T Cell Response After SARS-CoV-2 Vaccination in Immunocompromised Patients with Inflammatory Bowel Disease

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Abstract

Background: Vaccination is a promising strategy to protect vulnerable groups like immunocompromised inflammatory bowel disease [IBD] patients from an infection with SARS-CoV-2. These patients may have lower immune responses. Little is known about the cellular and humoral immune response after a SARS-CoV-2 vaccination in IBD patients.

Methods: Totals of 28 patients with IBD and 27 age- and sex-matched healthy controls were recruited at Jena University Hospital. Blood samples were taken before, after the first, and in a subgroup of 11 patients after second dose of a SARS-CoV-2 vaccination. Cellular immune response, including IFN-γ and TNF-α response and antibody titres, were analysed.

Results: Overall, 71.4% of the IBD patients and 85.2% of the controls showed levels of anti-SARS-CoV-2 antibodies above the cutoff of 33.8 BAU/ml [p = 0.329] after the first dose. Even in the absence of SARS-CoV-2 antibodies, IBD patients showed significant T cell responses after first SARS-CoV-2 vaccination compared with healthy controls, which was not influenced by different immunosuppressive regimens. Associated with the vaccination, we could also detect a slight increase of the TNF production among SARS-CoV-2-reactive TH cells in healthy donors [HD] and IBD patients. After the second dose of vaccination, in IBD patients a further increase of humoral immune response in all but one patient was observed.

Conclusions: Already after the first dose of a SARS-CoV-2 vaccination, cellular immune response in IBD patients is comparable to controls, indicating a similar efficacy. However, close monitoring of long-term immunity in these patients should be considered.

Key Words: IBD; immunosuppression; vaccination; SARS-CoV-2; COVID19; cellular immunity

1. Introduction

Since beginning of 2020, the severe acute respiratory syndrome coronavirus type 2 [SARS-CoV-2] pandemic has led to significant challenges in the treatment of patients with IBD. Although no increased susceptibility to SARS-CoV-2 infections or mortality is evident in patients with IBD, 17% of patients with IBD infected with
SARS-CoV-2 had to be hospitalised worldwide and patients with IBD express a great fear of becoming infected. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) and the COVID-19 European Crohn’s and Colitis Organisation (ECCO) taskforce recommended vaccinating all patients with IBD as soon as they are able to receive the vaccination, regardless of immune-modifying therapies. COVID-19 vaccines are safe in patients with IBD but they were excluded from COVID-19 vaccine trials and therefore, efficacy is largely unknown.

A plethora of scientific reports describe impaired immunity after vaccination in IBD patients with immunosuppressive therapy. However, data regarding the effect of immunosuppressive therapies on the immune response are inconsistent. Upon vaccination against influenza or pneumococci, IBD patients treated with immunosuppressive agents such as TNF-α-antibodies or receiving combination therapies developed lower humoral vaccine responses. In line with this, the immunogenicity of hepatitis B vaccinating combination therapies developed lower humoral vaccine responses. In patients with IBD and immunosuppressive therapies, in comparison with untreated controls.

Peripheral blood mononuclear cells [PBMCs] were separated on a Biocoll solution [Bio&SELL GmbH, Germany] by centrifugation at 800 g x g at room temperature [RT] for 20 min without brakes. The intermitting phase containing PBMCs was washed with PBS twice and subsequently cryoconserved in liquid nitrogen in medium containing penicillin/streptomycin [Sigma-Aldrich], 10 % DMSO [Sigma-Aldrich], and 50 % FCS [Sigma-Aldrich]. Upon thawing at RT, PBMCs were washed with cell culture medium (supplemented with 10% human AB serum [PAN Biotech, Germany], penicillin/ streptomycin) and let rest at 37°C for 1 h. Subsequently, a maximum number of 5 x 10⁶ PBMCs were restimulated in cell culture medium containing 1 µg/mL recombinant anti-human CD28 antibody [clone CD28.2, BioLegend] with either 0.2% DMSO [negative control], SARS-CoV-2 Spike glycoprotein PepMix 1 [S1, N-terminal coverage] or 2 [S2, C-terminal coverage] [both ipt, Germany]. As high controls, 10⁵ PBMCs were restimulated with 1 µg/mL TSST1 and 1 µg/mL SEB [both Sigma-Aldrich] in presence of 1 µg/mL recombinant anti-human CD28 or anti-human CD3/CD28 beads [Gibco/Thermo Fisher Scientific, Lithuania] at a ratio of one bead/PBMC. All samples were incubated for 2 h and Brefeldin A [BioLegend] was added for another 14 h of incubation. Upon centrifugation at 300 g x g at RT for 10 min, cells were recovered in 1 mg/mL beriglobin and stained with anti-human CD3 Pacific Blue [clone UCHT1, BioLegend] and anti-human CD4 Brilliant Violet 605 [clone RPA-T4, BioLegend]. After 5 min, Zombie Aquix fixable dead cells stain [BioLegend] was added and incubated for another 10 min. Upon washing with PBA/E, the cells were fixed in 2% formaldehyde/PBS at RT for 20 min, intracellularly stained with anti-human CD154 APC [clone 24-31, BioLegend], anti-human CD137 PE/Cy7 [clone 4B4-1, BioLegend], anti-human IFNγ APC/Cy7 [clone 4S.B3, BioLegend], anti-human TNFα PerCP/Cy5.5 [clone MBab11, BioLegend], anti-human IL-4 PE [clone MP4-25D2, BioLegend], and anti-human IL-17A FITC [clone BL168, BioLegend] in 0.5% Saponine [Sigma-Aldrich] in PBA/E at 4°C for 20 min. Cells were recovered in PBA/E and analysed with a FACs-Canto-Plus flow cytometer [BD]. Data were analysed with FlowJo V10.7 [BD, Ashland, OR, USA].

Serological analyses for SARS-CoV-2 antibodies were performed using the Liaison SARS-CoV-2 Trimerics IgG CLIA on the LiaisonXL [DiaSorin, Saluggia, Italy] following the manufacturer’s instructions. This assay detects IgG antibodies against SARS-CoV-2-specific trimeric spike glycoprotein with an estimated sensitivity of 98.7% [153/155] at ≥15 days after the first positive RT-PCR and an estimated specificity of 99.5% [1889/1899]. Results are defined as seropositive for measured values of ≥13 AU/ml or ≥33.8 BAU/ml, respectively. According to the manufacturer, this assay has shown a positive agreement of 100% (Wilson 95% confidence interval [CI]: 97.8-100%) when compared with a micro-neutralisation assay, and the negative agreement is stated as 96.9% (Wilson 95% CI: 92.9-98.7%).

2.2. Serological measurements

2.3. Statistical analysis

Statistical analysis was performed using SPSS v27 [IBM, Armonk, NY, USA] or Sigma Plot 13 [SYSTAT Software GmbH, Germany]. Normal distribution was tested using the Shapiro-Wilk test. If the test for normal distribution failed, the Mann-Whitney U test was performed; otherwise significance was tested using a two-sided, non-paired Student’s t test. Data are expressed as medians with interquartile range
3. Results

A total of 28 patients with IBD were included in the analysis, among them 17 patients with Crohn’s disease [CD], 10 patients with ulcerative colitis [UC], and one with not defined IBD. The median age was 42 years. Overall, nine patients had additional extraintestinal manifestations and nine patients had previous IBD-related complications including surgery. IBD was in remission in 20 patients and chronic-active in eight patients. All patients received immunosuppressive medication at inclusion. Two patients with UC had additional liver transplantation due to primary sclerosing cholangitis, and one patient received a heart transplantation due to non-IBD associated disease. Details on the baseline characteristics are presented in Table 1. Additionally, 27 healthy volunteers [HD = healthy donors] were included as a control group and were matched for age and sex. Both groups received either the AstraZeneca vaccine [ChAdOx1] in 18 patients and 14 controls or an mRNA-based vaccine in 10 patients and 13 controls [BioNTech/Pfizer, BNT162b2] as the first dose; all received an mRNA vaccine as the second dose.

3.1. Assessment of cellular immune response

To quantify SARS-CoV-2-specific T_{H} cells among CD4+ PBMCs, we incubated the PBMCs with two S-Protein-derived peptide mixes covering the whole sequence of the Spike protein [N- and C-terminally, S-Mix1 or S-Mix2, respectively]. When we analysed the CD137+CD154+ [antigen-specific] cells among living CD4+CD3+ cells [T_{H} cells, gating strategy is shown in Figure 1A] upon SARS-CoV-2 vaccination, we observed a comparable significant increase in frequencies of S-Protein-specific T_{H} cells in HD as well as in IBD patients [Figure 1B and C]. Although we detected slightly increased S-Mix2-specific T_{H} cells in naive patients, as described by Braun et al.,23 this was not significant in both cohorts [Figure 1C]. However, we observed the presence of S-Mix2-reactive T_{H} cells before vaccination at the level of IFN-γ-producing T_{H} cells in HD and IBD patients [Figure 1D]. Of note, the SARS-CoV-2 vaccination resulted in an increase in the frequencies of IFN-γ producers among SARS-CoV-2-reactive T_{H} cells in the HD as well as in the IBD cohort [Figure 1D]. Associated with the vaccination, we could also detect a slight increase of TNF-producing SARS-CoV-2-reactive T_{H} cells in HD and IBD patients [Figure 1E], but not of the IL-17A or IL-4 production [data not shown]. Such vaccine-related immunogenic effects were similar between HD and IBD cohorts when separated by their deficiency in generating a sufficient SARS-CoV-2-specific antibody response [Supplementary Figure 1A, available as Supplementary data at ECCO-JCC online]. IBD patients, who received an organ transplant did as well generate detectable SARS-CoV-2-specific T_{H} cell responses upon vaccination [Supplementary Figure 1B].

A subcohort of the vaccinated subjects was re-analysed after a second round of vaccination; in this group, the observed vaccine-related induction of SARS-CoV-2-reactive T_{H} cells did remain in IBD patients [Figure 1F], and thereby, this demonstrated that treated IBD patients did indeed develop a cellular SARS-CoV-2 specific immunity upon vaccination. In line with the results obtained from IBD patients after the first round of vaccination, these detected SARS-CoV-2-specific T_{H} cells contained non-significantly increased IFNγ producers [Figure 1G] and showed a pronounced increase of TNFα-producing T_{H} cells [Figure 1H].

In a general analysis of CD4+ T cells, which are predominantly CD8+ cytotoxic T cells [T_{C} cells], we did not detect a deficiency of very faint overall CD137 upregulation in IBD patients upon vaccination [Supplementary Figure 1C] or of the faintly induced IFNγ production among them [Supplementary Figure 1D]. Of note, a more detailed analysis of CD137+ Tc cells is necessary to study significant immunogenic effects of a SARS-CoV-2 vaccine in IBD patients on the T_{C} cell population, including detection of CD69 or specificity via pMHC multimers.24

3.2. Assessment of humoral immune response

Overall in both groups, one person showed positive SARS-CoV-2 IgG antibodies indicating a nonapparent infection before vaccination; these patients were excluded from further analysis. Three weeks after the first dose of the vaccine, 20 of the IBD patients [71.4%] had detectable levels of SARS-CoV-2 antibodies, indicating an immunological response to the vaccine, and 8 patients [28.6%] showed levels below the cutoff of 33.8 BAU/ml. Interestingly, there was a sufficient antibody production in 23 of the healthy controls [85.1%] as well, and it was still below the cutoff in four healthy controls [14.9%]. The difference between both groups was not statistically significant [Figure 2A, p = 0.329]. Furthermore, when looking at the levels of SARS-CoV-2 antibodies, they were slightly but non-significantly higher in the healthy controls [Figure 2B, median 57.2 vs 105.0 BAU/ml, p = 0.113]. Twelve patients and 12 controls already received the second dose of the vaccination. In these patients, antibodies markedly increased and were detectable in all samples of the healthy donors and all but one patient [91.7%]. Still, the antibody titres were slightly higher in the healthy donors. Of the patients analysed after the second vaccine dose [1119 vs 1570 BAU/
Figure 1. PBMCs from 16 healthy donors [healthy] or 23 patients with inflammatory bowel disease [IBD] were analysed for S-protein-specific T\(_H\) cells. DMSO [solvent of S-peptide mixes] was used as control. S-protein mixes 1 [S-Mix1] and 2 [S-Mix2] represent the S-protein N-terminal part and C-terminal part, respectively. A,B] Gating strategy is shown in [A] and S-protein-specific T\(_H\) cells are depicted as CD137\(^+\)CD154\(^+\) among living CD4\(^+\)CD3\(^+\) in [B]. C] Data of all 16 healthy donors and 23 IBD patients are summarised in the box plots. D, E] IFN\(_\gamma\)-producing cells [D] or TNF\(\alpha\)-producing cells [E] among CD137\(^+\)CD154\(^+\) TH cells are summarised in box plots. F-H] Upon a second round of vaccination, PBMCs from subjects of the IBD group were restimulated and analysed as in [A-E]. Statistics were analysed as described in Material and Methods section. *\(p<0.05\); **\(p<0.01\); ***\(p<0.001\); n.s., non-significant. PBMCs, peripheral blood mononuclear cells.
ml, \( p = 0.313 \), four did not have detectable antibodies after the first dose but, interestingly, three of these patients developed positive titres after the second dose. However, the levels were lower than in patients with already positive titres after the second dose and comparable to the levels found after the first dose in the already positive patients [Figure 2A].
To determine the impact of different types of immunosuppression, we stratified the patients according to their therapy. Unexpectedly, we could not observe any difference between anti-SARS-CoV-2 antibodies in patients with and without TNF-antibodies [Figure 3, \( p = 0.629 \)], with ustekinumab therapy [Figure 3, \( p = 0.371 \)]. Additionally, the number of systemic immunosuppressive drugs taken by a patient did not have an impact on the antibody levels post-vaccination [Figure 3, Spearman’s \( \rho = -0.216, \ p = 0.270 \)]. Patients taking only one immunosuppressive drug had comparable levels of SARS-CoV-2 antibodies to patients taking more than one drug [Figure 3, \( p = 0.566 \)].

We have included three patients with additional solid organ transplantation (two liver [LTX] and one heart [HTX] transplantation). As these patients have a more complex immunosuppressive therapy, we performed a separate analysis comparing the transplant and non-transplant IBD patients. The antibody response in these patients showed a huge variety between the lower limit of detection in the patients after HTX and one of the LTX patients, up to 1550 BAU/ml in the other LTX patient. The IBD patients without concomitant solid organ transplantation had a median level of 57.5 BAU/ml [Figure 3]. Notably, the patients without antibodies had a significant increase in SARS-CoV-2-specific T\(_H\) cells compared to patients without transplantation, indicating an effect of the vaccination.

4. Discussion

In this study, we demonstrate a significant SARS-CoV-2 specific cellular immune response in 27 immunocompromised patients with IBD after one dose of a SARS-CoV-2 vaccine. The T cell response was similar to that in healthy controls, indicating a protective effect of the vaccine in immunocompromised patients with IBD. The humoral response was sufficient in only 71.4% of the patients following the first dose and 91.7% after the second dose.

Recent studies raised concerns about the efficacy of the SARS-CoV-2 vaccination in immunosuppressed patients. Antibody levels after vaccination were found to be up to 20% lower compared with healthy controls after a single dose of a vaccine in transplant patients.\(^{10}\) In line with this, kidney transplant recipients showed positive SARS-CoV-2 antibodies after vaccination in only 5–10%\(^{10,13,15}\) and presented a weak T cell response measured by ELISPOT assay as well.\(^{11}\) A recent study in patients vaccinated with the BioNTech/Pfizer vaccine after liver transplantation [LTX] found antibodies in 47.5% of the patients and 100% of the controls.\(^{21}\) The authors identified co-medication with mycophenolate or steroids as a risk factor for vaccination failure: both were used only in the transplant patients in our cohort. Additionally, higher age was associated with an increased risk of vaccination failure.\(^{22}\) Another recent study found adequate antibody response in 86% of rheumatological patients following a SARS-CoV-2 vaccination, which is in line with our findings.\(^{20}\) The authors could identify treatment with rituximab as a risk factor for non-response to the vaccine; rituximab was not used in our cohort. We did include two patients with IBD and LTX due to PSC and one patient with HTX. Of these three patients, one patient developed antibodies. However, our patients with IBD were younger than the patients in the transplant cohorts. A recent study on transplant patients found positive antibodies in 40% of patients after the second dose and the authors were able to increase these proportion to 68% using a third dose of an mRNA SARS-CoV-2 vaccine.\(^{27}\) Data on the immune response in patients with IBD after vaccination are sparse. A recent study reported adequate humoral immune responses after the second dose or after one dose and previous infection, which is in line with our findings, but antibody titres in this study were lower in patients treated with infliximab compared with vedolizumab.\(^{18}\) Additionally, the same group reported the same differences in antibody titres in patients with IBD after confirmed SARS-CoV-2 infection.\(^{28}\) However, data on cellular immune response after SARS-CoV-2 vaccinations have thus far not been reported in patients with IBD. Thieme et al. have investigated SARS-CoV-2-specific immune responses in another population of immunosuppressed patients, i.e., transplant patients.\(^{22}\) Interestingly and in accordance with our data, they found no differences in humoral or cellular immune response between the transplant patients and controls.

In patients with negative antibody titres after the first vaccination, three out of four patients had detectable levels after the second dose, which were on the same level as titres after first vaccination in controls and IBD patients who had positive titres after the first dose. It is tempting to speculate that these patients might have a benefit from another booster vaccination dose as recently shown in transplant patients,\(^{27}\) but as the number of patients is small, a larger cohort of patients is needed.

Most importantly, we were able to show an increase in SARS-CoV-2-specific T\(_H\) cells in IBD patients already after the first SARS-CoV-2 vaccination. We found that these SARS-CoV-2-specific T\(_H\) cells were maintained or even enhanced upon a second dose of vaccine. In non-immunised, non-infected donors such SARS-CoV-2-reactive T\(_H\) cells have been described by Braun et al., who termed such subjects reactive healthy donors.\(^{23}\) However, little is known about SARS-CoV-2-specific T-cells in patients with IBD.\(^{24}\) In line with cross-reactive antigen-specific T-cells being present in up to 35% of healthy donors in other studies,\(^{21}\) we detected the presence of such reactive healthy donors in our HD as well as IBD cohorts before vaccination. The protective or pathogenic relevance of such pre-existing SARS-CoV-2 specific T\(_H\) cells is currently a matter of debate.\(^{10,12}\) They might represent either memory cells from a former encounter with SARS-CoV-2 [as in the additionally antibody-positive patient] or are cross-reactive T\(_H\) cells originating from other infections, e.g. previous infections with common coronaviruses. Collectively, we could show that IBD patients, independently from their medical history, do partially possess cross-reactive SARS-CoV-2-specific T\(_H\) cells comparable to healthy donors, and that vaccination of IBD patients did induce a robust T\(_H\) cell-mediated immune response against the viral spike protein.

Two of the IBD patients showed low levels of TNF- and IFN-producing CD137\(^+\)/CD154\(^+\)/CD4\(^+\) T cells following the vaccination, indicating a potential weaker response. However, low frequency of positive cells has to be taken into account in interpreting these results. Nevertheless, both of these patients had positive anti-SARS-CoV-2 antibodies following vaccination.

Our study has some limitations. First, we mainly examined the response following the vaccination after the first dose, and only in a smaller subcohort after the second dose. However, for all vaccines used in the participants, a second dose is strongly recommended. In line with other studies which detected a sufficient T cell response after one dose of a SARS-CoV-2 vaccine,\(^{13,14}\) we observed a robust increase of SARS-CoV-2-specific T\(_H\) cells in immunosuppressed IBD patients, which was preserved throughout a second vaccination. Second, we included both, AstraZeneca and BioNTech/Pfizer vaccines. In the current discussion about SARS-CoV-2 vaccinations, the recommendations regarding the AstraZeneca vaccine, which was used in the majority of the patients as the first dose, changed several times. As our patients were younger than 60 years, they will get another type of vaccine as
the second dose, following current German recommendations, which is the BioNTech/Pfizer vaccine in most cases. We therefore decided to include both types of vaccine in the current study. Third, data on the duration of the immune response are lacking and we cannot exclude a shorter duration of immunity following vaccination in immunosuppressed IBD patients. We still detected SARS-CoV-2-specific Th cells with an increased tendency of IFNγ production upon the second vaccination, but a monitoring of a robust long-term immune response is lacking. Fourth, the sample size is still small and larger cohort studies are needed to validate the observed vaccination-induced immune protection of immunosuppressed IBD patients from SARS-CoV-2.

Nevertheless, our data indicate an adequate humoral and cellular immune response in immunosuppressed patients with IBD, indicating a comparable efficacy to healthy controls. Therefore, monitoring of the vaccination effect and long-term immunity should be considered.

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**Conflict of Interest**

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**Author Contributions**

PAR and NA performed statistical analyses and wrote the manuscript. NA and SG performed experiments. PAR and AS conceived of the study. PAR, PG, and AS provided patient samples. AS and TK gave important intellectual input and interpreted the data. All authors critically revised the manuscript for important intellectual content.

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**Supplementary Data**

Supplementary data are available at ECCO-JCC online.

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