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SHORT REPORT

Serological response to vaccination against coronavirus disease-19 in patients with inflammatory bowel disease

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Abstract

Vaccination against coronavirus disease-19 (COVID-19) is effective in preventing the occurrence or reduction in the severity of the infection. Patients with inflammatory bowel disease (IBD) are on immunomodulators, which may alter serological response to vaccination against COVID-19. Accordingly, we studied (i) the serological response to vaccination against COVID-19 in IBD patients and (ii) a comparison of serological response in IBD patients with that in healthy controls. A prospective study was undertaken during a 6-month period (July 2021 to January 2022). Seroconversion was assessed among vaccinated, unvaccinated IBD patients and vaccinated healthy controls using anti-severe acute respiratory syndrome coronavirus 2 immunoglobulin G (anti-SARS-CoV-2 IgG) antibody detection enzyme-linked immunosorbent assay (ELISA) kit, and optical density (OD) was measured at 450 nm. OD is directly proportional to the antibody concentration. One hundred and thirty-two blood samples were collected from 97 IBD patients (85 [87.6%] ulcerative colitis and 12 [12.4%] Crohn's disease). Forty-one of the seventy-one (57.7%) unvaccinated and 60/61 (98.4%) vaccinated IBD patients tested positive (OD > 0.3) for SARS-CoV-2 IgG antibodies. Fourteen of the sixteen (87.5%) healthy controls tested positive for SARS-CoV-2 IgG antibodies. Vaccinated IBD patients had higher ODs than unvaccinated IBD patients (1.31 [1.09–1.70] vs. 0.53 [0.19–1.32], $p < 0.001$) and 16 vaccinated healthy controls (1.31 [1.09–1.70] vs. 0.64 [0.43–0.78], $p < 0.001$). Three of the seventy-one (4.2%) unvaccinated IBD patients reported having recovered from COVID-19. Most IBD patients seroconvert after vaccination against SARS-CoV-2, similar to a healthy population. A large proportion of IBD patients had anti-SARS-CoV-2 antibodies even before vaccination, suggesting the occurrence of herd immunity.

Keywords COVID-19, · Crohn's disease · Herd immunity · Pandemic · Ulcerative colitis · Vaccination

Akash Mathur and Shikha Sahu have contributed equally to the work and are joint first authors.

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Bullet points of the study highlights

What is already known?

- Inflammatory bowel disease (IBD) patients may have a worse coronavirus disease-19 (COVID-19) outcome.
- Vaccination against COVID-19 helps in preventing occurrence of infection and may reduce the severity of the disease.

What is new in this study?

- Both IBD patients and healthy controls had high seroconversion rates following vaccination against COVID-19.
- A large proportion of IBD patients develop herd immunity.

What are the future clinical and research implications of the study findings?

- Herd immunity is an important clinical consideration in developing and implementing the future vaccination strategy.

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a ribonucleic acid (RNA) virus belonging to the coronavirus family, began in Wuhan, Hubei province, China, in December 2019 and caused the current pandemic of the disease [1]. SARS-CoV2 affects the gastrointestinal tract, and gastrointestinal manifestations are fairly common in patients with coronavirus disease - 19 (COVID-19) [2]. Some studies have also shown that patients with inflammatory bowel disease (IBD), particularly active disease, might be at a higher risk of COVID-19 pneumonia and death [3].

Nearly a year after the beginning of the pandemic, India reported its first case of COVID-19; vaccines for the prevention of COVID-19 became available later and are being marketed currently. The first two vaccines approved by the drug regulator, Drug Controller General of India (DCGI), were Serum Institute of India's Covishield™, developed in partnership with the Oxford University and European firm AstraZeneca, and Bharat Biotech's homegrown Covaxin™, developed in collaboration with the top medical body, Indian Council of Medical Research (ICMR).

The country rolled out World's largest vaccination drive on January 16, 2021, starting the vaccination drive by vaccinating the healthcare workers. The second phase began on March 1, 2021, vaccinating all people above the age of 60 years and those above 45 years with comorbidities. Further vaccination was opened for all above the age of 45 in its third phase beginning in April 1, 2021. Subsequently, vaccination was opened for all individuals above the age of 18 years from May 1, 2021. As of August 1, 2022, India had administered 2.04 billion doses of the COVID-19 vaccine [4].

Initial studies with Covishield™ showed good efficacy of 76% after the first and 81.3% after the second dose [5]. Similarly, for Covaxin™, a large phase 3 clinical trial found the vaccine to be 64% effective against asymptomatic cases, 78% against symptomatic disease, and 93% effective against severe disease [6]. However, little is known regarding the immunogenicity of the vaccine in the unique population of IBD patients who are sometimes also on immunosuppressive treatment. So, we undertook this study to assess the vaccination response in IBD patients.

Multiple studies have shown that patients with IBD may have a worse COVID-19 outcome, more so in those with active disease [3, 7]. Vaccination against COVID-19 effectively prevents the occurrence of the infection and may even reduce the severity of the disease. Patients with IBD are on long-term immunomodulator therapy, which may alter the serological response to vaccination against COVID-19. Two vaccines became initially available in India as part of the Government-initiated World's largest free COVID-19 vaccination drive. India's indigenous whole virion inactivated Vero cell-derived vaccine (BBV 152) marketed as Covaxin™ (Bharat Biotech, Hyderabad, Telangana, India), and ChAdOx1 nCoV-19 (AZD1222) vaccine marketed as Covishield™ (Serum Institute of India Private Limited, Pune, Maharashtra, India) [8, 9]. While there are some data on seroconversion with ChAdOx1 nCoV-19 (AZD1222) in IBD patients, data with BBV 152 are scarce. Accordingly, we undertook a study to know (i) the serological response to vaccination against COVID-19 in IBD patients and (ii) a comparison of serological response in IBD patients with that in healthy controls.

Methods

This prospective study included a total of 132 blood samples collected from 97 IBD patients and 16 healthy controls during a 6-month period (July 2021 to January 2022) at a tertiary referral centre in northern India.

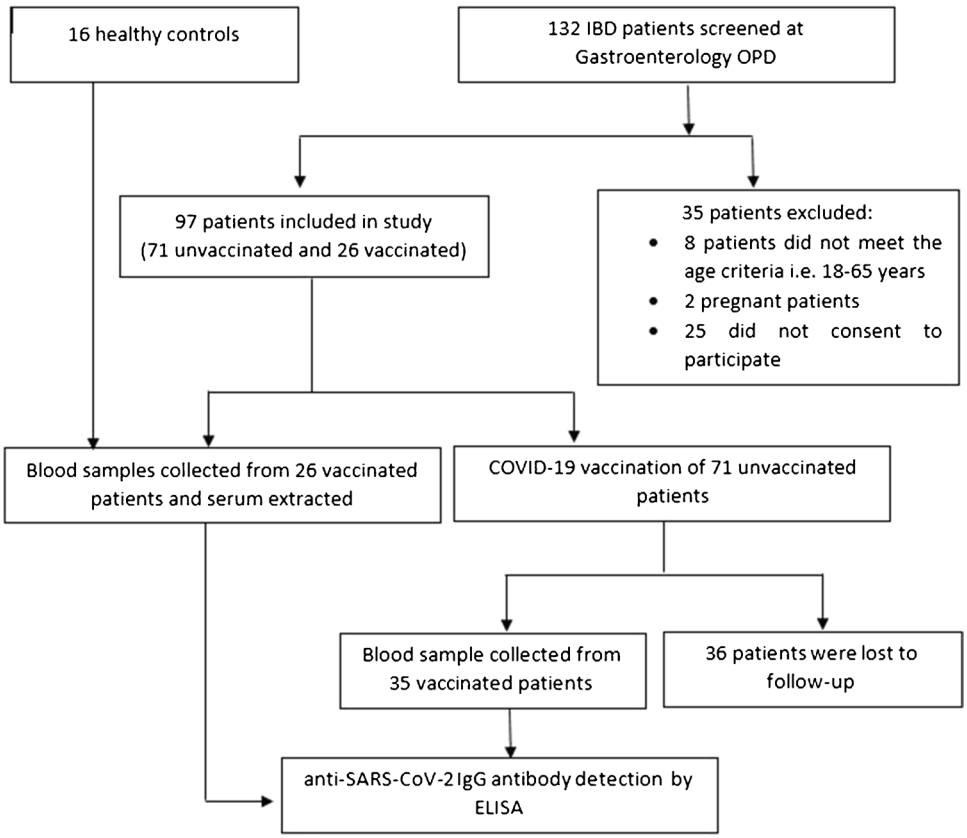

Fig. 1 Study flowchart: serological response to vaccination against coronavirus disease-19 in patients with inflammatory bowel disease. *IBD* inflammatory bowel disease, *OPD* outpatient department, *COVID-19* coronavirus disease-19, *anti-SARS CoV2 IgG* anti-severe acute respiratory syndrome coronavirus 2 immunoglobulin G, *ELISA* enzymelinked immunosorbent assay

The demographic and clinical data of the subjects were recorded in a structured questionnaire. After informed consent, each subject was vaccinated with two dosages of Covaxin™ (Bharat Biotech, Hyderabad, Telangana, India) or ChAdOx1 nCoV-19 (AZD1222) vaccine marketed as Covishield™ (Serum Institute of India Private Limited, Pune, Maharashtra, India) one or three months apart, respectively. None of the recruited subjects had received a booster dose of vaccine. Seroconversion was assessed using COVID Kawach SARS-CoV-2 immunoglobulin G (anti-SARS-CoV-2 IgG) antibody detection enzyme-linked immunosorbent assay (ELISA) (J. Mitra and Co. Pvt. Ltd., New Delhi, India), an indigenous qualitative antibody estimation kit, on sera obtained three weeks after the administration of the second dose of the vaccine (Fig. 1).

Statistical analysis

Statistical analysis was performed using R, Epicalc, and R-studio software (R development core team, Vienna, Austria) and MedCalc version 14 (Warandeberg 3, 1000 Brussels, Belgium). Continuous variables were presented as mean ± standard deviation (SD) or median and range or interquartile range (IQR). Categorical variables were analyzed by the Chi-squared (χ^2) test with Yates correction, wherever applicable. Continuous variables were analyzed using the Mann–Whitney *U* test and Wilcoxon signed rank test for unpaired and paired data, respectively. A *p*-value of less than 0.05 was considered significant.

Results

One hundred and thirty-two blood samples were collected from 97 IBD patients. Of them, 85 (87.6%) had ulcerative colitis, and 12 (12.4%) had Crohn's disease. The median age of IBD patients was 35 years (range 28–50), and 54 (55.6%) patients were males. Sixteen healthy controls were recruited in the control arm. The median age of controls was 27.5 years (range 24.2–35.7), and 4 (25%) were males.

Forty-one of the seventy-one (57.7%) unvaccinated and sixty of the sixty-one (98.4%) vaccinated IBD patients tested positive (OD > 0.3) for SARS-CoV-2 IgG antibodies ($p < 0.001$). The median OD value for the vaccinated patients was 1.3 (1.0–1.7), while in the unvaccinated group, it was 0.5 (0.1–1.3) (Fig. 2). Among the 16 vaccinated healthy controls (two were healthcare workers), 14 (87.5%) healthy controls tested positive (OD > 0.3) for SARS-CoV-2 IgG antibodies with a median OD value of 0.6 (0.4–0.7). The seropositivity rate was significantly higher

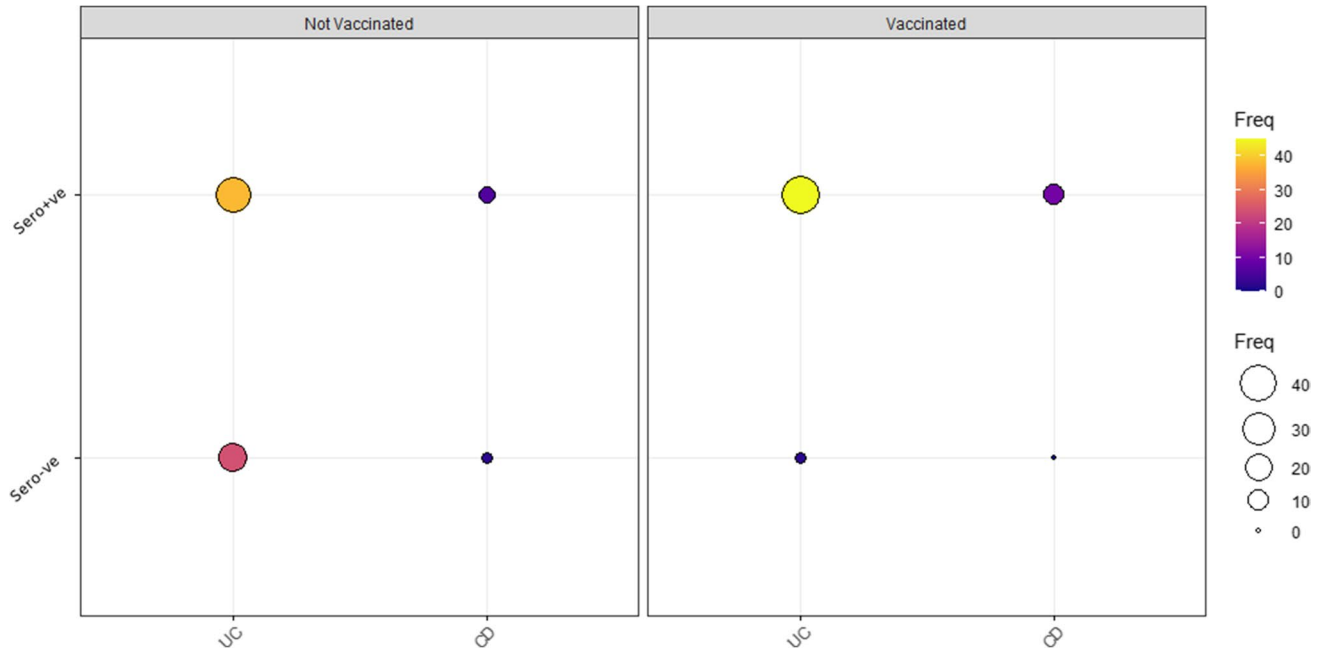

Fig. 2 Comparative analysis of seroprevalence of anti-severe acute respiratory syndrome coronavirus 2 immunoglobulin G (anti-SARS CoV2 IgG) antibody in inflammatory bowel disease patients (ulcerative colitis and Crohn's disease) pre- and post-vaccination showing increased antibody seroprevalence after vaccination. The circle represents the sample size, while the circle's color represents the frequency of presence of anti-SARS CoV2 IgG antibody. *Sero + ve* seropositive, *Sero-ve* seronegative, *UC* ulcerative colitis, *CD* Crohn's disease, *Freq* frequency

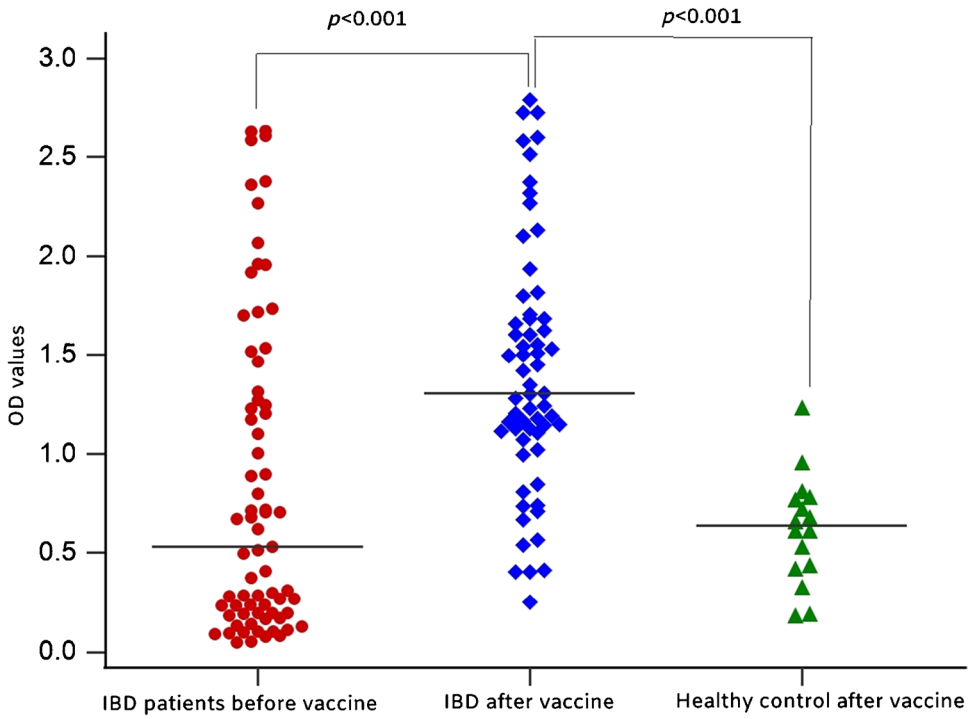

Fig. 3 Comparative analysis of the optical density (OD) values of the unvaccinated and vaccinated inflammatory bowel disease (IBD) patients and the healthy controls. OD values were significantly higher in vaccinated IBD patients than in unvaccinated IBD patients and healthy controls. A substantial proportion of unvaccinated patients also showed the presence of anti-severe acute respiratory syndrome coronavirus 2 immunoglobulin G antibodies, signifying herd immunity

among vaccinated IBD patients than among healthy controls ($p=0.047$). OD values were also significantly higher in vaccinated IBD patients than in unvaccinated IBD patients and healthy controls ($p<0.001$). OD values of vaccinated healthy controls and unvaccinated IBD patients were comparable (0.6 [0.4–0.7] vs. 0.5 [0.1–1.3], $p=0.882$) (Fig. 3). Three of the seventy-one (4.2%) unvaccinated IBD patients reported having recovered from COVID-19; all of them had mild disease, did not receive

any steroids or plasma transfusion, and none had long COVID syndrome. None of the IBD patients had breakthrough clinical COVID-19 until the last follow-up.

Paired data were available for 35 IBD patients. The median OD values before and after vaccination were 0.2 (0.1–1.1) and 1.3 (1.1–1.8), respectively. The median OD values increased substantially after vaccination in IBD patients ($p < 0.001$).

Overall, seven of 61 vaccinated patients had some forms of comorbidity. Seven patients with IBD with comorbidity had comparable median OD values of anti-SARS-CoV-2 antibody levels with that of 54 without comorbidity (1.2 [1.1–1.5] vs. 1.3 [1.0–1.8], $p = 0.666$).

The seroconversion rate was similar among 48 patients who received ChAdOx1 nCoV-19 (Covishield™) and 13 who received BBV 152 (Covaxin™) (97.9% and 100%, respectively; $p = 0.074$).

Five patients were on 5-amino salicylic acid (ASA) alone, and 56 were on immunomodulators in addition to 5-ASA. The median OD values of those with or without immunomodulators were comparable (1.6 [1.4–1.6] vs. 1.2 [1.0–1.6]; $p = 0.164$).

Discussion

The present study suggests that almost 98% of IBD patients seroconvert after vaccination against SARS-CoV-2 infection. Despite being on immunomodulator drugs, the seroconversion response among IBD patients was similar to that in healthy populations. A significant proportion (58%) of IBD patients had antibodies against SARS-CoV-2 even before vaccination, reflecting herd immunity.

Herd immunity refers to an indirect protective effect against an infectious disease that may occur via latent infection or vaccination and eventually reduces the likelihood of infection even without immunization [10]. Initially, it was suggested that herd immunity might not develop against COVID-19 due to various reasons, including uncertain efficacy of the vaccine to prevent transmission, uneven vaccine distribution, new emerging variants, and short-lasting immunity [11]. However, data from our small study show a high seroprevalence of anti-SARS-CoV-2 antibodies even in unvaccinated patients suggesting the development of herd immunity against COVID-19.

Some studies have previously estimated the seroprevalence of SARS-CoV-2 antibodies in unvaccinated subjects. One such study from Mexico found the seroprevalence of anti-SARS-CoV-2 antibodies in blood donors to be 45.2% during the third wave of SARS-CoV-2 infection. The seroprevalence was less than 15% before the second wave of the disease [12]. Another study from the USA before the second and third wave of COVID-19 found the seroprevalence of anti-SARS-CoV-2 antibodies among unvaccinated individuals who never had COVID-19 to be 11% only [13]. Our study found a higher seroprevalence, even after only the second wave of COVID-19 during the study period. In India, a seroprevalence survey conducted by the Indian Council of Medical Research (ICMR) in June–July 2021 found the seroprevalence of anti-SARS-CoV-2 antibodies to be 62.3% among unvaccinated subjects [14]. Our study presents data from a particular subset of patients with IBD. They are often on immunomodulator drugs, and it shows that there is a high anti-SARS-CoV-2 antibody seroprevalence even among these individuals.

While there are data to suggest that people with diabetes might have a lesser antibody response to COVID-19 vaccines, it has not been the case with patients with hypertension and obesity. Though our sample size was too small to study the effect of individual comorbidity on antibody response, overall, we did not find any difference in antibody response comparing to the median OD between the patients with and without comorbidities [15–17].

A significant difference was detected in our study among pre- and post-vaccination median OD values among patients for whom paired data were available. These data signify that despite being on immunomodulator drugs, these patients generate an excellent immune response. Though our study showed good seroconversion rates after vaccination against COVID-19 in both IBD patients and healthy controls, we found a significantly higher seropositivity rate in IBD patients than in healthy controls, possibly because of the small sample size, particularly that of the controls.

Covishield™ is an adenovirus vector-based vaccine, while Covaxin™ is made of adjuvanted inactivated viral particles. In various studies, Covishield™ and Covaxin™ showed nearly 90% and 80% effectiveness, respectively, with considerable efficacy against multiple variants as well [18]. The high efficacy of these vaccines has been associated with high seropositivity post-vaccination, 98.1% for Covishield™ and 80% for Covaxin™ [19]. Our study showed similar results even in IBD patients with high and comparable seropositivity rates for both the vaccines.

Some studies have previously shown that immunomodulatory drug therapy, particularly with anti-tumor necrosis factor α (TNFα), is associated with attenuated response to COVID-19 vaccination [20]. Recent studies and meta-analyses have suggested that the seroconversion rates for vaccines remain similar for various drugs [21, 22]. Our small study reiterates that seroconversion rates among different drug classes are high and similar, thus alleviating the scepticism around COVID-19 vaccination to reassure treating physicians and IBD patients.

This study showing the occurrence of herd immunity is critical to guide future vaccination dosing, schedules, and rollout of vaccination programs. None of the patients mentioned having ongoing symptomatic COVID-19 among the household contacts at the time of recruitment. Moreover, all the patients were also educated regarding using face masks, hand sanitization, and the importance of maintaining social distancing using telemedicine through regular group awareness for patients (GAP) sessions [23]. The small sample size, particularly that

of the controls, due to limited availability of antibody testing kits, unmatched cases and controls, and lack of paired data for all patients (as many patients found it difficult to travel for the second sample collection due to ongoing travel restrictions and COVID scare) and qualitative detection of anti-SARS-CoV-2 antibodies are some of the limitations of our study. However, we have used OD as a surrogate marker for antibody quantification to overcome the limitation of using qualitative kits.

In conclusion, most IBD patients seroconvert after vaccination against SARS-CoV-2, similar to a healthy population despite being on drugs used to treat IBD. A large proportion of IBD patients had anti-SARS-CoV-2 antibodies even before vaccination despite a low frequency of occurrence of clinically recognized COVID-19 in the past, suggesting the occurrence of herd immunity.

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Author contribution A. M., study design, care of the patients, data collection, analysis, and preparing the first draft of the paper; S. S.: laboratory work, collection of data, and help in data analysis and manuscript writing; U. C. G.: study design, care of the patients, data collection, analysis, and manuscript editing.

Declarations

Conflict of interest AM, SS, SR, UC, and UCG declare no competing interests in relation to this paper.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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