

**Cellular and humoral immune responses to SARS-CoV-2 vaccination in inflammatory
bowel disease patients**

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Abstract

Background and Aims

Knowledge on the immunogenicity of anti-SARS-CoV-2 vaccines in inflammatory bowel disease (IBD) patients is limited. Therefore, SARS-CoV-2-specific T-cell response and antibodies were analyzed in 60 IBD vaccine recipients and 30 controls.

Methods

SARS-CoV-2 IgG antibodies against the viral spike protein were measured at baseline and at 8 and 26 weeks after the second vaccine dose. SARS-CoV-2 IgG antibodies against the nucleocapsid antigens were measured at week 26. SARS-CoV-2 interferon-gamma released assay (IGRA) was performed in all vaccinees at week 26.

Results

At weeks 0 and 8, no differences were found in anti-spike antibodies between cohorts. At week 26, the decrease in antibody levels was more significant in the IBD cohort compared to the healthy cohort, and anti-nucleocapsid antibodies were not detected in either group. At week 26, 16 of 90 (18 %) vaccinated individuals had a negative IGRA test result, 7 of 90 (8 %) were borderline, and 67 (74 %) had a positive IGRA result; 22 of the 23 individuals with negative or borderline IGRA results belonged to the IBD cohort. However, the overall functional ability of T-lymphocytes to produce interferon-gamma after the unspecific mitogen stimulation was lower in IBD patients. In vaccinees with low or borderline IGRA, treatment with TNF-alpha inhibitors was the most frequent. In individuals with a significant drop in anti-spike antibody levels, plasmatic interferon-gamma concentrations after the specific SARS-CoV-2 stimulation were also insufficient.

Conclusions

Simple humoral and cellular post-vaccination monitoring is advisable in IBD patients so that repeated vaccine doses may be scheduled.

Key words

COVID-19; inflammatory bowel disease; vaccination.

Author's contributions

The authors confirm contribution to the paper as follows: study conception and design: MiL, KC, DD, MH; data collection: KC, DD, MaL, NM, VH, KM, KKu, VT, KKa, MiL; laboratory examinations: MH, JHH; interpretation of results: KC, MiL, DD, MH, JHH; manuscript preparation: KC, MiL, DD. All authors reviewed the results and approved the final version of the manuscript.

Disclosure of financial conflicts

KC has consulted for Biogen. DD: none. MH: none. JHH: none. MaL: has consulted for Takeda. NM: has consulted for Abbvie. VH: none. KM: none. KKu: none. VT: none. KKa: none. MiL: provided consultation and received fees for lectures by Celltrion, Abbvie, Janssen, Takeda and Ferring.

1. Introduction

Vaccine-established immunity to SARS-CoV-2 is acknowledged as the primary way to control the trajectory of the COVID-19 pandemic. As of the end of 2021, vaccination against SARS-CoV-2 has only been implemented for one year. The clear effectiveness of vaccination in different patient cohorts will therefore need to be proven with large and time-consuming efficacy trials. In the meantime, there is an urgent need for reliable immune correlates of anti-virus protection, as well as suitable laboratory tools to measure this protection in clinical practice.

Concerns have been raised about the susceptibility and increased risk of COVID-19 infection in inflammatory bowel disease (IBD) patients due to immune dysregulation, chronic inflammation, and immune-modifying treatment. Studies have shown that potential risk factors for SARS-CoV-2 infection in IBD patients include age, nutritional status, disease activity, numerous comorbidities, and high-dose systemic corticosteroid treatment. [1] Moreover, many studies have found post-vaccine seroconversion in IBD recipients of different anti-COVID-19 vaccines. [2-4] Our workgroup is one of several that has recently shown that positive levels of anti-SARS-CoV-2 IgG antibodies were achieved in all mRNA anti-SARS-CoV-2 vaccine IBD recipients and that a small percentage of vector-based vaccine recipients did not reach post-vaccination seroconversion, whereas vaccination with vector-based vaccines was associated with lower quantitative IgG antibody levels compared to mRNA vaccine-induced protection in an IBD cohort. [5]

However, there are legitimate concerns about the significance of anti-SARS-CoV-2 antibody levels since the cellular response from the T- and B-lymphocytes is more relevant. [6] Particularly, it remains unclear whether lower antibody response in IBD patients under

immunomodulatory regimens such as therapeutic monoclonal antibodies and their combination with thiopurines or methotrexate is also associated with an insufficient vaccine-induced SARS-CoV-2-specific T-cell response.

Recently, the diagnostic accuracy of interferon-gamma (IFN- γ) release assays (IGRA) to detect post-viral and post-vaccination T-cell antigen-specific response was proven. [7] IGRA assays, which perform a quantitative detection of plasmatic IFN- γ as a response to *in-vitro* stimulation by the S-protein of SARS-CoV-2 in human whole blood, are intended to be used as an aid in diagnosing specific T-cellular immune response of the SARS-CoV-2 spike protein after vaccination or infection. [8]

In the current study, we aimed to measure the immunological cellular response to the SARS-CoV-2 vaccine (both mRNA and vector-based) by applying IGRA and correlating it to the IgG humoral response against spike (anti-S) and nucleocapsid (anti-N) antigens in IBD patients on biological treatment after the completion of a two-dose vaccination regimen, comparing an IBD cohort with healthy fully vaccinated individuals.

2. Materials and Methods

A non-interventional observational trial was conducted in a single tertiary IBD center during the year 2021.

2.1. Examined cohorts

For the study results reported here, two cohorts were created: an IBD patient cohort (IBD, n = 60) and a healthy healthcare professionals' cohort (CTRL, n = 30). As can be seen in the size of the cohorts, a 2:1 matched pair case-control strategy was applied. The CTRL

cohort was matched to following criteria: (1) completed vaccination with COVID-19 vaccines approved by the European Medicines Agency; (2) 26 weeks had passed since the second vaccine dose; (3) gender, and (4) age. Individuals with PCR-proven SARS-CoV-2 infection during or after vaccination throughout 2021 were not eligible for the study; this was the only exclusion criterion for both cohorts. PCR-positive COVID-19 cases occurring more than 120 days prior to vaccination start were not excluded because such infections were contracted in 2020. Two cohorts could not be matched by vaccine type (mRNA or vector) due to over-time changes in Czech vaccination strategy during the year 2021.

Both cohorts consisted of fully vaccinated participants. Three vaccine brands were used for COVID-19 prevention: (1) mRNA BNT162b2 (Comirnaty; Pfizer-BioNTech, USA), (2) mRNA CX-024414 (Spikevax; Moderna, USA), and (3) vector ChAdOx1 nCoV-19 (Vaxzevria; AstraZeneca, UK). All vaccines were two-dosed. The study was conducted prior to the start of booster vaccine doses.

2.2. *Laboratory examinations*

Study start (week 0, W0) was the day of the first vaccine dose. Further monitoring time points were 8 (W8) and 26 (W26) weeks after completion of vaccination by second vaccine dose.

At W0, W8, and W26, anti-S serum IgG antibodies were measured by the SARS-CoV-2 IgG II Quant antibody test (Abbott, USA). Additionally, anti-N serum IgG antibodies were measured by the Anti-SARS-CoV-2 NCP ELISA IgG (Euroimmun, DE) at W26. Because all COVID-19 vaccines used in the study are constructed to encode virus S-protein, a positive test for anti-S IgG was used as a prior infection and/or vaccination indicator. The anti-N IgG

serological test was used to check for evidence of infection (i.e., direct contact with SARS-CoV-2 virus and subsequent antibody production) before, during, or after vaccination. The cut-off value of the anti-S IgG analysis was 50.0 AU/mL. After the release of a WHO standard preparation for SARS-CoV-2 binding antibodies [9], a conversion factor from Abbott AU became available ($1 \text{ BAU/mL} = 0.142 \times \text{AU/mL}$) [10] and the results obtained in this study have been expressed in BAU/mL. For anti-N IgG antibodies, a positivity index ratio of <0.8 was interpreted as negative, $0.8 - 1.1$ as borderline, and >1.1 as positive.

Quan-T-Cell SARS-CoV-2 and Quan-T-Cell ELISA (Euroimmun, DE) were performed at W26 in both cohorts. Quan-T-Cell SARS-CoV-2 is the stimulation tube set for heparinized whole blood stimulation with (1) antigens based on the SARS-CoV-2 spike protein (CoV-2 IGRA), (2) mitogen for unspecific T-cell stimulation for control of the stimulation ability (STIM IGRA), and (3) no additive for determination of the individual IFN- γ background (BLANK IGRA). After the stimulation process, the obtained plasma was analyzed by enzyme immunoassay. Optical density (OD) was measured as a logarithmic measurement of the light to be transmitted through the plasma sample, which corresponded to the amount of IFN- γ in the plasma specimen. Further, concentrations of IFN- γ in the CoV-2 IGRA samples were calculated from the calibration curve. Results were interpreted by the manufacturer's recommendations as follows: (1) plasmatic IFN- γ concentration $<100 \text{ mIU/mL}$ was negative, (2) $100 - 200 \text{ mIU/mL}$ was borderline, and (3) $>200 \text{ mIU/mL}$ was positive.

2.3. *Ethical aspects*

Data were analyzed in accordance with the ethical principles of the Declaration of Helsinki. The project was approved by institutional ethics committee No 2021/IIIa. All participants provided written informed consent.

2.4. *Statistical analysis*

Data were statistically evaluated using STATISTICA version 13 (Tibco, USA). Because a normal distribution of the data was not demonstrated with the Shapiro-Wilk test, non-parametric statistical approaches were adapted. Continuous variables were presented as medians and in upper and lower quartiles, while categorical variables were shown as numbers and percentages. A non-parametric Kruskal-Wallis test was carried out to analyze the agreement between quantitative data, and Cohen's kappa analysis was used to measure inter-rater reliability for categorical items. Fisher's exact probability test was used to determine nonrandom associations between categorical variables, with Freeman-Halton extension for more than two variables. P values of ≤ 0.05 were considered significant.

3. Results

Baseline characteristics of both IBD and CTRL cohorts are shown in Table 1.

Table 1

3.1. Plasmatic levels of IFN- γ after the whole-blood T-lymphocytes' stimulation with SARS-CoV-2 spike protein antigens

At W26, 16 of 90 (18 %) vaccinated individuals had a negative IGRA test result (<100 mIU/ml), 7 of 90 (8 %) were borderline, and 67 (74 %) had a positive IGRA result (>200 mIU/ml). Interestingly, 22 of the 23 individuals with negative or borderline IGRA test results belonged to the IBD cohort, and only one individual from the CTRL group, an 88-year-old woman, was IGRA-negative. However, the overall functional ability of T-lymphocytes to produce IFN- γ was significantly different between the IBD and CTRL cohorts. IFN- γ production after the unspecific mitogen stimulation (STIM IGRA) was lower in IBD patients, whereas baseline (BLANK IGRA) T-cell response was similar in the two cohorts, as shown in Table 2.

Table 2

In IBD patients with low or borderline IFN- γ plasmatic levels after the specific spike protein stimulation, treatment with the TNF-alpha inhibitors was the most frequent, as shown in Figure 1. Except of treatment with the TNF-alpha inhibitors, no other differences such as IBD characteristics (disease activity, localization, or duration of the disease) were seen in IGRA-negative/borderline patients compared to individuals with sufficient cellular immune response.

Figure 1

As can be seen in Table 3, an agreement was found between the IFN- γ plasmatic levels and serum anti-S IgG concentrations: in individuals with a significant drop in anti-S IgG levels, plasmatic IFN- γ concentrations after the specific CoV-2 IGRA stimulation were insufficient.

Table 3

3.2. *Over-time dynamics of the anti-SARS-CoV-2 IgG antibody response against spike and nucleocapsid viral antigens*

At W0 and W8, no significant differences were found in IgG anti-S serum concentrations between the IBD and CTRL cohorts. At W26, the decrease in anti-S IgG serum levels was more significant in the IBD cohort. Moreover, IgG anti-N antibodies were not detected in the IBD or CTRL groups (median positivity indexes of 0.2 and 0.1, respectively) at W26. Therefore, it can be assumed that no contact with viral nucleocapsid antigen occurred in study subjects until W26, and that for the 8 PCR-positive individuals from 2020, anti-nucleocapsid humoral immunity had already evolved (see Table 4).

Table 4

3.3. Rates of anti-SARS-CoV-2 cellular and humoral immune response in relation to the vaccines used

Vector vaccine Vaxzevria was used in 46.7 % of IBD patients and 30 % of CTRL individuals, whereas mRNA vaccines (Comirnaty or Spikevax) share was 53.3 % and 70 %, respectively. This difference in the proportions of vaccine types can be explained by the national vaccine prioritization strategy and vaccines availability in our country.

Negative or borderline IGRA test results at W26 were found in 23 individuals (22 from IBD and 1 from CTRL cohort), whereas most of them were vaccinated by vector vaccine Vaxzevria (16/23, 70 %).

At W8, the post-vaccination seroprevalence of anti-S IgG antibodies was 95.5 %. Four individuals (4.4 %) did not show sufficient anti-S IgG at W8, all of them were IBD patients vaccinated by the vector vaccine Vaxzevria. At W26, seronegativity expressed by the anti-S IgG levels lower than 352 BAU/mL was found in 17 individuals (18.9 %). Of them, 14 were IBD patients vaccinated by Vaxzevria, two IBD patient vaccinated by mRNA vaccines, and 1 CTRL individual vaccinated by Comirnaty. See Table 5.

Table 5

Discussion

Vaccination against SARS-CoV-2 is the most important strategy to protect against infection. Currently we know that early post-vaccination antibody production is robust in most IBD patients, even those on immune-modifying therapies, but that antibody production is blunted right at the beginning by anti-TNF therapy and its combination with immunomodulators such as azathioprine. [11] However, there is still little information available on post-vaccination cellular immunity. Assessing cellular immunity for SARS-CoV-2

(in addition to humoral immune response) appears important for several reasons. First, vaccinated patients undergoing immune-modifying therapy with positive post-vaccination cellular immunity against SARS-CoV-2 will probably have a lower risk of developing disease following infection than those who do not have detectable cellular immunity. [12] Some studies have reported T-cell response as a more sensitive indicator of anti-SARS-CoV-2 defense than antibody assays. [13] Moreover, cellular immunity against SARS-CoV-2 is emerging as a more resilient defense against mutated variants of SARS-CoV-2. [14,15]

Not enough information is available about post-vaccination cellular immunity in patients with immunopathological diseases such as IBD. A recent study of 28 German IBD patients [16] found that even in the absence of SARS-CoV-2 IgG antibodies, IBD individuals showed significant T-cell response after the first SARS-CoV-2 vaccination compared to healthy controls, and that this difference was not influenced by immunosuppressive regimens. On the contrary, impairment of CD4+ T-cell responses but normal memory CD8+ T-cell activation in CD patients after COVID-19 vaccination was recently reported in a single twin case. [17] In an Italian study on 35 rheumatoid arthritis (RA) patients, IFN- γ plasmatic levels after the specific stimulation by SARS-CoV-2 spike protein antigens were significantly lower in RA patients under TNF- α , IL-6, and CTLA-4 inhibitors. [18]

When comparing spike protein T-cell response between IBD and CTRL individuals, a significant difference was found in cellular reactivity between the groups: IBD vaccinees produced less IFN- γ than healthy vaccinated persons, which may suggest some degree of cellular dysfunction or exhaustion. This premise is supported by another finding, namely the decreased T-cell response in the IBD cohort, even after the unspecific mitogen stimulation. From a clinical perspective, it could be an important finding that there is a substantial

correlation between serum anti-spike IgG antibody levels and the functional cellular test results. Since antibody tests are already widely available and affordable, they could serve to some extent as a sufficient indicator of both antibody and cellular immune response.

There are some limitations to our study. The first one is the sample size, which was mainly influenced by the limited availability and costliness of SARS-CoV-2 IGRA assays. Deriving causal relationships in this setting is a challenge; the main concern is the effect of immune-modifying drugs. Cellular response primarily determines long-term postvaccination protection, but it is still less well understood. In anti-SARS-CoV-2 vaccinated IBD patients on immune-modifying therapy, the largest study with $n = 303$ patients is available as a preprint [19]. US workgroup has evaluated IBD patients who completed SARS-CoV-2 vaccination at four time points (1st vaccine dose, 2nd dose, 2 and 8 weeks after the 2nd dose). Consistently with our observations, S-specific T cellular and anti-S antibody responses were significantly correlated ($R = 0.19$ to 0.21) in this work. Among IBD patients with low antibody response, T cell clonal breadth and depth were low, suggesting that those with impaired humoral vaccine response have similarly impaired cellular responses. Moreover, similar observations on immune-modifying treatment and vaccine type (reduced cellular and humoral response in vector vaccines) were found. Despite these suggestive signals, those differences should be interpreted with caution due to the already small number of examined vaccinees.

However, several notable strengths are to be highlighted, including the utilization of a standardized high throughput IGRA assay and validated serological platforms to accurately measure antibody response.

Our results need to be confirmed in a larger population adopting a similar therapeutic strategy to draw definite conclusions. Future studies are needed to further

evaluate the longevity of humoral and T-cell response following vaccination. Meanwhile, it may be worthwhile to offer a booster SARS-CoV-2 vaccine dose, in particular to immunocompromised patients.

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Data Availability Statement

Cerna K, et al. **Cellular and humoral immune responses to SARS-CoV-2 vaccination in inflammatory bowel disease patients**

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

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Figure 1 SARS-CoV-2-reactive T-cells activity measured by IFN- γ release in different IBD treatment modalities

IFX, infliximab; ADA, adalimumab; VDZ, vedolizumab; UST, ustekinumab; AZA, azathioprine;

KW-H, Kruskal-Wallis H-test; cut-off, threshold interferon-gamma concentration.

