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Research Article

The Frequency Of SARS-Cov-2 Infection and The Impact Of COVID-19 Vaccination on The Disease Morbidity in Polish Pediatric Patients with Inflammatory Bowel Disease Treated with Biologic Therapies

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Abstract

Background: Little is known about morbidity of COVID-19 infection in pediatric patients with inflammatory bowel diseases (IBD) treated with biologic medications. The aim of this study was to evaluate the frequency of SARS-CoV-2 infection in children with IBD who received biologic therapies. **Methods:** A prospective, observational cohort study to evaluate coronavirus disease 2019 (COVID-19) vaccination state, and its effect on the disease course among pediatric patients with IBD. The questionnaire included information concerning numbers of vaccine doses, patients' medication and disease activity. Disease flare was defined by worsening IBD symptoms and change in IBD medications. Outcomes were stratified by vaccine type and IBD medication classes. **Results:** A total of 320 children with IBD, 169 with Crohn's disease (CD)-52,8%, 150 with ulcerative colitis (UC) - 46,9%, 1 unclassified -0,3%, responded to the questionnaire concerning COVI-19 vaccination. In our cohort 141 (49,7%) patients received biologic therapy: 13 patients (9,2%) adalimumab (ADA), 54 (38,3%) infliximab (IFX), 27 (19,1%) vedolizumasb (vedo), 29 (20,6%) ustekinumab (ust), 6 - vedo + ADA (4,3%), 1 - IFX + vedo (0,7%), 11 - ust + ADA (7,8%). 32 (22,7%) patients had COVID-19 infection during biological therapy (ust 6- 4,3%, vedo 7- 5,0%, ada 2-1,4%, ifx 12- 8,5%, ust + ada 2- 1,4%, vedo + ada 3- 2,1%). Among the patients on biologic treatment suffering from COVID-19, 25 (78,1%) children had mild course of the infection, 4 moderates (12,5%), 2 severe (6,3%), and 1 unknown (3,1%). A total of 127 (39,7%) patients received at least 1 COVID-19 vaccine, and among them 8 (6,3%) patients who received 1 dose of COVID-19 vaccine got the infection during biologic therapy. In our group, 193 (60,3%) patients have not been vaccinated against COVI-19, and 24 (12,4%) suffered from the disease during biologic therapy. **Conclusions:** Unvaccinated patients get COVID-19 infection more often than vaccinated ones, and the use of biological treatment has no impact on the frequency of SARS-CoV-2 disease or its course.

Key words: Inflammatory bowel disease; COVI-19; Vaccination

Abbreviations: IBD – Inflammatory Bowel Disease**;** CD – Crohn's Disease**;** UC - Ulcerative Colitis**;** IBDU – IBD unclassified

Introduction

The COVID-19 pandemic was declared by the World Health Organization (WHO) on 11 March 2020. The most common clinical manifestations are fever, cough and dyspnoea, which may be complicated by acute respiratory distress syndrome, multi-organ failure or death. Nonetheless, digestive symptoms (diarrhoea, vomiting or abdominal pain) are described in up to 20% of patients [1].

A potential risk groups that has required special attention during the pandemic were chronic diseases, particularly the ones with impaired immune system such as inflammatory bowel diseases (IBD). Not only altered immune response that plays a key role in the pathogenesis of IBD, but also the vast majority of drugs modulating immune system function, made IBD patients a high-risk group for SARS-CoV-2 infection and severe course of this disease [2]. However, current data do not demonstrate increased risk of infection or its severity in patients with IBD in comparison to the general population, except for those on corticosteroid therapy [3]. Active disease, age, and comorbidities are proven to be risk factors for COVID-19 mortality in patients with IBD [4].

It is known that the serological response to vaccination may be lower in immunocompromised patients [5]. Although overall in IBD the response to vaccination is not lower than in general population, there are several studies showing that the response to hepatitis B or anti-pneumococcal vaccination is lower in IBD patients treated with immunosuppressants and/or biological therapy [6,7].

Therefore, the aim of this study was to evaluate the frequency of SARS-CoV-2 infection in children with IBD who received biologic therapies, and thus assess the impact of these medications on the response to vaccination.

Patients and methods

Patients

Children with confirmed diagnosis of IBD, either UC or CD.

Methods

A prospective, observational cohort study to evaluate morbidity of COVID-19 and vaccination status among paediatric patients with IBD using the questionnaire filled by the patient and his or her caregiver. The included information concerned numbers of vaccine doses, patients' medication and disease activity. Disease flare was defined by worsening IBD symptoms and change in IBD medications. Outcomes were stratified by vaccine type and IBD medication classes.

Statistical analysis

All statistics tests were performed with Statistica 12 (StatSoft, Tulusa, OK, United States). Binary and categorical variables were shown as numbers and percentages. The level of statistical significance was assessed by chi-square test or Yates corrected chi-square test. A p value of less than 0.05 wasconsidered to be statistically significant.

Results

A total of 320 children with IBD including 169 with Crohn's disease (CD)-52,8%, 150 with ulcerative colitis (UC) - 46,9%, and 1 unclassified -0,3%, responded to the questionnaire concerning COVI-19 infection and vaccination status.

Among these children, 109 (34.6%) suffered from COVID19 (60 CD - 55.0%, 48 UC - 44.0%, 1 don't know - 0.9%).

1. One hundred twenty-two (38.9%) patients were treated with biological agents:

- 25 ustekinumab - 20.5%
- 8 ustekinumab + adalimumab (ADA)- %6.6
- 1 ustekinumab + vedolizumab (VEDO) - 0.8%
- 25 on VEDO- 20.5%
- 4 on VEDO + ADA- 3.3%
- 1 on infliximab (IFX) + VEDO- 0.8%
- 46 on IFX- 37.7%
- 12 on ADA- 9.8%

2. Seventy-five (68.8%) children were treated conventionally:

- 11 treated with nutritional therapy in combination with other drugs - 14.7%
- 6 received exclusive enteral nutrition - 8.0%
- 47 -treated with 5- aminoacylate (ASA) in combination with other drugs - 62.7%
- 34 treated with 5-ASA only - 45.3%
- 8 treated with steroids in combination with other drugs - 10.7%
- 5 treated with steroids without immunosuppression - 6.7%
- 10 treated with azathioprine (AZA) in combination with other drugs - 13.3%

- 8 treated with AZA without steroids - 10.7%
- 0 of those treated with cyclosporine - 0%
- 1 of those treated with methotrexate (MTX) - 1.3%
- 1 of those treated with MTX without steroids - 1.3%

Among patients who received conventional treatment, 17-22.7% were vaccinated against COVID-19 before developing SARS-CoV-2 infection, and majority (49-65.3%) of them had a mild course of this infection. While 25-33.3% have had moderate COVID disease, and 1-1.3% a severe one.

25 – 33.3%

3. Among children receiving biologic treatment, 34 (27.9%) had SARS-CoV-2 infection:

- 7 on ustekinumab - 20.6%
- 2 on ustekinumab + ADA- 5.9%
- 0 on usteninumab + VEDO 0.0%
- 7 on VEDO - 20.6%
- 2 on VEDO + ADA - 5.9%
- 1 on IFX + VEDO- 2.9%
- 13 on IFX - 38.2%
- 2 on ADA - 5.9%

Among these patients, 8-23.5% were vaccinated against COVID-19 before developing this infection, and majority of them (27-79.4%) have had a mild SARS-CoV-2 disease. While 5-14% have undergone moderate COVID-19 infection, and 2-5.9% had a severe one.

Factor/parameter	Total cohort (N=320)
Boys	32 (56%)
Type of IBD	
CD	169 (52,8%)
UC	150 (46,9%)
IBDU	1 (0,3%)
Treatment	
biologics	122 (38.9%)
conventional drugs	75 (68.8%)
COVID-19 vaccination	
biological treatment	8-25%
conventional treatment	7-22.7%
COVID-19 infection in vaccinated patients treated with biologics:	
mild	27-79.4%)
moderate	5-14%
severe	2-5.9%
COVID-19 infection in vaccinated patients treated with conventional drugs:	
mild	45-65.3%.
moderate	25-33.3%.
severe	1-1.3%

Table 1: presents characteristics of patients included in the study.

A statistically significant difference was reported in the incidence of COVID-19 infection in patients treated conventionally compared to those treated biologically - conventionally treated patients were more likely to have COVID-19 disease, p=.04576 (Chi-square test)

In the group of patients treated biologically, vaccination had no effect on the incidence of COVID-19 infection, p=.21416 (Chi-square test)

In the group of patients treated conventionally, vaccination had an impact on the incidence of COVID-19 disease - vaccinated patients were less likely to develop SARS-CoV-2 infection, p=.00250 (Chi-square test).

There is no statistical significance in the severity of COVID-19 infection in the conventionally treated vs biologically treated group, p=.13832 (Chi-square test).

Discussion

In our study, we have demonstrated that vaccination protects against COVID-19 infection even in IBD paediatric patients treated with either immunosuppressive agents or biologics, and biological medication does not influence the response to this vaccination. A similar finding was reported by observational Dutch cohort study which showed that neither IBD nor immunosuppressants were associated with increased risks of severe COVID-19 during one-year follow-up [8].

Although in our study the COVID-19 vaccine-induced antibodies in our patients were not assessed, we did not observe that immunosuppressive or biological treatment influenced the efficiency of vaccination - vaccinated patient had SARS-CoV-2 infection less often than the ones who were not vaccinated. However, in the study by Alexander et al to evaluate COVID-19 vaccine-induced antibody and T-cell responses in immunosuppressed patients with IBD, the authors observed that a third dose of COVID-19 vaccine induced a boost in antibody binding in immunosuppressed patients with IBD, but these responses were reduced in patients treated

with biologics [9]. These findings support continued prioritisation of immunosuppressed groups for further vaccine booster dosing. However, the Spanish study to study the Serological Response (SR) and tolerability of COVID-19 vaccine in patients with IBD and its relation with the treatment and type of vaccine showed that. immunosuppressants and biologicals did not decrease SR [10]. These findings are closer to our observations.

Burke et al published consistent results with the ones we observed. The authors aimed to define the effect of targeted biologic and immunomodulator therapy on risk of COVID-19 in a multi-institutional cohort of patients with IBD, and they concluded that these medications were not associated with an increased risk of COVID-19 [11]. In their study, older age and obesity but not immunosuppressive treatment was associated with severe COVID-19 infection [10].

Finally, Singh et al. performed a systematic review and meta-analysis to evaluate risk and outcomes of coronavirus disease in patients with IBD, and they concluded that SARS-CoV-2 infection risk in these patients is comparable to the general population. Outcomes of COVID-19-positive IBD patients are worse in UC, those on steroids or 5-ASA, but outcomes are better with biological agents [12]. These are very interesting observations. In our study, we did not report any difference between IBD types in the risk of COVID-19 morbidity, and there is no clear explanation why UC and 5-ASA medications may be risk factors for SARS-CoV-2 disease. While steroids are described as a risk factor for COVID-19, it was not expected that biological drugs would be associated with better outcomes of this infection [13,14].

The advantage of our study is relatively large group of patients and pediatric cohort, since to the best of our knowledge this is the only such study performed on children with IBD. There is still luck of data in this field in this group of age.

The disadvantage of this study is the lack of determination of post-vaccination antibodies, thus making it impossible to assess the post-vaccination response depending on the medications taken.

Conclusions

Based on the outcomes from our questionnaire concerning COVID-19 morbidity and vaccination status on the large cohort of pediatric patients with IBD, we conclude that unvaccinated patients get SARS-CoV-2 infection more often than vaccinated ones, and that the use of biological treatment has no impact on the frequency of COVID-19 disease or its course.

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