High Seroconversion Rate Against Severe Acute Respiratory Syndrome Coronavirus 2 in Symptomatic Pediatric Inflammatory Bowel Disease Patients

*†Wenly Ruan, *†Huyen Nguyen, *†Allyson Wyatt, *†Faith Ihekweazu, *†Bryan S. Vartabedian, *†Lina Karam, *†Seema Walsh, and *†‡Richard Kellermayer

ABSTRACT

Understanding coronavirus disease 2019 (COVID-19) in pediatric inflammatory bowel disease (PIBD) is important. We describe a single-center cohort of COVID-19 PIBD patients where seroconversion against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was examined. Immunosuppressed PIBD patients at Texas Children's Hospital who tested positive for SARS-CoV-2 by nasopharyngeal reverse transcriptase polymerase chain reaction were included in the study. The clinical course of IBD, concurrent medications, COVID-19 related symptoms, SARS-CoV-2 testing date, and SARS-CoV-2 immunoglobulin G (IgG) antibody testing date and result were examined. Of 14 SARS-CoV-2 positive PIBD patients, 12 were tested for qualitative anti-SARS-CoV-2 IgG (seven with transient COVID-19 symptoms, five asymptomatic). All symptomatic (7/7) and 60% of asymptomatic (3/5) patients seroconverted. No patients required hospitalization attributed to COVID-19. High rates of COVID-19 seroconversion occurred in immunosuppressed and symptomatic PIBD patients. More research to evaluate the significance of COVID-19 seroconversion is needed.

Key Words: coronavirus disease 2019, pediatric inflammatory bowel disease, seroconversion, severe acute respiratory syndrome coronavirus 2

(*JPGN* 2021;73: 363–366)

What Is Known

- Inflammatory bowel disease (IBD) patients with increasing age, comorbidities, and/or corticosteroid use may have more severe coronavirus disease 2019 (COVID-19) symptoms.
- Certain IBD treatments may lower the immune response to infectious agents.

What Is New

- This study is the first to selectively evaluate seroconversion after polymerase chain reaction-based COVID-19 infection in immunosuppressed pediatric IBD patients.
- High rates of COVID-19 seroconversion occurred in our case series.
- All symptomatic and 60% of asymptomatic patients demonstrated seroconversion by a clinical laboratory method to severe acute respiratory syndrome coronavirus 2.

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to have a major global impact. Most people infected by SARS-CoV-2 experience mild-moderate respiratory illness (1). Certain populations, however, may have a more serious course including those with underlying medical problems such as cardiovascular disease, respiratory disease, obesity, diabetes, cancer, autoimmune disease, and other immunosuppressed conditions (2). Therefore, it is important to understand how COVID-19 impacts specific patient populations to optimize prevention and care.

Inflammatory bowel disease (IBD) is a chronic inflammatory condition, where patients are commonly immunosuppressed with immunomodulators, biologics, and/or steroids. These treatments can increase the risk for serious viral and bacterial infections (3,4). As a result, IBD patients were thought to be at increased risk of severe disease in the setting of COVID-19. Emerging information, however, suggests that only those IBD patients with increasing age, comorbidities, and/or corticosteroid use may have more severe COVID-19 symptoms than the general age-matched population (5). Additionally, recent studies demonstrated that biologic use alone may not be associated with worse outcomes (6). As more is understood about the effects of COVID-19 in the IBD population, it

Received February 16, 2021; accepted May 5, 2021.

From the *Department of Pediatrics, Baylor College of Medicine, the †Section of Gastroenterology, Hepatology, and Nutrition, Texas Children's Hospital, and the ‡USDA ARS Children's Nutrition and Research Center, Houston, TX.

Address correspondence and reprint requests to Wenly Ruan, MD, Division of Pediatrics, Section of Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, Houston, TX; Texas Children's Hospital, Section of Gastroenterology, Hepatology and Nutrition, 6701 Fannin Street, D1010, Houston, TX 77030 (e-mail: wenly.ruan@bcm.edu).

Author Contributions: W.R. and R.K.: conception and design of study, analysis, and interpretation of data. W.R., H.N., A.W., F.I., B.V., L.K., S.W., R.K.: acquisition of data, checking the article for important intellectual content. All authors authorized the final approval of the version submitted.

W.R. was supported by the Pfizer Global Medical Grant #59570215. R.K. is the PI for Pfizer Global Medical Grant #59570215 and was also supported by the Wagner and Klaasmeyer family supported Gutsy Kids Fund, and the CCF ProKiids Network #585708.

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000003211

has been observed that those patients on thiopurine monotherapy, combination therapy with thiopurine and tumor necrosis factor (TNF) antagonist (anti-TNF) are associated with increased risk of severe COVID-19 (7).

It remains unclear how seroconversion against SARS-CoV-2 takes place post-COVID-19 infection in pediatric IBD patients based on disease severity and treatments. It has been previously demonstrated that IBD patients have lower response to vaccinations (8). In PIBD patients who were evaluated for response to the influenza vaccine, those on immunomodulator and anti-TNF combination therapy were at increased risk of inadequate response (9). Another study of influenza vaccination demonstrated a high prevalence of seroprotection in PIBD patients against strain A though this may be impaired for strain B for patients on anti-TNF therapy (10). Additionally, medications used for IBD treatment can affect the immune response to vaccines and infectious agents, which may impact the severity of disease. Two recent studies in adult patients suggested that anti-SARS-CoV-2 immunoglobulin G (IgG) is more pronounced in patients with more severe disease (11,12). It is therefore important to better understand the rate of seroconversion in IBD patients who develop COVID-19. A recent publication demonstrated that infliximab use attenuated seroconversion to COVID-19, which was furthered by concomitant immunomodulator use (13); however, seroconversion in PIBD patients alone needs to be better understood since immune response to SARS-CoV-2 varies with age. We describe a single center cohort of immunosuppressed PIBD patients with COVID-19, a subset of whom were tested for seroconversion after the laboratory test supported initial infection.

METHODS

The electronic medical records of PIBD patients on various immunosuppressive medications (patients on mesalamine monotherapy were excluded) who tested positive for SARS-CoV-2 by nasopharyngeal swab-based polymerase chain reaction (PCR) testing in 2020 were included in the study. The study received ethical approval of the Baylor College of Medicine Institutional Review Board (IRB), protocol H-48783. Patient demographics, clinical course of IBD, concurrent medications, COVID-19 related symptoms, SARS-CoV-2 testing date, and anti-SARS-CoV-2 IgG antibody testing date and results were examined. SARS-CoV-2 IgG immunoassay was performed at the same large commercial laboratory (CLIA certified Quest Laboratories, Secaucus, New Jersey, test code 39504). This test has an estimated assay sensitivity of 90.0% for specimens collected at least 15 days post-symptom onset, based on positive percent agreement of SARS-CoV-2 IgG serology results for specimens from patients positive for SARS-CoV-2 RNA. It has an estimated assay specificity of >99.9% based on negative percent agreement assessed by performing cross-reactivity studies utilizing serum samples positive for antibodies to other respiratory viruses pre- and post-COVID-19 (14).

RESULTS

A total of 14 PIBD patients at Texas Children's Hospital tested positive for SARS-CoV-2 with a nasopharyngeal SARS-CoV-2 real-time reverse transcriptase PCR (RT-PCR) test. Patient demographics and IBD characteristics are detailed in Table 1.

Five (35.7%) patients were primarily tested due to close contact with a COVID-19 positive person, four (28.6%) due to surveillance, three (21.4%) due to symptoms, and two (14.3%) due to both symptoms and close contact with a COVID-19 positive person. Management was altered in only one of these patients (methotrexate was held for one week) in response to the positive COVID-19 test. Seven (50.0%) ultimately developed symptoms attributed to COVID-19 infection, including fever, sore throat, headache, fatigue, loss of taste, loss of smell, dizziness, cough, nausea, vomiting, abdominal pain, and/or diarrhea; seven (50.0%) were asymptomatic. No patients required hospitalization attributed to COVID-19.

TABLE 1. Demographic characteristics of SARS-CoV-2 infected pediatric IBD patients

Characteristic	N (%)
Sex	
Female	8 (57.1%)
Male	6 (42.9%)
Ethnicity	
Hispanic	5 (35.7%)
Non-Hispanic	9 (64.3%)
Race	
White	11 (78.6%)
Black or African American	2 (14.3%)
Asian	1 (7.1%)
IBD diagnosis	
Crohn disease	10 (62.5%)
Ulcerative colitis	4 (28.6%)
Crohn's Disease Paris Classification (n = 10)	
Age at diagnosis	
A1a: 0 < 10	4 (40.0%)
A1b: 10 < 17	4 (40.0%)
A2: 17–40	2 (20.0%)
Location	
L1: Distal 1/3 ileum+ limited cecum	1 (10.0%)
L2: Colonic	2 (20.0%)
L3: Ileocolonic	6 (60.0%)
L3, L4a: Ileocolonic and upper disease	1 (10.0%)
Behavior	
B1: Nonstricturing, nonpenetrating	5 (50.0%)
B1, p: Nonstricturing, nonpenetrating, perianal	1 (10.0%)
B2: Stricturing	2 (20.0%)
B3: Penetrating	1 (10.0%)
B3, p: Penetrating, perianal	1 (10.0%)
Growth	
G0: No growth delay	6 (60.0%)
G1: Growth delay	4 (40.0%)
Ulcerative Colitis Paris Classification (n = 4)	
Extent	
E4: Pancolitis	4 (100%)
Severity	
S0: Never severe	2 (50.0%)
S1: Ever severe	2 (50.0%)
IBD treatment	
Biologic only	6 (42.9%)
Biologic and immunomodulator	2 (14.3%)
Biologic and steroid	2 (14.3%)
Immunomodulator and mesalamine	2 (14.3%)
Immunomodulator only	1 (7.1%)
Steroid and antibiotics	1 (7.1%)
Change in treatment course	
Yes	1 (7.1%)
No	13 (92.9%)
Seroconversion (12 patients tested)	
Yes, SARS-CoV-2 Ab (IgG) positive	10 (83.3%)
No	2 (16.7%)
Total population	14

IBD = inflammatory bowel disease; IgG = immunoglobulin G; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

TABLE 2. Pediatric inflammatory bowel disease patient clinical information tested for SARS-CoV-2 IgG

Patient	Age at diagnosis	IBD	IBD medications	Treatment modification	Reason for SARS- CoV-2 testing	COVID symptoms after testing	Time to SARS-CoV-2 IgG test	SARS-CoV-2 IgG result
1	7	CD	6-Mercaptopurine	No	Contact	Yes	18.1	Positive
2	10.5	CD	Methotrexate, mesalamine	No	Surveillance	No	10	Negative
3	15.6	CD	Infliximab	No	Symptoms	Yes	12.4	Positive
4	13.5	UC	Azathioprine, vedolizumab	No	Symptoms	Yes	4	Positive
5	3.4	UC	Prednisolone, ustekinumab	No	Surveillance	No	18.9	Negative
6	2.5	CD	Methotrexate, sulfasalazine	Methotrexate held for 1 wk	Symptoms	Yes	5.9	Positive
7	13.9	CD	Adalimumab	No	Contact	No	7.6	Positive
8	17.2	CD	Methotrexate, adalimumab	No	Contact, Symptoms	Yes	13.7	Positive
9	16.6	UC	Prednisone, vancomycin	No	Contact	No	2.9	Positive
10	2.8	UC	Infliximab	No	Surveillance	No	8.7	Positive
11	9.8	CD	Ustekinumab	No	Contact, Symptoms	Yes	4	Positive
12	6	CD	Prednisolone, ustekinumab	No	Contact	Yes	2.1	Positive

CD = Crohn disease; IBD = inflammatory bowel disease; IgG = immunoglobulin G; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UC = ulcerative colitis.

Of the 14 patients, 12 (75.0%) had testing for seroconversion completed. Detailed clinical information about these 12 patients is in Table 2. Seroconversion was tested between 2.1 and 18.9 weeks after initial positive SARS-CoV-2 PCR testing with a median of 8.1 weeks (interquartile range [IQR] 4.0–12.8 weeks). Ten (10/12, 83.3%) had positive SARS-CoV-2 IgG, of whom 7 of 10 (70.0%) had acute and resolved symptoms and three were asymptomatic. Therefore, while all symptomatic patients (7/7) had seroconversion, three of five (60%) asymptomatic patients seroconverted.

DISCUSSION

Much remains unknown about COVID-19 due to ambiguities in epidemiologic observations (15), RT-PCR based diagnosis (16), and serologic testing (17). Combining COVID-19 diagnostic and serology-based confirmation testing may improve our understanding and treatment of the disease, especially in potentially vulnerable populations (17,18). We describe a cohort of COVID-19 positive PIBD patients whose disease course was not significantly affected 1–6 months following infection, regardless of unaltered immunosuppression. No patients in this cohort were hospitalized. This reflects the recently observed low risk for severe COVID-19 in PIBD patients (19).

Twelve patients were subsequently tested for seroconversion. This is the first study to investigate the development of anti-SARS-CoV-2 antibodies selectively in PIBD patients after testing positive for COVID-19 by RT-PCR. All symptomatic (7/7, 100%), and most (3/5, 60.0%) asymptomatic patients mounted a detectable IgG-based immune response to SARS-CoV-2 regardless of immunosuppression (Table 2). Two asymptomatic patients did not demonstrate seroconversion, which may implicate either false positive initial nasopharyngeal SARS-CoV-2 RT-PCR, low level of antibodies, or decreased immune response in an asymptomatic patient, which has been previously reported (11,12). The majority (83.3%) of the COVID-19 PIBD cases had supporting evidence of infection by positive IgG based seroconversion. This finding indicates that especially symptomatic, but also asymptomatic SARS-CoV-2 RNA positive PIBD patients develop IgG antibodies against the virus, which demonstrates the induction of adaptive immunity against a true infection, at least in our population.

There are several limitations to this study. Due to this study's retrospective nature, SARS-CoV-2 IgG was tested at various times after the initial SARS-CoV-2 RT-PCR positive test. There are currently no standardized protocols, however, for SARS-CoV-2 antibody testing. The present study was conducted at a single center. Further prospective studies with a larger multi-center cohort would be beneficial to advance this area of research. Much remains unknown about SARS-CoV-2 antibody testing and its generalizability. Negative results may be related to imperfect testing methods, early testing in the course of infection, and/or lack/loss of immune response.

Seroconversion to SARS-CoV-2 was recently associated with significant protection against COVID-19 re-infection for 6 months, at least in healthcare workers (18). In IBD patients, seroconversion to SARS-CoV-2 was recently shown to be diminished in those who were on infliximab compared to those on vedolizumab. Concomitant immunodulator use further decreased this response. Our study, despite its limitations, adds to the current literature as it selectively evaluates seroconversion in an independent PIBD cohort after COVID-19 infection. This is important since immune response to COVID-19 varies with age which has been hypothesized to be a result of angiotensin- converting enzyme 2 receptor expression as one ages (20). Our findings may guide future studies on antibody sustainability and re-infection in this population. This work may also have implications regarding vaccination strategies in PIBD patients during the rapidly evolving pandemic. More research needs to be performed to evaluate the duration and clinical importance of seroconversion against SARS-CoV-2, and how patient, disease, and/or medication-related factors may modulate that in PIBD patients.

REFERENCES

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
2. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6.
3. Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155:337.e10–46.e10.
4. Long MD, Martin C, Sandler RS, et al. Increased risk of pneumonia among patients with inflammatory bowel disease. *Am J Gastroenterol* 2013;108:240–8.
5. Brenner EJ, Ungaro RC, Gearry 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;159:481–91.

6. Haberman R, Axelrad J, Chen A, et al. COVID-19 in immune-mediated inflammatory diseases—case series from New York. *N Engl J Med* 2020;383:83–5.
7. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2021;70:725–32.
8. Marín AC, Gisbert JP, Chaparro M. Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease. *World J Gastroenterol* 2015;21:11273–81.
9. Mamula P, Markowitz JE, Piccoli DA, et al. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;5:851–6.
10. Lu Y, Jacobson DL, Ashworth LA, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol* 2009;104:444–53.
11. Zhang B, Zhou X, Zhu C, et al. Immune phenotyping based on the neutrophil-to-lymphocyte ratio and IgG level predicts disease severity and outcome for patients with COVID-19. *Front Mol Biosci* 2020;7:1–7.
12. Huang M, Lu Q. Bin, Zhao H, et al. Temporal antibody responses to SARS-CoV-2 in patients of coronavirus disease 2019. *Cell Discov* 2020;6:1–22.
13. Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 2021;70:865–75.
14. VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG. Instructions for Use. Ortho-Clinical Diagnostics. Ortho-Clinical Diagnostics. 2020. Available at: https://www.fda.gov/media/137363/download [Accessed March 8, 2021].
15. Szigeti R, Kellermayer D, Trakimas G, et al. BCG epidemiology supports its protection against COVID-19? A word of caution. *PLoS One* 2020;15:1–9.
16. Basile K, Maddocks S, Kok J, et al. Accuracy amidst ambiguity: false positive SARS-CoV-2 nucleic acid tests when COVID-19 prevalence is low. *Pathology* 2020;52:809–11.
17. Peeling RW, Wedderburn CJ, Garcia PJ, et al. Serology testing in the COVID-19 pandemic response. *Lancet Infect Dis* 2020;20:e245–9.
18. Lumley S, O'Donnell D, Stoesser N, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020;384:533–40.
19. Brenner EJ, Pigneur B, Focht G, et al. Benign evolution of SARS-Cov2 infections in children with inflammatory bowel disease: results from two international databases. *Clin Gastroenterol Hepatol* 2020;19:394.e5–6.e5.
20. Bajaj V, Gadi N, Spihlman AP, et al. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections? *Front Physiol* 2021;11:1–23.