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Conception and reality: Outcome of SARS-CoV-2 infection and vaccination among Hungarian IBD patients on biologic treatments

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ABSTRACT

Introduction: Inflammatory bowel disease potentially elevates the risk of infections, independently from age, while the disease activity and medical treatment(s) can also increase the risks. Nevertheless, it is necessary to clarify these preconceptions as well during the COVID-19 pandemic.
Methods: An observational, questionnaire based study was conducted in Hungary between February and August 2021. 2 questionnaires were completed. The first questionnaire surveyed the impact of the pandemic on patients with biologic treatments and assessed the severity and outcome of the infection, whereas the second one assessed vaccination rate and adverse events.
Results: 472 patients participated in the study. 16.9 % of them acquired the infection and 6.3 % needed hospitalization. None of them required ICU care. Male sex elevated the risk of infection ($p = 0.008$), while glove ($p = 0.02$) and mask wearing ($p = 0.005$) was the most effective prevention strategy. Nevertheless, abstaining from community visits or workplace did not have an impact on the infection rate. Smoking, age, and disease type did not elevate the risk. UC patients had poorer condition during the infection ($p = 0.003$); furthermore, the disease activity could potentially worsen the course of infection ($p = 0.072$). The different biological treatments were equally safe; no difference was observed in the infection rate, course of COVID-19. Azathioprine and corticosteroids did not elevate the infection rate. 28 patients (35.0 %) suspended the ongoing biologic treatment, but it had no impact on the disease course. However, it resulted in changing the current treatment ($p = 0.004$). 9.8 % of the respondents were sceptic about being vaccinated, and 90 % got vaccinated. In one case, a serious flare-up occurred.
Discussion: Most patients acquired the infection at workplace. Biologic therapies had no effect on the COVID-19 infection, whereas male sex, an active disease, and UC could be larger threat than treatments. Vaccination was proved to be safe, and patient education is important to achieve mass vaccination of the population.

1. Introduction

SARS-CoV-2 is a single-stranded, RNA coronavirus, which is a predominantly respiratory pathogen that causes severe respiratory distress syndrome, pneumonia, and pulmonary embolism with high morbidity and mortality rates [1].

Since its one and half a year outbreak declared by the World Health Organization on 11th March 2020, [2] there has still been no effective control for the COVID-19 pandemic. Inflammatory bowel disease (IBD; ulcerative colitis [UC], and Crohn's disease [CD]) potentially elevates the risk of viral infections, independently from age; moreover, disease activity and medical treatment(s) can increase the risk as well. IBD patients under 35 years of age are 5

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times as likely to have experienced a severe viral infection requiring hospitalization as the background population, whereas the presence of IBD alone increases the risk 3 times [3].

Based on the nationwide, multicenter study of Derikx LAAP et al. conducted in Netherlands and published in October 2020, only 0.29 % of the IBD population was diagnosed with COVID-19. This finding is apparently in contrast with the expected results. However, 20 % of the IBD population had a severe course of the disease, and 13 % of them passed away. Except for one patient, all of them were above 65 years of age, and all had comorbidities [4].

Obviously, immunomodulation potentially elevates the risk of infection and serious disease course, in addition, immunosuppressants can elevate the risk of severe viral and bacterial infections [5–7]. Opportunistic infections are more common in patients treated with biologic agents, especially in combination with immunosuppressants. While anti-TNF increases the chance to pneumonia in monotherapy as well as in viral infections, mesalazine is a much safer therapeutic option with lower risk rates [8–9]. It would be obvious that patients on biologics are more likely to get COVID-19, and the course of the disease is more severe. However, based on recent studies, the relative risks of hospitalization, the need of hospitalization at an intensive care unit, and the mortality rates have been lower for patients on biological agents. Nevertheless, mortality rates have been higher in case of the administration of steroids and 5-aminosalicylate [10–11].

On the one hand, the main objective of the present study was to evaluate the subjective status of patients during the infection beyond the traditional outcomes (e.g., hospitalization rate or admission to ICU/ventilator use) and to assess potential factors influencing the infection rate and the severity of the disease course (including age, gender, smoking, changes in daily habits, personal protective strategies, therapeutic interventions, conventional treatments [azathioprine, budesonide, methylprednisolone], and biologic therapies). On the other hand, the study also aimed to measure the vaccination rate and the risk and benefit ratio of the various vaccinations.

As the available study results are contradictory, more data are needed and more results published and made accessible.

2. Methods

2.1. Study design and setting

This was a Hungarian, multicenter, observational, cross-sectional, questionnaire-based study, conducted between the February 1, 2021 and August 1, 2021. 4 Hungarian centers were involved in our study, one at each of the following sites: University of Szeged, Szeged, Hungary, University of Pécs, Pécs, Hungary, Semmelweis University, Budapest, Hungary, and the Hungarian Crohn's and Colitis Association, Budapest, Hungary. The collaborating centers were reached out via e-mail.

In our study, all four centers took part in compiling the questionnaires, and it was also approved by the president of the Hungarian Society of Gastroenterology. The questionnaires were sent randomly to some patients who provided feedback on comprehensibility, and they could also suggest some changes.

2.2. Participants

The questionnaires were sent to patients with IBD on biologic treatments. The questionnaires were sent to the patients the e-mail contact details of who were available in the centers. Nevertheless, participants who could not be reached via e-mail, could fill out the questionnaire in person on the occasion of follow-up visits to reduce potential bias as elderly patients might not have e-mail address.

Patients obtained an invitation letter and the inform consent form, which contained the aims of the survey, and that data would only be used anonymously and with strict confidentiality during the statistical analysis. We emphasized that the participation was voluntary, and that they consented to the use of the data for only scientific purposes.

Partially completed or repeatedly submitted questionnaires were excluded from the study.

2.3. Questionnaires

The study consisted of 2 different questionnaires. The first one was sent to all IBD patients on biologic treatments in each center, while the second one was sent to only the one at the University of Szeged.

The first questionnaire was sent out in February 2021, and it consisted of 53 questions to assess the source of the infection, prevention strategies, the infection/hospitalization rate, the patients' symptoms, and the impact of the pandemic including changes in daily habits, e.g., avoiding public places or missing out from job; personal protective strategies, e.g., regular mask wearing, change in therapy, or vaccine hesitancy; and therapeutic interventions.

As half of the Hungarian population had been vaccinated until July 2021, a second questionnaire was sent out in July 2021, which consisted of 23 questions. It assessed the rate of the vaccinated IBD patients and the risk and benefit ratio of the different vaccinations (Pfizer®, ModeRNA®, Sputnik V®, Astra Zeneca®, or Sinopharm®). It also compared the course of the COVID-19 infection with the adverse events of the vaccinations.

In Hungary, a PCR or an antigen test is performed if the patient develops symptom(s) of the COVID-19 infection or in case of contact tracing.

2.4. Data analysis

The patients' demographic and clinical data were collected by the questionnaires. Statistical analysis was performed by using R statistical software version 4.0.3 (R Foundation for Statistical Computing Vienna, Austria) and Statistical Package for the Social Sciences software version 24 (SPSS Inc., Chicago, IL, USA). During the analysis, a p value of < 0.05 was considered to indicate statistical significance. Mean values were given with ± SDs. Risk factors, such as sex, disease type, smoking, vitamin supplementation, mask wearing, glove wearing, avoiding public places, and missing from job were assessed with odds ratio (95 % CI was calculated), while age was calculated with linear regression. The impact of treatments on the infection and the hospitalization rate was assessed by the Pearson's chi-squared test, whereas the impact of the biologics and the corticosteroid treatment on the general condition during the infection was calculated by the ANOVA test. The impact of the immunomodulator (azathioprine) on the general condition during the course of the infection was calculated by the Welch Two Sample *t*-test. The impact of the disease activity on the infection rate was assessed by the Welch Two Sample *t*-test as well, whereas the impact of the disease activity on the general condition during the infection was assessed by the Spearman's correlation.

2.5. Ethical considerations

Ethical approval for the study was obtained from the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB) (IV/2678–3 /2021/EKU). The research was carried out according to The Code of Medical Ethics of the World Medical Association (Declaration of Helsinki), and informed con-

sent was obtained from the enrolled patients. Patient consent form was included at the beginning of the questionnaires, and by completing the questionnaire, patients agreed to participate in the study.

3. Results

The questionnaire was sent to 607 patients receiving biologic therapy, and 472 of them (77.8 %; male/female ratio: 39.2 %/60.8 %) filled out the first questionnaire. The mean age was 38.7 years (±11.8 yrs). Mean disease duration was 12.4 years (±8.9 yrs). Overall, 80 patients (16.9 % [95 % CI: 13.82–20.61]) went through the COVID-19 infection, and 5 patients (6.3 %) were hospitalized. No patients were in the ICU or needed invasive ventilation (Table 1).

3.1. Demographic data

In our cohort, male IBD patients were exposed to a higher risk to SARS-CoV-2 infection, as significantly more men had a positive test result than women (p = 0.008). Age (p = 0.823) and disease duration (p = 0.586) did not influence the risk. 132 patients (28.0 %) smoked cigarettes, and 73 of them did it regularly. In our cohort, regular smoking did not elevate the infection rate (p = 0.09) compared to occasional smokers and nonsmokers (Table 2).

3.2. General attitude to the pandemic, prevention strategies

In total, 262 patients (55.5 %) claimed that the COVID-19 pandemic was a serious, life-threatening disease, while 109 patients (23.1 %) claimed that SARS-CoV-2 was like an influenza virus, and 99 patients (21.0 %) said that it was far less serious than it was dealt with, and 2 patients (0.4 %) claimed that there was no such virus.

A total of 76.7 % of the patients claimed that they were at increased risks, and nearly half of them (47.3 %) thought that they were at very high risk. 41.2 % of the patients visited their physician less frequently.

Except for 13 patients, all of the participants (97.2 %) wore their mask regularly, and it seemed to be one of the most effective equipment against the virus, as it reduced the infection rate significantly (p = 0.005). 20.8 % of the patients claimed that they wore disposable gloves regularly, and it decreased the COVID-19 infection rate as well (p = 0.02). A relatively huge proportion (51.9 %) of the respondents declared that due to the pandemic, they no longer visited public places, while 15.9 % quit their job or changed to work in home-office due to health reasons (e.g., chronic disease or elderly age) (Table 1). 38.8 % of the infected patients declared that they had been infected at their workplace. Nevertheless, avoiding public places (p = 0.08) and missing out from job (p = 0.337) did not have a significant impact on the infection rate (Table 2). 28.8 % assumed that they got the infection via a family member, and 16.3 % claimed that they did not know where they got the infection from (Table 3).

Overall, 60.9 % of the patients took vitamins/dietary supplements to prevent the infection, 47.5 % vitamin C and 51.7 % vitamin D. Based on our cohort results, vitamin C supplementation did not mean protection against the infection (p = 0.117), and surprisingly, vitamin D seemed to increase the risk (p = 0.027, OR = 1.71).

In total, 47.5 % of the patients who went through the COVID-19 infection claimed that nobody got infected in their family, and 56.3 % responded that nobody caught the infection at the workplace. 5 % of the patients claimed that>3 patients got the infection in their family, and 16.3 % declared that>3 patients at their workplace (Table 3).

Table 1
Demographic and clinical data of the respondents of the first questionnaire.

Number of patients (n)	472
Sex	
M (n; %)	185 (39.2 %)
F (n; %)	287 (60.8 %)
Age (mean ± SD) > 65 yrs (n; %)	38.7 yrs ± 11.8 yrs 13 (2.75 %)
Smoking	
Yes (n; %)	73 (15.5 %)
Occasionally (n; %)	59 (12.5 %)
No (n; %)	340 (72.0 %)
UC / CD (n; %)	163 (34.5 %) / 309 (65.5 %)
Disease duration (mean ± SD)	12.4 ± 8.9 yrs
Wearing a mask	459 (97.2 %)
Surgical mask (n; %)	305 (64.6 %)
Cotton mask (n; %)	240 (50.8 %)
FFP2/FFP3 (n; %)	111 (23.5 %)
Glove use	98 (20.76 %)
Vitamin supplementation	
Vitamin C (n; %)	234 (49.6 %)
Vitamin D (n; %)	253 (53.6 %)
Avoiding public places (n; %)	245 (51.9 %)
Missing from job (n; %)	75 (15.9 %)
Biologic treatment	
infliximab (n; %)	132 (28.0 %)
adalimumab (n; %)	185 (39.2 %)
vedolizumab (n; %)	83 (17.6 %)
ustekinumab (n; %)	53 (11.2 %)
tofacitinib (n; %)	19 (4.0 %)
COVID-19 positive (n; %)	80 (16.9 %)
Hospitalization (n; %)	5 (6.3 %)
ICU care (n; %)	0 (0 %)
Willing to be vaccinated	
Yes (n; %)	269 (57.0 %)
Depending on the physician (n; %)	33 (7.0 %)
Uncertain (n; %)	137 (29.0 %)
No (n; %)	33 (7.0 %)

3.3. Clinical data

3.3.1. IBD type / activity

In total, 34.5 % of the patients had UC and 65.3 % had CD. There was no significant difference in the incidence of the COVID-19 infection (p = 0.701); however, UC patients who went through the COVID-19 infection felt worse during the infection measured on a 1 to 5 self-assessment scoring scale (1: good, 5: very poor). (p = 0.003) (mean UC score was 3.6 and CD score was 2.8). No other significant difference was observed in our cohort between the two diseases.

Based on our cohort, the disease activity of the IBD seemed to have an impact on the general condition (close to the significance level) during the COVID-19 infection (p = 0.072); however, it did not elevate the infection rate.

3.3.2. Biologic therapies

Most of the patients (67.2 %) received anti-TNF agents (infliximab [IFX] 28.0 % or adalimumab [ADA] 39.2 %). In total, 17.6 % of patients were on vedolizumab (VDZ), 11.2 % on ustekinumab (UST), and 4.0 % on tofacitinib therapy (Table 1). In most cases, where it was possible, we aimed to change IFX to ADA in order to reduce the number of doctor–patient visits, as patients could use ADA at home. Therefore, 24 patients (5.1 %) claimed that they had a change in their therapy.

In total, 80 patients (16.9 %) went through the infection, and 24 patients were administered IFX, 34 ADA, 16 VDZ, 3 UST, and 3 tofacitinib therapy. Based on our cohort, the different biologic treatments did not elevate the infection rate (p = 0.349). Furthermore, no significant difference was detected during the infection (p = 0.094) regarding the general condition measured on a 1 to 5

Table 2
Risk factors in IBD to develop COVID-19 infection (n = 80).

		COVID negative (N = 392)	COVID positive (N = 80)	COVID prevalence	p-value
Age (mean ± SD)		38.6 ± 12.0	39.0 ± 11.0	–	p = 0.823
Male		143	42	22.7 %	**p = 0.008**
Disease duration (mean ± SD)		13.7 ± 9.0	13.2 ± 4.5		p = 0.586
CD/UC		255 / 137	54 / 26	17.5 % / 16.0 %	p = 0.701
Smoking		66	7	9.6 %	p = 0.09
Protective factors	Wearing a mask	385	74	14.2 %	**p = 0.005**
	Glove use	91	7	7.1 %	**p = 0.02**
	Avoiding public places	211	34	13.9 %	p = 0.08
	Missing from job	66	9	12.0 %	p = 0.337
Biologic therapies	vedolizumab	67	16	19.3 %	p = 0.349
	ustekinumab	50	3	5.7 %	
	tofacitinib	16	3	15.8 %	
	adalimumab	151	34	18.4 %	
	infliximab	108	24	18.2 %	
Steroid	altogether	52	11	17.5 %	p = 0.995
	budezonide	30	8	21.1 %	p = 0.482
	methylprednisolone	22	3	12.0 %	p = 0.498
Immunomodulator	azathioprine	93	16	14.67 %	p = 0.56

self-assessment scoring scale. No additional differences were observed regarding the different biologic treatments (Table 3).

3.3.3. Conventional therapy

38 patients were administered budesonide therapy (8.1 %), and 25 patients (5.3 %) methylprednisolone therapy. Based on our cohort, there was no significant difference between the two groups, and steroid treatments did not elevate the infection rate (p = 0.675) and did not have an impact on the course of the infection (p = 0.071).

In total, 109 patients (23.1 %) received azathioprine therapy, and it neither elevated the infection rate (p = 0.56), nor worsened the course of the infection (p = 0.153). No further significant difference was observed (Table 3).

3.3.4. COVID-19 disease course

Overall, 80 patients (16.9 %) went through the COVID-19 infection. No one was admitted to the ICU or put on a ventilator. Respondents reported several symptoms, and the five most common ones were anosmia/parosmia (66.3 %), headache (55.0 %), cough (48.8 %), fever (50.0 %), and ageusia/parageusia (51.3 %) (Table 3).

After the establishment of the diagnosis, 28 patients (35.0 %) suspended the ongoing biologic treatment for a mean of 34 days, and it did not cause flare-ups in the primary disease (p = 0.158). Nevertheless, 13.75 % of the patients reported that after all, they needed a change in their medical therapy due to deterioration as a consequent of the infection. Patients who ceased their ongoing biological treatment for prophylactic purposes in case of infection were more likely to have to change therapy due to relapse (p = 0.004). Patients did not specify the change in their treatment. In total, 5 patients (6.3 %) were hospitalized with the COVID-19 infection. Flare-ups were relatively frequent in our cohort. Nearly half of the patients (46.25 %) claimed to have an increase in the number of defecations per day.

3.4. Willingness to be vaccinated

Overall, 56.9 % of the participants claimed that they would get vaccinated (in general, no brand names were given), and 7.0 % claimed that it would depend on the advice of their physician. Patients with primary education and university degree were more about to take the vaccination compared to patients with secondary education (p = 0.02).

3.4.1. Comparison of the COVID-19 infection and the vaccination

112 patients (CD 74 and UC 38; females 53.6 %) filled out the second questionnaire, and the mean age was 41 years (±14.7). Until July 2021, half of the Hungarian population received the second dose of the vaccine. 90 % of the IBD patients got vaccinated (66 Pfizer®, 12 Astra Zeneca®, 9 ModeRNA®, 8 Sinopharm®, and 5 Sputnik V®), and 60 % of them claimed that it was the only solution to overcome the pandemic. 9.8 % of the respondents were sceptic about the vaccines, as these vaccines were developed too rapidly. 10.7 % would only take the preferred vaccine. 106 patients (94.6 %) received biologic therapy (IFX 27, ADA 31, VDZ 16, tofacitinib 9, and UST 19), and 23 were administered azathioprine, 9 budesonide, and 6 methylprednisolone (Table 4).

A total of 30 patients had SARS-CoV-2 infection, while 28 of them developed some symptoms. The 5 most common symptoms were headache (63.3 %), olfactory disturbance (56.7 %), cough (53.3 %), fever (50.0 %), and parageusia (46 %). No patient was hospitalized. Patients rated their disease activity on a 1 to 5 self-assessment scale. Following the COVID-19 infection, the self-assessment score increased from 1.63 to 2.07; consequently, 6 patients (20 %) reported a relapse after the course of the infection. The existing biological therapies (p = 0.553) and conventional therapies, azathioprine (p = 0.384), budesonide (p = 0.285), methylprednisolone (p = 0.553), did not affect the prevalence of post-infection relapse.

In contrast, 10 of the vaccinated respondents (10 %) reported deterioration in their disease after vaccination, but the symptoms were mild, and persistent complaints with blood stained stools, diarrhea, and abdominal cramps were present only in 2 cases (2 %). The vaccination type did not affect the prevalence of the relapse (p = 0.235). The existing biological therapies (p = 0.488) and conventional therapies, azathioprine (p = 0.875), budesonide (p = 0.625), and methylprednisolone (p = 0.477), did not affect the prevalence of the relapse after vaccination. In addition, several people (49 %) reported post-vaccination side effects, but they were mild and resolved within a few days (e.g., headache, fatigue, or malaise). Based on the responses, the prevalence of the adverse events after both vaccinations differed between the various vaccines (p < 0.001). Most of the side effects developed after the administration of the Sputnik V® vaccination (100 %), fewer side effects were present after the administration of the Sinopharm® (25 %) vaccination, while after the second vaccination, the most side effects were present in ModeRNA® (55.5 %) vaccinated patients, and the fewest side effects were reported after the Sinopharm® (37.5 %) vaccination.

Table 3
Characteristics of the COVID-19 infection.

		N (80)	% (100)
Symptoms	Parosmia	49	61.3 %
	Headache	43	53.8 %
	Fever	40	50.0 %
	Parageusia	37	46.3 %
	Cough	37	46.3 %
	Diarrhea	33	41.3 %
	Dyspnea	13	16.3 %
	Abdominal pain	4	5.0 %
How bad did you feel in general? (Mark it on a 1–5 scale; the higher number indicates poorer condition)	1	10	12.5 %
	2	14	17.5 %
	3	29	36.3 %
	4	15	18.8 %
	5	12	15.0 %
How active was your disease before the infection? (Mark it on a 1–5 scale; the higher number indicates poorer condition)	1	36	45.0 %
	2	26	32.5 %
	3	9	11.3 %
	4	6	7.5 %
	5	3	3.8 %
Where/Who do you think you get the infection from?	workplace	31	38.8 %
	family	23	28.8 %
	don't know	13	16.3 %
	other	6	7.5 %
	hospital	4	5.0 %
	friends	3	3.8 %
How many people have been infected in your household?	0	38	47.5 %
	1	18	22.5 %
	2	14	17.5 %
	3	5	6.3 %
	>3	4	5.0 %
	don't know	1	1.3 %
How many people have been infected at your workplace?	0	45	56.3 %
	1	5	6.3 %
	2	4	5.0 %
	3	4	5.0 %
	>3	13	16.3 %
	don't know	9	11.3 %
Did you have any relapse during infection?	yes	22	27.5 %
	no	56	70.0 %
	cannot tell due to similar symptoms	2	2.5 %
Did the number of passed stools increase during the infection?	yes, 1–2	18	22.5 %
	yes, 2–3	11	13.8 %
	yes, >3	9	11.3 %
	no	41	51.3 %
	don't know	1	1.3 %
Modification in IBD treatment		11	13.75 %
Cessation of biologic treatment due to the infection		28	35.0 %
Treatment due to COVID-19 infection	yes	14	17.5 %
	favipiravir	7	8.8 %
	antibiotic	5	6.3 %
	LMWH	4	5.0 %
Hospitalization	5	6.3 %	
Ventilator/ICU care	0	0 %	

Table 4
Demographic and clinical data of the respondents of the second questionnaire assessing, e.g., the vaccination rate and adverse events).

Number of patients (n)	112
Sex	
M (n; %)	52 (46.4 %)
F (n; %)	60 (53.6 %)
Age (mean ± SD) > 65 yrs (n; %)	38.7 yrs ± 11.8 yrs 13 (2.75 %)
UC / CD (n; %)	163 (34.5 %) / 309 (65.5 %)
Vaccination rate	99 (90 %)
Pfizer (n; %)	66 (66.7 %)
ModeRNA (n; %)	8 (6.1 %)
Astra Zeneca (n; %)	12 (9.7 %)
Sputnik V (n; %)	5 (4.5 %)
Sinopharm (n; %)	8 (7.5 %)
Biologic treatment	106 (94.6 %)
infliximab (n; %)	27 (25.5 %)
adalimumab (n; %)	31 (29.2 %)
vedolizumab (n; %)	16 (15.1 %)
ustekinumab (n; %)	19 (17.9 %)
tofacitinib (n; %)	9 (8.5 %)
Steroid (n; %)	15 (13.4 %)
budesonide	9 (8.0 %)
methylprednisolone	6 (5.3 %)
Immunosuppressant	
AZA (n; %)	23 (20.5 %)

4. Discussion

The COVID-19 pandemic still poses challenges to health care one year after its outbreak. Patients with inflammatory bowel disease are considered as risk groups considering the infection [3]. Because of it, several international recommendations/guidelines have been published; however, many of these publications are based on observations. For this reason, efforts ought to be made by both researchers and physicians to collect and analyze as many data as possible, in order to overcome the pandemic.

Almost twice as many people were infected in our cohort until the end of the study period as in the Hungarian background population. 810,046 infections (approximately 8.53 % of the Hungarian population) had been reported until August 8, 2021 [12]. This result does not support previous observations according to which there is no increase in the prevalence of the COVID-19 infection in IBD patients [13] or biologics do not have an impact on the increase of the infection rate [14]. In contrast with previous studies, such as the nationwide study conducted by Derikx et al. (4), the higher infection rates can be explained by the different study population, as our study focused on patients with biological treatments. In addition, patients who paid no attention to the pandemic, and those who were not infected by the virus were potentially uninterested in filling out the questionnaire.

In accordance with previous studies [15–16], male patients seemed to have an increased risk of the infection. Consequently, they should be treated with greater precaution. Despite the preliminary expectations and previously published data, [17] and age [15] were not found to have an impact on the infection. A possible explanation may be that study patients with IBD were younger, that is, only a very small percentage of the patients were older than 65 years. In addition, as smoking has an anti-inflammatory effect in UC [18], it may even have a beneficial effect on the prevalence of the COVID-19 infection. Nonetheless, in our cohort, it did not affect the infection rate.

A high amount of patients took vitamin supplementations, especially vitamins C and D. Yet it should be highlighted that the respondents did not state the type and the quantity of the supplementation. Based on our cohort, vitamin C did not tend to be an effective prophylactic therapy, and vitamin D even seemed to elevate the infection rate. As previously published studies have described the protective role of vitamin D administration both in the prevalence of the COVID-19 infection and in the severity of the course of the disease, we presume that the findings of this study concerning this supplement are probably accidental. Nevertheless, in the future, more studies should focus on the role of vitamin D [19–21].

Most of the patients claimed that SARS-CoV-2 was a life-threating virus, and they thought that they were at high risk as well. In accordance with these observations, almost every participant wore the mask regularly, which still seemed to be one of the most effective protective factors, besides wearing gloves, against the infection.

Most of the patients claimed that they acquired the infection at their workplace, or from a family member. Nonetheless, more than half of the patients declared that no one got the infection in their

workplace or in their family, which can be partly due to the fact, that the patients did not pass the infection on, or that the infection was asymptomatic in their environment, and consequently no COVID-19 antigen testing was performed. However, based on the results in our cohort, it seems that the infection spreads more in the family. It is evident that the pandemic has a huge effect on the daily life of the patients, as more than half of the participants responded that they did not attend public places, or worked in home-office (or even quit their job) because of health considerations. Nevertheless, these preventive strategies did not tend to decrease the infection rate.

Patients with UC seemed to experience poorer general health; however, they did not tend to develop more serious problems than CD patients. Compared to previous data, UC was identified as a single risk factor in the development of severe COVID-19 infection [4].

Previous presumptions seemed to be supported by our findings as increased disease activity was associated, close to the significance level, with potential aggravation in the course of the infection [3,22]. Nevertheless, the disease activity itself did not elevate the infection rate.

Based on our first questionnaire, the different types of biological treatments seemed to be equally safe, as no difference was observed in the infection rate and the course of COVID-19 infection [11]. Suspending the biological treatments did not seem to be effective against the COVID-19 infection; however, it did not cause flare-ups either in the primary disease. Nevertheless, after the cessation of the treatment, more patients needed a change in the therapy. In addition, after the infection, relapses were common, and several patients had to change the therapy they were on because of having flare-ups, however, changes in the medical treatments were not specified by the patients. We would like to emphasize, that so far, data are scarce, which would have looked at the rate of relapse and deterioration following infection. Nevertheless, another study has already confirmed the high infection rates, in about a third of the cases, which is quite higher than in our cohort. In addition, it also emphasized, that biological treatment should not be suspended during the infection, in order to avoid IBD relapse [22].

Azathioprine seemed to be favorable during the infection, furthermore, it did not have an impact on the infection rate, in accordance with previously published data [23–24]. A possible explanation for the positive effect of AZA may be that the reduction of disease activity is favorable. In contrast with international data [11], steroid treatment did not have impact on the patients with COVID-19. Moreover, there was no significant difference between budesonide and methylprednisolone therapies. However, it has to be highlighted that only a few patients were administered these therapies.

Cessation of the ongoing biologic treatment was not more favorable; in fact, patients who suspended it needed a change in the treatment because of some health-related problem. Furthermore, after the infection, a relatively huge amount of the patients claimed that their general health was poorer, and they also admitted to having flare-ups.

After all, patients with IBD are still considered to be a risk group, and they are afraid of getting infected with COVID-19, but only half of these patients would be willing to get vaccinated. On the other hand, the high vaccine rejection rate is not surprising, as acceptance of the influenza vaccination was low as well. However, the acceptance of the vaccination correlated with the patients' education level.

Deterioration in health also occurred after the vaccination; however, with the exception of 2 cases, the complaints resolved within a few weeks. In these two cases, remission did not occur, and in one case, frequent bloody diarrhea, abdominal cramps, and signs of the active inflammation were seen on colonoscopy. Although worsening of the condition could occur after vaccination, severe deterioration was much less common. Further studies with a larger number of participants would be needed to elucidate the effect of both the infection and the vaccination on IBD.

A possible limitation of the study may be that in the cases where patients filled out the questionnaire at the beginning of the study period and got infected afterwards, they did not complete the questionnaire again. The Hungarian database gives a report on the number of registered cases of the infection, and not the number of patients who did go through it. In addition, patients who developed the COVID-19 infection were presumably more willing to complete the questionnaire, which may result in bias of the results as well. However, we aimed to reduce bias, as patients could fill out the questionnaire in person as well, and not only via internet. As it was an anonymous questionnaire based study, presumably the responses cover the reality, and many patients could be reached, which increased the size of the cohort. However, we would like to emphasize, that patients' claims may not fully reflect or represent the reality. Furthermore, we could also examine subjective parameters, which could not be retrieved from the medical databases. However, it can be a source of bias as well. No statistical correction was made for multiple comparisons of simple variables.

Nevertheless, it raises further questions whether in other cohorts, hospitalization/ICU/mortality rates are higher or not.

5. Conclusions

Our questionnaire based survey found that regular mask and glove wearing seemed to be the most effective form of prevention against the infection. The results show that male patients and patients with UC seemed to have poorer condition during the infection.

Different biologic therapies appeared to be equally safe, and suspending the ongoing biologic therapy should be a matter of individual judgment. Azathioprine and corticosteroids did not tend to increase the infection rate, and IBD disease activity did not result in poorer condition during the infection. However, we suggest that poorer general condition and flare-ups in IBD may mean higher risk for COVID-19 infected patients than biologic treatments.

Furthermore, we wish to highlight that patient education towards vaccination is an enormously relevant factor during the pandemic, as the vaccinations cause fewer side effects compared to the COVID-19 infection.

To sum up, we aimed at answering relevant questions in IBD patient care; nonetheless, further questions to clarify emerged during the study.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100253.

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