-19 vaccine. **c.** either the BNT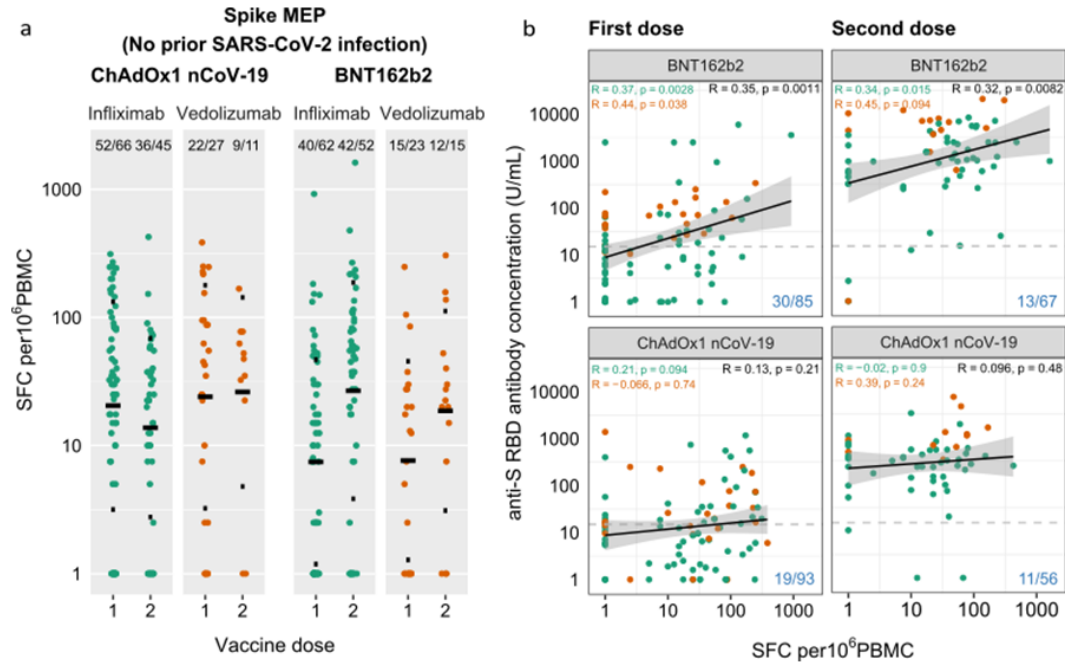162b2 or ChAdOx1 nCoV-19 vaccine. The resultant values represent the fold change of antibody concentration associated with each variable. Each vaccine was modelled separately, and then a further model was created using all available data. Horizontal dotted line represents a fold change of 1. Abbreviations: UC = ulcerative colitis, IBDU = IBD unclassified

682

Figure 3. Anti-SARS-CoV-2 spike T cell responses stratified by vaccine platform (BNT162b2 vs

ChAdOx1 nCoV-19), biologic therapy (infliximab vs vedolizumab), and vaccine dose (one vs two).

a. Spike MEP T cell responses SFC per 10^6 PBMC stratified by vaccine platform, biologic therapy

(infliximab vs vedolizumab) and number of vaccine doses. The horizontal bar represents the

geometric mean and the narrow bars represent one geometric standard deviation either side of the

geometric mean. The number of T cell responders / total number of individuals tested are shown in

black at the top of each panel. **b.** Scatterplot demonstrating the correlation between T cell responses

against spike MEP pool (SFC per 10^6 PBMC) and anti-SARS-CoV-2 spike antibody concentration after

the first (LHS) and second (RHS) dose of BNT162B2 (top) and ChAdOx1 nCoV-19 (bottom) vaccine.

The number of non-T cell responders / total number of individuals tested is shown in blue on the

bottom RHS of each panel. The horizontal dotted line in **b**. represents a threshold of 15 U/mL of anti-

S1 SARS-CoV-2 antibody. The biologic infliximab is show in green and vedolizumab is shown in

orange. R, Spearman's rank correlation. SFC, spot forming cells. PBMC, peripheral blood

mononuclear cell. MEP, mapped epitope peptide.

697

698
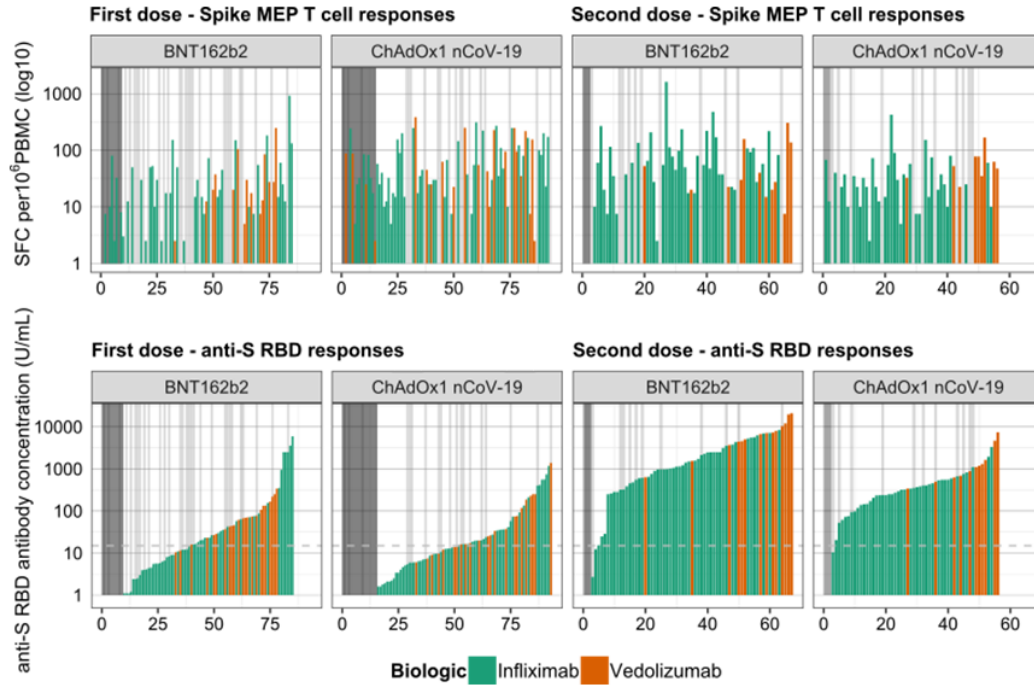
Figure 4: Anti-spike T cell responses ordered by cumulative magnitude of anti-S RBD following two

doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccine shows uncoupling of the T cell and antibody

responses

Top panel shows T cell responses to spike, and bottom panel shows anti-S RBD responses plotted for

individual study participants ordered by increasing magnitude of anti-S RBD antibody concentration

(U/mL). The vertical dark grey bars at the LHS of the panels indicate individuals with no anti-S RBD

response. The vertical light grey bars in the panels indicate individuals with no T cell response. The

horizontal dotted line represents a threshold shown of 15 U/mL of anti-S RBD.

707
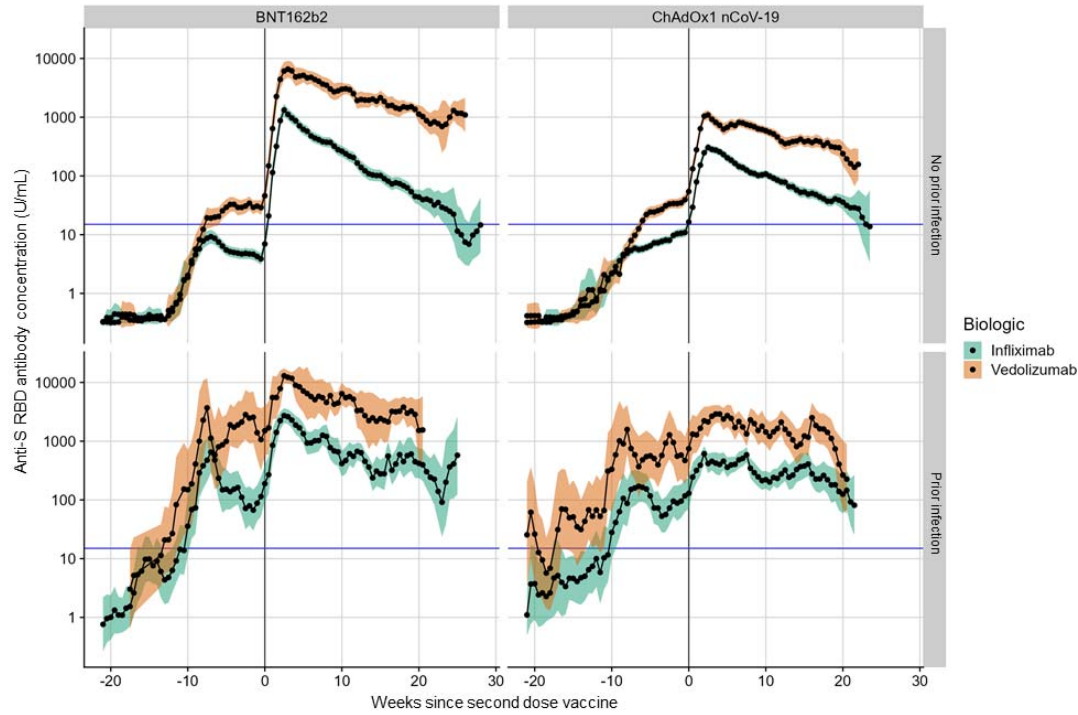
Figure 5: Rolling geometric mean antibody concentration over time from the date of the second dose of the SARS-CoV-2 vaccine (week 0) stratified by biologic therapy (infliximab vs vedolizumab), vaccine, and history of prior SARS-CoV-2 infection. Geometric means are calculated using a rolling 15-day window (i.e. 7 days either side of the day indicated). The shaded areas represent the 95% confidence intervals of the geometric means. The horizontal blue line represents the seroconversion threshold (15 U/mL). The number of participants included at each time point is presented in Supplementary Figure 3. Overall, data from 4429 participants with no history of prior infection (2999 on infliximab and 1430 on vedolizumab) and 1170 participants with a history of prior infection (825 on infliximab and 345 on vedolizumab) were included in this graph between 22 weeks before and 29 weeks after the second vaccine dose. The biologic treatment infliximab is shown in green and vedolizumab is shown in orange.
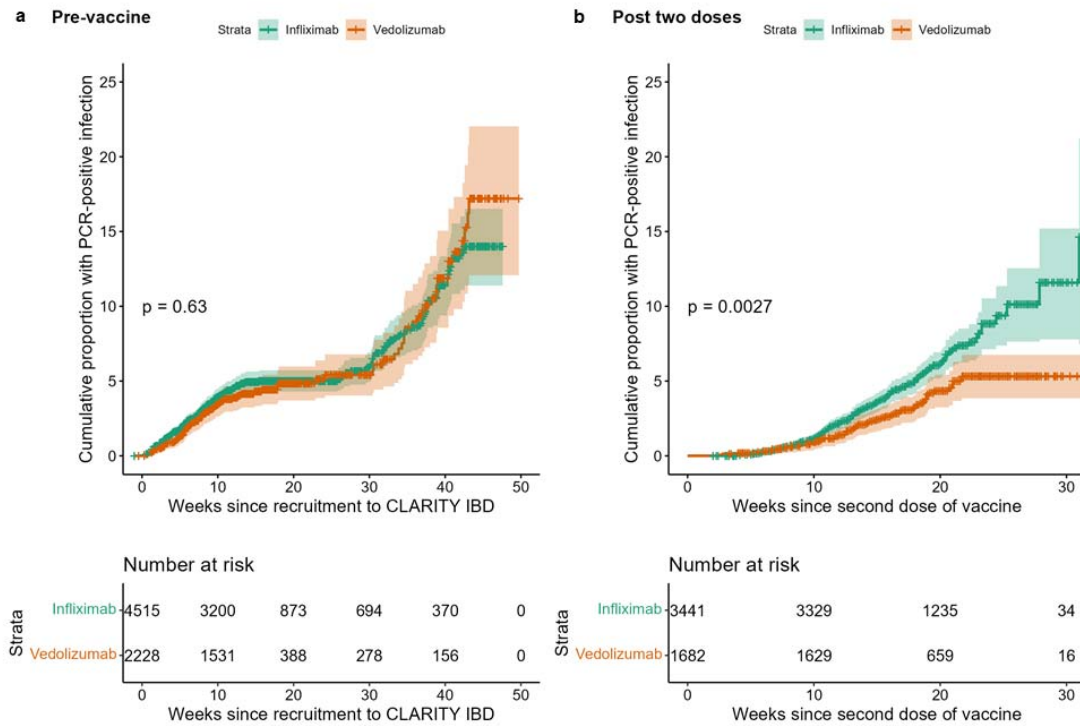
Figure 6: Kaplan-Meier graphs comparing the time to PCR-confirmed SARS-CoV-2 infection stratified by biologic therapy (infliximab vs vedolizumab) in participants before vaccination and after receiving two doses of vaccine.

a) The time to PCR-confirmed SARS-CoV-2 infection in participants who have not received any dose of either vaccine stratified by biologic therapy (infliximab vs vedolizumab). b) The time to a PCR-confirmed SARS-CoV-2 breakthrough infection in participants following two doses of either vaccine stratified by biologic therapy. The biologic treatment infliximab is shown in green and vedolizumab in orange. The number of participants at each time point are displayed in black at the bottom of each figure. P-values are calculated using log-rank test.