J Gastroenterol (2023) 58:1015–1029
https://doi.org/10.1007/s00535-023-02029-z

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

Trajectory analyses to identify persistently low responders to COVID-19 vaccination in patients with inflammatory bowel disease: a prospective multicentre controlled study, J-COMBAT

Kenji Watanabe[1,2] · Masanori Nojima[3] · Hiroshi Nakase[4] · Toshiyuki Sato[1] · Minoru Matsuura[5] · Nobuo Aoyama[6] · Taku Kobayashi[7] · Hirotake Sakuraba[8] · Masakazu Nishishita[9] · Kaoru Yokoyama[10] · Motohiro Esaki[11] · Fumihito Hirai[12] · Masakazu Nagahori[13] · Sohachi Nanjo[14] · Teppei Omori[15] · Satoshi Tanida[16] · Yoshihiro Yokoyama[4] · Kei Moriya[17] · Atsuo Maemoto[18] · Osamu Handa[19] · Naoki Ohmiya[20] · Kiichiro Tsuchiya[21] · Shinichiro Shinzaki[1,22] · Shingo Kato[23] · Toshio Uraoka[24] · Hiroki Tanaka[25] · Noritaka Takatsu[26] · Atsushi Nishida[27] · Junji Umeno[28] · Masanao Nakamura[29] · Yoshiyuki Mishima[30] · Mikihiro Fujiya[31] · Kenji Tsuchida[32] · Sakiko Hiraoka[33] · Makoto Okabe[34] · Takahiko Toyonaga[35] · Katsuyoshi Matsuoka[36] · Akira Andoh[27] · Yoshio Hirota[37] · Tadakazu Hisamatsu[5] · on behalf of the J-COMBAT study group

Received: 18 May 2023 / Accepted: 18 July 2023 / Published online: 10 August 2023

Abstract

Background The degree of immune response to COVID-19 vaccination in inflammatory bowel disease (IBD) patients based on actual changes in anti-SARS-CoV-2 antibody titres over time is unknown.

Methods Data were prospectively acquired at four predetermined time points before and after two vaccine doses in a multicentre observational controlled study. The primary outcome was humoral immune response and vaccination safety in IBD patients. We performed trajectory analysis to identify the degree of immune response and associated factors in IBD patients compared with controls.

Results Overall, 645 IBD patients and 199 control participants were analysed. At 3 months after the second vaccination, the seronegative proportions were 20.3% (combination of anti-tumour necrosis factor [TNF]α and thiopurine) and 70.0% (triple combination including steroids), despite that 80.0% receiving the triple combination

Conference presentation: Partial data contained within this manuscript have been previously presented at the European Crohn's and Colitis Organisation (ECCO 2022, virtual, 2022, digital oral poster 24) and Digestive Disease Week (DDW2022, San Diego, 2022, poster Tu1546) meetings.

Yoshio Hirota and Tadakazu Hisamatsu contributed equally to this work.

✉ Kenji Watanabe
kenjiw@med.u-toyama.ac.jp

1 Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hyogo Medical University, 1-1, Mukogawa-cho, Nishinomiya, Hyogo, Japan

2 Department of Internal Medicine for Inflammatory Bowel Disease, University of Toyama, 2630, Sugitani, Toyama 930-0194, Japan

3 Center for Translational Research, The Institute of Medical Science Hospital, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, Japan

4 Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo, Japan

5 Department of Gastroenterology and Hepatology, Kyorin University School of Medicine, Shinkawa 6-20-2, Mitaka-shi, Mitaka, Tokyo, Japan

6 Aoyama Clinic, 3-3-9, Tamondouri, Kobe, Japan

7 Center for Advanced IBD Research and Treatment, Department of Gastroenterology, Kitasato University Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo, Japan

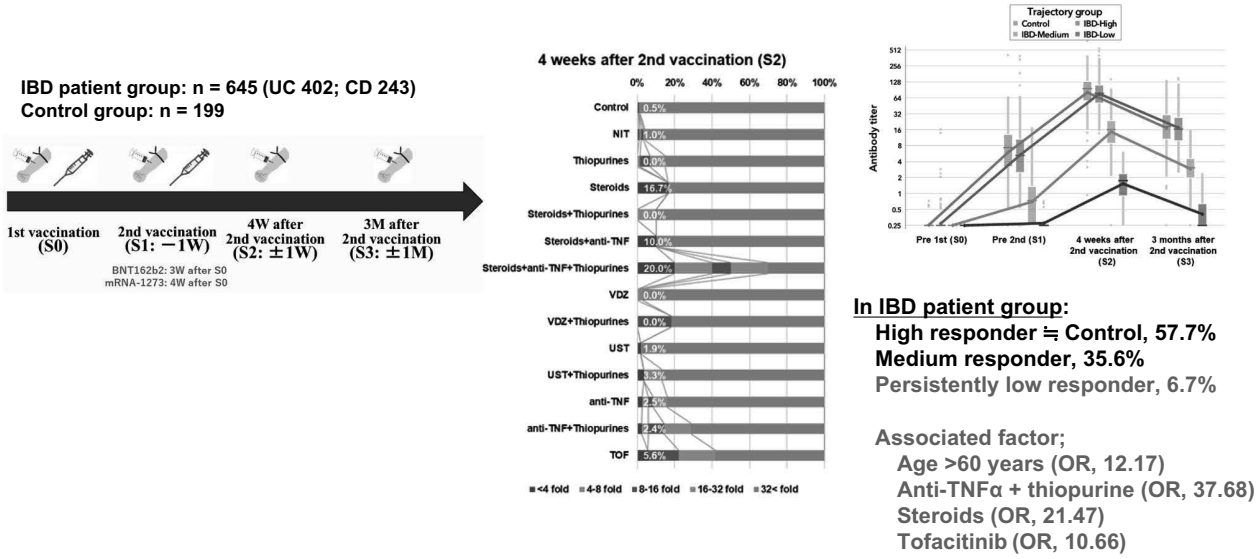
8 Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori, Japan

9 Nishishita Gastrointestinal Hospital, 4-15, Kitakawahori-cho, Tennoji-ku, Osaka, Japan

therapy were seropositive at 4 weeks after the second vaccination. Trajectory analyses indicated three degrees of change in immune response over time in IBD patients: high (57.7%), medium (35.6%), and persistently low (6.7%). In the control group, there was only one degree, which corresponded with IBD high responders. Older age, combined anti-TNFα and thiopurine (odds ratio [OR], 37.68; 95% confidence interval [CI], 5.64–251.54), steroids (OR, 21.47; 95%CI, 5.47–84.26), and tofacitinib (OR, 10.66; 95%CI, 1.49–76.31) were factors associated with persistently low response. Allergy history (OR, 0.17; 95%CI, 0.04–0.68) was a negatively associated factor. Adverse reactions after the second vaccination were significantly fewer in IBD than controls (31.0% vs 59.8%; $p < 0.001$).

Conclusions Most IBD patients showed a sufficient immune response to COVID-19 vaccination regardless of clinical factors. Assessment of changes over time is essential to optimize COVID-19 vaccination, especially in persistently low responders.

Graphical abstract



Keywords COVID-19 · Vaccine · Inflammatory bowel disease · Trajectory analyses · Responder

Abbreviations

5-ASA	5-Aminosalicylate
BCG	Bacillus Calmette–Guerin
CD	Crohn's disease
CI	Confidence interval

[10] Department of Gastroenterology, Kitasato University School of Medicine, 1-15-1, Kitasato, Minami-ku, Sagamihara, Kanagawa, Japan

[11] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Saga University, 1-1,5-Chome, Nabeshima, Saga, Japan

[12] Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, Japan

[13] Clinical Research Center, Tokyo Medical and Dental University Hospital, 1-5-45 Yushima Bunkyo-ku, Tokyo, Japan

[14] Third Department of Internal Medicine, University of Toyama, 2630 Sugitani, Toyama-shi, Toyama, Japan

[15] Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan

[16] Education and Research Center for Community Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Japan

[17] Department of Gastroenterology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara, Japan

[18] IBD Center, Sapporo Higashi Tokushukai Hospital, 3-1, Kita 33-Jo Higashi 14-Chome, Higashi-ku, Sapporo, Japan

[19] Department of Internal Medicine, Division of Gastroenterology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama, Japan

[20] Department of Advanced Endoscopy, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake City, Aichi, Japan

CLARITY	Impact of biologic therapy on SARS-CoV-2 infection and immunity
COVID-19	Coronavirus disease 2019
GMT	Geometric mean titre
IBD	Inflammatory bowel disease
JAK	Janus kinase
J-COMBAT	Japan prospective multicentre study for the optimization of COVID-19 vaccination based on the immune response and safety profile in inflammatory bowel disease patients
LLOQ	Lower limit of quantification
mRNA	Messenger ribonucleic acid
NIT	Non-immunosuppressive treatment
OR	Odds ratio
RFC	Relative fold change
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SECURE-IBD	Surveillance Epidemiology of Coronavirus under Research Exclusion for Inflammatory Bowel Disease
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
UMIN	University hospital medical information network
VIP	Vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease

Introduction

The global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has dramatically influenced daily clinical practice [1]. Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a typical immune-mediated inflammatory disease treated with several immunosuppressive agents, such as steroids, immunomodulators, biologics, or Janus kinase (JAK) inhibitors, and its incidence continues to increase globally [2, 3] IBD doctors worldwide have collaborated on several issues related to COVID-19, including the international registry (SECURE-IBD) [4–7]. The efficacy and safety of COVID-19 vaccination have been investigated in several situations. For example, the CLARITY study and VIP study from the UK investigated the influence of commonly used immunosuppressive drugs on immune responses to COVID-19 vaccination in patients with IBD [8–10]. In general, infliximab, infliximab combination therapy with immunomodulators, and tofacitinib attenuate immune responses. However, some issues with these studies remain. For instance, the vaccination schedule did not follow the vaccine manufacturers' dosing recommendations. The second vaccination was delayed due to the UK government's policy. The interval between the first and second vaccinations varied between studies (10–14 weeks in the CLARITY study and 42–90 days in the VIP study). The timing of blood sample collection also varied.

Most previous studies have focused on the influence of individual variables related to patient clinical background or therapeutic drugs for IBD on the immune response to COVID-19 vaccination at particular time points [8–10].

[21] Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki, Japan

[22] Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, Japan

[23] Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama, Japan

[24] Department of Gastroenterology and Hepatology, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi, Gunma, Japan

[25] Sapporo IBD Clinic, 1-18, Minami-19, Nishi-8, Chuo-ku, Sapporo, Hokkaido, Japan

[26] Inflammatory Bowel Disease Center, Fukuoka University Chikushi Hospital, 1-1-1, Zokumyoin, Chikushino, Fukuoka, Japan

[27] Department of Medicine, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga, Japan

[28] Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka, Japan

[29] Department of Endoscopy, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Japan

[30] Department of Internal Medicine II, Faculty of Medicine, Shimane University, 1060 Nishikawatsu-cho, Matsue,, Shimane, Japan

[31] Gastroenterology and Endoscopy, Division of Metabolism and Biosystemic Science, Gastroenterology, and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, 2-1-1-1 Midorigaoka Higashi, Asahikawa, Hokkaido, Japan

[32] Gastroenterology, Nagoya City University West Medical Center, 1-1-1, Hirate-cho, Kita-ku, Nagoya, Aichi, Japan

[33] Department of Gastroenterology and Hepatology, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, 2-5-1 Shikata-cho, Kita-ku, Okayama, Japan

However, some patients administered an anti-tumour necrosis factor (TNF) α agent coupled with an immunomodulator exhibit insufficient immune responses after COVID-19 vaccination, but some develop a sufficient response. To date, no study has analysed the degree of humoral immune response to COVID-19 vaccination and associated factors in patients with IBD based on the actual change in anti-SARS-CoV-2 antibody titres over time. Therefore, in this study, we performed trajectory analysis to identify the degree of immune response to COVID-19 vaccination and the influence of individual variables in patients with IBD compared with healthy controls. In a nationwide multicentre study, we prospectively investigated changes in humoral immune responses over time to COVID-19 vaccination at predetermined time points before and after the first and second doses according to the vaccine manufacturers' recommendations.

Methods

Patient and settings

The Japan prospective multicentre study for optimization of COVID-19 vaccination based on the immune response and safety profile in inflammatory bowel disease patients (J-COMBAT) is a Japan-wide, physician-initiated, multicentre, prospective observational controlled study investigating the humoral immune response and safety profile in patients with IBD or healthy controls who wish to receive SARS-CoV-2 vaccination (UMIN registration No. 000043545).

Patients and controls were recruited from 33 institutes associated with university hospitals, specialized IBD hospitals, or private clinics from February 2021 to October 2021. Participants in the healthy control group were mainly recruited from staff working at the institutes involved in the study. The inclusion criterion was an IBD (UC or CD) patient or healthy control who wished to receive a COVID-19 vaccination. The exclusion criteria were age less than 12 years and active COVID-19. An additional exclusion criterion for healthy controls was a diagnosis of IBD.

In Japan, three COVID-19 vaccines have been approved: BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) in February 2021; mRNA-1273 mRNA COVID-19 vaccine (Moderna)©; and adenovirus vector COVID-19 vaccine ChAdOx1-S (Oxford-AstraZeneca) in May 2021. The required age is ≥ 12 years for BNT162b2 and mRNA-1273 and ≥ 40 years for ChAdOx1-S. The most popular vaccine in Japan is BNT162b2, followed by mRNA-1273.

Study design

Essentially, all participants who were analysed received two doses of the COVID-19 vaccine according to the vaccine manufacturers' dosing recommendations. The interval between vaccinations was 3 weeks for BNT162b2, 4 weeks for mRNA-1273, and 8 weeks for ChAdOx1-S. Collection of clinical data and blood samples was performed prospectively at each predetermined time point: before the first vaccination (S0), ≤ 1 week before the second vaccination (S1), 4 (± 1) weeks after the second vaccination (S2), and 3 (± 1) months after the second vaccination (S3) (Fig. 1).

Outcome measures

The primary outcome was humoral immune response, including changes over time and differences according to therapeutic drug use for COVID-19 vaccination in patients with IBD. We compared each data set between the IBD and control groups or between IBD group subgroups, including non-immunosuppressive treatment (NIT) patients. We also performed trajectory analysis to identify the degree of model for immune response by measuring the change of anti-SARS-CoV-2 antibody titres over time and its associated factor to COVID-19 vaccination in patients with IBD compared with healthy control.

Variables

Variables recorded included demographics (disease, age, sex, height and weight, smoking history, allergy history, drinking history, Bacillus Calmette–Guerin (BCG) and influenza vaccination history, adverse events related to past vaccination, comorbidity, past medical history), IBD disease activity (partial Mayo score for UC, with ≥ 3 defined as an active case; Harvey–Bradshaw index for CD, with ≥ 4 defined as an active case), therapeutic drugs for IBD, blood test results (white blood cell count, lymphocyte count, serum albumin and serum C-reactive protein),

[34] Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, Japan

[35] Division of Internal Medicine, Department of Gastroenterology and Hepatology, The Jikei University School of Medicine, 3-19-18 Nishi-Shimbashi, Minato-ku, Tokyo, Japan

[36] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Sakura Medical Center, 564-1, Shimoshidu, Sakura, Chiba, Japan

[37] Clinical Epidemiology Research Center, SOUSEIKAI Medical Group (Medical Co. LTA), 3-6-1, Kashii-Teriha, Higashi-ku, Fukuoka, Japan

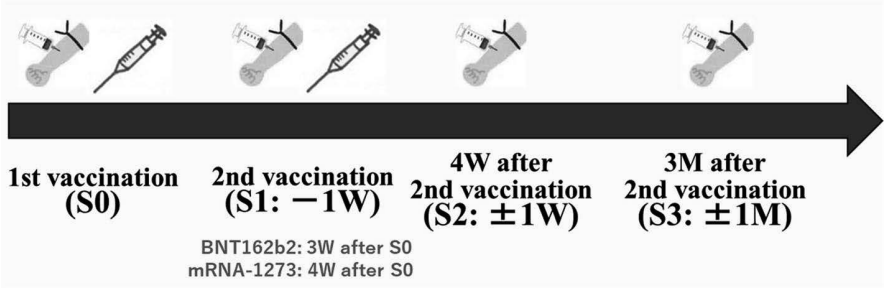


Fig. 1 Study design for each time point. *W* week, *M* month

history of COVID-19 and/or testing, COVID-19 vaccine formulation, date of COVID-19 vaccination, and adverse reactions to COVID-19 vaccination according to the guidance of the Toxicity Grading Scale For Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials by the Food and Drug Administration of the USA [11]. All data were entered electronically into a purpose-designed electronic data capture system hosted by APO PLUS STATION Co., Ltd. (Tokyo, Japan).

Laboratory methods

Measurement of anti-SARS-CoV-2 spike protein antibody titres for all samples was performed centrally by Fukuyama Medical Laboratory Co., Ltd. (Hiroshima, Japan). We used the Siemens SARS-CoV-2 IgG (COV2G) antibody assay with the Advia Centaur XP platform (Munich, Germany) to detect antibodies against SARS-CoV-2 in serum samples [12]. The COV2G antibody assay detects IgG antibody titres for the receptor-binding domain (RBD) of the S1 subunit of the spike protein. All samples were processed by trained laboratory staff according to the manufacturers' procedures with the specified controls and calibrators. Public Health England reported that compared with other commercially available assays, the Siemens SARS-CoV-2 IgG (COV2G) antibody chemiluminescent immunoassay can detect a wide range of antibody titres when assessing antibody formation after COVID-19 vaccination [13]. The humoral immune response was assessed by using the fold change or geometric mean titre (GMT) of anti-SARS-CoV-2 spike antibody titres.

Target sample size

In this study, the target sample size was 750, including more than 400 patients receiving immunosuppressive treatment and 200 NIT patients in the IBD group and 250 individuals in the control group. The number of IBD cases was set mainly based on feasibility and the amount required to obtain a sufficient number of cases with different types of immunosuppressive treatment (e.g. 50 cases each). Precision and power were estimated as follows. In a clinical trial in the early phase of the BNT162b2 vaccine [14], the mean log of the 50% neutralizing antibody titre (normal log) was 2 to 3, with a 95% confidence interval (95%CI) of approximately 0.5 for each treatment group ($N = 12$). The standard deviation (SD) was estimated to be 0.44. Based on this, the 95%CI of the logarithmic antibody titre was estimated to be $\pm$ 0.10 SD for the target number of 400 cases in the immunosuppressive treatment patient group in this study, which is considered to be a high precision estimation. Similarly, the 95%CI for 200 patients of the NIT group was $\pm$ 0.14 SD.

When comparing the 400 immunosuppressive and 200 NIT patients, the 95%CI will be approximately 3–5% of the mean value. A difference of 0.25 SD in log antibody titre can be detected at $\alpha = 0.05$ with a power of 80% based on t-distribution testing. Because this was an observational study conducted for exploratory research, a multiplicity adjustment for multiple items was not performed.

Statistical analyses

The lower limit of quantification (LLOQ) of the measured anti-SARS-CoV-2 antibody titres in this study was 0.5, and values lower than the LLOQ were set to 0.25 for every calculation. Box plots were created for antibody titres stratified by age, sex, and treatment group. The fold change in the antibody titre was determined as the titre divided by the baseline value. For comparisons between cases with different treatments, we did not distinguish between those treated with or without 5-aminosalicylate (5-ASA) because most NIT patients received 5-ASA (97/107 = 90.7%). Analysis using a multivariate linear regression model was performed to estimate the effect of clinical and background demographic factors on log-transformed antibody titres at a single time point as a dependent variable. Trajectory classes for a time series of antibody titres were generated (nonarbitrary manner) using latent class linear mixed models in the R package "lcmm" (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Logistic regression analysis was then applied to estimate the risk of the lowest trajectory class with the factors listed in Table 1, and $p < 0.05$ was considered

statistically significant. SAS 9.4 (Cary, North Carolina, USA) was used for all analyses.

Ethical considerations

The trial complied with the Declaration of Helsinki. The protocol of the clinical study was approved by the institutional review board at each participating institution, and informed consent to participate in the study was obtained from each participant prior to enrolment. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient characteristics

Overall, 897 participants (694 cases [428 UC cases and 266 CD cases]) in the IBD group and 203 participants in the control group) were registered in the J-COMBAT study (Fig. 2). Among the initial participants, unvaccinated participants the first vaccination (35 cases [18 UC cases and 17 CD cases] in the IBD group and one participant in the control group) were excluded from the analyses. We also excluded unvaccinated participants at the second vaccination (9 cases [5 UC cases and 4 CD cases] in the IBD group and two participants in the control group) and breakthrough infection cases (5 cases [3 UC cases and 2 CD cases] in the IBD group and one participant in the control group) from the analyses. Ultimately, 645 patients (402 UC cases and 243 CD cases) in the IBD group and 199 participants in the control group were analysed in the current study. We decided to end recruitment at the end of October 2021 because that is when the second vaccination rate plateaued and booster vaccination was scheduled to begin in December 2021 in Japan.

The baseline characteristics of the participants are shown in Table 1. Age, smoking history, and allergy history were similar between the groups. Allergic rhinitis/hay fever was more common in the control group (22.1% vs. 7.9%), whereas drug allergy was more frequent in the IBD group (11.4% vs. 4.5%). BNT162b2 was the most common vaccine, with a second vaccination rate of 82.3% (517/628) in the IBD group and 100% (199/199) in the control group. The second vaccination rate was 18.3% for mRNA-1273 (110/628) and 0.2% for ChAdOx1-S (1/628) in the IBD group.

Trajectory analyses of the degree of changes over time assessed by genomic mean titres of measured anti-SARS-CoV-2 spike protein antibody titres: comparison between IBD patients and controls

Before trajectory analyses, we analysed our raw data related to fold changes in anti-SARS-CoV-2 spike protein antibody titres stratified by therapeutic drug in the IBD group compared with the control group (Fig. 3). After the first vaccination and prior to the second vaccination, at S1 (Fig. 3a), several combination therapies at baseline were associated with a higher proportion of seronegative (< fourfold change in the genomic mean titre) cases. Some treated patients were still seronegative at 4 weeks after the second vaccination, at S2 (Fig. 3b). At 3 months after the second vaccination, at S3 (Fig. 3c), the proportion of seronegativity increased among treated patient: 10.0% for tofacitinib, 13.1% for anti-TNFα agents, 20.0% for anti-TNFα agents and steroids, 20.3% for anti-TNFα agents and thiopurine, and 70.0% for triple combination therapy (steroids, thiopurine, and anti-TNFα agents). Therefore, 30.0% of cases receiving triple combination therapy were seropositive at S3.

Next, we confirmed the observed changes in anti-SARS-CoV-2 spike antibody titres over time in the IBD and control groups. As a broad distribution of the degree of changes over time was observed in the IBD group compared with the control group (Fig. 4a, b), we performed trajectory analysis to identify the actual degree of changes over time using the GMT of the measured anti-SARS-CoV-2 spike antibody titres. These trajectory analyses indicated three degrees of change in humoral immune responses in patients with IBD over time: high (Fig. 4c), medium (Fig. 4d), and persistently low (Fig. 4e). Persistently low responders consisted of IBD patients who had an increased average GMT $\leq$ twofold from S0 throughout the disease course. Overall, 6.7% (43/640 cases: 20 UC cases and 23 CD cases) of IBD patients were persistently low responders, 35.6% (228/640 cases: 129 UC cases and 99 CD cases) were medium responders, and 57.7% (369/640 cases: 249 UC cases and 120 CD cases) were high responders. The medium responders were also sufficient responders according to the seroconversion by the fourfold rise of antibody titre. In contrast, by assessing the whole GMT, the control group was found to only consist of one degree of change over time, corresponding to the IBD group high responders (Fig. 4b). The overlaid line chart for the three degrees in the IBD group and one degree in the control group by trajectory analysis is illustrated in Fig. 4f.

Table 1 Baseline characteristics of participants in the IBD and control groups

		IBD group						Control group	
		All IBD patients		Ulcerative colitis		Crohn's disease			
N, %		645	100.0%	402	62.3%	243	37.7%	199	100.0%
Sex (*n*, %)	Female	304	47.1%	202	50.2%	102	42.0%	151	75.9%
Age group, years (*n*, %)	≤ 29	105	16.3%	52	13.0%	53	21.8%	50	25.1%
	30–39	111	17.2%	59	14.7%	52	21.4%	37	18.6%
	40–49	157	24.3%	99	24.7%	58	23.9%	57	28.6%
	50–59	123	19.1%	71	17.7%	52	21.4%	37	18.6%
	60–69	86	13.3%	69	17.2%	17	7.0%	13	6.5%
	≥ 70	62	9.6%	51	12.7%	11	4.5%	5	2.5%
BMI (*n*, %)	< 18.5	71	11.0%	39	13.1%	32	16.6%	19	9.8%
	18.5- < 25	326	50.5%	205	68.8%	121	62.7%	144	74.6%
	25-	94	14.6%	54	18.1%	40	20.7%	30	15.5%
BCG vaccination history (*n*, %)	No	131	20.3%	85	32.3%	46	29.7%	20	10.8%
	Yes	287	44.5%	178	67.7%	109	70.3%	165	89.2%
Smoking history (*n*, %)	Non-smoker	430	66.7%	263	70.9%	167	72.3%	152	76.4%
	Current smoker	49	7.6%	25	6.7%	24	10.4%	22	11.1%
	Former smoker	123	19.1%	83	22.4%	40	17.3%	25	12.6%
Allergic history (*n*, %)	Yes	189	29.3%	122	32.8%	67	29.0%	68	34.3%
Allergic rhinitis/hay fever	Yes	51	7.9%	37	9.3%	14	5.8%	44	22.1%
Atopic dermatitis	Yes	4	0.6%	1	0.3%	3	1.2%	1	0.5%
Allergic dermatitis	Yes	4	0.6%	1	0.3%	3	1.2%	3	1.5%
Contact dermatitis	Yes	4	0.6%	4	1.0%	0	0.0%	1	0.5%
Food allergy	Yes	35	5.4%	17	4.3%	18	7.4%	15	7.5%
Drug allergy	Yes	73	11.4%	53	13.3%	20	8.2%	9	4.5%
Allergy to contrast agent	Yes	9	1.4%	4	1.0%	5	2.1%	1	0.5%
Metallic allergy	Yes	4	0.6%	3	0.8%	1	0.4%	1	0.5%
Alcohol allergy	Yes	17	2.6%	8	2.0%	9	3.7%	4	2.0%
Others	Yes	12	1.9%	8	2.0%	4	1.6%	12	6.0%
Drinking history (*n*, %)	No	463	71.8%	284	74.0%	179	76.8%	89	45.6%
	≤ 1/month	39	6.0%	21	5.5%	18	7.7%	25	12.8%
	2–4/month	42	6.5%	26	6.8%	16	6.9%	27	13.8%
	2–3/week	32	5.0%	24	6.3%	8	3.4%	23	11.8%
	≥ 4/week	41	6.4%	29	7.6%	12	5.2%	31	15.9%
Comorbidity									
Hypertension (*n*, %)	Yes	8	1.2%	8	2.0%	0	0.0%	5	2.5%
Diabetes (*n*, %)	Yes	5	0.8%	3	0.7%	2	0.8%	0	0.0%
Asthma (*n*, %)	Yes	10	1.6%	6	1.5%	4	1.7%	7	3.5%
Previous history of COVID-19 (*n*, %)	Yes	4	0.6%	2	0.5%	2	0.8%	1	0.5%
Vaccine formulations (*n*, %)	BNT162b2 (Pfizer/BioNTech)	517	80.2%	330	84.2%	187	79.2%	199	100.0%
	ChAdOx1 nCoV-19 (Oxford/AstraZeneca)	1	0.2%	1	0.3%	0	0.0%	0	0.0%

Table 1 continued

		IBD group						Control group	
		All IBD patients		Ulcerative colitis		Crohn's disease			
	mRNA-1273 (Moderna)	110	17.1%	61	15.6%	49	20.8%	0	0.0%
Blood test results (mean, SD)									
White blood cells (/μl)		5276.4	5131.0	5144.4	3516.9	5453.1	6847.5	NA	NA
Lymphocytes (/μl)		34.6	107.5	38.5	135.8	28.2	9.9	NA	NA
C-reactive protein (mg/dl)		2.0	42.3	3.1	53.6	0.2	0.4	NA	NA
Serum albumin (g/dl)		4.2	0.4	4.2	0.4	4.1	0.4	NA	NA
IBD disease activity									
Partial Mayo score (mean, SD)		NA	NA	0.9	1.4	NA	NA	NA	NA
Active UC (n, %)		NA	NA	59	14.7%	NA	NA	NA	NA
Harvey–Bradshaw index (mean, SD)		NA	NA	NA	NA	2.7	3.6	NA	NA
Active CD (*n*, %)		NA	NA	NA	NA	76	31.3%	NA	NA
Therapeutic agent for IBD									
Oral 5-ASA formulation (*n*, %)	Yes	488	75.7%	320	80.0%	168	69.4%	NA	NA
Systemic steroids (*n*, %)	Yes	62	9.6%	34	8.5%	28	11.6%	NA	NA
Thiopurines (azathioprine/6-MP) (*n*, %)	Yes	241	37.4%	145	36.3%	96	39.7%	NA	NA
Vedolizumab (*n*, %)	Monotherapy	45	7.0%	36	9.0%	9	3.7%	NA	NA
	Combination therapy with thiopurine	14	2.2%	9	2.3%	5	2.1%	NA	NA
Ustekinumab (*n*, %)	Monotherapy	62	9.6%	23	5.8%	39	16.1%	NA	NA
	Combination therapy with thiopurine	42	6.5%	27	6.8%	15	6.2%	NA	NA
Anti-TNFα agent (*n*, %)	Monotherapy	141	21.9%	54	13.5%	87	36.0%	NA	NA
	Combination therapy with thiopurine	95	14.7%	37	9.3%	58	24.0%	NA	NA
Infliximab	Monotherapy	73	11.4%	21	5.3%	52	21.5%	NA	NA
	Combination therapy with thiopurine	64	10.0%	25	6.3%	39	16.1%	NA	NA
Adalimumab	Monotherapy	46	7.2%	11	2.8%	35	14.5%	NA	NA
	Combination therapy with thiopurine	24	3.7%	5	1.3%	19	7.9%	NA	NA
Golimumab	Monotherapy	22	3.4%	22	5.5%	0	0.0%	NA	NA
	Combination therapy with thiopurine	7	1.1%	7	1.8%	0	0.0%	NA	NA
Tofacitinib (*n*, %)	Yes	40	6.2%	40	10.0%	0	0.0%	NA	NA
Adverse reactions after the second vaccination (*n*, %)	Yes	200	31.0%	118	31.2%	82	33.9%	119	59.8%
IBD flare after the second vaccination (*n*, %)	Yes	23	3.9%	15	4.0%	8	3.3%	NA	NA
IBD flare at 4 weeks after the second vaccination (*n*, %)	Yes	31	5.2%	20	5.2%	11	4.5%	NA	NA
IBD flare at 3 months after the second vaccination (*n*, %)	Yes	19	3.4%	17	5.0%	2	0.8%	NA	NA

There were more females and drinkers in the control group compared with the IBD group. Only four cases in the IBD group and one participant in the control group had a history of COVID-19 prior to the first vaccination. At the first vaccination, 21.0% (135/644) (14.7% [59/401] of UC cases and 31.3% [76/243] of CD cases) in the IBD group were in the active phase. *5-ASA* 5-aminosalicylate, *6-MP* 6-mercaptopurine, *BCG* Bacillus Calmette–Guerin, *BMI* body mass index, *CD* Crohn's disease, *IBD* inflammatory bowel disease, *NA* not applicable, *TNF* tumour necrosis factor, *UC* ulcerative colitis

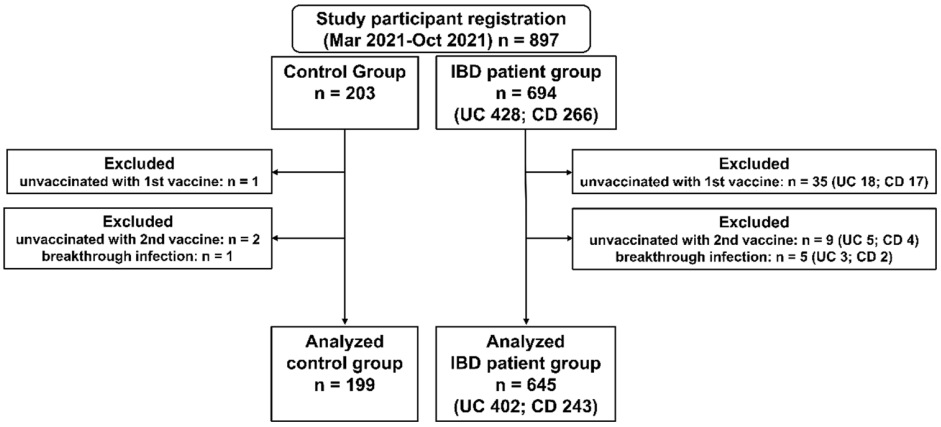


Fig. 2 Flow diagram of the participants analysed. *CD* Crohn's disease, *IBD* inflammatory bowel disease, *UC* ulcerative colitis

Trajectory analyses of factors associated with persistently low or high responders in the IBD group

Forest plots show the level of association of each variant for the persistently low responders (Fig. 5) and high responders (Supplementary Fig. 1). Age > 60 years (odds ratio [OR], 12.17; 95% confidence interval [CI], 1.55–95.31, $p = 0.017$) or > 50 years (OR, 9.13; 95%CI, 1.28–64.99; $p = 0.027$) was associated with persistently low response. Stratification by therapeutic drug showed that combination therapy with anti-TNFα agents and thiopurine (OR, 37.68; 95%CI, 5.64–251.54; $p < 0.001$), systemic steroids (OR, 21.47; 95%CI, 5.47–84.26; $p < 0.001$), and tofacitinib (OR, 10.66; 95%CI, 1.49–76.31; $p = 0.019$) were associated with persistently low response. In contrast, allergy history (OR, 0.17; 95%CI, 0.04–0.68; $p = 0.013$) was not associated with persistently low response.

Influence of independent clinical factors on measured anti-SARS-CoV-2 spike antibody titres at 4 weeks after the second COVID-19 vaccination

To identify independent clinical factors for the measured anti-SARS-CoV-2 spike antibody titres at 4 weeks after the second COVID-19 vaccination (S2) as a one-point analysis of the highest antibody titre over time, we performed multivariate analyses adjusting for known confounders using a multivariable model with exponentiated coefficients of linear regression models of relative fold change of anti-SARS-CoV-2 spike antibody titres. The forest plot in Fig. 6 depicts the adjusted relative fold change for each factor. A sequential negative influence was indicated according to increasing age group compared with the ≤ 20 year age group (Fig. 6a), and allergy history increased the fold change (relative fold change [RFC], 1.41; 95%CI, 1.17–1.69; $p < 0.001$). Vaccine formulation also influenced the antibody titre, which was significantly higher for mRNA-1273 than for BNT162b2 (RFC, 2.51; 95%CI, 1.89–3.33; $p < 0.001$).

Regarding therapeutic treatment, systemic steroids (RFC, 0.44; 95%CI, 0.32–0.61; $p < 0.001$), thiopurine (RFC, 0.63; 95%CI, 0.43–0.92; $p = 0.018$), anti-TNFα agent monotherapy (RFC, 0.55; 95%CI, 0.39–0.77; $p < 0.001$), and combination therapy with anti-TNFα agents and thiopurines (RFC, 0.37; 95%CI, 0.25–0.55; $p < 0.001$) negatively influenced the antibody titre, with tofacitinib having the strongest impact (RFC, 0.20; 95%CI, 0.12–0.31; $p < 0.001$).

Some components of allergy history also influenced the antibody titre (Fig. 6b), including food allergy (RFC, 1.40; 95%CI, 1.00–1.95; $p = 0.048$), alcohol allergy (RFC, 1.72; 95%CI, 1.02–2.89; $p = 0.043$), and drug allergy (RFC, 1.48; 95%CI, 1.12–1.96; $p = 0.006$). Conversely, adverse events did not influence the antibody titre at S2.

Safety profile

The rates of IBD flare after the second vaccination are shown in Table 1. IBD flare was observed in 3.9% of IBD patients (4.0% of UC and 3.3% of CD) during less than 4 weeks after the second vaccination. IBD flare was also observed in 5.2% of IBD patients (5.2% of UC and 4.5% of CD) at 4 weeks and 3.4% of IBD patients (5.0% of UC and 0.5% of CD) at 3 months after the second vaccination.

Adverse reactions after the second vaccination were significantly fewer in IBD patients (31.0% [31.2% of UC and 33.9% of CD]) compared with control participants (59.8%; $p < 0.001$). We analysed adverse reactions (fatigue, headache, muscle pain, swelling, fever, diarrhoea, tenderness, and redness) stratified by age group with comparison between IBD patients and controls for first and second vaccination (Supplementary Fig. 2). We also analysed adverse reactions stratified by therapeutic drug in IBD patients for the first and second vaccination (Supplementary Fig. 3). However, we could not identify the specific feature or trend.

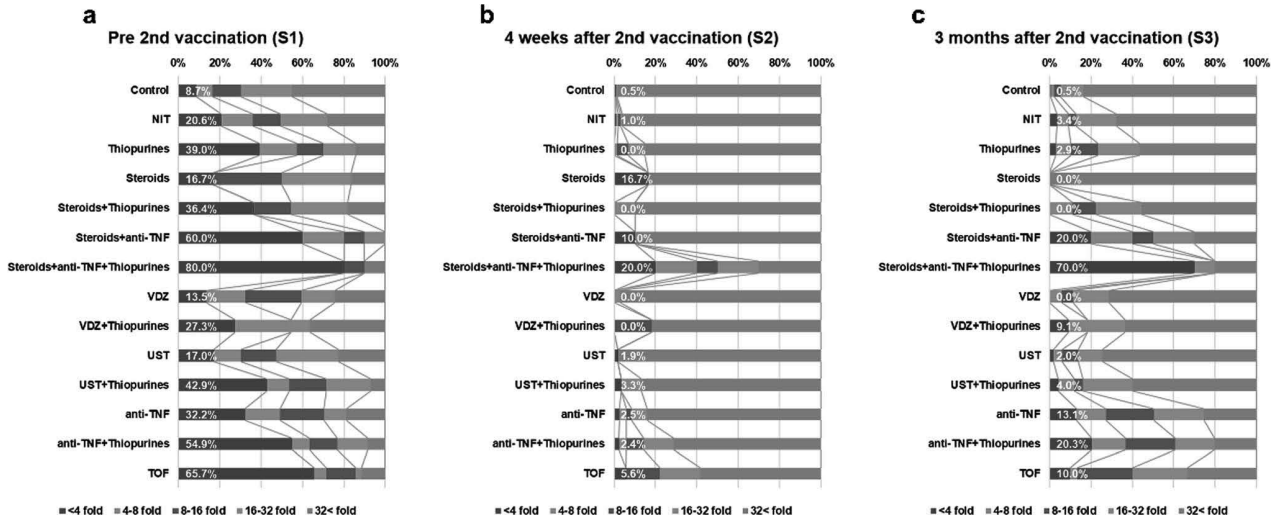


Fig. 3 Seronegative proportion according to fold change in the geometric mean titre stratified by treatment group at each time point. *NIT* non-immunosuppressive treatment, *TNF* tumour necrosis factor, *TOF* tofacitinib, *UST* ustekinumab, *VDZ* vedolizumab

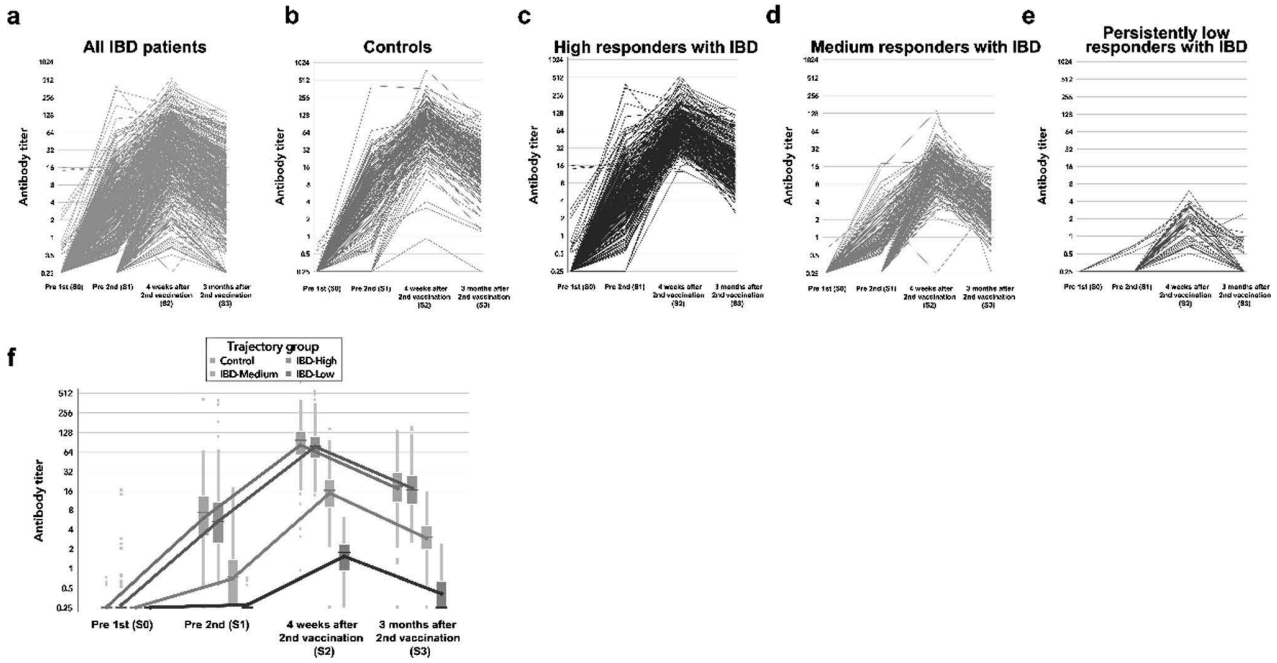


Fig. 4 Changes in the geometric mean titre over time by anti-SARS-CoV-2 spike protein antibody titres measured according to the model of trajectory analyses in IBD patients and controls. The changes over time of measured anti-SARS-CoV-2 spike protein antibody titres for all samples from all IBD patients (Fig. 4a, grey line) and all participants in the control group (Fig. 4b, green line). The trajectory analyses indicated three degrees of immune response, high responders (Fig. 4c, blue line), medium responders (Fig. 4d, orange line), and persistent low responders (Fig. 4e, red line) in patients with IBD. The line chart shows three merged models in the IBD group and one model in the control group assessed by trajectory analysis (Fig. 4f). IBD, inflammatory bowel disease

Discussion

The results of this prospective study with precise assessments at predetermined time points before and after the first and second COVID-19 vaccinations indicate that the changes over time occurring in anti-SARS-CoV-2 spike antibody titres after COVID-19 vaccination in IBD patients are broadly distributed compared with those in healthy controls. The present trajectory analysis clearly showed the existence of three degrees of response to COVID-19 vaccination in IBD patients compared with only one in the control group. We found 57.7% of IBD patients to be high

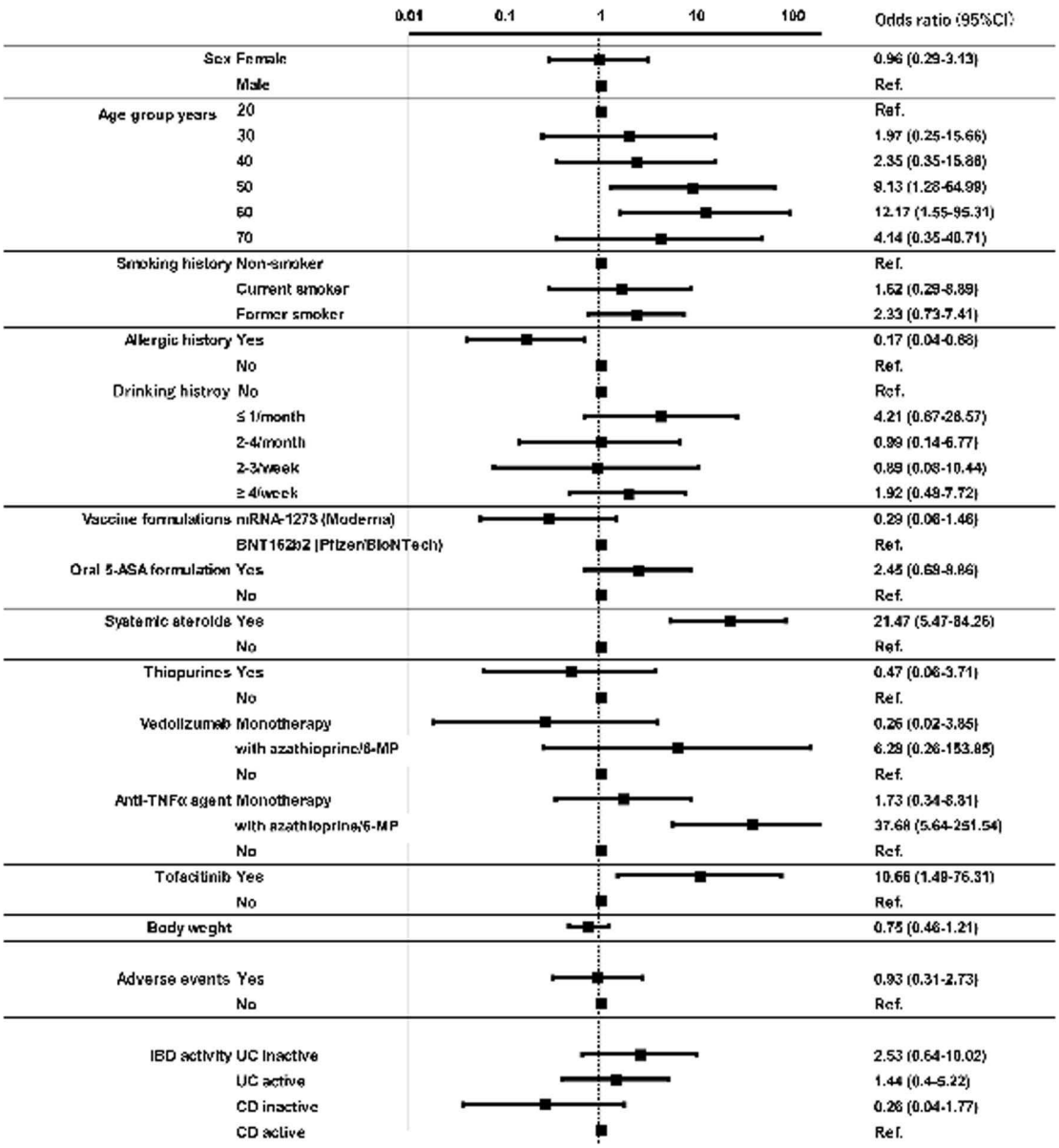


Fig. 5 Risk level of factors associated with persistently low response determined by trajectory analyses in patients with IBD. Fixed effects of ChAdOx1 nCoV-19 vaccination, history of COVID-19, ustekinumab use, and baseline anti-SARS-CoV-2 S1-RBD titre were not estimated due to non-convergence. *5-ASA* 5-aminosalicylate, *6-MP* 6-mercaptopurine, *CD* Crohn's disease, *CI* confidence interval, *IBD* inflammatory bowel disease, *TNF* tumour necrosis factor, *UC* ulcerative colitis, *Ref* reference

responders, with a response rate similar in magnitude to that of the control group; 35.6% of IBD patients were medium responders. Thus, 93.3% of IBD patients showed a sufficient response to two doses of the COVID-19 vaccine regardless of their clinical background or treatment. Nonetheless, 6.7% of IBD patients were persistently low responders. Logistic regression analysis was applied to identify factors associated with persistently low response. Older age, combination therapy with anti-TNFα agents and thiopurine, systemic steroids, and tofacitinib contributed to persistently low response. To the best of our knowledge, no previous study has reported the degree of actual change in immune response over time to COVID-19 vaccination in patients with IBD by trajectory analysis. By individually measuring anti-SARS-CoV-2 spike protein antibody titres at different time points, we detected sufficient and insufficient responders among patients with IBD compared with controls. The computer assessed induvial raw data at each visit, and then divided into three groups based on the pattern of individual time course change for antibody titre

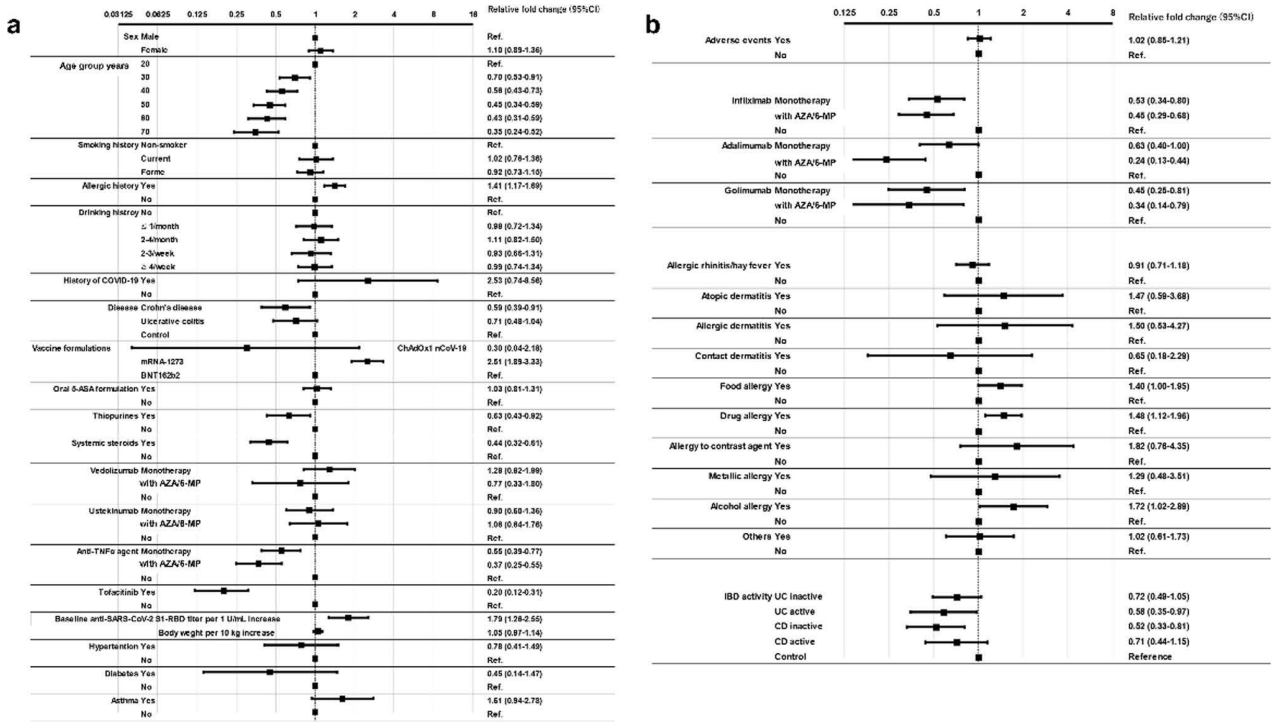


Fig. 6 Influence of independent clinical factors on measured anti-SARS-CoV-2 spike protein antibody titres at 4 weeks after the second vaccination. Multivariate analyses (for demographic and clinical factors [Fig. 6a]; adverse events, each anti-TNFα agent, allergic history, and IBD activity [Fig. 6b]) were adjusted for known confounders by a multivariable model showing exponentiated coefficients of linear regression models of relative fold change of anti-SARS-CoV-2 spike protein antibody titres. *5-ASA* 5-aminosalicylate, *6-MP* 6-mercaptopurine, *AZA* azathioprine, *CD* Crohn's disease, *CI* confidence interval, *UC* ulcerative colitis, *Ref* reference, *RFC* relative fold change, *CI* confidence interval

without arbitrary manner. So, there is no definition for each responder group.

Of note, even combination therapy with anti-TNFα agents and thiopurine or triple combination therapy (steroids, thiopurine, and anti-TNFα agents) do not attenuate antibody titres after two doses of vaccination in all IBD patients. One systematic review and meta-analysis by Sakuraba et al. reported attenuation of humoral immune responses after two doses of mRNA vaccination in patients with IBD (event rate, 0.937; 95%CI, 0.863–0.972) [15]. They also reported that compared to control patients, a significantly smaller proportion of patients with immune-mediated inflammatory diseases achieved a serologic response after two doses of vaccine (OR, 0.086; 95%CI, 0.036–0.206). Immune responses to COVID-19 vaccination depend on humoral and cellular immunity. However, IBD is an immune-mediated inflammatory disease associated with immune disorders [16]; thus, IBD itself may increase the risk of an insufficient immune response to vaccination.

Several previous studies investigating immune responses to COVID-19 vaccination by group analysis with stratification by variables including clinical background or therapeutic treatment at particular assessment time points have demonstrated that anti-TNFα agents or other immunosuppressive agents attenuate immune responses in IBD patients. [8–10] However, it cannot be concluded that all IBD patients administered anti-TNFα agents and thiopurine respond insufficiently to COVID-19 vaccination. From the viewpoint of real-world clinical management, some patients receiving combination therapy with anti-TNFα agents and thiopurine in fact exhibit sufficient humoral immune responses after COVID-19 vaccination. [17, 18].

Interestingly, allergy history negatively contributed to persistently low response. Chiba et al. reported that perennial allergic rhinitis is a predictor of post-vaccination fever after BNT162b2 vaccination and that BNT162b2-vaccinated subjects with post-vaccination fever have high antibody titres after vaccination [19, 20]. Therefore, not only assessment of general risk factors, including therapeutic drugs, but also individual assessment on a case-by-case approach is essential for optimizing COVID-19 vaccination because breakthrough infections may occur in persistently low responders with IBD. Further investigation of the immunological mechanisms related to persistently

low response to COVID-19 vaccination should be performed to prevent an epidemic of COVID-19 in patients with IBD.

At the one-point analysis 4 weeks after the second vaccination, increasing age group, systemic steroids, thiopurines, anti-TNFα agent monotherapy, combination therapy with an anti-TNFα agent and thiopurine, and tofacitinib negatively influenced the antibody titre by analyses of a multivariate linear regression model. These results were compatible with previous published data. However, tofacitinib had the strongest negative influence on the antibody titre. Differences in the genetic backgrounds of Asian IBD patients might explain the differences observed between previously published results from Western countries and the present results [21]. In addition, allergy history and receiving the mRNA-1273 vaccine formulation positively influenced the antibody titre. Adverse events did not influence the antibody titre 4 weeks after the second vaccination. Thus, not only a conventional one-point assessment coupled with summarized group analysis stratified by clinical background or treatment contents, but also an analysis of changes of time with the assessment of individual measured antibody titres by trajectory analysis, is essential to evaluate the immune response to COVID-19 vaccination in patients with IBD.

Weaver et al. reported 2.1% IBD flare was found after vaccination among 3316 individuals in the USA [22]. Our results were, a little higher rate, 3.9% IBD flare after the first vaccination and 5.2% IBD flare after the second vaccination. Adverse reactions after the second vaccination were significantly fewer in IBD patients than controls. Originally, we were interested with association between adverse reactions and clinical background including treatment contents. Weaver et al. also reported anti-TNFα agent and vedolizumab were positively associated with severe systemic reactions to second vaccination [22]. We performed several analyses for the safety profile from the perspective of age, each adverse event, treatment contents, or time point of vaccination. However, we could not identify the specific feature or trend.

There were some limitations in our study. First, most participants received mRNA vaccine, the most common COVID-19 vaccine in Japan. Second, the number of participants did not reach the target; however, our statistical analyses, including the influence of each IBD therapeutic drug, were considered feasible based on preliminary analyses by a statistician (MNo). Third, it was not possible to estimate statistically the association of ustekinumab with persistently low response. Finally, there was a small number of paediatric participants because all investigators were adult IBD doctors.

Assessment of changes over time, and not only a one-point snapshot, is essential to optimize COVID-19 vaccination in individuals. Trajectory analysis is a useful approach to identify the degree of immune response sufficiency according to individual differences [19, 20] because breakthrough infections may occur in persistently low responders with IBD. Further investigation of the immunological mechanisms related to persistently low response to COVID-19 vaccination should be performed to prevent an epidemic of COVID-19 in patients with IBD. In conclusion, most IBD patients showed a sufficient immune response to COVID-19 vaccination regardless of clinical factors. Assessment of changes over time is essential to optimize COVID-19 vaccination, especially in persistently low responders.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00535-023-02029-z.

Acknowledgements Nagase K (Hyogo Medical University) and Fujii A (Medical System Research Corp.) kindly supported this work. We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contributions KW, MNo, HN, YH, and TH participated in the conception and design of this study and were involved in the acquisition, analysis, or interpretation of data. KW was the project manager and coordinated patient recruitment and serological analyses. The drafting of the manuscript was performed by KW, MNo, HN, and TH. KW, YH, and TH obtained funding for the study. All authors contributed to the critical review and final approval of the manuscript. KW and MN accessed and verified the study data. All authors were responsible for the decision to submit the manuscript.

Funding This work was supported by research grants for Research on Emerging/Re-emerging Infectious Diseases and Promoting Vaccination Policy from the Ministry of Health, Labour and Welfare, Japan (Hirota Y, 20HA2001), Health and Sciences Research Grants for research on intractable diseases from the Ministry of Health, Labour and Welfare of Japan (Hisamatsu T, 20316729), and a JSGE (The Japanese Society of Gastroenterology) grant (Watanabe K).

Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest KW has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd.; received research grants from EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., EP-CRSU Co., Ltd., received scholarship grants from AbbVie GK, EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, JIMRO Co., Ltd., Nippon Kayaku Co., Ltd.; and has been an endowed chair for AbbVie GK, EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Zeria Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Otsuka Pharmaceutical Factory, Inc., Asahi Kasei Medical Co., Ltd., Mochida Pharmaceutical Co., Ltd. HN has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma

Corporation, Mylan EPD G.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd.; received research grants from AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., PENTAX Medical, AYUMI Pharmaceutical Corporation; and received scholarship grants from AbbVie GK, EA Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Nippon Kayaku Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd. MM has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Janssen Pharmaceutical K.K. TK has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc.; received research grants from AbbVie GK, Activaid, Alfresa Pharma Corporation, JMDC, Gilead Sciences, Nippon Kayaku Co., Ltd., Eli Lilly Japan K.K., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Google Asia Pacific Pty. Ltd.; received scholarship grants from Mitsubishi Tanabe Pharma Corporation, Zeria Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd.; and was an endowed chair for Otsuka Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., JIMRO Co., Ltd., AbbVie GK, Zeria Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd. HS has received scholarship grants from LAVIEPRE Co., Ltd, Yakult Honsha Co., Ltd, Bristol-Myers Squibb Company. KY has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd. ME has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K.; received research grants from Mitsubishi Tanabe Pharma Corporation, EA Pharma Co., Ltd., AbbVie GK, Pfizer Japan Inc., Alfresa Pharma Corporation. FH has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Janssen Pharmaceutical K.K., Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd.; received research grants from Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., and AbbVie GK; and received scholarship grants from AbbVie GK, EA Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation. MNag has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd., AbbVie GK, Pfizer Japan Inc., Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K. and received scholarship grants from Takeda Pharmaceutical Co., Ltd. TO has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd. ST has received scholarship grants from AbbVie GK, EA Pharma Co., Ltd. AM has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Janssen Pharmaceutical K.K., Nippon Kayaku Co Ltd, Eli Lilly Japan KK; received research grants from EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Eli Lilly Japan KK, Gilead Sciences Inc, Nippon Boehringer Ingelheim Co Ltd, AbbVie GK, Kaken Pharmaceutical Co Ltd, Mochida Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Kissei Pharmaceutical Co., Ltd.; and has been an endowed chair for AbbVie GK. KiT has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd., AbbVie GK., Janssen Pharmaceutical K.K., and received research grants from AIMO Pharmaceutical. SS has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Nippon Kayaku Co., Ltd., Gilead Sciences, JIMRO Co., Ltd., Nippon Kayaku Co., Zeria Pharmaceutical Co., Ltd., Alfresa Pharma Corporation, Astra Zeneka K.K., Eisai Co., Ltd., Sekisui Medical Co., Ltd. and received research grants from Sekisui Medical Co., Ltd. SK has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation. TU has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Takeda Pharmaceutical Co., Ltd. and received research grants from Janssen Pharmaceutical K.K., Eli Lilly Japan KK, NIHON PHARMACEUTICAL Co., Ltd. HT has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Eisai Co., Ltd., Nikkiso Co., Ltd., Nippon Kayaku Co., Ltd. and received research grants from EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., AbbVie GK, Janssen Pharmaceutical K.K. JU has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Nippon Kayaku Co., Ltd., JIMRO Co., Ltd., EA Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., AbbVie GK, Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd. MF has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for EA Pharma Co., Ltd., AYUMI Pharmaceutical Corporation, AbbVie GK, Otsuka Pharmaceutical Factory, Inc., Zeria Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Nippon Kayaku Co., Ltd., elpharma Co., Ltd., Pfizer Japan Inc., Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., Olympus Corporation, Celltrionhealthcare.jp, Alfresa Pharma Corporation, Mylan Inc., Boston Scientific Corporation, Covidien Japan, Inc., FUJIFILM Corporation, Fuji Chemical Industries Co., Ltd., JIMRO Co., Ltd. and received research grants from EA Pharma Co., Ltd., AYUMI Pharmaceutical Corporation, AbbVie GK, Otsuka Pharmaceutical Factory, Inc., Zeria Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Nobelpharma Co., Ltd., Pfizer Inc., Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Yakult Honsha Co., Ltd., JIMRO Co., Ltd., Kamui Pharma. Inc. SH has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd. TT has received research grants from AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd. Pfizer Inc. KMa has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., AbbVie GK, EA Pharma Co., Ltd., Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd.; received research grants from Janssen Pharmaceutical K.K.; and received scholarship grants from Mitsubishi Tanabe Pharma Corporation, AbbVie GK, EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd. AA has received honouraria and had expenses paid to attend or give a presentation or advice at a meeting for AbbVie GK, Takeda Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co., Ltd. TH has received honouraria and had expenses paid to attend or give a

presentation or advice at a meeting for EA Pharma Co. Ltd., AbbVie GK, Celgene K.K., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Nichi-Iko Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, AbbVie GK, EA Pharma Co. Ltd., Kyorin Pharmaceutical Co., Ltd., JIMRO Co., Ltd., Janssen Pharmaceutical K.K., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Pfizer Japan Inc.; received research grants from Alfresa Pharma Corporation, EA Pharma Co., Ltd.; and received scholarship grants from Mitsubishi Tanabe Pharma Corporation, EA Pharma Co., Ltd., AbbVie GK, JIMRO Co. Ltd., Zeria Pharmaceutical Co., Ltd., Daiichi-Sankyo, Kyorin Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Takeda Pharmaceutical Co., Ltd., Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd.

References

1. Danese S, Cecconi M, Spinelli A. Management of IBD during the COVID-19 outbreak: resetting clinical priorities. Nat Rev Gastroenterol Hepatol. 2020;17:253–5.
2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–78.
3. Murakami Y, Nishiwaki Y, Oba MS, et al. Estimated prevalence of ulcerative colitis and Crohn's disease in Japan in 2014: an analysis of a nationwide survey. J Gastroenterol. 2019;54:1070–7.
4. Ungaro RC, Brenner EJ, Agrawal M, et al. Impact of medications on COVID-19 outcomes in inflammatory bowel disease: analysis of more than 6000 patients from an international registry. Gastroenterology. 2022;162:316–9.
5. Nakase H, Matsumoto T, Matsuura M, et al. Expert opinions on the current therapeutic management of inflammatory bowel disease during the COVID-19 pandemic: Japan IBD COVID-19 taskforce, intractable diseases, the health and labor sciences research. Digestion. 2021;102:814–22.
6. Hayashi Y, Nakase H, Hisamatsu T, et al. Should we continue or discontinue inflammatory bowel disease medication in patients with coronavirus disease 2019? Gastroenterology. 2022;163:338–9.
7. Nakase H, Hayashi Y, Hirayama D, et al. Interim analysis of a multicenter registry study of COVID-19 patients with inflammatory bowel disease in Japan (J-COSMOS). J Gastroenterol. 2022;57:174–84.
8. Lin S, Kennedy NA, Saifuddin A, et al. Antibody decay, T cell immunity and breakthrough infections following two SARS-CoV-2 vaccine doses in inflammatory bowel disease patients treated with infliximab and vedolizumab. Nat Commun. 2022;13:1379. https://doi.org/10.1038/s41467-022-28517-z.
9. Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. Gut. 2021;70:1884–93.
10. Alexander JL, Kennedy NA, Ibraheim H, et al. COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study. Lancet Gastroenterol Hepatol. 2022;7:342–52.
11. Food and Drug Administration. Guidance for Industry. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. URL: https://www.fda.gov/media/73679/download. Accessed: 3rd Dec 2022
12. Irsara C, Egger AE, Prokop W, et al. Clinical validation of the Siemens quantitative SARS-CoV-2 spike IgG assay (sCOVG) reveals improved sensitivity and a good correlation with virus neutralization titers. Clin Chem Lab Med. 2021;59:1453–62.
13. Public Health England. Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898437/Evaluation__of_sensitivity_and_specificity_of_4_commercially_available_SARS-CoV-2_antibody_immunoassays.pdf Accessed: 3rd Dec 2022
14. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-Based Covid-19 vaccine candidates. N Engl J Med. 2020;383:2439–50.
15. Sakuraba A, Luna A, Micic D. Serologic response to coronavirus disease 2019 (COVID-19) vaccination in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Gastroenterology. 2022;162:88–108.
16. Wellens J, Colombel JF, Satsangi JJ, Wong SY. SARS-CoV-2 vaccination in IBD: past lessons, current evidence, and future challenges. J Crohns Colitis. 2021;15:1376–86.
17. Wong SY, Dixon R, Martinez Pazos V, et al. Serologic response to messenger RNA Coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. Gastroenterology. 2021;161:715–8.
18. Lev-Tzion R, Focht G, Lujan R, et al. COVID-19 vaccine is effective in inflammatory bowel disease patients and is not associated with disease exacerbation. Clin Gastroenterol Hepatol. 2022;20:e1263–82.
19. Chiba S, Shinohara K. A predictive model to estimate fever after receipt of the second dose of Pfizer-BioNTech coronavirus disease 2019 vaccine: an observational cohort study. Health Sci Rep. 2022;5:e742. https://doi.org/10.1002/hsr2.742.
20. Uwamino Y, Kurafuji T, Sato Y, et al. Young age, female sex, and presence of systemic adverse reactions are associated with high post-vaccination antibody titer after two doses of BNT162b2 mRNA SARS-CoV-2 vaccination: an observational study of 646 Japanese healthcare workers and university staff. Vaccine. 2022;40:1019–25.
21. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47:979–86.
22. Weaver KN, Zhang X, Dai X, et al. Impact of SARS-CoV-2 vaccination on inflammatory bowel disease activity and development of vaccine-related adverse events: results from PREVENT-COVID. Inflamm Bowel Dis. 2022;28:1497–505.
23. Stankiewicz Karita HC, Dong TQ, Johnston C, et al. Trajectory of viral RNA load among persons with incident SARS-CoV-2 G614 infection (Wuhan strain) in association with COVID-19 symptom onset and severity. JAMA Netw Open. 2022;5:e2142796. https://doi.org/10.1001/jamanetworkopen.2021.42796.
24. Sonabend R, Whittles LK, Imai N, et al. Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. Lancet. 2021;398:1825–35.