Original paper

Assessment of the activity of the immune system in patients with inflammatory bowel diseases and asymptomatic COVID-19

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Abstract

Introduction: Although the phenomenon of cytokine storm is well described in patients with severe COVID-19, little is known about the role of the immune system in asymptomatic patients, especially in the group with autoimmune diseases, such as inflammatory bowel disease (IBD).

Aim: To assess the stimulation of the immune system expressed through the production of cytokines in IBD patients with asymptomatic COVID-19.

Material and methods: This is a multi-centre, prospective study in which the concentration of many cytokines (IL-1a, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL- 15, IL-17, IL-23, IFN-γ, TNF-α, TNF-β) was assessed in patients with IBD and asymptomatic SARS-CoV-2 infection diagnosed by serological tests.

Results: In the group of patients with a recent SARS-CoV-2 infection, defined as positive antibodies in the IgA + IgM class, a higher percentage of patients with the presence of interleukin (IL) 2 (IL-2) was found. No association with other cytokines or effects of IBD activity or treatment was found. However, the effect of the applied treatment on the concentration of some cytokines was found: a negative association of infliximab, vedolizumab, and prednisone with IL-2, a positive correlation of steroids, thiopurines with IL-10, and in the case of tumor necrosis factor-α (TNF-α), negative with infliximab, and positive with vedolizumab.

Conclusions: The increased concentration of IL-2 may result from its regulatory role in inhibiting excessive activation of the immune system; however, considering the studies of patients with severe COVID-19, its role in the initial phase of SARS-CoV-2 infection requires further research.

Introduction

The course of SARS-CoV-2 infection, which led to the outbreak of the COIVD-19 pandemic, varies greatly – from asymptomatic infection to a severe course, often ending in death [1]. We no longer have any doubts about the important role of immunological processes in the course of infections, which is best seen in the most severe ones [2]. Most studies to date have focused on this stage of the disease. Understanding the mechanism of severe infection gives an opportunity to develop methods of early diagnosis and treatment, and thus reduce the number of victims of the pandemic. But mild and asymptomatic infections are just as important to keeping the pandemic going. They are largely responsi-

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ble for the rapid spread of the virus, despite attempts to contain it through social distancing and other non-specific methods [3]. The situation has also changed with the introduction of vaccination and the dominance of new variants of the virus, which have led to a reduction in the number of the most severe cases. Mild and asymptomatic patients predominate; therefore, it is important to better understand the mechanisms, including immunological ones, of these stages of the disease.

SARS-CoV-2 virus infection can be divided into three main phases: the viral infection phase, the pulmonary phase, and the systemic hyperinflammation phase [4]. Previous research has revealed the key role of the immune system, especially in the last phase, when its excessive, uncontrolled stimulation leads to damage to many organs. The phenomenon of overstimulation, expressed by the production of many cytokines, is called cytokine storm and is quite well known and described in the literature [5]. These studies led to the formulation of specific recommendations for diagnosis (the prognostic role of IL-6 concentration) [6] and treatment (the use of tocilizumab in severe cases) [7] of COVID-19.

Much less is known about the role of the immune system in mild and asymptomatic infections. But even in these patients, symptoms of immune system stimulation were found.

Inflammatory bowel diseases (IBDs), which include Crohn's disease (CD) and ulcerative colitis (UC), are a group of autoimmune diseases, and therefore the role of the immune system is also significant in their pathogenesis. In the initial phase of the pandemic, many concerns were expressed about the safety of this group of patients, especially due to their widespread use of immunosuppressive drugs. However, these hypotheses were not confirmed, and studies in this group of patients allowed for a better understanding of the immunological mechanisms during SARS-CoV-2 infection [8–10].

Aim

The aim of this study is to assess the stimulation of the immune system expressed through the production of cytokines in IBD patients with asymptomatic COVID-19.

Material and methods

This is a multicentre prospective study evaluating serum cytokine levels in IBD patients who have had asymptomatic SARS-CoV-2 infection. Three tertiary centres (from Warsaw, Lodz, and Poznan) recruited participants for the study from 1 May to 30 September 2020, from patients who came to the centres for the next dose of a biological drug or due to an exacerbation of IBD. During the recruitment period, regulations limiting the movement of people were in force in Poland, and access to outpatient care as well as to planned hospitalisations was limited. Patients with symptoms of respiratory tract infection could not enter the centres – such people were sent home or directed to hospital wards treating COVID-19. For this reason, none of the patients in the study had symptomatic COVID-19.

Patient characteristics

The study involved 473 patients who made 1180 visits to the centres during the study. During each visit, patients filled in a form that was obligatory for the whole country, which assessed the occurrence of symptoms of respiratory tract infections in the last 7 days. In addition, information on IBD was collected, both the history of the disease and current activity. On this basis, demographic data (age, sex), type of disease, duration, history of surgeries, current treatment, and disease activity expressed by partial Mayo score (for UC) and Crohn's Disease Activity Index (CDAI) (for CD) were assessed.

Laboratory analysis

At each visit, the patient had serum collected, which was divided into 2 samples. In the first one, the concentration of SARS-CoV-2 antibodies in the IgA + M and IgG classes was determined. SARS-CoV-2 IgG and IgM+IgA antibodies were measured by using the ELISA method, targeting viral spike (S) and nucleocapsid (*N*) antigens (Vircell Microbiologists®, Granada, Spain). Positive cut-off values were established according to the manufacturer's instructions. The value expressed was the antibody index, which was defined as sample optical density/cut-off serum mean optical density × 10. It was 8 for antibodies in the IgA + M class and 6 for antibodies in the IgG class. All tests were performed in the Coronavirus Laboratory Diagnostic Unit of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw.

The second sample was frozen at –80°C immediately after collection for possible further testing.

All patients with positive IgA + M (n = 50) and IgG (n = 46) antibodies were included in the analysis. Eighteen patients had a positive result in 2 classes. Forty-one antibody-negative patients randomly selected from the remaining patients were also included in the analysis. In these patients, a panel of cytokines was tested from the second serum sample.

The concentration of the following cytokines was determined in these samples: interleukin (IL) 1a (IL-1a), IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL- 15, IL-17, IL-23, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and TNF-β (measured by using the ELISA method, Quansys Biosciences®). All tests were

performed in the Diagnostic Laboratory Unit of the Central Clinical Hospital of Ministry of Internal Affairs in Warsaw. According to the manufacturer's recommendations, samples with a concentration below the detection limit were considered negative. Detection of a given cytokine at any concentration marked a positive result.

Table I. Group characteristics

Variables	Values, *n* (%)
Patients	119
Sex, male	70 (58.8)
Age, Me (Q1; Q3)	30.00 (27.00; 44.00)
Crohn's disease	90 (75.6)
CDAI, Me (Q1;Q3)	119.78 (62.00; 227.04)
Ulcerative colitis	29 (24.4)
Mayo Score, Me (Q1; Q3)	3.00 (2.00; 4.00)
Smokers	19 (16.0)
SARS-CoV-2 IgG positive	46 (38.7)
SARS-CoV-2 IgA+M positive	50 (42.0)
IL-1α positive	10 (8.4)
IL-1β positive	4 (3.4)
IL-2 positive	65 (54.6)
IL-4 positive	0 (0.0)
IL-5 positive	1 (0.8)
IL-6 positive	39 (32.8)
IL-8 positive	110 (92.4)
IL-10 positive	37 (31.1)
IL-12 positive	3 (2.5)
IL-13 positive	8 (6.7)
IL-15 positive	13 (10.9)
IL-17 positive	9 (7.6)
IL-23 positive	2 (1.7)
IFN-γ positive	5 (4.2)
TNF-α positive	44 (37.0)
TNF-β positive	11 (9.2)
Treatment:	
5-ASA	106 (89.1)
Thiopurines	74 (62.2)
Methotrexate	5 (4.2)
Infliximab	54 (45.4)
Adalimumab	13 (10.9)
Vedolizumab	35 (29.4)
Ustekinumab	5 (4.2)
Prednisone	18 (15.1)
Budesonide	5 (4.2)

N and % were given for qualitative variables; median with quartile 1 and 3 were given for quantitative variables.

Statistical analysis

The analysis was conducted in statistical software R, ver. 4.2.1, with $\alpha = 0.05$. The χ^2 test and Fisher's exact test were used to analyse whether the presence of cytokines was related to selected variables. The level of quantitative variables was compared between 2 groups using Mann-Whitney's *U* test. Univariate logistic regression models were built, in which the presence of selected cytokines was considered as dependent variables. Multivariate models were built by a stepwise method. Initial models included variables that had a *p*-value lower than 0.25 [11] in the univariate models. Odds ratios were calculated with 95% confidence intervals. Nagelkerke's Pseudo R^2 and χ^2 tests were calculated to evaluate multivariate models.

Ethics approval

This study was approved by the Ethics and Supervision Committee for Human and Animal Research at the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw (No. 66/2020). All patients provided written informed consent to participate in the study.

Results

Of the 119 patients, 58.8% were male, the mean age was 30 years. Of these, 75.6% had CD and 24.4% had UC. Most patients were in remission of IBD: median CDAI was 119.78, and median Mayo score was 3.00. Most were treated with 5-ASA (89.1%). There was a high percentage of patients treated with thiopurines (62.2%), as well as biologically: anti-TNF drugs (56.3%) and vedolizumab (29.4%); 19.3% were treated with steroids. Smoking was declared by 16% of patients.

Of all the cytokines tested, only in the case of IL-2, IL-6, IL-8, IL-10, and TNF-α were sufficient positive samples obtained to qualify these results for further statistical analysis.

Patients' characteristics and antibody and cytokine results are presented in Table I.

IL-2

In the group of patients with the presence of SARS-C0V-2 antibodies in the IgA + M class, a significantly higher percentage of people with an increased presence of IL-2 was found (52.3% vs. 29.6%; $p = 0.021$). This relationship did not apply to IgG antibodies (35.4% vs. 42.6%; $p = 0.539$). There were also significantly more smokers in this group (24.6% vs. 5.6%; $p = 0.010$). Ana-

lysing the use of drugs, a significantly higher percentage of patients taking adalimumab was found. However, the univariate and multivariate regression analysis showed a lower percentage of patients taking another anti-TNF drug – infliximab. In addition, a negative effect of taking vedolizumab and prednisone was found (Tables II–IV).

Table II. Comparison of selected variables between subjects with and without IL-2

Variables	IL-2		*P*-value
	Negative *n* = 54	Positive *n* = 65	
SARS-CoV-2 IgG	23 (42.6)	23 (35.4)	0.539
SARS-CoV-2 IgA + M	16 (29.6)	34 (52.3)	0.021
Sex, male	33 (61.1)	37 (56.9)	0.783
Age, Me (Q1; Q3)	30.00 (27.25; 43.75)	33.00 (26.00; 44.00)	0.771
Type of disease:			
Crohn`s disease	38 (70.4)	52 (80.0)	0.315
Ulcerative colitis	16 (29.6)	13 (20.0)	
5-ASA	50 (92.6)	56 (86.2)	0.409
Thiopurines	35 (64.8)	39 (60.0)	0.727
Methotrexate	2 (3.7)	3 (4.6)	> 0.999[1]
Infliximab	28 (51.9)	26 (40.0)	0.268
Adalimumab	0 (0.0)	13 (20.0)	0.001
Vedolizumab	19 (35.2)	16 (24.6)	0.290
Ustekinumab	1 (1.9)	4 (6.2)	0.375[1]
Prednisone	11 (20.4)	7 (10.8)	0.231
Budesonide	2 (3.7)	3 (4.6)	> 0.999[1]
Smokers	3 (5.6)	16 (24.6)	0.010
CDAI, Me (Q1; Q3)	131.68 (58.55; 224.10)	117.78 (63.50; 204.79)	0.906
Mayo Score, Me (Q1; Q3)	2.50 (2.00; 4.00)	4.00 (1.00;5.00)	0.511

N and % were given for qualitative variables; median with quartile 1 and 3 were given for quantitative variables. Dependencies between qualitative variables were analysed with chi-square test or with Fisher's exact test[1]. Differences in the level of quantitative variables were analysed with Mann-Whitney's U test.

Table III. Univariate logistic regression models for IL-2

Variables	IL-2		*P*-value
	OR	95% CI for OR	
SARS-CoV-2 IgG (positive vs. negative)	0.74	0.35; 1.55	0.422
SARS-CoV-2 IgA + M (positive vs. negative)	2.60	1.23; 5.67	0.014
Sex (male vs. female)	0.84	0.40; 1.75	0.644
Age	1.00	0.96; 1.03	0.797
Type of disease (UC vs. CD)	0.59	0.25; 1.38	0.225
5-ASA (yes vs. no)	0.50	0.13; 1.63	0.269
Thiopurines (yes vs. no)	0.81	0.38; 1.71	0.590
Infliximab (yes vs. no)	0.62	0.30; 1.28	0.197
Vedolizumab (yes vs. no)	0.60	0.27; 1.33	0.210
Prednisone (yes vs. no)	0.47	0.16; 1.30	0.151
Smokers (yes vs. no)	5.55	1.72; 24.93	0.009
CDAI (quantitative)	> 0.99	> 0.99; 1.00	0.990

OR 95% CI – odds ratio with 95% confidence intervals.

Table IV. Multivariate logistic regression models for IL-2

Variables	IL-2		*P*-value
	OR	95% CI for OR	
SARS-CoV-2 IgA + M (positive vs. negative)	2.80	1.21; 6.78	0.018
Infliximab (yes vs. no)	0.26	0.08; 0.80	0.024
Vedolizumab (yes vs. no)	0.23	0.06; 0.74	0.017
Prednisone (yes vs. no)	0.22	0.06; 0.72	0.017
Smokers (yes vs. no)	3.83	1.07; 18.40	0.056

OR 95% CI – odds ratio with 95% confidence intervals.

IL-6

In the group of patients with the presence of IL-6, a statistically significantly higher median CDAI index was found (158.5 vs. 108.6; $p = 0.042$). However, it should be emphasised that both these values are within the limits considered as clinical remission. No other relationships were found in this group.

IL-8

No significant dependency was detected between the presence of IL-8 and any of the selected variables, also in univariate logistic regression models.

IL-10

In the group of patients with the presence of IL-10, there were more taking steroids: budesonide (10.8% vs. 1.2%; $p = 0.032$), prednisone (multivariate logistic regression models, OR = 3.09; $p = 0.041$), and thiopurines (OR = 2.63; $p = 0.036$). No other relationships were found.

TNF-α

In the group with the presence of TNF-α there was a greater proportion of men (72.7% vs. 50.7%; $p = 0.030$), fewer patients were treated with infliximab

Table V. Comparison of selected variables between subjects with and without TNF-α

Variables	TNFα		*P*-value
	Negative *n* = 75	Positive *n* = 44	
SARS-CoV-2 IgG	27 (36.0)	19 (43.2)	0.561
SARS-CoV-2 IgA + M	28 (37.3)	22 (50.0)	0.246
Sex, male	38 (50.7)	32 (72.7)	0.030
Age, Me (Q1; Q3)	32.00 (27.00; 45.00)	30.00 (26.75; 42.25)	0.956
Type of disease:			
Crohn's disease	56 (74.7)	34 (77.3)	0.922
Ulcerative colitis	19 (25.3)	10 (22.7)	
5-ASA	66 (88.0)	40 (90.9)	0.765[1]
Thiopurines	49 (65.3)	25 (56.8)	0.466
Methotrexate	3 (4.0)	2 (4.5)	> 0.999[1]
Infliximab	42 (56.0)	12 (27.3)	0.004
Adalimumab	8 (10.7)	5 (11.4)	> 0.999[1]
Vedolizumab	16 (21.3)	19 (43.2)	0.021
Ustekinumab	3 (4.0)	2 (4.5)	> 0.999[1]
Prednisone	14 (18.7)	4 (9.1)	0.253
Budesonide	2 (2.7)	3 (6.8)	0.357
Smokers	10 (13.3)	9 (20.5)	0.445
CDAI, Me (Q1; Q3)	114.46 (54.80; 203.05)	135.72 (71.87; 225.00)	0.362
Mayo Score, Me (Q1; Q3)	2.00 (1.00;4.00)	3.50 (2.00; 5.00)	0.325

N and % were given for qualitative variables; medians with quartile 1 and 3 were given for quantitative variables. Dependencies between qualitative variables were analysed with chi-square test or with Fisher's exact test[1]. Differences in the level of quantitative variables were analysed with Mann-Whitney's U test.

(27.3% vs. 56.0%; $p = 0.004$), but not with adalimumab, and there were more patients treated with vedolizumab (43.2% vs. 21.3%; $p = 0.021$). These data were confirmed in univariate and multivariate logistic regression models (Tables V–VII).

Discussion

To the best of our knowledge, this is the first study that attempts to assess the immune system response, expressed by multiple cytokine concentrations, to asymptomatic SARS-CoV-2 infection in a group of patients with IBD, and possibly in any other group.

In our study, we assessed the concentration of 15 cytokines in a group of patients with IBD and asymptomatic SARS-CoV-2 infection defined by a positive serological test. None of the patients had symptoms of COVID-19 and most were in clinical remission from IBD. We found a higher concentration of IL-2 in the group of patients with a recent infection, which was expressed in the relationship between the concentration of this cytokine and the concentration of SARS-CoV-2 antibodies in the IgA + IgM class.

We found no relationship between other cytokines and asymptomatic SARS-CoV-2 infection.

In our study, there was no effect from the type and severity of IBD and the treatment applied on the course of the early phase of SARS-CoV-2 infection. However, a relationship was observed between the treatment and the concentration of some cytokines. Thus, in the case of IL-2, a negative association with infliximab, vedolizumab, and prednisone was found. Interestingly, the effect for adalimumab was the opposite. As for IL-10, a positive correlation was found with the intake of steroids and thiopurines. In the case of the presence of TNF-α, the percentage of patients treated with infliximab was significantly lower, and the percentage of patients treated with vedolizumab was higher.

In our study, we included a wide range of cytokines. These included those thought to be part of the innate immune system, but also the adaptive and chemokines, pro- and anti-inflammatory. It should be emphasised that a characteristic feature of cytokines is their pleiotropy, i.e. the ability of each of them to affect many different cells and show different actions. Therefore, qualifying a particular cytokine as appropriate for a given

Table VI. Univariate logistic regression models for TNF-α

Variables	TNF-α		*P*-value
	OR	95% CI for OR	
SARS-CoV-2 IgG (positive vs. negative)	1.35	0.63; 2.90	0.438
SARS-CoV-2 IgA + M (positive vs. negative)	1.68	0.79; 3.59	0.178
Sex (male vs. female)	2.60	1.18; 5.96	0.020
Age	1.00	0.96; 1.03	0.889
Type of disease (UC vs. CD)	0.87	0.35; 2.05	0.749
5-ASA (yes vs. no)	1.36	0.41; 5.30	0.624
Thiopurines (yes vs. no)	0.70	0.32; 1.50	0.356
Infliximab (yes vs. no)	0.29	0.13; 0.65	0.003
Adalimumab (yes vs. no)	1.07	0.31; 3.45	0.906
Vedolizumab (yes vs. no)	2.80	1.25; 6.40	0.013
Prednisone (yes vs. no)	0.44	0.12; 1.32	0.168
Smokers (yes vs. no)	1.67	0.61; 4.53	0.309

OR 95% CI – odds ratio with 95% confidence intervals.

Table VII. Multivariate logistic regression models for TNF-α

Variables	TNF-α		*P*-value
	OR	95% CI for OR	
SARS-CoV-2 IgA + M (positive vs. negative)	2.11	0.91; 5.05	0.085
Sex (male vs. female)	2.86	1.22; 7.09	0.019
Infliximab (yes vs. no)	0.28	0.11; 0.64	0.003
Prednisone (yes vs. no)	0.23	0.06; 0.78	0.027

OR 95% CI – odds ratio with 95% confidence intervals.

function is difficult and is based on the main direction of action.

Research to date has focused on understanding the role of the immune system in severe COVID-19. In many studies, a significant stimulation of the immune system was found, which is reflected, among others, in a significant increase in the concentration of pro-inflammatory cytokines. This phenomenon is called a cytokine storm.

A study by Qin *et al.* [12] found significantly elevated levels of IL-6, IL-8, IL-10, and TNF-α in patients with severe COVID-19 compared to patients with a milder course. The concentration of these cytokines, among many other factors, was associated with a higher risk of respiratory failure and death.

Similarly, Del Valle *et al.* [13] found elevated levels of IL-6, IL-8, and TNF-α in patients hospitalised for COVID-19. Moreover, high concentrations of these cytokines at admission was a prognostic factor.

In our study, we did not observe elevated levels of these cytokines. The asymptomatic course of COIVD-19 did not cause significant stimulation of the immune system or this stimulation was inhibited by anti-inflammatory mechanisms effectively and in the early stages. This may be shown by the elevated concentrations of IL-2 observed in our study. This cytokine is one factor responsible for regulating the activity of T lymphocytes, and it protects against autoimmunity; it is a strong growth factor of regulatory T lymphocytes. This is probably not the only mechanism inhibiting the development of excessive stimulation of the immune system leading to the symptomatic form of COVID-19, but it should be considered, because it is noticeable even in patients with asymptomatic forms of SARS-CoV-2 infection.

However, the role of IL-2 in COVID-19 infection is not clear. In the Fawzy *et al.* [14] study, high concentrations of this cytokine were also found in patients with severe COVID-19. Other authors (Kalfaoglu *et al.* [15], Silva *et al.* [16]) postulate dysfunction of IL-2 as a result of dysregulation of T lymphocytes in severe COVID-19 infection. As a result, the regulatory function of these cytokine decreases and the activation function of NK cells, T helper, and B lymphocytes increases.

Our work has some limitations. The diagnosis of SARS-Cov-2 infection is based on serological tests that were available in the initial phase of the pandemic. As we know, serological diagnostics is not the optimal tool for diagnosing a past SARS-CoV-2 infection, but due to its simplicity, it is most often used for this purpose. In our study, the time since infection could not be accurately determined because all patients were asymptomatic. The study group was relatively small, which could have resulted in too few patients with the presence of many cytokines, and thus the lack of reliable statistical analysis.

Our study is the first to assess the impact of asymptomatic SARS-CoV-2 infection on the immune system of IBD patients. We found a positive correlation between early infection markers (IgA + M antibodies) and the presence of IL-2. Immune disorders mediated by this cytokine have already been described in severe infections. Its impact on the course of COVID-19, and especially its role in the progression of the infection towards a severe form, requires further research.

Conflict of interest

The authors declare no conflict of interest.

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