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Editorial

COVID-19 Vaccines in IBD Patients: Particularities and Future Perspectives

COVID-19 vaccines have emerged as a shelter after the storm. Currently, four vaccines have been approved in the European Union, two of them mRNA-based [BNT162b2 and mRNA-1273] and the remaining based on an adenoviral vector [ChAdOx1 nCoV-19 and Ad26.COV2-S]. These vaccines are designed to elicit an immune response against the viral S1 spike protein, generating both an antibody- and a T-cell-based response. Even though immunocompromised patients were excluded from phase 3 trials, International Inflammatory Bowel Disease [IBD] Societies unanimously recommend vaccinating all patients as soon as possible, regardless of the level of disease activity or the use of therapies affecting the immune system.[1,2] Moreover, recent observational studies have shown that IBD patients are not more prone to develop adverse events than the general population, and that vaccination is unlikely to promote flares.[3]

In this issue of the *Journal of Crohn's and Colitis*, Doherty and colleagues[4] have published a prospective multi-centre study evaluating how prior SARS-CoV-2 exposure, vaccine class, current IBD-related medication and biomarkers for disease activity impact vaccine response. In their study,[4] the presence of IBD by itself affected humoral immunity, regardless of the use of IBD-related medication. Indeed, the seroconversion rate in IBD patients was 80% and 97% after receiving the first and second doses, respectively, whereas this rate reached 97% and 100% in healthy controls. Likewise, the median levels of IgG against the spike protein were significantly lower in IBD patients in comparison to healthy controls [266.0 vs 837.8 AU/mL after the first dose, and 2613.3 vs 6871.8 AU/mL after the second]. An important finding was that mRNA-based vaccines were superior in both healthy controls and IBD patients, generating anti-spike IgG levels that were 78% higher. Regarding IBD therapeutics, patients receiving anti-tumour necrosis factor [TNF], anti-IL 12/23 or Janus kinases [JAK] inhibitors had significantly lower median levels of anti-spike IgG—approximately half of the amount measured in patients without IBD-specific medication, under vedolizumab or aminosalicylates. Notably, the levels observed in patients under immunomodulators or steroids were not significantly reduced. In addition, the levels in patients under anti-TNF monotherapy and in those on combination therapy were similar. A limited reserve of antibodies, defined as < 4000 AU/mL, was detected after two vaccine doses in 70–75% of the patients receiving anti-TNF [$n = 101$], anti-IL 12/23 [$n = 6$] and JAK inhibitors [$n = 4$]. Strikingly, half of the patients receiving 5-aminosalicylic acid [5-ASA], immunomodulators or steroids [but not IBD-related medication] also exhibited a limited antibody reserve. Regarding the durability of the immune response, a significant drop in IgG levels [~77%] was observed after 12 weeks in all IBD patients, and a tendency towards an even greater reduction was detected in patients receiving anti-TNF therapy.

The currently available evidence on the impact of classic immunosuppressors and/or targeted therapies on antibody levels is contradictory. Evidence of a neutral effect of aminosalicylates and ustekinumab on humoral responses was provided by several studies,[5] including the largest prospective study to date evaluating humoral immunity to SARS-Cov-2 vaccines in IBD patients.[6] Regarding corticosteroids, their impact on humoral immunity has been previously suggested.[6] However, no significant attenuating effects were detected by Doherty and colleagues,[4] which may be related to the low number of patients receiving steroids in their study [$n = 10$] or to the dosage [not reported]. Concerning anti-TNF therapy, while some studies failed to find any effect on humoral response,[5] others reported an attenuated response in IBD patients under infliximab[2,7] and, in contrast to the study by Doherty and colleagues, also detected lower levels of anti-spike IgG in patients under combination therapy.[7] Indeed, in the study by Kennedy and colleagues,[7] the use of immunomodulators was an independent predictor of lower seroconversion rates. Similar results were obtained by Kappelman and colleagues,[6] who reported that combination therapy [anti-TNF combined with thiopurines or methotrexate] was associated with a significant odds ratio for lack of antibody response. Regarding anti-integrin therapy, anti-spike IgG levels were lower in vedolizumab-treated IBD patients in comparison to healthy controls in the only comparative study currently available,[2] but these results may have been biased by the small sample size [$n = 12$] and the fact that IBD itself affects seroconversion.

An important limitation of the study by Doherty and colleagues is that it did not assess T-cell-specific immunity. T-cell responses are independent of humoral immunity and have been reported to be crucial in long-term immunological memory and protection against [re]infection, including with the new SARS-CoV-2 variants.[1] Until now, only two reports[1,8] [one of them only available as a preprint[8]] have focused on T-cell responses to COVID-19 vaccines in IBD patients. In the study by Reuken and colleagues,[1] the frequencies of SARS-CoV-2-specific T helper cells and the increase in TNF and interferon-gamma production were similar among IBD patients and healthy controls, regardless of the immunosuppres-

sive regime. Although the sample size was small [28 patients with the first dose only, and 11 with both doses], the findings corroborate those obtained in other immunosuppression settings.[9] On the other hand, Lin and colleagues[8] described that one-fifth of the patients treated with infliximab and vedolizumab did not mount T-cell responses after receiving both doses of the vaccine.

The accumulating evidence has led to some adjustments in the vaccination schedule. Indeed, in several countries, a third primary dose at least 8 weeks after the second dose was proposed for patients under immunosuppressors [including those with IBD]—a strategy that differs from the booster dose programme defined for the general population.[10]

Nevertheless, several issues remain to be clarified: [i] the relevance of a limited antibody reserve, as well as the association between anti-spike IgG levels, resistance to COVID-19 and severity of the disease in case of infection; [ii] the relationship between anti-spike IgG levels, patient-related factors and the neutralizing ability of the antibodies; [iii] the mechanisms underlying the altered immune response in IBD patients; [iv] the impact of genetics on the immune response, including human leukocyte antigen [HLA] subtypes, which may be associated with IBD susceptibility and/or lack of response to the vaccine; [v] the association between the gut microbiome and vaccination outcomes; [vi] the role of vitamin D, not only as a regulator of microbiome diversity but also as a negative regulator of the angiotensin-converting enzyme 2 axis; [vii] the impact of drug dosage on the humoral and cellular immune responses; [viii] the potential usefulness of higher vaccine doses or passive immunization strategies in IBD patients; and [ix] the pertinence of tailored immunization strategies, with periodic boosters based on the measurement of IgG titres. In summary, further efforts are needed to understand and optimize the immunological response to the SARS-CoV-2 vaccine in IBD patients.

Conflict of Interest

F.M. has served as speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira and Biogen. M.M.E. has no conflicts of interest to disclose.

Author Contributions

M.M.E. drafted the manuscript. F.M. coordinated the drafting and critically reviewed the manuscript.

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References

1. Reuken PA, Andreas N, Grunert PC, Glöckner S, Kamradt T, Stallmach A. T cell response after SARS-CoV-2 vaccination in immunocompromised patients with inflammatory bowel disease. *J Crohns Colitis* 2022;**16**:251–8.
2. 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**:715–18.e4.
3. Ellul P, Revés J, Abreu B, *et al.* Implementation and short-term adverse events of anti-SARS-CoV-2 vaccines in inflammatory bowel disease patients: an international web-based survey. *J Crohns Collitis*; in press. doi:10.1093/ecco-jcc/jjac010
4. Doherty J, O Morain N, Stack R, *et al.* Reduced serological response to COVID-19 vaccines in patients with IBD is further diminished by TNF inhibitor therapy; Early results of the VARIATION study [VAriability in Response in IBD Against SARS-COV-2 ImmunisatiON]. *J Crohns Colitis*; in press. doi:10.1093/ecco-jcc/jjac029
5. Pozdnyakova V, Botwin GJ, Sobhani K, *et al.* Decreased antibody responses to Ad26.COV2.S relative to SARS-CoV-2 mRNA vaccines in patients with inflammatory bowel disease. *Gastroenterology* 2021;**161**:2041–3.e1.
6. Kappelman MD, Weaver KN, Zhang X, *et al.* Factors affecting initial humoral immune response to SARS-Cov-2 vaccines among patients with inflammatory bowel diseases. *Am J Gastroenterol* 2022;**117**:462–9.
7. 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.
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 infliximab- and vedolizumab-treated patients. *medRxiv* 2021. doi:10.1101/2021.11.10.21266168.
9. Bitoun S, Henry J, Desjardins D, *et al.* Rituximab impairs B-cell response but not T-cell response to COVID-19 vaccine in autoimmune diseases. *Arthritis Rheumatol*; in press. doi:10.1002/art.42058
10. Alexander JL, Selinger CP, Powell N. Third doses of SARS-CoV-2 vaccines in immunosuppressed patients with inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2021;**6**:987–8.