Humoral response to COVID-19 infection in immunosuppressed patients with inflammatory bowel disease

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The course of coronavirus 19 (COVID-19) might be determined by certain comorbidities (e.g. diabetes, hypertension and other cardiovascular diseases) and advanced age. Because the impact of immunosuppression on disease severity is not entirely clear, management of patients under immunosuppressive treatment remains controversial. Six cases of inflammatory bowel disease (IBD) patients with COVID-19 on immunosuppressive medication are presented. The aim of this study was to describe patients' clinical manifestation and chronologic development of virus-specific antibodies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection before and after restart with immunosuppressive/biological therapy as an indicator for a specific immune response. All patients were tested for the presence of SARS-CoV-2-RNA with PCR, were in clinical remission prior to COVID-19 and only one patient continued his immunosuppressive treatment during the COVID-19 infection. Initial symptoms of COVID-19 were pyrexia, diarrhea, cephalea, and dysgeusia and anosmia. No patient needed admission to hospital or ICU. The SARS-CoV-2 antibody development was described to be late in three of the six patients. Late antibody development seems to be more frequent in older patients and in patients with combined immunosuppressive treatment. In this scenario, SARS-CoV-2 antibody testing could be useful prior to restarting immunosuppressive therapy. Eur J Gastroenterol Hepatol 33: 443–447

Introduction

Since December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified on 7 January 2020 in Wuhan, China, as the cause of coronavirus disease 2019 (COVID-19)[1–3], accounting for more than 600 000 deaths worldwide [4].

Most cases have a favorable clinical evolution with only mild symptoms, whereas around 14% of patients do develop severe symptoms with critical illness present in approximately 6% of cases [5]. Fever, a dry cough, common flu-like symptoms, anosmia and dysgeusia are the most frequently reported symptoms [5–8]. Furthermore, gastrointestinal manifestations such as diarrhea, nausea and abdominal pain have been present in nearly 50% of affected patients [9].

Elderly patients and those with comorbidities, such as cardiovascular or pulmonary disease, arterial hypertension, diabetes mellitus and obesity, have been associated with the highest morbidity and mortality [10,11]. The association of immunosuppressive therapy in inflammatory bowel disease (IBD) patients with SARS-CoV-2 infection and its disease severity has been controversial. Some recent studies have found neither an increased susceptibility to SARS-CoV-2 in IBD patients, nor an association between immunosuppressive therapies and an increased risk of clinically manifest COVID-19 [12–14]. Currently, international IBD groups recommend that immunosuppressive and biological drugs should not be discontinued as a preventive strategy in patients with IBD without symptoms suggestive of COVID-19 [14,15].

Like with other viral infections, virus-specific antibodies can be detected after an elapsed SARS-CoV-2 infection[16], with the currently available tests at the earliest 5–7 days postonset of symptoms [17]. The observed kinetics of antibody responses, however, vary among individuals and strongly depend on the applied test system, the antigen-specificity and probably on the clinical severity of the infection. Multiple antibody tests have recently become available, their variable test sensitivities and specificities had been reported in different cohorts but not in IBD with COVID-19 [18]. It remains unclear whether the SARS-CoV-2 antibodies grant permanent immunity, additional studies on immunity to SARS-CoV-2 and eventual reinfection are therfore critical [19,20].

Here, we report the clinical evolution in six patients with IBD and immunosuppressive treatment that were infected with SARS-CoV-2, particularly focusing on longitudinal antibody development as an indicator for a specific immune response. Demographic, clinical and laboratory data of six IBD patients with SARS-CoV-2 caused COVID-19 are presented.

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Table 1. Demographic and clinical data of six IBD patients with COVID-19

	Patient characteristics					
Patient #	1	2	3	4	5	6
Actual age (years)	48	22	19	45	71	25
Gender	Female	Male	Male	Female	Female	Male
IBD type	Crohn's disease	Crohn's disease	Crohn's disease	Ulcerative colitis	Crohn's disease	Crohn's disease
Duration of disease (years)	38	2	5	18	16	16
Montreal classification	L1	L3	L3+L4	E3	L2	L2
Prior intestinal surgery	Yes[a]	No	No	No	No	No
SARS-CoV-2 infection source	Husband	Brother	University	Husband	Nephew	Father
Last fCP prior to COVID-19	315	1350	103	79	110	171
fCP during COVID-19 (mg/kg)	291	464	N/A	375	44	57
Activity score prior to COVID-19	HBI: 1	HBI: 0	HBI: 0	Mayo: 0	HBI: 0	HBI: 0
Biologic therapy	Adalimumab 40 mg q10d	Adalimumab40mg q10d	None	Ustekinumab 90 mg q3 w	Infliximab 300 mg q8w	Vedolizumab 300 mg q 8 w
Trough level biologics (mcg/ml)	ADA: 13.7	ADA: 15.3	/	/	IFX: 5.5	VDZ: 9.0
Immunomodulators	AZA 50 mg 2×/wk	AZA 150 mg/d	AZA 100 or 150 mg/d alternating	None	None	None
6-TGN (pmol/8×10E8 RBC)	226	87	N/A	/	/	/
Flu-like symptoms	Pyrexia	/	/	Pyrexia and cough	Sore throat and runny nose	Pyrexia
Gastrointestinal symptoms	Nausea, diarrhea, dysgeusia and anosmia	Dysgeusia and anosmia	Dysgeusia and anosmia	Nausea and diarrhea	Dysgeusia and anosmia	/
Neurological symptoms	Cephalea	/	/	/	Cephalea	/
Symptom duration (days)	21	7	7	7	10	2
Suspension/delay of therapy (days)	36	10	0	35	14	0
SARS-CoV-2 IgA from symptom onset[b]	2w: 0.710 4w: 0.800 5w: 0.480 8w: 0.470	3w: 1.570 5w: 1.330 9w: 1.180	N/A	4w: 8.500	4w: 1.140 5w: 0.950 6w: 1.430	5w: 1.400 7w: 1.680
SARS-CoV-2 IgG from symptom onset[b]	2w: 0.150 4w: 0.460 6w: 0.710 8w: 1.560	3w: 0.570 5w: 0.700 9w: 5.600	9w: 5	4w: 3.940	4w: 0.750 5w: 0.900 6w: 1.490	5w: 2.110 7w: 4.030

ADA, adalimumab; AZA, azathioprin; COVID-19, coronavirus disease 2019; fCP, fecal calprotectin; IBD: inflammatory bowel disease; IFX, infliximab; N/A, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 6-TGN, 6-thioguanine nucleotides; VDZ, vedolizumab; w: weeks; /, not applicable.
[a]Strictureplasty and jejunal resection.
[b]Anti-SARS-CoV-2-IgA- and IgG ELISA (Euroimmun, Lübeck, Germany), reference value: ratio <0.8 (negative), ratio 0.8–1.1 (borderline) and ratio >1.1 (positive).

Patients and methods

Study population

Of the six patients in our cohort, five had Crohn's disease and one ulcerative colitis, all in clinical remission prior to COVID-19 (Harvey–Bradshaw Index ranging between 0 and 1 and a Mayo score of 0). The demographic and all the clinical and laboratory data are summarized in Table 1. Fecal calprotectin prior to COVID-19 infection ranged from 79 to 1350 mg/kg (normal <50). COVID-19 was confirmed by real-time reverse-transcriptase PCR of nasal and pharyngeal swab specimens for SARS-CoV-2-RNA by local health authorities using different primers. SARS-CoV-2 antibodies IgA and IgG were determined by a commercial ELISA from Euroimmun (Euroimmun, Lübeck, Germany) using the recombinant S1 protein as antigen.

The objective of the present study was to describe the clinical evolution in six patients with IBD and immunosuppressive treatment that were infected with SARS-CoV-2, particularly focusing on longitudinal antibody development as an indicator for a specific immune response.

Data collection

We retrospectively collected all data of IBD patients with COVID-19 who were on immunosuppressive medication and visiting our outpatient clinic for IBD between 01 March 2020 and 01 June 2020. If the treating gastroenterologist (H.V.) got information on ongoing COVID-19, the immunosuppressive therapy was stopped in accordance with the recommendations of OEGGH and ECCO, and the patient was carefully monitored clinically, additional laboratory tests were performed if necessary, and calprotectin in stool was determined.

Patients' serum was quantitatively analyzed for SARS-CoV-2-specific antibodies, IgA and IgG, as the indicator for the virus-specific immune response, and with the intention to choose the right time point for restart/continuation of immunosuppression.

Ethical considerations

Informed consent was obtained from all participants concerning retrospective anonymous reporting of the cases.

Results

Patient characteristics

Initial symptoms of COVID-19 infection were diarrhea (reported in two patients), cephalea (reported in two patients), and dysgeusia and anosmia (reported in four patients). In spite of recent/ongoing immunosuppressive or biological therapy, none of our patients developed respiratory symptoms or had to be hospitalized. One patient continued his azathioprine treatment during his COVID-19 infection because of lacking tight medical control (case 3) without further problems. The antibody results are depicted in Figs. 1 and 2 where we categorized patients by weeks according to the date of antibodies test after the onset of symptoms. Clinical course of COVID-19 is summarized for the six patients in Table 1.

Individual cases

Case 1

A 48-year-old female with a 38-year history of Crohn's disease, no other comorbidities and prior related surgeries (strictureplasties and jejunal resection due to intestinal stenosis), treated with adalimumab (q10d) and azathioprine was in clinical remission when a PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. The last injection of adalimumab was administered subcutaneously 1 day before she experienced first symptoms which persisted for a total of 21 days. Immunosuppressive therapy was suspended upon diagnosis of COVID-19. Antibodies were determined 17, 31 (borderline IgA), 34 and 53 days (positive IgG) after the onset of symptoms. Finally, 33 days after onset, a negative PCR test (nasal and pharyngeal swab) was obtained prior to restart of medication on day 34.

Case 2

A 22-year-old male with a 2-year history of Crohn's disease and no further comorbidities was receiving adalimumab and azathioprine 150 mg/d. A PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. Prior to COVID-19, the patient was in clinical remission. The last injection of adalimumab was administered 1 day and

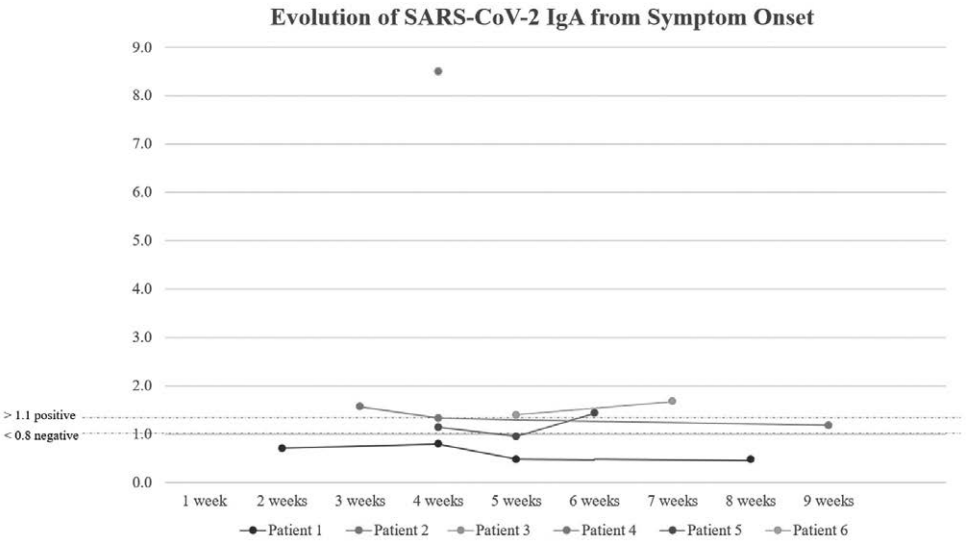

Fig. 1. Evolution of SARS-CoV-2 IgA antibodies.

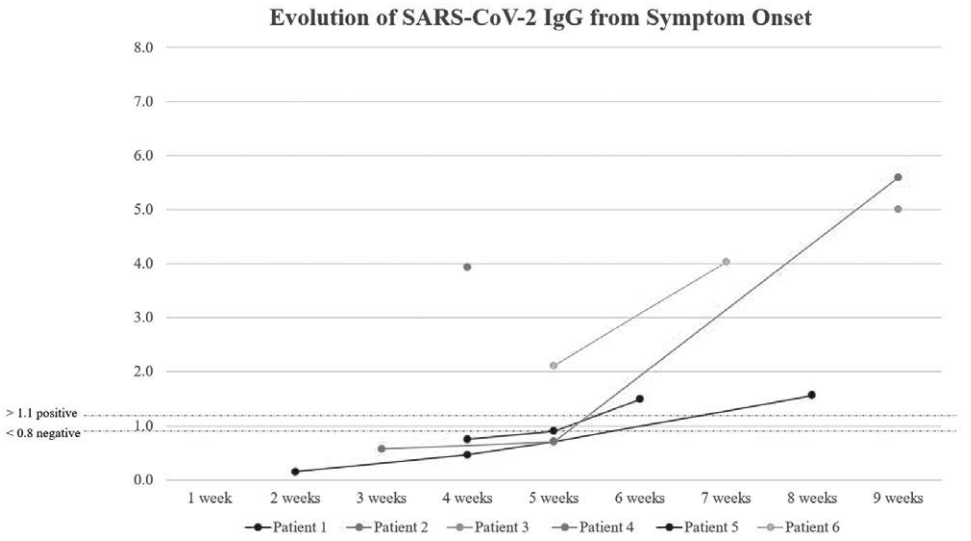

Fig. 2. Evolution of SARS-CoV-2 IgG antibodies.

the last intake of azathioprine 11 days after start of symptoms. The symptoms persisted for 1 week. Adalimumab was restarted 22 days and azathioprine 37 days after start of symptoms. Antibody tests were performed 21 days (positive IgA), 37 days and 63 days (positive IgG) after the symptom onset. A negative PCR (nasal and pharyngeal swab) was obtained prior to restart on day 21.

Case 3

A 19-year-old male with a 5-year history of Crohn's disease and no other comorbidities was receiving azathioprine 150 mg/d. A PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. Prior to COVID-19, the patient was in clinical remission. Symptoms persisted for 7 days. The first antibody test was made 64 days after symptom onset and was positive in IgG (no IgA available). Due to lack of medical supervision, the patient did not suspend azathioprine.

Case 4

A 44-year-old female with an 18-year history of ulcerative colitis without other comorbidities was receiving ustekinumab 90 mg q3w. A PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. Prior to COVID-19, the patient was in clinical remission. Symptoms persisted only for 1 day. The last injection of ustekinumab was administered 11 days before start of symptoms. Immunosuppressive therapy was suspended and restarted 27 days after the symptom onset. SARS-CoV-2 antibodies were determined 27 days after start of symptoms and were both positive.

Case 5

A 71-year-old female with a 16-year history of Crohn's disease, without other comorbidities, was receiving infliximab 300 mg q8w. A PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. Prior to COVID-19, the patient was in clinical remission. The last dose of infliximab was administered 25 days prior to start of symptoms. The patient's COVID-19 symptoms persisted for 13 days. Due to two additional positive PCR tests (nasal and pharyngeal swab) which took place 26 and 34 days after start of symptoms, immunosuppressive therapy was delayed. The first negative PCR test (nasal and pharyngeal swab) was obtained 44 days after symptom onset. Antibody tests were performed 26 (positive IgA), 34 and 44 days (positive IgG) after symptoms started. The next application of infliximab took place 46 days after symptom onset (15 days later than scheduled).

Case 6

A 25-year-old male with a 16-year history of Crohn's disease and no other comorbidities was receiving vedolizumab 300 mg q8w. A PCR test (nasal and pharyngeal swab) confirmed SARS-CoV-2 infection. Prior to COVID-19, the patient was in clinical remission. The last dose of vedolizumab was administered 7 days prior to symptom onset. The patient's COVID-19 symptoms persisted only for 2 days, and antibody tests were performed 37 and 49 days after start of symptoms. Treatment with vedolizumab was resumed 49 days after start of symptoms after proven positivity of antibodies (both IgA and IgG) on day 37.

Discussion

In our observation, positive antibody detection was delayed, since IgG initially tested positive in 50% of patients (cases 1, 2 and 5) only after 6 weeks after onset of symptoms. Contrarily, in the younger patient (22 years of age) with combined immunosuppressive treatment (case 2), SARS-CoV-2 IgA antibodies were already positive after 2 weeks compared to 4 weeks in the two other slower responders (cases 1 and 5).

Following infection with SARS-CoV-2, initially either IgA or IgM antibodies can be measured first. A Cochrane review summarized sensitivities of SARS-CoV-2 IgA antibodies in non-IBD patients to range from 0.67 (95% CI, 0.38–0.88) to 1.00 (95% CI, 0.94–1.00) after 15–21 days of infection [18]. Recently, SARS-CoV-2 IgG antibody dynamics following initial infection were described among 45 non-IBD patients, and IgG development was 96.7% at 37 days postexposure [21]. In the said study, no further description of comorbidities or concomitant medication was given. One of the first studies to report specific SARS-CoV-2 antibodies observed the outcome of 34 hospitalized patients with a total observation time of 7 weeks. At the end, all patients had positive SARS-CoV-2 IgG titers, whereas two patients (33.3%) had negative IgM antibodies [22].

In general, SARS-CoV-2 IgG antibodies are usually detected in the middle and later stages of the disease, currently seen as a diagnostic addition due to the ranges in specificities [23]. An outbreak of COVID-19 occurred during deployment in the western pacific of a US Navy air craft carrier: only 15 (6.4%) of 235 service members had a history of asthma, hypertension, diabetes or immunosuppression. The median age was 30 years [interquartile range (IQR) = 24–35 years], and 212 (90.2%) members had positive ELISA results (OR = 75.5; 95% CI = 38.5–148.1) [24].

Although comprehensive data on SARS-CoV-2-specific IgA and IgG kinetics, detected with the antibody assay we used in our cases, are still missing, our observations indicate that the humoral immune response to SARS-CoV-2 might indeed be delayed in immunosuppressed patients. On the other hand, it is well known that the serological response rate to immunization in immunocompromised patients might be lower, for example for hepatitis B [25]. A study by Altunoz *et al*. showed that patients with IBD under immunosuppression (corticosteroids, azathioprine and anti-TNF) develop lower protective anti-HBs titers; further studies have also confirmed such findings [26,27]. Similarly, response rates to pneumococcal vaccination are significantly lower when patients received anti-TNF therapy alone or in combination with azathioprine, in comparison to the group which only received mesalamine [28]. This has led to the recommendation to vaccinate patients prior to initiating immunosuppressive treatment. Contrarily, a study comparing measles, mumps and rubella vaccine-induced antibody concentrations in a cohort of IBD patients receiving immunosuppressive treatment found comparable results to healthy controls [29].

The main limitation of our study is the descriptive observational nature of this data; hence, we were not able

to compare the results to a control group consisting of persons also infected with COVID-19 but no ongoing immunosuppression. Furthermore, antibodies were not determined at the same time points in all patients because it required attending the hospital in such uncertain times, which is the reason why some of them have only one antibody determination. The main strength of our observation is the description of the clinical evolution of immunosuppressed patients in largely uncharted territory where recommendations of whether to halt immunosuppressive treatment, clinical outcomes, antibody development and long-term immunity remain to be fully elucidated.

Conclusion

Late antibody development seems to be more frequent in older patients and in patients with combined immunosuppressive treatment. In this scenario, SARS-CoV-2 antibody testing could be useful prior to restart of immunosuppressive therapy.

Acknowledgements

Conflicts of interest

C.P. has served as a speaker/consultant/advisory board member for AbbVie, MSD, Takeda, Janssen, Merck, Ferring and Astro Pharma. H.V. has served as a speaker/consultant/advisory board member for AbbVie, Amgen, Gilead, MSD, Takeda, Janssen, Merck, Ferring, Astro Pharma, Pfizer, Roche, Sandoz, Panaceo, Covidien, Falk Pharma GmbH, and Montavit. SS, MK, and LW have nothing to disclose.

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