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THE EFFECT OF THE CORONAVIRUS DISEASE 2019 PANDEMIC ON DIFFERENT AREAS OF GASTROENTEROLOGY

Ph.D. Thesis

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LIST OF ABBREVIATIONS

5-ASA – 5-aminosalicilates

ACE-2 – angiotensin-converting enzyme 2

ADA - adalimumab

AZA – azathioprine

B – Standardized Coefficients Beta

BMI – body mass index

BT – biological therapy

CD – Crohn's disease

CDAI – Crohn's disease activity index

CI – confidence interval

COMB – combination therapy

COVID-19 – coronavirus disease 2019

ECCO – European Crohn's and Colitis Organisation

ERCP – endoscopic retrograde cholangiopancreatography

ESGE – European Society of Gastrointestinal Endoscopy

ESGENA – European Society of Gastroenterology and Endoscopy Nurses and Associates

ETT TUKEB – Hungarian Scientific and Research Ethics Committee of the Medical Research Council

GI – gastrointestinal

IBD – inflammatory bowel disease

ICU – intensive care unit

IFX – infliximab

HSG – Hungarian Society of Gastroenterology

mRNA – messenger RNA

NONE – no treatment

pMayo – partial Mayo score

PGA – physician's global assessment

PPE – personal protective equipment

RNA – ribonucleic acid

S – spike

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

SD – standard deviance

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

TNFα – tumor necrosis factor alpha

TOFA – tofacitinib

UAE – United Arabian Emirates

UC – ulcerative colitis

UST – ustekinumab

VDZ - vedolizumab

WHO –World Health Organization

SUMMARY

Introduction: The coronavirus disease 2019 (COVID-19) pandemic posed a challenge to healthcare, thus in the field of gastroenterology and endoscopy. Staff and patients are at increased risk during an endoscopic examination, so certain restrictions were ought to be introduced. Additionally, inflammatory bowel diseases (IBD) potentially elevate the risk of infections, independently from age, while the disease activity and medical treatment(s) can also increase the risks. Data showed reduced seroprevalence and seroconversion in patients with IBD following COVID-19 infection, therefore, decreased efficacy was hypothesized following vaccination. Additionally, no data was present regarding the level of anti-severe respiratory syndrome disease coronavirus 2 (SARS-CoV-2) spike antibodies among immunosuppressed patients following vaccinations. Therefore, we **aimed** to measure the effect of the pandemic on endoscopy units in real-life settings. Furthermore, to clarify the effect of the COVID-19 pandemic on patients with IBD, and to assess the efficacy of different anti-SARS-CoV-2 vaccines under different treatments and identify predictive factors associated with lower serological response, including anti-tumor necrosis factor (anti-TNF) drug levels.

Methods: The first study was an international, multi-centre observational, cross-sectional, questionnaire-based study. The survey contained 40 questions, which evaluated the effect of the COVID-19 pandemic on the endoscopy units and assessed the infection control. The second study was an observational, questionnaire-based study conducted in Hungary between February and August 2021. The questionnaire surveyed the impact of the pandemic on patients with biologic treatments and assessed the severity and outcome of the infection. The third study was a prospective, double-center study of IBD patients conducted following messenger ribonucleotide acid (mRNA) and non-mRNA anti-SARS-CoV-2 vaccination. Healthy control (HC) patients were enrolled to reduce bias. Baseline and control samples were obtained 14 days after the second dose to assess the impact of conventional and biological treatments. Clinical and biochemical activity, serological response level, and anti-TNF drug levels were measured.

Results: A total of 312 questionnaires were filled in the first study, 120 from Hungary, and 192 internationally. 54 questionnaires (17.3 %) were sent from high-risk countries; 84.9 % of the gastroenterologists declared that they read the European Society of Gastrointestinal Endoscopy (ESGE) statement. Overall, 92.1 % of gastroenterologists realized risk stratification, and 72.1 % claimed to have enough protective equipment. In 52.6 % of the endoscopy units, at least one endoscopist had to discontinue the work due to any risk factor, while 40.6 % reported that the reduced staff did not affect the workflow. Five most important indications considered by

gastroenterologists correlated well with the ESGE recommendation. Significant correlation was found in the usage of the necessary protective equipment in high-risk patients depending on the countries ($p < 0.001$). In the second study 472 patients participated. Almost twice as many patients with IBD (16.9 %) acquired the infection compared to background population. In total, 6.3 % needed hospitalization, but no ICU care. The frequency and disease course of COVID-19 infections did not differ between the different biological therapies. Azathioprine and corticosteroids did not elevate the infection rate. Male sex elevated the risk of infection ($p = 0.008$), while glove ($p = 0.02$) and mask wearing ($p = 0.005$) were the most effective prevention strategy. 9.8 % of the respondents were sceptic about being vaccinated, and 90 % got vaccinated. In one case, a serious flare-up occurred. In the thirds study we included 199 IBD (mean age, 40.9 ± 12.72 years) and 77 HC participants (mean age, 50.3 ± 12.36 years). Most patients (76.9 %) and all HCs received mRNA vaccines. Half of the IBD patients were on biological treatment (anti-TNF 68.7 %). Biological and thiopurine combined immunomodulation and biological treatment were associated with lower serological response ($p < 0.001$), and mRNA vaccination promoted better antibody levels ($p < 0.001$). Higher adalimumab (ADA) levels caused lower serological response ($p = 0.006$). W8 persistence of anti-SARS-CoV-2 level was equal in IBD and HC groups. Vaccination did not aggravate clinical disease activity ($p = 0.65$).

Conclusions: In the first study the survey found weak correlation in preliminary training depending on countries; nevertheless, in Hungary during the examined period, endoscopists considered the recommendations more strictly than in other countries. Although many physicians left the endoscopy lab, the workflow was not affected, probably due to the reduced number of examinations. In the second study, the prevalence of the COVID-19 infection in patients on biologic therapies was higher compared to the background population, but no difference was observed between the different type of biological treatments. Male sex, active disease, and UC could be larger threat than treatments. In the third study, vaccination was proved to be safe. Anti-SARS-CoV-2 vaccination is considerably efficacious in IBD patients, with mRNA vaccines promoting better antibody levels. The negative impact of combined biological treatment, especially with high ADA drug levels, on serological response to vaccination should be considered. Although midterm durability of vaccination is encouraging, more data are needed to expand the existing understanding on this issue.

INTRODUCTION

Inflammatory bowel diseases (IBD: ulcerative colitis [UC], Crohn's disease [CD], inflammatory bowel disease unclassified [IBD-U]) are immune-mediated chronic, relapsing inflammatory conditions of the gastrointestinal tract affecting 2.5 to 3 million people in Europe. (1–3) Despite the increasing incidence worldwide predominantly in young adulthood, the aetiology remains mostly unknown. (4) Current evidence suggests that the pathogenesis involves genetic, environmental, microbial and immune-mediated factors. (5) Patients with IBD have an altered gut microbiota and reduced diversity compared to healthy patients. The healthy colon contains an outer and inner mucus layer, which play an important role in maintaining gut microbiota, however, these structures alongside with the intercellular junctions are usually damaged in IBD resulting higher permeability. As a consequence, the commensal bacteria promotes CD4+ T-cell expansion and interleukin 17A production, which are involved in the pathogenesis of IBD. (6,7) As a consequence of the disrupted barrier function, the altered immune cell functions and malabsorption, patients with IBD are considered immunocompromised, and more susceptible to infections. (4,7,8) Furthermore, the primary aim of the currently available treatments is to modulate the immune-response as well, resulting in higher susceptibility to infectious diseases. Based on the recommendation published by the European Crohn's and Colitis Organisation (ECCO) immunosuppressing agents are systemic corticosteroids, thiopurines, methotrexate, calcineurin-inhibitors and biologic therapies (including the gut selective α4β7 integrin inhibitor vedolizumab [VDZ]) at varying degree, and using them in combination increases even more the chance of opportunistic infections. In addition, active disease, malnutrition, comorbidities, older age and higher body mass index (BMI) were associated with opportunistic infections. (9–11)

Serious viral infections (defined as infections requiring hospitalization or resulting in death) are found to be 3 times higher among the IBD patients compared to the background population, furthermore, under 35 years, the incidence rate was found to be 5 times higher. (12) In addition, the prevalence of pneumonia is also elevated in IBD, enhancing, that the relative risk is the highest in the younger population (≤ 30 years), while the absolute risk is the highest among the elderly (61-64 years). (13) Several studies confirmed, that the clinically active disease is one of the most relevant risk factors in developing serious infectious disease, furthermore, the therapeutic agents, in particular thiopurines, corticosteroids and tumor necrosis factor alpha (TNFα) inhibitors to different extent. (12,14,15) The combination of thiopurines

and corticosteroids, and the triple combination of thiopurines, corticosteroids and infliximab (IFX) were found to result in the greater risk. (9,15,16)

The World Health Organization (WHO) declared the pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11th March 2020, which was first identified in Wuhan, China. (17,18) SARS-CoV-2 is a single stranded ribonucleic acid (RNA) virus belonging to the genus of Coronavirus, and is predominantly a respiratory pathogen causing mostly pneumonia, severe respiratory distress syndrome and pulmonary embolism. (19,20) The prevalence and incidence rates, the hospitalization, intensive care unit (ICU) admission and mortality rates varied between countries and regions, and the severity of the infection differed between subjects, however, almost 7 million patients died due to confirmed COVID-19 infection reported by the WHO until 20th October 2023. (21,22) The pandemic has challenged the health care and also the care of the IBD patients.

The human-to-human transmission of SARS-CoV-2 is predominantly by exhaled respiratory droplets, and the virus enters to the host cell via the angiotensin-converting enzyme 2 (ACE-2) receptors, mostly expressed in the epithelial cells of the lung. (23–26) However, these receptors are also found in the epithelial cells of the small and large intestine, moreover, the virus was detectable in endoscopic biopsies and faecal specimens, which raises the possibility of faecal-oral transmission as well. (27,28) Consequently, endoscopies procedures should be concerned as risk factors regarding the transmission of the virus, e.g., via faecal droplets from patients. Furthermore, additional concerns should be taken, as these methods are considered as potentially aerosol-generating, as patients are coughing and gagging during upper gastrointestinal (GI) endoscopies, in addition, the staff may contact with liquid stool during a lower GI endoscopy. (26) Consequently, based on these considerations, the workflow of the endoscopic units was restricted to varying degrees depending on the regulations of the particular hospitals and countries. (29–31)

Therefore, during the first wave of the pandemic, the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) published a statement regarding GI endoscopies during the COVID-19 pandemic on April 2020. The guideline includes recommendations regarding the appropriate performance of the GI endoscopies, the adequate indications of the procedures and the protection of the personnel (e.g., equipment) during the pandemic. The statement emphasizes that patients should be stratified to a low-, and a high-risk category, moreover, the

adequate clothing and protective equipment of the endoscopic staff should be based on it. The health professional personnel should wear surgical mask, gloves, disposable hairnet, protective eyewear and waterproof disposable gowns in case of low-risk patients, while examining high-risk patients instead of surgical mask filtering face piece (FFP) 2/3 is recommended, and plus one extra glove should be added. In addition, the recommendation lists the endoscopic procedures by priority. (31) Nevertheless, data were lacking regarding the compliance with recommendations and the efficacy of them in a real-life setting.

Patients with chronic diseases, such as IBD were initially considered to bear a potentially greater risk in relation to the chronic inflammation process and/or medications. Following the outbreak of the COVID-19 pandemic, the risk and the severity of the infection was uncertain. However, based on previous data, patients with IBD were considered as at-risk and a vulnerable population, particularly elderlies, patients with active disease and on immunomodulatory therapy compared with the background population. (32,33) Though, data from the early phase of the pandemic were contradictory with these hypotheses.

In the background population, it was well defined, that elder age and comorbidities were identified as risk factors in developing severe COVID-19. (34,35) An international cohort study published in May 2020 found that older age and comorbidities were identified as risk factors in IBD as well, furthermore, systemic corticosteroid use were also identified as deteriorating factors regarding the course of the infection. However, this particular study found, that the age-standardized mortality ratio of IBD patients did not differ from the background population. In addition, TNFα antagonists were not associated as an independent risk factor regarding severe outcomes, moreover, these agents appeared to be more secure even in comparison with 5-aminosalicilates (5-ASA) / sulfasalazine. (36) It should be highlighted, that this study was criticised for selection bias, as patients on anti-TNFα were over-represented in the sample. (37,38)

Further studies predominantly confirmed, that IBD did not increase the infection rate and the risk of developing severe COVID-19 infection. (33,39–44) The risk of the infection did not differ between CD and UC, however, UC patients were at greater risk regarding developing severe COVID-19.(38,41) Comorbidities were identified as an independent risk factor in various publications. (36,38,45) The impact of different medications on severity varied between studies. However, a meta-analysis published in March 2021 demonstrated, that 5-ASA and corticosteroid resulted in increased risk of hospitalization, ICU admission and mortality rate, while biological treatments were identified as protective factors. (41) Based on the SECURE-

IBD trial (46), thiopurines were associated with poor outcomes, however, a further meta-analysis conducted by Tripathi et al. (39) did not support these findings. In addition, IBD disease activity was identified as a risk factor in developing severe COVID-19, especially in younger patients. (47,48) To conclude, data were contradictory regarding the effect of the treatment on the severity of the COVID-19, in addition, no particular investigation was conducted to assess further potential predictive and protective factors on both acquiring the infection and the outcome, including clothing (e.g., mask, gloves), social interactions. Moreover, more data were essential to help patient care during the pandemic.

Vaccinations were considered playing a key role in overcoming the COVID-19 pandemic, and physicians and professional organizations recommended patients to take the vaccination, as both safety and efficacy data were promising in the general population, however, clinical trials excluded immunosuppressed patients. (49–52) It was previously hypothesised, that IBD patients will potentially have an impaired serological response to vaccinations, as patients on anti-TNFα treatment experienced lower antibody levels following pneumococcal, influenza and viral hepatitis vaccinations. (13,53–55) A multicentre prospective observational cohort study in the United Kingdom (CLARITY) had shown that IFX significantly attenuated seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity after SARS-CoV-2 infection, especially in the combination therapy group, compared to VDZ. (55) Moreover, a cohort study reported reduced incidence of seroconversion among patients with immune-mediated inflammatory diseases (including IBD, rheumatoid arthritis, spondyloarthritis and psoriasis) receiving cytokine modulating agents, like TNFα-, interleukin-6-, interleukin-23-, interleukin-17- and Janus kinase inhibitors. (56)

In contrast with previous assumptions, the first published meta-analysis reported high seroconversion rate among patients with IBD. Following the second dose of vaccine it was 96 %. Otherwise, no difference was observed between different immunosuppressant treatments. (57)

In Hungary the population-based vaccination program was introduced relatively early, with adenovirus vector vaccines (Sputnik®, Gamaleya Research Institute of Epidemiology and Microbiology and Astra Zeneca®, University of Oxford), inactivated virus vaccine (Sinopharm®, Sinopharm's Beijing Institute of Biological Products) in addition to messenger RNA (mRNA) vaccines. However, physicians promoted mRNA vaccinations among IBD patients. Latter meta-analysis confirmed the superiority of mRNA vaccines over adenovirus vector vaccines with a seroconversion rate of 96-98 % and 78-90 %, respectively. (58)

However, data on the efficacy of the vaccinations were limited, as these publications predominantly focused explicitly on mRNA and adenovirus vector vaccines. Moreover, data on the relationship between anti-TNFα serum levels and the rate of seroconversion are limited, and no further predictive factors were identified influencing the anti-SARS-CoV-2 antibody levels. In addition, safety concerns were issued regarding the impact of the vaccines on the activity of IBD.

AIMS

The aims of these comprehensive studies were:

Study 1. To evaluate the effect of the COVID-19 pandemic on the endoscopic units and the impact of the regulations and recommendations on both patient care and healthcare workers in an international multicentre cross-sectional study. Furthermore, to assess the indications of endoscopic procedures which cannot be postponed during the pandemic and comparing the responds with the ESGE guidelines.

Study 2. To assess the prevalence and the severity of the SARS-CoV-2 infections among IBD patients on biological therapies, and to evaluate possible preventive strategies used by them in a cross-sectional, self-reported multicentre questionnaire-based study.

Study 3. To measure the level of seroconversion and persistence of specific anti-SARS-CoV-2 spike (S) antibodies following the administration of various SARS-CoV-2 vaccines among IBD patients on different types of treatments and to compare them with healthy subjects in a prospective multicentre cohort study. Furthermore, we aimed to identify predictive factors regarding ineffective serological response, and whether the serum anti-TNFα levels influence it.

PATIENTS AND METHODS

Study 1. To evaluate the effect of the COVID-19 pandemic on the endoscopic units and the impact of the regulations on both patient care and healthcare workers in an international multicentre cross-sectional study. Furthermore, to assess the indications of endoscopic procedures which cannot be postponed during the pandemic and comparing the responds with the ESGE guidelines.

1.1. Study design, settings, participants and data collection

This first study was an observational, cross-sectional, questionnaire-based study conducted between April and June 2020. Gastroenterologists from Europe, Israel, United Arabian Emirates (UAE) and Canada working in endoscopic units were invited to contribute to the study. The participation in the study was voluntary. Centres were reached out via e-mails, and they distributed the questionnaire to further centres in their country. The participating centres were divided into 3 groups, based on the SARS-CoV-2 infection rate of the country (cases per million people until September 2020)(59):

- low risk countries (0 – 2000 cases/million)
- moderate risk countries (2000 – 5000 cases/million)
- high risk countries (>5000 cases/million)

Furthermore, the participating endoscopic units were clustered by the size of the lab, defined by the number of the employed gastroenterologists:

- small (≤ 3 endoscopists)
- medium (4 to 6 endoscopists)
- large (≥7 endoscopists)

Countries with a minimum of 20 completed questionnaires were eligible to further analysis.

The questionnaire consisted of 40 questions evaluating the effect of the COVID-19 pandemic on the endoscopic units' workflow and the infection control, respectively. The questionnaire was revised by the president of the Hungarian Society of Gastroenterology (HSG – Hungarian Society of Gastroenterology). Partially or incorrectly completed questionnaires were excluded. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. (60)

1.2. Outcomes and variables

The primary outcome was the usage of the appropriate protective equipment, while the secondary outcome was the adequate indication of the endoscopic procedures following the risk stratification as specified in the ESGE and ESGENA guidelines, and how preliminary trainings influenced achieving these outcomes. Further analyses were performed to assess the impact of the pandemic and to assess the quality of infection prevention and control strategies on the endoscopic units as well. (31)

1.3. Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences software version 24 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were performed on all studied variables which were expressed as means and medians with ranges. During the analysis, the differences between achieving the outcomes the workflows of endoscopy units were assessed by chi-square tests and complemented with Fisher's exact tests (if the expected frequency is below 5). A p value of <0.05 was considered to indicate statistical significance.

1.4. Ethical approval

The study protocol and the questionnaire were approved by the Scientific Research Ethics Committee of the Hungarian Medical Research Council. The study was carried out under the Declaration of Helsinki. Number of ethical license: IV/4669-2/2020/EKU.

Study 2. To assess the prevalence and the severity of the SARS-CoV-2 infections among IBD patients on biological therapies, and to evaluate possible preventive strategies used by them in a cross-sectional, self-reported multicentre questionnaire-based study.

2.1. Study design and settings

The second study was a Hungarian, multicentre, questionnaire based cross sectional study, carried out between February and August 2021. The collaborating centres were tertiary IBD referrals from the Semmelweis University, University of Pécs and University of Szeged, furthermore, the questionnaire was sent to the Hungarian Crohn's and Colitis Association. The questionnaire was approved by the president of the HSG and was sent out via e-mail to the centres. The reporting of this study conforms to the STROBE statement. (60)

2.2. Participants, data collection, variables and outcomes

The inclusion criteria were adult patients (≥ 18 years) on biological treatment. Patients were enrolled consecutively and were reached out via e-mail or they could fill in the

questionnaire in person to reduce potential selection bias, as the access to the internet among the elderly is limited.

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

The primary outcome was the prevalence of SARS-CoV-2 infection among IBD patients on different biological treatment, while secondary outcomes were severity, hospitalisation, ICU admission. Furthermore, preventive strategies and risk factors were analysed as well.

2.3. Statistical 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, 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 immunomodulatory (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.

2.4. 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).

Study 3. To measure the level of seroconversion and persistence of specific anti-SARS-CoV-2 spike (S) antibodies following the administration of various SARS-CoV-2 vaccines among IBD patients on different types of treatments and to compare them with healthy subjects in a prospective multicentre cohort study. Furthermore, we aimed to identify predictive factors regarding ineffective serological response, and whether the serum anti-TNFα levels influence it.

3.1. Study design, settings and participants

This 3rd study was a Hungarian double-centre, prospective cohort study conducted between March 2021 and February 2022 at the University of Szeged and the Semmelweis University. The reporting of this study conforms to the STROBE statement. (60)

The inclusion criteria were adult (≥18 years) patients with IBD presented in outpatient setting. Healthy controls (HC) were involved from the H-UNCOVER randomized trial. (61) Serological test was performed before inclusion, and patients with elevated anti-SARS-CoV-2 S antibody levels were excluded. Participation was voluntary and data was collected anonymously.

Enrolled patients were divided into four groups based on their treatment, those receiving biologic therapy (BT), azathioprin monotherapy (AZA), both BT and AZA in combination (COMB), and those, who did not receive neither of these treatments.

3.2. Data source, variables and measurements

Demographic and clinical data were obtained at baseline, including sex, age at inclusion, type of IBD, ongoing treatment, disease classification according to the Montreal classification and clinical disease activity assessed by Crohn's disease activity index (CDAI) in patients with CD and partial Mayo (pMayo) score in UC. Biochemical activity was assessed by C-reactive protein (CRP). (62–64) The type of vaccine was collected and patients were divided into two subgroups, those with messenger RNA (mRNA) and those with non-mRNA vaccinations, furthermore, the serum level of anti-TNFα agents were measured at this point. Furthermore, anti-SARS-CoV-2 S antibody levels were measured at baseline (before vaccination) and 4 and 8 weeks following the second vaccination.

The anti-SARS-CoV-2 S antibody levels were measured using the Elecsys Anti-SARS-CoV-2 Spike Antibody Immunoassay® (Roche®, Basel, Switzerland), with the cut-off value set at 0,8 U/mL according to the manufacturer's protocol. The assay had a sensitivity of >99.5 % for confirming SARS-CoV-2 infection on the 14th day following polymerase chain reaction

(PCR) as per the product's label. Serum IFX (#Ridascreen IFX Monitoring®, R-Biopharm®, Darmstadt, Germany) and ADA (#Ridascreen ADM Monitoring®, R-Biopharm®, Darmstadt, Germany) concentrations were determined using the ELISA method as per the manufacturer's protocol (R-Biopharm®, Darmstadt, Germany). The sensitivity of the IFX and ADA assays was <1 ng/mL, respectively. The intra- and inter-assay coefficients of variation for both assays were <15 %.

3.3. Statistical analysis

Statistical analysis was performed via IBM SPSS software (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp., Armonk, NY, USA). Normality was tested using visual interpretations. Descriptive statistics were interpreted as mean ± standard deviation of the mean (SD) for continuous variables and count + percentages for categorical variables. After checking assumptions, the Welch test or Mann–Whitney test and Kruskal–Wallis test were applied to compare groups described with continuous variables. Significance values had been adjusted using the Bonferroni correction for multiple tests. On the other hand, groups described with categorical variables were compared using the chi-squared test and Fisher's exact test. A p value of < 0.05 indicated statistical significance. To reduce bias, propensity score matching (using age, sex, and type of vaccine as variables) was used to select HC patients. To examine predictive factors associated with serological response, linear regression models were constructed using age, BT, vaccine type, disease type, concomitant corticosteroid treatment, disease duration, extended disease, and clinical and biochemical activities as variables. Linear regression models were constructed to assess the relationship between anti-TNF drug levels and serological response. To measure serological persistence, the Welch test was used based on ln + 1 values of anti-SARS-CoV-2 S antibody levels.

3.4. Ethical approval

The study was approved by the National Institute of Pharmacy and Nutrition according to the Scientific Research Ethics Committee of the Hungarian Medical Research Council's proposal (Registration No. ETT TUKEB IV/861-1/2021/ EKU) and by the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged (approval No.: RKEB 4937).

RESULTS

1.1. Data of participant centres

In the first study, a total of 312 questionnaires were filled, 120 from Hungary, and 192 internationally, predominantly from Europe (including Belgium, Canada, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Romania, Slovakia, Slovenia, Switzerland, and United Arabian Emirates). Fifty-four questionnaires (17.3 %) were sent from high-risk, 81 from medium-risk (26 %) and 177 from low-risk (56.7 %) COVID-19 prevalence countries. The proportion of large, medium, and low-capacity endoscopy units were 40.7 % (N = 127), 29.5 % (N = 92) and 29.8 % (N = 93), respectively. **(Table 1.)**

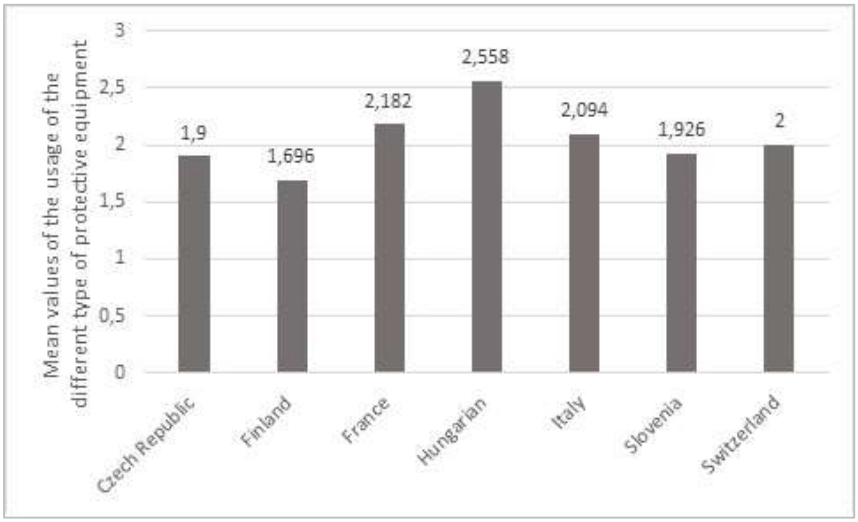
Country	Questionnaires filled	COVID-19 prevalence
Belgium	2 (0.6 %)	**High**
Canada	2 (0.6 %)	**Medium**
Croatia	12 (3.8 %)	**Medium**
Czech Republic	20 (6.4 %)	**Medium**
Finland	23 (7.4 %)	**Low**
France	22 (7.1 %)	**High**
Germany	2 (0.6 %)	**Medium**
Hungary	120 (38.5 %)	**Low**
Israel	7 (2.2 %)	**High**
Italy	32 (10.3 %)	**Medium**
Romania	13 (4.2 %)	**Medium**
Slovakia	7 (2.2 %)	**Low**
Slovenia	27 (8.7 %)	**Low**
Switzerland	22 (7.1 %)	**High**
United Arabian Emirates	1 (0.3 %)	**High**
Overall	**312**	

1. Table The distribution of responses among countries. COVID-19 prevalence (cases per one million people, since the outbreak until 1 September) is classified to low- (0-2000 cases/million), medium- (2000-5000 cases/million), and high-risk (>5000 cases/million) countries.

1.2. Preliminary trainings, usage of the appropriate protective equipment and infection prevention and control strategies

In total, 84.9 % of the gastroenterologists claimed to have read the ESGE statement, while only 32.1 % reported to have attended or participated in any further, advanced training at their workplace on the management of the endoscopy lab during the pandemic. No difference was observed regarding the participation rate between Hungary and other countries ($p = 0.701$).

Furthermore, no significant difference was found between countries (with at least 19 filled questionnaires) in terms of preliminary trainings ($p = 0.531$). Nevertheless, the numbers of usage of the necessary protective equipment [FFP2 (N95)/FFP3 (N99), protective eyewear, double gloves] used during the examination of a high-risk patient differed depending on the country ($p < 0.001$). Therefore, post-hoc analysis comparing each country in terms of protective equipment was performed. Based on our data, Hungarian gastroenterologists significantly used the most of the different types of necessary clothing **(Figure 1 and Table 2).**



1. Figure Usage of available necessary protective equipment (FFP2/3, protective eyewear, double gloves) in endoscopic labs. 1 point when only one was used, 2 when two of them, and 3 when all of them. (Mean values based on countries) ($p < 0.001$)

	Czech Republic	**Finland**	**France**	**Hungary**	**Italy**	**Slovenia**
Finland	0.999	-	0.494	**<0.001**	0.7503	0.999
France	0.999	0.494	-	0.494	0.999	0.999
Hungary	**0.0065**	**<0.001**	0.494	-	**0.03547**	**0.00199**
Italy	0.999	0.7503	0.999	**0.03547**	-	0.999
Slovenia	0.999	0.999	0.999	**0.00199**	0.999	-
Switzerland	0.999	0.999	0.999	**0.02733**	0.999	0.999

2. Table Post-hoc analysis of the usage of necessary protective equipment when examining high-risk, or COVID-19 positive patients between countries.

The preliminary training rates provided by institutes was independent of the COVID-19 rate of the particular countries ($p = 0.483$), in addition, it was also independent of the capacity of the endoscopy units ($p = 0.402$).

Overall, 72.1 % of the participants claimed to have enough protective equipment. Based on our results, there is a significant correlation between the COVID-19 infection rate of a country and the usage of the protective equipment in accordance with the ESGE statement (i.e., when a gastroenterologist wears all the necessary gear during an endoscopy of a high-risk or SARS-CoV-2 positive patient; $p < 0.001$). **(Table 2.)** FFP2 (N95) or FFP3 (N99) masks are provided in 83.0 % of the labs, protective eyewear in 69.2 %, plexiglass face-shield in 63.5 %, double gloves in 69.9 %, while 22.1 % of the respondents still use a surgical mask during an examination of a SARS-CoV-2 positive or high-risk patient **(Figure 2)**.

A negative pressure room was available in 10.6 % of the endoscopy units. Based on our results, adequate ventilation and/or air purification was provided in 80.1 % of the cases by natural ventilation through opened windows (50.6 %), ventilation on the outside (9.3 %) or by air filter (19.9 %).

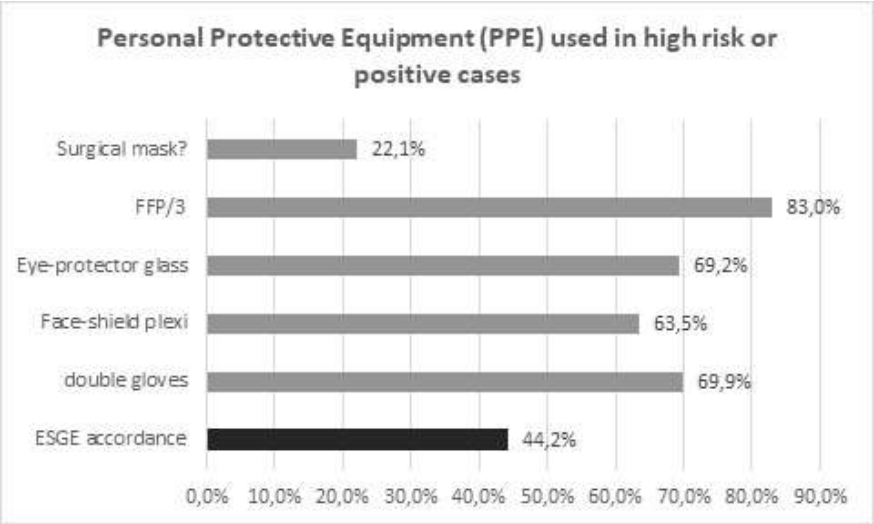
1.3. The effect of the COVID-19 pandemic on the endoscopic workflow

A total of 99.4 % of the gastroenterologists claimed that the COVID-19 pandemic had an impact on the operation of the healthcare system and their endoscopy units. In 52.6 % of the endoscopy units (N = 164) at least one endoscopist had to discontinue the work due to any risk factor (age over 65 years, chronic disease, for example), while 40.6 % reported that the reduced staff did not affect the workflow. In addition, more than 40 % of the doctors ceased the work in 10.3 % of the endoscopy units (N = 32); 63.8 % of the endoscopy labs at least halved their endoscopic capacity; moreover, in 37.5 % of the labs the reduction exceeded 75 %. Colonoscopy was reduced in 83 % of the cases, and gastroscopic examinations were diminished to a slightly greater extent (86.2 %), while ERCP and endoscopic ultrasound (EUS) was reduced in a lower proportion (63.5 % and 61.9 %). A possible explanation is that ERCP and EUS are performed in fewer endoscopy labs.

1.4. Indication of endoscopic procedures in endoscopy units compared to ESGE and ESGENA guidelines

A total of 91.7 % of the respondents claimed that they perform patients' risk stratification prior to the examination. Endoscopists considered that the five most important examinations are the following in a low-risk patient: lower/upper GI bleeding with hemodynamic instability (93.9 %), ERCP in obstructive jaundice (91.0 %), foreign body in the oesophagus (89.7 %), ERCP in acute biliary pancreatitis (79.2 %), and iron deficiency anaemia with hemodynamic instability (78.8 %), which correlates well with the ESGE recommendation. Based on our results it seems to influence the indications of the necessary examinations

performed, but still the five most important indications remained unchanged: lower/upper GI bleeding with hemodynamic instability (95.2 %), ERCP in obstructive jaundice (69.6 %), foreign body in the oesophagus (76.9 %), ERCP in acute biliary pancreatitis (49.4 %), and iron deficiency anaemia with hemodynamic instability (32.1 %). Still, more than 20 % of the responders stated that they would perform endoscopy in high-risk or SARS-CoV-2 positive patients in the case of lower/upper GI bleeding without hemodynamic instability (28.5 %), endoscopically confirmed malignant adenoma (27.6 %), and dysphagia (24.0 %). Only 19.9 % declared that they would perform colonoscopy in severe flare-ups of therapy-refractory inflammatory bowel disease, which is included in the ESGE statement, due to potentially permanent health damage.



2. Figure Personal Protective Equipment (PPE) used in high risk or positive cases

1.5. Endoscopists' perspective on risk of infection

A total of 85.3 % of the responding endoscopists think that the endoscopy staff is at higher risk, but there is no clear consensus among participants which procedure poses the highest risk. Most of them (46.5 %) claimed that gastroscopy carries the highest risk, while 27.9 % assigned ERCP to be the most hazardous. Overall, 26.6 % consider that each examination poses the staff the same level of risk, while nearly everyone agreed (except 0.6 %) that colonoscopy is not the most hazardous procedure.

2.1. Participants, demographic and clinical data, COVID-19 prevalence, hospitalization and ICU rate

In this second study, the questionnaire was sent to 607 patients receiving biologic therapy, and 472 of them (77.8 %; male/female ratio: 39.2 %/60.8 %, UC/CD ratio: 34.5 %/65.5 %) filled out the 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, therefore, approximately almost twice as many IBD patients on biological treatments were infected compared to the Hungarian general population (8.5 %) until the end of the study period (August 8th 2021). In total, 5 patients (6.3 %) were hospitalized. No patients were admitted to ICU and no one needed invasive ventilation. No patients were admitted to ICU and no one needed invasive ventilation.

2.2. Biologic therapies on the prevalence of COVID-19 infections and disease course

Most of the patients (67.2 %) received anti-TNF agents (IFX 28.0 % or ADA 39.2 %). In total, 17.6 % of patients were on VDZ, 11.2 % on ustekinumab (UST), and 4.0 % on tofacitinib therapy **(Table 3).** 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, no difference was observed in the prevalence of the infection between biological therapies ($p = 0.349$). Furthermore, no significant difference was detected between treatments regarding the general condition measured on a 1 to 5 self-assessment scoring scale ($p = 0.094$). No additional differences were observed regarding the different biologic treatments **(Table 4)**.

2.3. Conventional therapy

38 patients were administered budesonide therapy (8.1 %), and 25 patients (5.3 %) methylprednisolone therapy. Based on our cohort, neither methylprednisolone ($p = 0.498$) nor budesonide ($p = 0.482$) did not elevate the prevalence of the infection.

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**).

2.4. Risk factors and preventive strategies

Male IBD patients were exposed to a higher risk acquiring SARS-CoV-2 infection (prevalence among males 22.7 % / females 15.3 %; $p = 0.008$). 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 regularly. In our cohort, regular smoking did not elevate the infection rate ($p = 0.09$) (Table 4).

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 (1: good, 5: very poor) self-assessment scoring scale (mean UC score was 3.6 and CD score was 2.8; p = 0.003). 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.

Number of patients (n)	472
Sex	
M (n; %)	185 (39.2 %)
F (n; %)	287 (60.8 %)
Age (mean ± SD)	38.7 yrs ± 11.8 yrs
>65 yrs (n; %)	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 %)
Avoiding public places (n; %)	245 (51.9 %)
Missing from job (n; %)	75 (15.9 %)
Biologic treatment	
IFX (n; %)	132 (28.0 %)
ADA (n; %)	185 (39.2 %)
VDZ (n; %)	83 (17.6 %)
UST (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; %)	
No (n; %)	137 (29.0 %)
	33 (7.0 %)

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

Abbreviations: ADA: adalimumab; CD: Crohn's disease; COVID-19: coronavirus disease 2019; F: female, ICU: intensive care unit; IFX: infliximab; M: male; n: number of elements, UC: ulcerative colitis; UST: ustekinumab; VDZ: vedolizumab

Nearly all of the participants (97.2 %) wore their mask regularly, and it seemed to be one of the most effective preventive 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-related reasons (e.g., chronic disease or elderly age) **(Table 4).** 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 4 and 5)**. 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 5).**

		COVID-19 negative (N=392)	**COVID-19 positive (N=80)**	**COVID-19 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	VDZ	67	16	19.3 %	p=0.349
	UST	50	3	5.7 %	
	tofacitinib	16	3	15.8 %	
	ADA	151	34	18.4 %	
	IFX	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

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

Abbreviations: ADA: Adalimumab; CD: Crohn's disease; COVID-19: coronavirus disease 2019; IFX: infliximab; n: number of patients; SD: standard deviance; UC: ulcerative colitis; UST: ustekinumab; VDZ: vedolizumab

		N (80)	%
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 %

5. Table Characteristics of the COVID-19 infection based on patients' responds

Abbreviations: IBD: inflammatory bowel disease; ICU: intensive care unit; LMWH: low molecular weight heparin; n: number of patients

2.5. Patients' perspective on the COVID-19 pandemic

In total, 262 patients (55.5 %) claimed that the SARS-CoV-2 was a serious, life-threatening disease, while 109 patients (23.1 %) claimed that like an influenza virus, and further 99 patients (21.0 %) said that it was far less serious than it was dealt with. 2 patients (0.4 %) denied the existence of the 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.

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 more than 3 patients got the infection in their family, and 16.3 % declared that more than 3 patients at their workplace **(Table 5)**.

2.6. COVID-19 symptoms and the impact of the infection on IBD disease course

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 %).

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 (either dosage and type) 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 ($p = 0.004$). Flare-ups were relatively frequent in our cohort following the infection, as nearly half of the patients (46.25 %) claimed to have an increased stool number per day.

3.1. Baseline characteristics

In the third study we included 199 IBD patients (male/female ratio 95/104, mean age 40.9 ± 12.72 years). More patients had CD than UC (n = 127, 63.8 % vs. n = 72, 36.2 %). Moreover, propensity score matching from a database including 105 patients was used to select 77 HCs. HCs were older than IBD patients (50.3 ± 12.36 vs. 40.94 ± 12.72 years; $p < 0.001$). Most of the patients received mRNA-type vaccines (n = 153, 76.9 %), whereas 46 patients (23.1 %) received non-mRNA vaccines. Healthy control (HC) participants received mRNA-type vaccines. Baseline demographic data are shown in **Tables 6 and 7.**

	IBD (n = 199)	HC (n = 77)
age, mean (± SD)	40.9 (± 12.72)	50.3 (± 12.36)
gender, male N (%)	95 (47.7 %)	21 (27.3 %)
vaccine type N (%)		
mRNA	153 (76.9 %)	77 (100 %)
Pfizer	120 (78.4 %)	77 (100 %)
Moderna	33 (21.6 %)	0 (0 %)
non-mRNA	46 (23.1 %)	0 (0 %)
Astra Zeneca	23 (50.0 %)	0 (0 %)
Sputnik V	11 (23.9 %)	0 (0 %)
Janssen	1 (2.2 %)	0 (0 %)
Sinopharm	11 (23.9 %)	0 (0 %)

6. Table Baseline demographic data of IBD patients

Abbreviations: HC: healthy control; IBD: inflammatory bowel disease; mRNA: messenger ribonucleotide acid; N: number of subjects; SD: standard deviation of mean

	IBD (n = 199)
Disease type, CD N (%)	127 (63.8 %)
Disease duration, years, median (IQR)	12 (6-18)
Disease location*, N (%)	
Ileum	37 (29.1 %)
Colon	40 (31.5 %)
Ileocolic	49 (38.6 %)
Upper GI involvement	4 (2.5 %)
Disease behavior*, N (%)	
Inflammatory disease	62 (48.8 %)
Stricturing disease	25 (19.7 %)
Penetrating disease	40 (31.5 %)
Age classification*, N (%)	
<16 years	9 (7.9 %)
17-39	82 (64.6 %)
40+	36 (28.3 %)
Disease extension*, N (%)	
E1 proctitis	9 (12.5 %)
E2 distal colitis	29 (40.28 %)
E3 pancolitis	34 (47.22 %)
Biological therapy group N (%)	99 (49.7 %)
IFX	36 (36.4 %)
ADA	32 (32.3 %)
VDZ	7 (7.1 %)
UST	14 (14.1 %)
tofacitinib	10 (10.10 %)
Azathioprine group N (%)	23 (11.6 %)
Combined group N (%)	44 (22.1 %)
None group N (%)	33 (16.6 %)
Disease activity mean (± SD)	
CDAI	85.66 (58.803)
pMayo	1.27 (1.127)
CRP	6.371 (13.336)

7. Table Baseline clinical data of IBD patients

Abbreviations: CD: Crohn's disease, CDAI: Crohn's disease activity index, CRP: C-reactive protein, IQR: interquartile range, mRNA: messenger ribonucleotide acid, N: number of subjects, SD: standard deviation of mean

*Assessed by Montreal classification

In total, 63.8 % of the patients had CD, with most cases having ileocolonic localization and inflammatory phenotype (38.6 % and 48.8 %, respectively). Almost half of the UC patients had pancolitis (47.22 %). Moreover, 49.7 % of the patients were in the biological therapy group (BT), whereas more than two third were on anti-TNF therapy (68.7 %). In total, 11.6 % of the patients received azathioprine as monotherapy (AZA group), 22.1 % received it in combination with biological agents (COMB group), and 16.6 % received neither biologics nor azathioprine (NONE group). Based on the clinical activity indexes, most of the CD patients were in clinical remission (mean CDAI 85.66 ± 58.8), whereas UC patients showed remission to mild disease activity (mean pMayo 1.27 ± 1.3) **(Table 7.).**

3.2. Serological response to vaccination across different groups

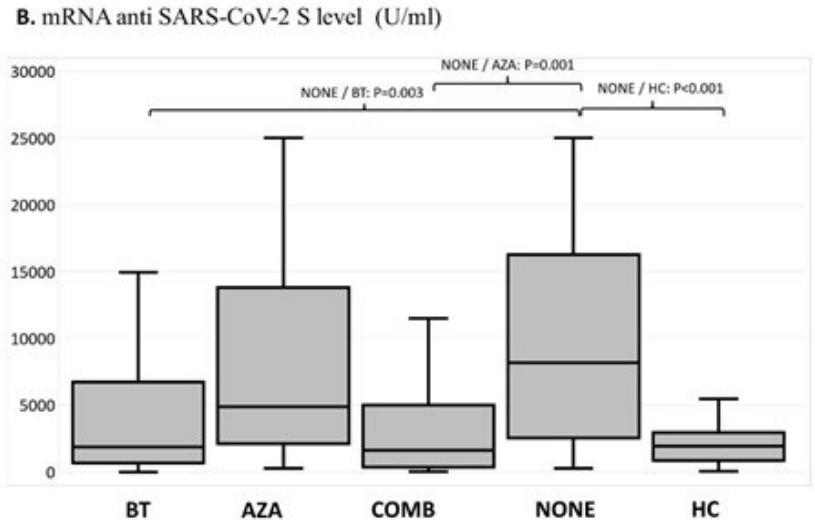
Following all-type and mRNA vaccinations, anti-SARS-CoV-2 S antibody levels were significantly higher in the NONE group ($p < 0.001$); however, no significant difference between the groups was observed among cases receiving non-mRNA vaccination ($p = 0.447$). Further details are available in **Table 8**.

Anti-SARS-CoV-2 S antibody titers in patients showed a decreasing trend in the following order of treatment: NONE, AZA, HC, BT and COMB (mean values of mRNA vaccination subgroup: NONE group: 8179 U/mL, AZA group: 4880 U/mL, HC group: 1931 U/mL, BT group: 1861 U/mL, COMB: 1624.5 U/mL; $p < 0.001$). Anti-SARS-CoV-2 S antibody levels were significantly higher in the NONE group compared to the BT group ($p = 0.003$), COMB ($p < 0.001$) and HC ($p < 0.001$). No other significant differences were observed during comparisons. **Table 8** and **Figure 3.** provide further data further data regarding the serological response to vaccination.

	BT group (n=99)	AZA group (n=23)	COMB group (n=44)	NONE group (n=33)	HC group (n=77)	p value
age, mean (± SD)	43.3 (11.80)	40.7 (15.12)	35.7 (9.43)	41.0 (15.63)	50.3 (12.36)	<0.001
mRNA vaccine N (%)	73 (73.7 %)	17 (73.9 %)	34 (77.3 %)	29 (87.9 %)	66 (85.7 %)	0.214
non-mRNA vaccine N (%)	26 (26.3 %)	6 (26.1 %)	10 (22.7 %)	4 (12.1 %)	11 (14.3 %)	
anti SARS-CoV-2 S level (U/ml)	1147 (302-4678)	3381 (251-7988)	976.5 (251-3937)	6122 (2334 - 13808)	1629 (588-2815)	<0.001
mRNA anti SARS-CoV-2 S level (U/ml)	1861 (666-6617)	4880 (2767-13500)	1624.5 (384-4750)	8179 (2765 - 14471)	1931 (868-2934)	<0.001
non-mRNA anti SARS-CoV-2 S level (U/ml)	175 (38.4-1009)	73.3 (1.8-3354)	230.1 (39.8-533.5)	1562.8 (298.8 – 3400.5)	-	0.447

8. Table Serological response in different groups.

Abbreviations: AZA: azathioprine, BT: biological therapy, COMB: biological therapy and azathioprine combination, HC: healthy control, mRNA- messenger ribonucleotide acid, n: number of subjects, SD: standard deviation of mean



3. Figure Comparison of anti-SARS-CoV-2 S antibody levels following mRNA vaccinations between groups.

Anti-SARS-CoV-2 S antibody levels of the NONE group were significantly higher compared to the BT ($p = 0.003$), COMB ($p < 0.001$) and HC groups ($p < 0.001$). No significant difference was observed between the NONE and AZA groups ($p = 0.99$).

mRNA vaccination ($p < 0.05$) promoted better serological compared to non-mRNA vaccination ($p = 0.571$) in all cases except the VDZ treatment group.

According to our model, mRNA vaccines were associated with higher serological response ($B = -0.523$; $p < 0.001$). In addition, age had a negative impact on anti-SARS-CoV-2 S antibody levels ($B = -0.169$; $p = 0.014$), and biological treatment was associated with lower serological response ($B = -0.163$; $p = 0.016$). Clinical and biochemical (CRP and lymphocyte count) activities and disease type did not influence anti-SARS-CoV-2 S antibody levels according to the same model. Concomitant corticosteroid usage, disease duration and disease extent had no significant impact on serological response ($B = -0.130$, $p = 0.074$; $B = -0.102$, $p = 0.205$; $B = 0.017$, $p = 0.813$). Coupling data are shown in **Tables 8-9**. Model details with selected variables are available in **Table 10**.

	mRNA (n = 219)	non-mRNA (n = 57)	p value
All subjects	2540 (758-5822)	188 (40.4-772)	<0.001
BT group	1861 (666-6617)	175 (38.4-1009)	<0.001
IFX (n = 36)	1147 (386-3839)	198.5 (39.8-772.0)	<0.001
ADA (n = 32)	1556 (523-4108)	209.1 (124.8 - 251.0)	<0.001
VDZ (n = 7)	3207 (650.5-7764)	2167.5 (835.25-5332)	0.571
UST (n = 14)	10328 (8359.5-20488.5)	102.7 (22.84 - 3533)	0.005
Tofacitinib (n = 10)	1339.5 (747-3018)	113 (20.8 - 174)	<0.001
AZA group (n = 23)	4880 (2767-13500)	73.30 (1.8-3354)	0.008
COMB group (n = 44)	1624.5 (384-4750)	230.1 (39.8-533.5)	0.001
NONE group (n = 33)	8179 (2765-14471)	1562.8 (298.8-3400.5)	0.027
HC group (n = 77)	1931 (868-2934)	167 (125-358)	<0.001

9. Table Anti-SARS-CoV-2 (S) levels according to the type of the vaccine across different treatments.

Abbreviations: ADA: Adalimumab; AZA: azathioprine, BT: biological therapy, , COMB: biological therapy and azathioprine combination, HC: healthy control, IFX: infliximab; n: number of subjects, SD: standard deviation of mean; UST: ustekinumab, VDZ: vedolizumab

	B	t	p value.	95.0 % CI for B	
(Constant)		10.362	0.000	7.586	11.164
Age	-0.169	-2.497	0.014	-0.054	-0.006
Biological treatment (0: no, 1: yes)	-0.163	-2.442	0.016	-1.623	-0.171
Vaccine category (1: mRNA; 2:non-mRNA)	-0.523	-7.729	0.000	-3.493	-2.070
ln CRP	0.112	1.643	0.103	-0.049	0.530
Disease (UC, CD)	-0.041	-0.603	0.548	-0.843	0.449
Lymphocyte count	0.111	1.617	0.108	-0.004	0.042
Clinical activity	-0.089	-1.316	0.190	-1.214	0.244

10. Table Linear regression model to assess higher serological response. Modell summary: R = 0.627, R2 = 0.393, F = 12.779, p < 0.001.

Abbreviations: B: Standardized Coefficients Beta, CD: Crohn's disease, CI: Confidence interval, CRP: C-reactive protein, UC: ulcerative colitis

3.3. Serological response and anti-TNF serum level

Given that no significant difference was observed in the type of vaccinations between the IFX and ADA-treated groups (mRNA vs. non-mRNA; p = 0.73, **Table 11**), we assessed the impact of the serum IFX and ADA levels on anti-SARS-CoV-2 S antibody titers.

	mRNA (n = 219)	non-mRNA (n= 57)	p value
IFX (n = 30)*	23	7	0.730
ADA (n = 45)*	36	9	

11. Table Ratio of patients according to type of vaccination treated with anti-TNF agents.

Abbreviations: ADA: Adalimumab, IFX: infliximab

*Number of patient to assess data

Accordingly, we found no significant correlation between serum IFX levels and serological response (B = 0.332; p = 0.078). However, higher ADA levels were associated with lower anti-SARS-CoV-2 S antibody levels (B = −0.404; p = 0.006). Data are summarized in **Tables 12 and 13.**

	B	t	p value.	95.0 % CI for B	
(Constant)		5.922	0.000	4.988	10.308
IFX level	0.332	1.829	0.078	-0.091	1.582

12. Table Linear regression model to assess serological response influence of IFX level. Model summary: n=29, R = 0.332, R2 = 0.110, F = 3.347, p < 0.078.

Abbreviations: B: Standardized Coefficients Beta, CI: Confidence interval, IFX: infliximab

	B	t	p value.	95.0 % CI for B	
(Constant)		8.162	0.000	6.754	11.196
ADA level	-0.404	-2.897	0.006	-1.664	-0.298

13. Table Linear regression model to assess serological response influence of ADA level. Model summary: n=45, R = 0.404, R2 = 0.163, F = 8.395, p < 0.001.

Abbreviations: B: Standardized Coefficients Beta, CI: Confidence interval, ADA: adalimumab

3.4. Persistence of SARS-CoV-2 S antibody levels following mRNA vaccination

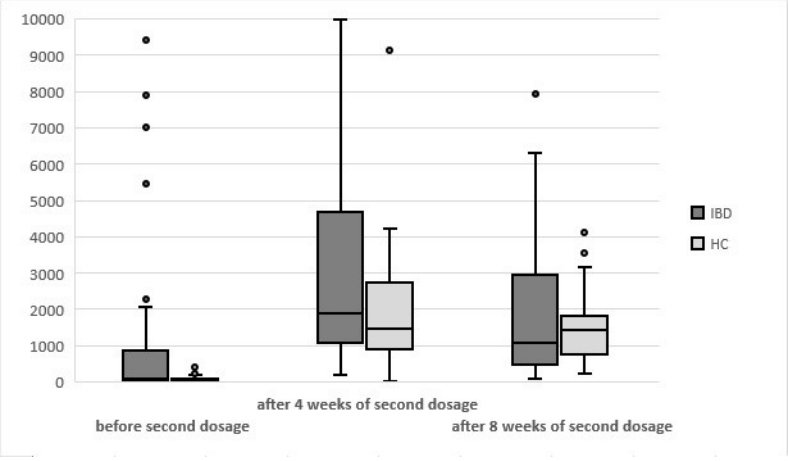
Based on the results of our single center sub-analysis, follow-up data of 100 participants were collected (IBD n = 61, HC n = 39) after mRNA vaccination. Age was statistically similar in both groups (p = 0.53). No significant difference was observed between the IBD and HC groups either before the second dose (p = 0.091) or at weeks 4 (p = 0.084) and 8 (p = 0.953) after the second dose of the vaccine. Coupling data are detailed in **Table 14 and Figure 4**.

	IBD mean (± SD) n = 61	HC mean (± SD) n = 39	p value
age, years	47.2 (12.5)	48.6 (10.4)	0.534
before second dosage	1181.84 (2939)	75.16 (90)	0.091*
after 4 weeks of second dosage	4114.79 (5515)	2278.35 (3090)	0.084*
after 8 weeks of second dosage	2860.53 (5068)	1464.54 (943)	0.953*

14. Table Anti-SARS-CoV-2 levels during follow-up among IBD and HC participants who received mRNA vaccines.

Abbreviations: HC: healthy control, SD: standard deviation of mean

*Comparisons of groups based on ln + 1 values



4. Figure Persistence of anti-SARS-CoV-2 S antibody levels during follow-up period in IBD patients after mRNA vaccination. No significant difference was observed before (p = 0.091), after 4 weeks (p = 0.084) and after 8 weeks (p = 0.953) of the second vaccine dose.

3.5. Impact of anti-SARS-CoV-2 vaccination on disease activity

Follow-up data for 81 and 66 IBD participants were analysed at baseline and 8 weeks after the second dose of anti-SARS-CoV-2 vaccination, respectively. CRP levels, a marker of biochemical activity, significantly decreased from a mean baseline level of 5.65 ± 8.34 mg/L to a mean level of 4.02 ± 3.45 mg/L at week 8 after the second vaccine dose (p = 0.038). No significant difference in clinical disease activity was observed between baseline and follow-up measurements (p = 0.65). Related data are summarized in **Table 15**.

	Baseline n = 81	after 8 weeks of second dosage n = 66	p value
CRP, mg/l, mean (± SD)	5.65 (8.34)	4.02 (3.45)	0.038
PGA, n (%)			
inactive	56 (69.1)	43 (65.2)	0.65
mild	17 (21.0)	19 (28.8)	
moderate	6 (7.4)	3 (4.5)	
severe	2 (2.5)	1 (1.5)	

15. Table Change in clinical and biochemical (CRP) activity during follow-up
Abbreviations: CRP: C-reactive protein, PGA: patient global assessment score, SD: standard deviation of mean

DISCUSSION

The COVID-19 pandemic posed challenges to the health care system. Because both health-care professionals and patients were at increased risk for the infection, doctor-patient contacts and further examinations were aimed to be reduced. Nevertheless, as data and recommendations were lacking, especially during the first phases of the pandemic, there was an uncertainty at some degree, which examinations and interventions should and ought to be omitted. This was also the case for endoscopic procedures, however, the ESGE and ESGENA guidelines were published relatively early in April 2020, though, compliance was questionable. To refine recommendations and to adapt the best to the SARS-CoV-2 pandemic collecting more data and feedbacks on the workflows of endoscopic units was not an issue. In this thesis, an attempt was made to fulfil these relevant voids in order to establish better regulations and recommendations and to overcome the issues raised by the pandemic.

Additionally, IBD patients were hypothesized to be at increased risk, especially patients on biological treatments, however, data were lacking regarding the impact of different treatments and preventive strategies on both acquiring the infection and the disease course. Furthermore, following the introduction of COVID-19 vaccines in the general population, both

efficacy and safety concerns were uncertain, as clinical trials did not include immunosuppressed patients. (65) Publications were somewhat contradictory; therefore, more data were essential to be collected.

In the first study, it was found, that the majority of gastroenterologists made certain efforts to apply changes in their laboratories, and intended to read, or be informed about the recommendations. However, it should be pointed out, that only a few of the responders participated in preliminary training. Although a lot of gastroenterologists had to leave the labs, the workflow did not seem to be affected that much, based on the responds. This can be explained by the decreased number of examinations performed since the outbreak of the pandemic.

A great variability was observed among gastroenterologists regarding the election of indications for endoscopic procedures and the protective equipment among countries. However, the most urgent indications for an endoscopic examination/ intervention coincided with the ESGE and ESGENA statement regarding acute life-threatening gastrointestinal diseases. In contrast, the accordance was lower regarding clinical conditions with potential permanent health damage, in case of postponed endoscopy. A high proportion reported, that endoscopic examination would be performed in case of potential malignancy in patients with a low risk of SARS-CoV-2 infection (including also a change in bowel habits without hematochezia, as more than 15 % of the participants would perform endoscopy in this scenario), and more than one-third of the endoscopists would continue the Faecal Occult Blood Test-based Colorectal Cancer screening programme. According to our questionnaire, the participants claimed that upper gastrointestinal endoscopy (including ERCP) poses a much higher risk than colonoscopy; nevertheless, as we mentioned above, the indications were principally acute life-threatening or potential health damage-causing conditions. Selection of the protective equipment varied depending on the patient's risk-status. During an examination of a low-risk patient, surgical mask, gloves, disposable hairnet, protective eyewear and waterproof disposable gowns are sufficient during an examination, but in case of a high-risk or SARS-CoV-2 positive patient, the necessary equipment contains FFP-2/3 mask, two pairs of gloves, disposable hairnet, protective eyewear and waterproof disposable gowns. (66) According to our results, the presence/usage of the necessary equipment during an examination of a high-risk patient differs between countries, and in Hungary significantly more endoscopy labs use the prescribed protective clothing. However, as participants from Hungary were overrepresented, these results should be treated with care due to potential selection bias.

Limitations of this particular study was the cross-sectional setting, and the questionnaire-based data collection, due to source of recall bias, however, we intended to decrease bias, as, participating centres were reassured that data was treated anonymously. Hungarian participants were overrepresented in our data, this could be a potential source of selection bias.

However, the questionnaire-based data collection was also a strength of this study, as participants could report real-life experiences. Furthermore, we would like to highlight, that in a novel pandemic situation, cross-sectional settings are the fastest way to achieve data and to provide feedback on them. Additionally, data was immensely lacking, and our publication was the first international study reflecting on the pandemic situation and the workflow of endoscopic units.

In the second study, we found, that almost twice as many IBD patients on biological treatments were infected with SARS-Cov-2 compared to the Hungarian general population until the end of the study period (August 8th 2021). (67) This result was contradictory with previous data, that there is no increase in the prevalence of COVID-19 infection among IBD patients and biologics did not have an impact on the increase of the infection rate. (39,41,44,68,69) It should be highlighted, that only patients on biological treatments were included in this study, additionally, due to the questionnaire-based data collection, both selection and recall bias could be present, as patients who were previously infected could have been more motivated to participate in our study. The hospitalization rate was small, and no patient was admitted to the ICU.

No difference was observed between different biological treatments on the infection rate and the course of COVID-19 infection, confirming previous data. (36) Suspending the biological treatments did not seem to be effective against the COVID-19 infection, which supports published data and recommendation, however, it neither caused flare-ups in the primary disease. Following the infection, patients reported common relapse rates, and several patients had to change the ongoing therapy due to flare-ups. (44,70) Changes were not specified by patients. It should be emphasized, that data were lacking investigating the relapse rate following SARS-CoV-2 infection. In accordance with further data, AZA did not have impact on the infection rate. (45,71) Our study confirmed, that steroid treatment did not result in worse outcomes during the infection. (72) However, it has to be highlighted that only a few patients were administered these therapies.

In accordance with previous studies, male patients were at an increased risk of acquiring the infection, consequently, they should be treated with greater precaution. (73–76) Unlike previous data, age was not an independent risk factor of the infection rate. (74,77) However, patients with IBD are generally younger, compared to the background population, so the mean age was 38.9 years in our study, and only few participants were older than 65 years. (78)

Patients with UC experienced worse disease course and general condition, but not elevated hospitalization and ICU admission rates. Compared to previous data, UC was identified as a single risk factor in the development of severe COVID-19 infection. (38,45) Our findings supported that increased disease activity tended to be associated – close to the significance level - with potential aggravation in the course of COVID-19 infection. (12,47,48,70)

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. Our study showed, that almost every participant wore the mask regularly and it still seemed to be one of the most effective protective factors decreasing the infection rate in accordance with previous data. (79,80) Additionally, wearing gloves was found to be protective as well, however, only a few amount of patients used them. The pandemic had a huge effect on the daily life of patients, as more than half of the participants responded that they did not attend to public places, or worked in home-office (or even quit their job) due to health considerations. However, these preventive strategies were ineffective in decreasing the infection rate, though, recommendations advised social distancing at some degree. (44)

Limitations of this second study were the cross-sectional setting, and the questionnaire-based data collection, resulting in both selection and recall bias. As patients who have experienced COVID-19 infection could have been more motivated participating in this study, which could have distorted the data, and patients, who got infected afterwards did not complete the questionnaire again. Furthermore, the questionnaires were based on patients' responds, consequently, no standard clinical activity indexes could be assessed. However, we aimed to reduce potential selection bias with the possibility to fill out the questionnaire in person.

Additionally, strengths of this study were that physicians could see patients' perspective and the size of the study sample in a questionnaire-based analysis. Although the cross-sectional study setting could be a limitation of the study, we would like to highlight in this particular study as well, that the cross-sectional study designs are the fastest way to collect data effectively in a novel pandemic situation. Furthermore, we could also examine subjective parameters,

which could not be retrieved from the medical databases. As data were treated anonymously, it covered the reality potentially better.

The third study focused on the serological response following anti-SARS-CoV-2 immunization, as contradictory and limited data have been published regarding immunocompromised patients. To our knowledge, our prospective cohort analysis has been the first unique study to compare different types of vaccines (mRNA and non-mRNA including inactivated virus vaccine) and biological and/or immunosuppressive treatment on serological response in a well-defined cohort. Our two-centre, prospective cohort study included 199 IBD and 77 HC participants. Based on Hungarian IBD recommendations, most patients received mRNA-type anti-SARSCoV-2 vaccines; however, to compare our findings to internationally existing data, we also analysed the non-mRNA vaccines. In accordance with clinical practice guidelines, anti-TNF therapy was the most common biological treatment among our enrolled patients. (81,82) mRNA vaccines were found to promote superior seroconversion levels than non-mRNA vaccines did among immunocompromised IBD patients, in accordance with previous data. Comparing non-mRNA vaccinations, no difference was observed between attenuated adenovirus vaccines and inactivated whole virion vaccines, according to an Indian prospective cohort study. (83) However, data were still lacking regarding non-mRNA vaccinations in IBD populations. In our cohort, ongoing biological, and/or immunomodulatory treatment resulted in lower antibody response. Higher ADA trough levels were associated with lower serological response; however, no significant difference was observed in subjects receiving IFX. The durability of anti-SARS-CoV-2 S antibody levels did not differ between the IBD and HC groups 8 weeks following the administration of mRNA vaccines. Our results suggest no causal relationship between disease flares and immunization based on clinical and biochemical parameters.

Previous studies have analysed the possible effects of biologic treatments on serological response in IBD following both infection and vaccination, and found attenuated seroprevalence and seroconversion among patients on IFX and especially on combination therapy, compared to VDZ. (84) A retrospective study in the same population showed that the negative effects of ADA on serological response were similar to those of IFX. In cases with undetectable TNF inhibitor levels, the seropositivity rate was comparable to VDZ. (85) After recruiting consecutive IBD patients, the CLARITY study investigated the immunogenicity to BNT162b2 and ChAdOx1 nCoV-19, and found, that IFX therapy promoted a lower serologic response not only after infection but also after a single vaccine dose, especially in those receiving

combination treatment, compared to VDZ monotherapy. This effect was blunted after the second dose of the vaccine. (84)

A prospective multicentre study conducted in Israel found that although two doses of BNT162b2 seroconverted all IBD patients, TNF inhibitor therapy resulted in significantly lower anti-SARSCoV-2 S Ig antibody levels. Older age also independently showed a negative association with anti-SARS-CoV-2 S Ig antibody levels. (86)

In our cohort, both biological treatment and combined therapy were associated with lower serological response compared to AZA and patients without ongoing treatment, however significant differences were not proved during VDZ and UST treatment. Although, the low number of patients in VDZ/UST groups should be enhanced during interpretation of the results. The difference between ongoing treatments was more prominent in participants receiving mRNA-type vaccines. Our post hoc analysis showed similarity of serological response between UST/VDZ and the NONE group which highlights the dissimilarity of different biological agents. However, interpretation of data is limited by low sample sizes in each treatment groups. Notably, the serological response was higher in the NONE group compared to the HC group. A possible explanation for this phenomenon could be the significantly higher age in the HC group, in accordance with the study mentioned above, higlighting the potential role of age regarding serological response. (86)

The VARIATON study investigated the effects of mRNA (BNT162b2, CX-024414) and vector (ChAdOx1 nCoV-19, Ad26.CoV2.S) vaccines in IBD patients. (87) SARS-CoV-2 S antibody levels were significantly higher following two doses of mRNA vaccines compared to vector vaccines. Furthermore, IBD itself proved to have a negative impact on anti-spike protein IgG levels. Anti-TNFα, anti-IL 12/23 therapy, and Janus kinase (JAK) inhibitors were associated with significantly lower median SARS-CoV-2 S levels compared to patients receiving 5-ASA, immunomodulators, or steroids. Older age and TNFα inhibitory therapy were independent negative confounding factors in the IBD group. No significant difference was observed between TNF inhibitor monotherapy and combination therapy. (87)

Results from a single tertiary IBD centre that compared the effects of two doses of mRNA BNT162b2 (Comirnaty; Pfizer-BioNTech, USA), mRNA CX-024414 (Spikevax; Moderna, Cambridge, Massachusetts, USA), or vector ChAdOx1 nCoV-19 (Vaxzevria; AstraZeneca, UK) vaccines on serological response showed that neither biological monotherapy (IFX, ADA, VDZ, UST) nor trough levels were associated with lower SARS-CoV-2 IgG antibody levels. In contrast, variables, such as older age and the combination of

biological and immunosuppressive treatment were identified as attenuating factors on seroprevalence. The lowest antibody levels were found in patients receiving TNFα inhibitor and concomitant immunosuppressive treatment (azathioprine/methotrexate). The vector vaccine Vaxzevria was unable to promote seroconversion in 2.2 % of IBD patients and induced significantly lower levels of antibodies either in IBD patients or the control group compared to mRNA vaccines. (88)

Our data showed that mRNA vaccines were superior to non-mRNA types in all groups, excluding VDZ treatment. However, the low number of patients receiving VDZ precluded us from drawing significant conclusions. In line with existing international data, our study confirmed the negative effects of older age, combined biological treatment and non-mRNA vaccines on serological response. (85, 86) Based on our results, we therefore highlight the importance of treatment over disease activity on antibody response.

A study by Edelman–Klapper revealed no correlation between anti-TNF drug levels and serological response. (86) Our data showed that higher ADA serum levels had a negative effect on anti-SARS-CoV-2 S antibody levels; however, no correlation was observed in subjects who received IFX treatment. Our possible hypothesis for this discordance is that the dosage regimen during ADA therapy provides relatively stable drug levels in contrast to IFX, which promotes alternating serum levels. A limitation of the study protocol is that standardizing the time of the sampling of the drug levels was not possible due to the real-world setting.

It was found, that anti-SARSCoV-2 S antibody levels persisted for up to 8 weeks after the second dose of the mRNA vaccine. We found no difference between IBD and HC participants during the follow-up period, in contrast to the data published in a few existing studies. (84, 87) Our analysis revealed that vaccination had no significant impact on clinical disease activity based on PGA. Although a statically significant decrease in biochemical activity was observed during follow-up, no clinically significant decrease was noted. A multicentre study by Lev-Tzion et al. showed similar exacerbation rates after vaccination between vaccinated and non-vaccinated IBD patients. (91)

The strength of this study was the two-centre, prospective setting with a relatively high number of enrolled patients. Only a few studies have examined the possible correlation between anti-TNFα drug levels and serological response. Multivariable analysis has allowed us to review multiple connections. Furthermore, during the study period, Hungary was characterized as one of the countries with highest COVID-19 incidence rates both in Europe and the world, resulting in ingenuous and objective patient selection and enrolment. (92) Notably, only mRNA

vaccinations were available in most of the European countries during this period; thus, studies only reported on such vaccines. The pandemic situation overruled some viewpoints on scientific methodology, resulting in certain limitations in this study. Testing of serological and therapeutic drug levels in anti-TNFα treated patients was performed at the day of the first vaccination according to the Hungarian immunization protocol, regardless of the treatment cycle. Separated analysis of VDZ, UST, and TOFA groups were not performed due to the low number of patients and potentially misleading results. Biochemical activity was measured by CRP due to its excessive availability; however, faecal calprotectin could provide more accurate data. Potential selection bias was that almost three times more patients received mRNA vaccines compared to those who received non-mRNA vaccines. The proportion of patients enrolled in the study subgroups differed, reflecting the financial protocols in Hungary.

CONCLUSIONS

In the first study, we found that the COVID-19 pandemic had an effect on the endoscopic units at some degree, as half of the participants claimed to work with decreased number of endoscopists, however, due to the reduced number of examinations it did not affect the workflow in each cases. Most of the participants have read the ESGE and ESGENA guidelines, however, there was still a variability in applying them, regarding the adequate indications of endoscopic procedures following risk stratification of SARS-CoV-2. A variability was presence also in the usage/presence of protective equipment, as participants in high-risk countries are more likely to wear the necessary ones. Although there was a difference between Hungary and other countries regarding the personal protective equipment, due to the variability in the number of participating centres from each country, further investigations could clarify this result. Due to the alterations in daily practice during the pandemic, we would suggest keeping more training, and occasional forums, in order to get relevant feedback from the endoscopists, as regulations should reflect real-life issues. In our second study we found that the prevalence of infection was approximately 2 times higher in our cohort compared to the background population. However, 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. Additionally, regular mask and glove wearing seemed were the most effective form of prevention against the infection. The results show that male and UC patients seemed to have poorer condition during the infection, but not worse hospitalization rates. However, we suggest that poorer general condition and flare-ups in IBD may mean higher risk for COVID-19 infected patients than biologic treatments. However, we suggest that poorer general condition and flare-ups in IBD may mean higher risk for COVID-19 infected patients than biologic treatments. To sum up, we aimed at answering relevant questions in IBD patient care; nonetheless, further questions emerged to clarify during the study. Based on our third, double-centre, prospective cohort study, anti-SARS-CoV-2 vaccination has considerable effectiveness in IBD patients, with mRNA-type vaccines being superior to non-mRNA vaccines. The negative impact of combined biological treatment, especially with high ADA drug levels, on serological response to vaccination should be considered with adjustment of vaccination to ADA trough level. Mid-term durability of vaccination is encouraging; however, more data are needed to expand our existing data in the field of this issue.

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