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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 FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS:

I. **Resál, T.,** Matuz, M., Keresztes, C., Bacsur, P., Szántó, K., Sánta, A., Rutka, M., Kolarovszki-Erdei, D., Bor, R., Fábián, A., Szepes, Z., Miheller, P., Sarlós, P., Zacháry, A., Farkas, K., & Molnár, T. (2023). Conception and reality: Outcome of SARS-CoV-2 infection and vaccination among Hungarian IBD patients on biologic treatments. Vaccine: X, 13, 100253. *D1, IF: 3.8*

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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

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. Patients with IBD are considered immunocompromised, and more susceptible to infections, in addition, 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.

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. In addition, the prevalence of pneumonia is also elevated in IBD. 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, tumor necrosis factor alpha (TNFα) inhibitors and combinational treatment to different extent.

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, and is predominantly a respiratory pathogen causing mostly pneumonia, severe respiratory distress syndrome and pulmonary embolism. The prevalence and incidence rates, the hospitalization, intensive care unit (ICU) admission and mortality rates varied, however, almost 7 million patients died due to confirmed COVID-19 infection reported by the WHO until 20th October 2023.

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. 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. Consequently, endoscopies procedures should be concerned

as risk factors regarding the transmission of the virus, e.g., via faecal droplets from patients, gagging and coughing. The guidelines published by the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) states appropriate indications and personnel protection during pandemic based on patient stratification to a low-, and a high-risk category. 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. However, data were lacking regarding the compliance with recommendations and the efficacy of them in a real-life setting.

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, though, data from the early phase of the pandemic were contradictory with these hypotheses. An international cohort study found that older age and comorbidities were identified as risk factors in IBD, furthermore, systemic corticosteroid use were also identified as deteriorating factors regarding the course of the infection. 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. Further studies predominantly confirmed, that IBD did not increase the infection rate and the risk of developing severe COVID-19 infection. The risk of the infection did not differ between CD and UC, however, UC patients were at greater risk regarding developing severe COVID-19. 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. Based on the SECURE-IBD trial, thiopurines were associated with poor outcomes, however, a further meta-analysis conducted by Tripathi et al. 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. 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.

Vaccinations were considered playing a key role in overcoming the COVID-19 pandemic, however, clinical trials excluded immunosuppressed patients. 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. Furthermore, IFX significantly attenuated seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity after SARS-CoV-2 infection, especially in the combination with thiopurines. 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 %.

In Hungary the population-based vaccination program was introduced relatively early, with adenovirus vector vaccines, inactivated virus vaccine and messenger RNA (mRNA) vaccines, however, physicians promoted mRNA type vaccines. Latter meta-analysis confirmed the superiority of mRNA vaccines over adenovirus vector vaccines with a seroconversion rate of 96-98 % and 78-90 %, respectively. 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

1.1. Study design, settings, participants and variables

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):

- 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 (MGT – Magyar Gasztroenterológiai Társaság). Partially or incorrectly completed questionnaires were excluded. The reporting of this study conforms to the STROBE statement.

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.

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 MGT and was sent out via e-mail to the centres. The reporting of this study conforms to the STROBE statement. (55)

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.

This third 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 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

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. Serological test was performed before inclusion, and patients with elevated anti-SARS-CoV-2 S antibody 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), immunosuppressant monotherapy (AZA), both BT and AZA in combination (COMB), and those, who did not receive neither of these treatments (NONE).

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 Crohn's disease and partial Mayo (pMayo) score in ulcerative colitis. Biochemical activity was assessed by C-reactive protein (CRP). 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 infliximab (IFX; #Ridascreen IFX Monitoring®, R-Biopharm®, Darmstadt, Germany) and adalimumab (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 %.

1.2. Statistical analysis

In the first study, the 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.

In the second study 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 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.

In **this third study**, the 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.

1.3. Ethical approval

Ethical approvals for the above mentioned studies were obtained from the Medical Research Council – Research and Ethics Committee (TUKEB), Hungary (Appr. no: IV/4669-2/2020/EKU, IV/2678–3 /2021/EKU, IV/861-1/2021/ EKU).

RESULTS

1.1. Data of participant centres

In the first study evaluating the effect of the COVID-19 pandemic on the endoscopic units, 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.

1.2. Usage of the appropriate protective equipment and infection prevention and control strategies

No significant difference was found between countries 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 ($p<0.001$), with highest rates in Hungary. Furthermore, appropriate protective equipment was associated with the higher COVID-19 prevalence rates.

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

In total, 84.9 % of the gastroenterologists claimed to have read the ESGE statement. 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 %). 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 %).

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

In this second study assessing the prevalence and the severity of the SARS-CoV-2 infections among IBD patients on biological therapies, 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, 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.

2.2. Biologic and conventional 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. 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.

Biological therapies combined with different conventional therapies did not have an impact on the prevalence and disease course of COVID-19.

2.3. 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 and disease duration did not influence the risk ($p = 0.823$, $p = 0.586$, respectively). In our cohort, regular smoking did not elevate the infection rate ($p = 0.09$).

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.

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 ($p = 0.02$). 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.

2.4. 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, 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 this third study assessing the effectiveness and safety of the different type of vaccinations among IBD patients compared to healthy controls, we included 199 IBD patients (male/female ratio 95/104, mean age 40.9 ± 12.72 years, CD/UC: 127/72). 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.

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).

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 ($p = 0.447$).

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.

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 activities and disease type did not influence anti-SARS-CoV-2 S antibody levels. Concomitant corticosteroid usage ($p = 0.074$), disease duration ($p = 0.205$) and disease extent ($p = 0.813$) had no significant impact on serological response.

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; $p = 0.73$), we assessed the impact of the serum IFX and ADA levels on anti-SARS-CoV-2 S antibody titers.

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 ($B = -0.404$; $p = 0.006$).

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.

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 ($p = 0.65$).

DISCUSSION

The COVID-19 pandemic posed challenges to the health care system. 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. 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. 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, 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.

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). 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. It should be highlighted, that 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. Suspending the biological treatments did not seem to be effective against the COVID-19 infection. Following the infection, patients reported common relapse rates, and several patients had to change the

ongoing therapy due to flare-ups. 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. Our study confirmed, that steroid treatment did not result in worse outcomes during the infection. 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, however, age was not an independent risk factor of the infection rate. 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.

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. 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.

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. Additionally, wearing gloves was found to be protective as well, however, only a few amount of patients used them. Avoiding communities or public places were ineffective in decreasing the infection rate, though, recommendations advised social distancing at some degree.

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 all 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. 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 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. 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, highlighting the potential role of age regarding serological response.

The VARIATON study found mRNA vaccines superior to vector vaccines in IBD patients. Additionally, 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.

In accordance with the VARIATION study, 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.

Results from a single tertiary IBD centre that compared the effects of two doses of vector 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.

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. 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.

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. 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

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. 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. Furthermore, 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. 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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