Humoral Immunogenicity After Vaccination Against SARS-CoV-2 Infection in Inflammatory Bowel Disease Patients Under Immunosuppressive Therapy: Should We Prioritize an Additional Booster Injection?

Vítor Macedo Silva, MD,*†‡, Tiago Lima Capela, MD,*†‡, Marta Freitas, MD,*†‡, Tiago Cúrdia Gonçalves, MD,*†‡ Pedro Boal Carvalho, MD,*†‡, Francisca Dias de Castro, MD,*†‡, Maria João Moreira, MD,*†‡, and José Cotter, MD, PhD*†‡,

From the *Gastroenterology Department, Hospital da Senhora da Oliveira, Guimarães, Portugal †Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal ‡Life and Health Sciences Research Institute/3B’s – Research Institute on Biomaterials, Biodegradables and Biomimetics, PT Government Associate Laboratory, Braga/Guimarães, Portugal

Address correspondence to: Vítor Macedo Silva, MD, Hospital da Senhora da Oliveira, Rua dos Cutileiros, Creixomil. 4835-044, Guimarães, Portugal (vitorbmacedo@gmail.com).

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may lead to the development of the novel coronavirus disease (coronavirus disease 2019 [COVID-19]). Scarce data are available regarding safety and efficacy of SARS-CoV-2 vaccination in inflammatory bowel disease (IBD) patients, which may present differences between subgroups. Lower humoral immunological response could require additional booster injections.

Methods: This is a prospective study including adult patients with IBD after complete vaccination against SARS-CoV-2 infection with BioNTech vaccine. Patients with previous SARS-CoV-2 infection were excluded. A control group with healthy individuals matched for age and sex was also analyzed. Blood samples were collected 30 days after complete vaccination to quantify immunoglobulin G (IgG) antibody titers against SARS-CoV-2 in both groups.

Results: The final sample included 81 IBD and 32 non-IBD patients, 55 (48.7%) of them women, with a mean age of 40.2 ± 13.0 years. From IBD patients, 58 (71.6%) had Crohn’s disease and 23 (28.4%) had ulcerative colitis. IBD patients had significantly lower median anti-SARS-CoV-2 IgG levels when compared with the control group (6479 [interquartile range (IQR) 1830-11883, 10 053] AU/mL vs 13 061 [IQR 2826-21427, 15 539] AU/mL; P = .003). Regarding IBD medication, significant lower levels of SARS-CoV-2 IgG antibodies when compared with control subjects were observed in patients treated with thiopurines (5423 [IQR 3109-13369, 10 260] AU/mL; P = .011), methotrexate (834 [IQR 507-3467, 4155] AU/mL; P = .002), anti-tumor necrosis factor α agents (5065 [IQR 1033-11669, 10 636] AU/mL; P = .001), and corticosteroids (548 AU/mL; P = .001). The incidence of SARS-CoV-2 infection after vaccination was also significantly higher in patients treated with these agents.

Conclusions: IBD patients treated with immunomodulators, anti-tumor necrosis factor α agents and corticosteroids presented significantly lower anti-SARS-CoV-2 IgG levels following complete vaccination when compared with healthy control subjects. These findings support the benefit of additional booster injections in this population.

Lay Summary

This is a prospective study quantifying antibody titers against severe acute respiratory syndrome coronavirus 2 after complete vaccination in adult patients with inflammatory bowel disease. Immunomodulators, infliximab, and corticosteroid treatment were associated with lower antibody levels. This could support the benefit of an additional booster injection in this population.

Key Words: inflammatory bowel disease, SARS-CoV-2, vaccination

Introduction

For the last 2 years, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has rapidly spread around the world.1 In humans, the infection may ultimately lead to the development of the novel coronavirus disease 2019 (COVID-19), with the immunological system playing 2 crucial roles in the disease: controlling viral replication in an earlier phase, and overproducing proinflammatory cytokines in patients who eventually progress to a severe disease course.2 Since the beginning of the COVID-19 pandemic, more than 500 million cases and 6 million deaths related to the disease have been confirmed worldwide, according to the World Health Organization data.3

The tremendous impact of this pandemic has driven multiple efforts in order to develop effective and safe vaccines against SARS-CoV-2 infection, with multiple options being now commercially available and already being administered...
worldwide.4 Considering the need for a fast establishment of SARS-CoV-2 vaccination programs, scarce information is still available regarding their effect in specific populations, namely patients with inflammatory bowel disease (IBD).1 IBD patients, such as those with ulcerative colitis (UC) or Crohn’s disease (CD), are characterized by abnormal functioning of the innate and adaptive immune systems.6 Additionally, currently available therapies for IBD often consist of agents that suppress the immune system, leaving IBD patients with an increased susceptibility to viral and bacterial infections.7 For that reason, international consensus guidelines have been published, aiming to standardize immunization protocols in patients with IBD under immunosuppressive therapy.8

Currently available investigations present discordant information regarding the course of SARS-CoV-2 infection in IBD patients. Despite emerging data suggesting that SARS-CoV-2 infection incidence and prevalence in IBD patients are not different from those in general population,9,10 some authors have reported that disease activity or treatment with certain medications, such as corticosteroids or thiopurines, are significant risk factors for adverse outcomes in case of COVID-19 disease.11,12 The SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease) database is an international collaborative database created to monitor COVID-19 outcomes in patients with IBD, which has been recently updated by including more substantial analyses evaluating a wider range of IBD medication classes and adjusting results for as much covariates as possible.13 Significant conclusions stated in this report included the association between systemic corticosteroids with increased odds of severe COVID-19. On the other hand, tumor necrosis factor α (TNFα), interleukin-12/23, and integrin antagonists were not significantly associated with adverse outcomes in IBD patients with COVID-19. The same was concluded for mesalamine or sulfasalazine. As of combined therapies, the combination of anti-TNFα agents and methotrexate was not significantly associated with risk of adverse COVID-19 outcomes, differently from the combination of anti-TNFα agents and thiopurines.

Patients with immune conditions (including IBD) were excluded from the SARS-CoV-2 vaccine clinical development programs.14 Therefore, many questions regarding the safety and effectiveness of SARS-CoV-2 vaccination in IBD patients have emerged with urgent clinical relevance.15 Nevertheless, research has consistently shown that most IBD patients achieve significant antibody responses after SARS-CoV-2 vaccination. The CORALE (Coronavirus Risk Associations and Longitudinal Evaluation) study, including more than 500 patients with IBD, reported that 99% of IBD patients achieved positive levels of antibodies 2 weeks after complete vaccination.16 Similar results were described in the PREVENT-COVID (Partnership to Report Effectiveness of Vaccination in Populations Excluded from Initial Trials of COVID) and HERCULES (Humoral and Cellular initial and Sustained immunogenicity in patients with IBD) cohort studies, regardless of IBD treatment classes.17,18

In Portugal, a disseminated vaccination campaign culminated in more than 95% of the adult population being vaccinated, offering an adequate setting to investigate the short- and long-term effects of the immunization in different populations.

In this study, we aimed to assess the 30-day humoral immunogenicity after SARS-CoV-2 vaccination in IBD patients. The primary aim was to evaluate significant differences between these patients and healthy individuals. The secondary aim was to assess differences in antibody levels, occurrence of adverse events, and development of SARS-CoV-2 infection between distinct medications frequently used to treat IBD.

Methods

Ethical Considerations

This study follows the ethical guidelines of the revised 1975 Helsinki Declaration, and was additionally approved by the institution’s Ethics and Human Research committee.

This study is an observational, prospective, and anonymous study, not meeting the criteria for clinical trial. The article includes anonymous data from 113 individuals. An informed consent to participate was obtained from each individual.

Study Design and Patients Selection

We conducted a prospective observational cohort study, aiming to include IBD patients and control individuals (with no significant pathologies), with every participant being voluntarily enrolled. Eligible participants were adults (≥18 years of age) who had complete vaccination against SARS-CoV-2 infection for <30 days at the moment of enrollment. These individuals agreed to participate in the study, with anonymity being assured during data collection and analysis, and with an informed consent being obtained.

CD and UC diagnoses were established based on a combination of clinical, biochemical, endoscopic, and histological investigations, as defined in the European Crohn’s and Colitis Organisation guidelines.19

Exclusion criteria for both IBD and non-IBD individuals were history of previous SARS-CoV-2 infection, diagnosis of any acquired or innate immunodeficiency, cancer, chronic kidney disease, pregnancy or breastfeeding, and treatment with any immunosuppressive drug for indications other than IBD.

In order to be included in the study, IBD patients needed to be on stable medication for at least 3 months before vaccination.

Key Messages

What is already known?

Most inflammatory bowel disease patients achieve significant antibody responses after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination; however, available information regarding different medications is inconsistent.

What is new here?

Inflammatory bowel disease patients treated with immunomodulators, anti-tumor necrosis factor α agents, and corticosteroids presented significantly lower anti-SARS-CoV-2 immunoglobulin G levels following complete vaccination, as well as higher SARS-CoV-2 infection rates.

How can this study help patient care?

Our findings support the benefit of prioritizing these patients for additional booster injections against SARS-CoV-2 infection when available.
Humoral Immunogenicity After Vaccination Against SARS-CoV-2

Study Variables
Anonymized data were collected from the electronical medical records of every individual. The following variables were registered: sex, age in years, CD or UC diagnosis, CD classification according to the Montreal classification, UC proximal extension, and IBD current medication (salicylates, thiopurines, methotrexate, infliximab, adalimumab, vedolizumab, ustekinumab, and systemic corticosteroids defined as ≥5 mg prednisolone daily).

Vaccination Against SARS-CoV-2 Infection
In order to assure a homogeneous sample, only individuals vaccinated with the Pfizer-BioNTech vaccine were included. The schedule for administration of this vaccine consisted of 2-dose series separated by 21 days. Complete vaccination was defined as 2 doses of the Pfizer-BioNTech vaccine 3 weeks apart without additional booster injections. All included patients and healthy control subjects were included on the same vaccination phase.

Asymptomatic SARS-CoV-2 Infection
In order to avoid bias, asymptomatic SARS-CoV-2 infection was tested by nucleocapsid antigen test. Patients with positive tests were not included in the final sample.

Serological Response to Vaccination Against SARS-CoV-2 Infection
Blood samples were collected 30 days after the second dose of the BioNTech vaccine. A measurement of immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike protein was then carried out by using a chemiluminescent microparticle immunoassay technique (SARS-CoV-2 IgG Quant II; Abbott), with the result being labeled in arbitrary units (AU) per milliliter.

A significant humoral response to vaccination was defined as IgG levels of >50 AU/mL, as recommended by the manufacturer reference levels.

Assessment of Adverse Events After SARS-CoV-2 Vaccination
On the day of the blood sample collection, a questionnaire including a list of described adverse events after SARS-CoV-2 vaccination was applied to every participating patient.

Statistical Analysis
Statistical analysis was performed using SPSS software version 23 (IBM Corp). Categorical variables are presented as frequency and percentage, and continuous variables are presented as mean ± SD or median (interquartile range [IQR]) when appropriate. Reported P values were 2-tailed, with statistical significance considered with a P value <.05.

Comparison between the IBD and non-IBD groups was conducted with the chi-square or Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables.

Results
Our final sample included 81 IBD patients and 32 non-IBD individuals, with 58 (51.3%) being men, and a mean age of 40.1 ± 13.0 years. IBD and non-IBD groups were homogeneous for age and sex. Table 1 summarizes the characteristics of the IBD and non-IBD groups.

Regarding IgG antibodies against SARS-CoV-2 virus, the overall sample presented a median level of 8403 (IQR 3125-14746, 11 621) AU/mL. The median levels in the IBD group were significantly lower when compared with the control group (6479 [IQR 1830-11883, 10 053] AU/mL vs 13 061 [IQR 2826-21427, 15 539] AU/mL; P = .003).

The SARS-CoV-2 IgG antibody levels of the control subjects and IBD patients according to specific different therapies are graphically described in Figure 1. Significantly lower levels of SARS-CoV-2 IgG antibodies when compared with control individuals were found in IBD patients regularly treated with thiopurines (median 5423 [IQR 3109-13369, 10 260] AU/mL; P = .011), methotrexate (median 834 [IQR 507-3467, 4155] AU/mL; P = .002), anti-TNFα agents (median 5063 [IQR 1033-11669, 10 636] AU/mL; P = .001), and corticosteroids (median 548 AU/mL; P = .001). Additionally, patients undergoing combination therapy (thiopurines plus anti-TNFα agent) presented significantly lower IgG antibody levels when compared with patients treated with thiopurines alone (median 4853 [IQR 1353-12077, 10 723] AU/mL vs

| Variable Data |
|-------------|
| IBD group n = 81 |
| Male 41 (50.6) |
| Age, y 39.0 ± 14.2 |
| Crohn’s disease 58 (71.6) |
| Disease location according to Montreal classification |
| L1—ileal disease 31 (55.4) |
| L2—colonic disease 2 (3.6) |
| L3—ileocolonic disease 22 (39.3) |
| L4—upper GI tract disease 1 (1.8) |
| Ulcerative colitis 23 (28.4) |
| Disease proximal extension |
| E1—proctitis 2 (8.7) |
| E2—left-sided colitis 11 (47.8) |
| E3—extensive colitis 10 (43.5) |
| Current IBD medication |
| Salicylates 15 (18.5) |
| Thiopurines 40 (49.4) |
| Methotrexate 4 (4.9) |
| Anti-TNFα agents |
| Infliximab 42 (51.9) |
| Adalimumab 6 (7.4) |
| Vedolizumab 10 (12.3) |
| Ustekinumab 10 (12.3) |
| Corticosteroids 3 (3.7) |
| Combination therapy (thiopurines + anti-TNFα) 28 (34.6) |
| Non-IBD group n = 32 |
| Male 17 (53.1) |
| Age, y 43.2 ± 8.8 |

Values are mean ± SD or n (%).

Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease; TNFα, tumor necrosis factor α.
9996 [IQR 5573-14808, 9234] AU/mL; P = .039). Compared with anti-TNFα monotherapy, antibody levels were lower, despite not having statistically significant differences (median 4853 [IQR 1353-12077, 10 723] AU/mL vs 3868.4 [IQR 793-11705, 10 520.5] AU/mL; P = .628).

No significant differences were found in patients regularly treated with salicylates (median 9621 [IQR 5092-14736, 9644] AU/mL; P = .226), vedolizumab (8713 [IQR 4972-13797, 8870] AU/mL; P = .286), and ustekinumab (8205 [IQR 4491-17463, 12 972] AU/mL; P = .390) when compared with healthy individuals.

A significant humoral response (IgG anti-SARS-CoV-2 ≥50 AU/mL) was achieved in all but 2 IBD patients, who were treated with combination therapy with thiopurines plus anti-TNFα agents. All non-IBD patients achieved positive humoral responses.

Regarding adverse events, no major events were reported in both control or IBD patients. Minor adverse events (fever for <24 hours, myalgia and inflammatory reaction on the injection site) did not significantly differ between both groups (40.7% vs 46.9%; P = .434).

SARS-CoV-2 infection between second and third dose administration was assessed. A total of 8 (25%) patients of the control group developed the infection after complete vaccination. Compared with healthy individuals, the incidence of SARS-CoV-2 infection was significantly higher in patients treated with agents who were associated with significantly lower SARS-CoV-2 antibody levels: thiopurines (50.0%; P = .025), anti-TNFα agents (43.8%; P = .040), methotrexate (75.0%; P = .041), and corticosteroids (100.0%; P = .027). As of infection severity, there were only 3 (3.7%) reported cases of severe infection (respiratory failure requiring hospitalization) in patients with IBD. From these, 2 patients were treated with combined therapy and 1 patient was treated with corticosteroids. There were no cases of severe infection in the healthy control subjects group. Additionally, no death related to COVID-19 was reported in either group.

**Discussion**

Both CD and UC are characterized by chronic intestinal inflammation due to immune dysregulation, often treated with immune-modifying therapies including immunomodulators, corticosteroids, and biologic agents such as monoclonal antibody inhibitors of TNFα. Previous investigations have evaluated the safety and effectiveness of various vaccines in patients with IBD, focusing on the impact of immune-modifying agents on serologic responses, as it has been shown that specific treatment regimens at the time of vaccination may result in attenuated immune responses.

Patients with immune disorders, including IBD patients, were excluded from the SARS-CoV-2 vaccines clinical development programs, a fact that leaves many questions unanswered regarding vaccination consequences (both safety and effectiveness) in these individuals. Nevertheless, recommendations from an international consensus meeting endorsed vaccination against SARS-CoV-2 in IBD patients as soon as they are able to receive the vaccine, regardless of concomitant immunomodifying therapies. Despite this, the panel of experts stated that prospective evaluations of IBD patients receiving SARS-CoV-2 vaccines were urgently needed in order to quantify the amplitude and duration of immune responses in this setting.

In our prospective investigation, we aimed to assess the SARS-CoV-2 vaccination humoral immunogenicity in IBD patients when compared with healthy individuals. Additionally, we aimed to assess differences when considering distinct IBD therapies, in order to better understand the effects of immune-modifying agents and to hypothesize which patients could eventually benefit the most from an additional booster injection of the vaccine.

Median levels of anti-SARS-CoV-2 IgG antibodies in our IBD sample were less than half of sex- and age-matched healthy individuals. This finding is supported by previous reports for other immunizations in IBD, as response to vaccination in these patients is thought to be impaired not only due to immunological alterations generated by the disease itself, but also due to the common use of immunomodulating drugs. Certain agents, such as corticosteroids, immunomodulators, and anti-TNFα agents, are associated with a suboptimal overall response to vaccination in IBD.

In previously available trials investigating humoral response to SARS-CoV-2 vaccination in IBD patients, such as the CORALE, PREVENT-COVID, and HERCULES cohort studies, most individuals achieved a humoral response after complete vaccination, which is in line with our sample. Despite this, our group aimed to assess not only the achievement of a humoral response, but also how intense that response would be, and how it varied between available IBD treatments.
In a recent systematic review by Jena et al., corticosteroids have already been shown to be associated with lower seroconversion rates (70%-90% compared with healthy individuals) after SARS-CoV-2 vaccination in patients with immune-mediated inflammatory diseases. Our study has confirmed this particular association in IBD patients, as those treated with corticosteroid treatment had significantly lower IgG antibodies after vaccination. However, current recommendations emphasize that this is not an indication to delay vaccination or suspend treatment in IBD patients, but rather a reason to warn patients receiving systemic corticosteroid treatment that vaccination efficacy may be decreased in this scenario.

In our sample, treatment with anti-TNFα agents was also associated with significantly lower antibody titers in response to SARS-CoV-2 vaccination. These results agree with previous investigations that have inclusively shown that anti-TNFα treatment is associated with lower SARS-CoV-2 nucleocapsid seroprevalence and antibody reactivity when compared with other therapies, such as vedolizumab.

In relation to immunomodulators, such as thiopurines (azathioprine and 6-mercaptopurine) and methotrexate, our group has also found significantly lower antibody titers after SARS-CoV-2 vaccination. In our sample, a synergism between thiopurines and anti-TNFα agents was confirmed for SARS-CoV-2 vaccination, as patients with combination regimens of thiopurines plus anti-TNFα agents presented significantly lower antibody titers when compared with patients treated with thiopurines alone (4853 AU/mL vs 9996 AU/mL; P = .039). The fact that no significant differences were found between patients undergoing combination therapy and patients with anti-TNFα agents monotherapy may indicate that the impact on antibody levels is greater for anti-TNFα agents than for thiopurines.

Finally, patients treated with salicylates had a response to SARS-CoV-2 vaccination which was similar to that of healthy individuals. Salicylates’ mechanism of action relies mainly on local effects, such as interaction with epithelial cell receptors. Therefore, the degree of immune system modulation is largely insignificant with these agents. Knowing this, the fact that no significantly different antibody titers in response to SARS-CoV-2 vaccination were found in our investigation was highly expected.

In our sample, the medications associated with significantly lower anti-SARS-CoV-2 antibody levels were also associated with a significantly higher incidence of SARS-CoV-2 infection after the second dose of the vaccine. Regarding infection severity, there was a low incidence of severe COVID-19 disease in our sample, which may underline conclusions regarding infection severity in overall IBD patients. However, further prospective investigations specifically focusing on the therapeutic agents found to be associated with lower antibody levels would be interest in order to complement our investigation on this field.

Despite our sample being underpowered to assess vaccination effects on the development of breakthrough SARS-CoV-2 infection, these findings may eventually pave the way for prioritization of this set of patients for additional booster injections when available. This seems to be an effective way to overcome the lower humoral immunogenicity found in these patients, as recent articles have shown that all IBD patients displayed a humoral immune response after a third vaccination dose, and median antibody concentrations were higher after the third dose than after completion of the 2-dose series.

It must be noticed that in our sample no major adverse events were reported in IBD patients after complete vaccination against SARS-CoV-2. Additionally, the frequency of minor adverse events did not significantly differ from the control group. Therefore, we consider that SARS-CoV-2 vaccination in IBD patients, including eventual additional booster injections to assure long-term immunization, must not be delayed based on hypothetical concerns regarding its safety in this specific population.

Our investigation presents some limitations, namely the impossibility to exclude every possible previous asymptomatic infection, as not all patients have undergone nucleocapsid antibody testing before vaccination, and the preclusion of assessment of antibody levels after a third dose, owing to the high incidence of SARS-CoV-2 infection after this phase in our region. Nevertheless, this was outbalanced by the valuable findings about humoral responses and comparisons between different IBD medications and with healthy individuals, which is innovative.

It is of crucial importance to better understand the effects of SARS-CoV-2 vaccination on IBD patients, an understudied population in previous vaccine development trials, not only because these patients are a high-risk group considering disease outcomes, but also due to hypothetical different responses to vaccination. Facing our results, it is reasonable to assume that immunogenicity after complete SARS-CoV-2 vaccination is attenuated in IBD patients treated with immunomodulators, anti-TNFα agents, and systemic corticosteroids. Therefore, physicians who follow-up these specific individuals must assure a tight follow-up throughout SARS-CoV-2 vaccination process. Furthermore, these particular patients should be counseled to engage in more restrict sanitary measurements, in order to avoid SARS-CoV-2 infection. In the scenario of available additional booster injections, these patients could be prioritized to prevent failed immunization.

Author Contribution
All authors contributed to and agreed on the content of the manuscript. V.M.S. designed the study, collected and carried out data analysis and drafted the manuscript. T.L.C. and M.F. collected and carried out data analysis. T.C.G., P.B.C., F.D.C., and M.J.M. critically revised the manuscript. J.C. critically revised and approved the final version of the manuscript.

Conflicts of Interest
All authors have no conflicts of interest to declare.

Funding
Nothing to declare.

References
1 Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270-273.
2 Neurath MF. COVID-19 and immunomodulation in IBD. Gut 2020;69(7):1335-1342.
3 WHO Coronavirus (COVID-19) Dashboard. Accessed January 3, 2022. https://covid19.who.int/
Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis.* 2021;21(2):e26-e35.

Selim R, Wellens J, Marlow L, Satsangi JJ. SARS-CoV-2 vaccination uptake by patients with inflammatory bowel disease on biological therapy. *Lancet Gastroenterol Hepatol.* 2021;6(12):989.

Bezio C, Aruzuzi A, Furfaro F, et al. Therapies for inflammatory bowel disease do not pose additional risks for adverse outcomes of SARS-CoV-2 infection: an IG-IBD study. *Aliment Pharmacol Ther.* 2021;54(11-12):1432-1441.

Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155(2):337-346.e10.

Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol.* 2017;112(2):241-258.

Derikx L, Lantinga MA, de Jong DJ, et al. Clinical outcomes of COVID-19 in patients with inflammatory bowel disease: a nationwide cohort study. *J Crohns Colitis* 2021;15(4):529-539.

Allocca M, Chaparro M, Gonzalez HA, et al. Patients with inflammatory bowel disease are not at increased risk of COVID-19: a large multinational cohort study. *J Clin Med* 2020;9(11):3533.

Brenner EJ, Ungaro RC, Geary RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159(2):481-491.e3.

Ungaro RC, Brenner EJ, Geary RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2021;70(4):725-732.

Ungaro RC, Brenner EJ, Agrawal M, Zhang X, Kappelman MD, Colombel JF. Impact of medications on COVID-19 outcomes in inflammatory bowel disease: analysis of more than 6000 patients from an international registry. *Gastroenterology* 2022;162(1):316-319.e5.

Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383(27):2603-2615.

Siegel CA, Melmed GY, McGovern DP, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut* 2021;70(4):635-640.

Melmed GY, Botwin GJ, Sobhani K, et al. Antibody responses after SARS-CoV-2 mRNA vaccination in adults with inflammatory bowel disease. *Ann Intern Med.* 2021;174(12):1768-1770.

Caldera F, Knutson KL, Saha S, et al. Humoral immunogenicity of mRNA COVID-19 vaccines among patients with inflammatory bowel disease and healthy controls. *Am J Gastroenterol.* 2022;117(1):176-179.

Kappelman MD, Weaver KN, Boccati M, Fireistine A, Zhang X, Long MD. Humoral immune response to messenger RNA COVID-19 vaccines among patients with inflammatory bowel disease. *Gastroenterology* 2021;164(4):1340-1343.e2.

Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13(2):144-164.

Andrisani G, Frasca D, Romero M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-α agents: effects of combined therapy with immunosuppressants. *J Crohns Colitis* 2013;7(4):301-307.

Marin AC, Gisbert JP, Chaparro M. Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease. *World J Gastroenterol.* 2015;21(40):11273-11281.

Jena A, Mishra S, Deepak P, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. *Autoimmun Rev.* 2021;21(1):102927.

Chanchlani N, Lin S, Chee D, et al. Adalimumab and infliximab impair SARS-CoV-2 antibody responses: results from a therapeutic drug monitoring study in 11 422 biologic-treated patients. *J Crohns Colitis* 2022;16(3):389-397.

Travis SP, Jewell DP. Salicylates for inflammatory bowel disease. *Baillieres Clin Gastroenterol* 1994;8(2):203-231.

Long MD, Weaver KN, Zhang X, Chun K, Kappelman MD. Strong response to SARS-CoV-2 vaccine additional doses among patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2022;20(8):1881-1883.e1.

Schell TL, Knutson KL, Saha S, et al. Humoral immunogenicity of 3 COVID-19 messenger RNA vaccine doses in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* Published online April 9, 2022. doi:10.1093/ibd/zizac082