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The clinical course of SARS-CoV-2 infection among children with rheumatic disease under biologic therapy: a retrospective and multicenter study

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Abstract

The effects of biological disease-modifying antirheumatic drugs (bDMARDs) in the clinical course of COVID-19 on children with underlying rheumatologic diseases have not been fully demonstrated. To evaluate the course of COVID-19 infection in patients with rheumatic disease receiving bDMARD treatment. This was a retrospective, multicenter study conducted in pediatric patients infected by SARS-CoV-2 and under bDMARDs therapy. The study population consisted of 113 patients (72 female/41 male). The mean age of the patients was 12.87 ± 4.69 years. The primary diagnosis of the cohort was as follows: 63 juvenile idiopathic arthritis, 35 systemic autoinflammatory diseases, 10 vasculitides, and five cases of connective tissue diseases. The mean duration of the primary disease was 4.62 ± 3.65 years. A total of 19 patients had additional comorbid diseases. Thirty-five patients were treated with canakinumab, 25 with adalimumab, 18 with etanercept, 10 with infliximab, nine with tocilizumab, six with rituximab, four with anakinra, three with tofacitinib, and one with abatacept. The median exposure time of the biological drug was 13.5 months. Seventy-one patients had symptomatic COVID-19, while 42 were asymptomatic. Twenty-four patients required hospitalization. Five patients presented with MIS-C. The hospitalized patients were younger and had a shorter duration of rheumatic disease compared to ambulatory patients, although the difference was not statistically significant. Steroid usage, presence of fever, and dyspnea were more common among the hospitalized patients. A worsening in the course of both COVID-19 and current disease was not noticed under bDMARDs, however, to end with a strong conclusion multicentric international studies are required.

Keywords COVID-19 · Rheumatic disease · Biologic drugs · Pediatrics

Introduction

Coronavirus disease 19 (COVID-19) has been the foremost cause of morbidity and mortality in the world during the past 2 years. Initially, a cluster of unexplained pneumonia was reported from Wuhan, Hubei province, China in December 2019. Subsequently, a new type of coronavirus named SARS-CoV-2 was found to be the causative viral agent; this new disease was declared as COVID-19 on February 11, 2020 [1, 2]. Until date (accepted date: September 3, 2021), 218.9 million confirmed cases of COVID-19 have been reported, of which 4.5 million confirmed death have been reported globally by the World Health Organization (WHO). In our country, 6.4 million infected cases and 57.283 cumulative deaths have been announced in the same time period [3]. The most common symptoms during the SARS-CoV-2 infection are fever, cough, shortness of breath, fatigue, myalgia, loss of taste or smell, and sore throat. However, it is well-known now that COVID-19 is clinically characterized

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by a varying spectrum, ranging from an asymptomatic course to life-threatening multi-organ failure [1, 2]. Initial reports showed that children with COVID-19 were prone to develop a mild or asymptomatic course. However, children with a rheumatic disease or those receiving immunosuppressant treatments may be vulnerable to SARS-CoV-2 infection.

It is well-known that patients with rheumatic disease are at risk of serious infection due to both immune dysfunctions resulting from their diseases and the usage of immunomodulatory drugs. Biological disease-modifying anti-rheumatic drugs (bDMARDs), which are often used in treatments, act by targeting the pathways of the immune system through cytokine blockade and can cause immune dysregulation in the body. Increased risk of serious infections in both adults and children has been reported with the use of bDMARDs [4]. Therefore, the presence of a rheumatic disease or the usage of anti-rheumatic drugs is of interest in terms of whether or not they affect the course of SARS-CoV-2 infection. A meta-analysis by Akiyama et al. [5] showed that having a rheumatic disease increased the risk of the symptomatic course of COVID-19, rate of hospital admission, and death due to COVID-19 in adult patients when compared to that in the general population. On the other hand, conflicting results have been reported that suggest that patients with rheumatic diseases and SARS-CoV-2 express milder symptoms of COVID-19 without any severe complications due to the usage of corticosteroids and bDMARDs [6]. Although the number of studies published on COVID-19 is increasing every day, the data on pediatric patients remain insufficient. Recently, a study from Italy [7] concluded that pediatric patients with chronic diseases who were treated with bDMARDs did not carry an increased risk for respiratory or life-threatening complications of COVID-19 relative to the general population. Restricted reports with a small number of patients [8, 9] have been introduced from our country; however, relevant multicentric data from developing countries are still lacking.

Herein, we aimed to determine the course of SARS-CoV-2 infection in children with rheumatic diseases under bDMARD treatment.

Methods

This retrospective, multicenter study was conducted by 14 pediatric rheumatology centers in Turkey. The medical records of patients who were diagnosed with a rheumatic disease according to the previously accepted criteria and treated with bDMARDs were reviewed.

Inclusion and exclusion criteria

Patients with rheumatic diseases and receiving bDMARDs were evaluated, and of these, the patients who were diagnosed with COVID-19 were included in the study. Case definition of COVID-19 was made according to the following criteria:

a) In asymptomatic patient, the detection of SARS-CoV-2 RNA was performed using molecular amplification test [e.g., nasal polymerase chain reaction (PCR) test].
b) In asymptomatic patients, the detection of SARS-CoV-2 RNA was performed using PCR. The patient had a history of contact with a confirmed case.
c) In patients, the detection of positive SARS-CoV-2 antibody [immunoglobulin (Ig) M and IgG] ELISA test after suspected COVID-19 symptoms, but without SARS-CoV-2 PCR confirmation during the symptomatic period.
d) In patients, the detection of SARS-CoV-2 antibody IgM and IgG after a close contact with a person infected with SARS-CoV-2.

The diagnosis of COVID-19 was confirmed in 103 patients by nasal SARS-CoV-2 PCR and in 10 patients by SARS-CoV-2 antibody IgM and IgG ELISA test.

Patients infected with SARS-CoV-2, but not receiving bDMARDs were excluded from the study. Furthermore, patients who had suspected symptoms, but refused to undertake PCR or antibody test for confirmation of the diagnosis were excluded.

Data collection

This real-life study was based on secondary data collection from medical records of patients between April 2020 and 2021. Demographic and clinical data, laboratory findings, information about the course of COVID-19, and the outcomes were retrospectively recorded.

The present study was approved by the Institutional Review Board (IRB) at xxxx via waiver of informed consent (IRB number STUDY00000771).

Statistical analysis

The SPSS version 21.0 (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using the proportion

for categorical variables; mean and standard deviation (SD) were used for normally distributed numerical variables; and median and range (R) were used for non-normally distributed numerical variables. Differences in the proportions between groups were compared by Chi-squared test or Fisher's exact test, whichever was appropriate. The Student's *t* test (for normally distributed variables) or the Mann–Whitney *U* test (for non-normally distributed variables) was performed to evaluate the differences between the two groups when comparing numerical data. $P \leq 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics of the patient group

We included 113 pediatric patients infected with SARS-CoV-2 who were receiving bDMARD for the treatment of their primary rheumatic diseases. The study population consisted of 72 female (63.7%) and 41 (36.3%) male. The mean age of the patients was 12.87 ± 4.69 years. Among 113 patients, 63 (55.8%) were diagnosed with juvenile idiopathic arthritis (JIA), 35 (30.9%) with systemic autoinflammatory disease (AID), 10 (8.9%) with vasculitides, and 5 (4.4%) with connective tissue diseases. The mean duration of the primary rheumatic disease was 4.62 ± 3.65 years. Nineteen (16.8%) patients had additional comorbid diseases (Table 1).

Prior to SARS-CoV-2 infection, 35 patients (30.9%) were receiving canakinumab, 26 (23.0%) were treated with adalimumab, 19 (16.8%) with etanercept, 10 (8.9%) with infliximab, 9 (8.0%) with tocilizumab, 6 (5.3%) with rituximab, 4 (3.5%) with anakinra, 3 (2.7%) with tofacitinib, and 1 (0.9%) with abatacept. Furthermore, 42 (37.1%) patients were using conventional DMARD, concomitantly and 27 (23.8%) patients were also receiving corticosteroids with a median dose of 0.16 mg/kg (Table 1). The median time of exposure to a biological drug was 12 months. The median time of duration between diagnosis of COVID-19 and the last biologic drug administration was 15 days.

COVID-19 test results

In the cohort, 101 (89.4%) patients had a history of close contact with COVID-19 patients. Among them, 18 patients had an infected person in their family. At the time of diagnosis, SARS-CoV-2 PCR was positive in 103 (91.1%) patients. The diagnosis of COVID-19 was confirmed by SARS-CoV-2 antibody test in the remaining 10 patients (8.9%). Of these 10 patients, all had COVID-19-suspected symptoms, but SARS-CoV-2 PCR test was not performed when they were symptomatic.

Table 1 Baseline characteristics of the patients infected with SARS-CoV-2 while receiving a bDMARD

Rheumatic disease, *n* (%)	
Juvenile idiopathic arthritis	63 (55.8%)
Autoinflammatory diseases	35 (30.9%)
Familial Mediterranean fever	21
Cryopyrin associated periodic syndrome	5
Hyperimmunoglobulin D syndrome	4
Chronic recurrent osteomyelitis	3
Idiopathic recurrent pericarditis	1
Pyogenic arthritis, pyoderma gangrenosum and acne syndrome	1
Vasculitis	10 (8.9%)
Adenosine deaminase 2 deficiency	4
Takayasu arteritis	3
Polyarteritis nodosa	1
Other	2
Connective tissue diseases	5 (4.4%)
Systemic lupus erythematosus	3
Sjögren's disease	1
Juvenile dermatomyositis	1
Comorbidities, *n* (%)	19 (16.8%)
Hypertension	4
Inflammatory bowel disease	3
Scoliosis	3
Chronic renal failure	2
Hereditary spherocytosis	1
Asthma	1
Cardiomyopathy	1
Adrenal insufficiency	1
Celiac disease	1
Growth hormone insufficiency	1
Hypothyroidism	
Disease-modifying antirheumatic drugs, *n* (%)	42 (37.1%)
Methotrexate	27
Mycophenolate mofetil	5
Leflunomide	4
Azathioprine	3
Cyclosporine	1
Sulfasalazine	1
Hydroxychloroquine	1

The clinical course of patients during the SARS-CoV-2 infection

At the time of diagnosis of COVID-19, 71 (62.8%) patients had at least one COVID-19-related symptom, while 42 (37.2%) were asymptomatic. The most common symptom was fever ($n = 42$), followed by myalgia ($n = 34$) and cough ($n = 29$) (Table 2). The median duration of fever was 4 (1–16) days. Twenty-nine patients (25.6%) presented with respiratory symptoms such as cough and dyspnea. Abnormal

Table 2 Clinical findings of the patients at the time of diagnosis of COVID-19

Asymptomatic, *n* (%)	42 (37.2%)
Symptomatic, *n* (%)	71 (62.8%)
Fever	42
Myalgia	34
Cough	29
Anosmia/ageusia	15
Diarrhea	11
Abdominal pain	9
Dyspnea	8
Rash	5
Anorexia/nausea/emesis	4
Fatigue/malaise	3
Chest pain	3

thorax computerized tomography findings revealed COVID-19 in 7 (6.2%) patients.

Twenty-four (21.2%) patients required hospitalization. The median time of hospitalization was 8 (2–10) days. Of these 24 patients, two were admitted to the intensive care unit with the requirement of mechanical ventilation. The remaining 89 (78.8%) patients received ambulatory care. Treatment was applied to 35 (30.9%) patients. Among these 35 patients, 21 were hospitalized. Twenty-two received favipiravir, 10 received azithromycin, and seven received oseltamivir. Ten patients required steroid treatment, concomitantly.

Five (4.4%) patients of whom two with the diagnosis of JIA, two with vasculitis, and one with AID presented with MIS-C. These two patients with vasculitis were receiving anti-tumor necrosis factor (TNF)-α drugs (etanercept = 1, infliximab = 1). Two patients with JIA were using anti-interleukin (IL)-1 agents (canakinumab = 1, anakinra = 1). The patient with AID was receiving canakinumab. Among these five patients, four were treated with IVIG and anakinra, two patients also received tocilizumab. Two patients died. Of these two patients, one was diagnosed with vasculitis and treated with etanercept before MIS-C, and the other was diagnosed with JIA and was receiving anakinra.

None of the patients reported disease flare after COVID-19 or the occurrence of any additional late complication after post-COVID-19 during the follow-up.

Comparison of clinical findings of patients requiring hospitalization with others

The comparison of clinical and laboratory findings of patients requiring hospitalization and receiving ambulatory care are depicted in Table 3. No differences were noted in terms of the type of rheumatic diseases or biological drugs used as well as the median duration time of biologic drug administration. Patients requiring hospitalization were younger and had a shorter duration of rheumatic disease when compared to others, while these findings did not reach any statistical significance. Furthermore, steroid usage was more common among patients requiring hospitalization.

On evaluation, the risk factor associated with hospitalization, the presence of fever [OR 3.05 (95% CI 1–7.7), $P = 0.01$], and dyspnea [OR 4. 25 (95% CI 0.97–18.46), $P = 0.04$] increased the odds of hospitalization. However, not statistically different, patients treated with rituximab and tofacitinib were hospitalized for a longer time (Table 3).

Discussion

Immunomodulatory drugs or underlying diseases may influence the clinical course of SARS-CoV-2 infection. However, it remains debatable whether medications worsen or improve the symptoms of COVID-19 and the clinical outcomes. Furthermore, the effect of SARS-CoV-2 infection on the disease activity of the underlying rheumatic disease remains unclear. We believe that clarifying these issues will guide clinicians when dealing with rheumatic diseases. This multicenter study presents the clinical characteristics and outcomes of patients infected with SARS-CoV-2 who were receiving bDMARD due to their primary rheumatic diseases. The overall hospitalization rate was 21.2%, while 78.8% of the patients received ambulatory care. The presence of fever and dyspnea were found to be risk factors for hospitalization. Hospitalized patients had younger age, shorter disease duration, and a higher rate of steroid usage when compared to ambulatory patients.

It is well-known that patients with comorbidities such as cardiovascular disease, liver disease, kidney disease, or malignancies are more vulnerable to SARS-CoV-2 infection [10, 11]. Correspondingly, a large pediatric cohort from our country revealed an association between having an underlying disease and a severe course of COVID-19 [12]. However, the course of COVID-19 in patients with a rheumatic disease or those using antirheumatic drugs remains unclear. Hyrich et al. [6] reported an increased risk of death among patients with rheumatic arthritis (RA), systemic lupus erythematosus, and psoriasis when infected with SARS-CoV-2. Gianfrancesco et al. [13] found that 10 mg/day or a higher dose of glucocorticoid exposure increased the risk of hospitalization, while the hospitalization rate was lower in patients using anti-TNF. By the same group, it was also shown that patients with RA receiving rituximab or Janus kinase inhibitors presented with a more severe course of COVID-19 than those treated with anti-TNF [14]. Haberman et al. [15] confirmed that COVID-19 outcomes were worse in patients with inflammatory arthritis receiving glucocorticoids, but it did not differ in patients using anti-cytokine therapy. The data

Table 3 The comparison of clinical findings of patients with requiring hospitalization and others

	Patients who were ambulatory ($n=89$)	Patients who were hospitalized ($n=24$)	P value
Female/male, *n*	57/32	15/9	0.53
The mean of age (years)	14.4	11.5	0.44
Distribution of rheumatic disease, *n*			0.27
Juvenile idiopathic arthritis	51	12	
Systemic autoinflammatory diseases	29	6	
Vasculitis	7	3	
Connective tissue diseases	2	3	
The mean ± SD duration of primary rheumatic disease (months)	41.5 ± 43.5	35.2 ± 45.04	0.30
Comorbid disease, *n*	14	5	0.42
Usage of corticosteroids, *n*	17	10	**0.03**
Median dose of steroid, mg/kg	0.16 (0.05–2)	0.15 (0.02–0.6)	0.34
Usage of DMARD, *n*	38	8	0.27
Distribution of biologic drugs, *n*			0.33
Canakinumab	26	9	
Infliximab	9	1	
Adalimumab	22	4	
Etanercept	16	3	
Tocilizumab	8	1	
Anakinra	2	2	
Rituximab	4	2	
Abatacept	1	0	
Tofacitinib	1	2	
The median exposure time of a biologic drug (months)	12.8 (1–95)	13.0 (1–84)	0.65
Fever, *n*	14	28	**0.01**
Myalgia, *n*	25	9	0.37
Cough, *n*	19	10	0.06
Anosmia/ageusia, *n*	15	0	**0.03**
Diarrhea, *n*	9	2	0.79
Abdominal pain, *n*	7	2	0.94
Dyspnea, *n*	4	4	**0.04**
Rash, *n*	2	3	0.06
Anorexia/nausea/emesis, *n*	3	1	0.62

The statistical significant parameters were presented in bold

about the clinical course of pediatric patients infected with SARS-CoV-2 who were receiving bDMARD is limited. A study from Turkey evaluated 39 children with a rheumatic disease who were infected with SARS-CoV-2 while receiving biological drugs. Among these 39 patients, 21 were symptomatic and 18 were asymptomatic. The hospitalization rate was 51.3%, and the mortality rate was 2.5% [8]. Villacis-Nunez et al. [7] reported 55 cases with rheumatic diseases and laboratory-confirmed COVID-19. In this cohort, the hospitalization rate was 18.2%. Afro-American ethnicity, presence of cardiovascular diseases, active rheumatic disease, and the usage of medium/high-dose corticosteroid or mycophenolate or rituximab were found to be associated with an increased odds ratio of hospitalization. Furthermore, fever, dyspnea, chest pain, and rash were more common among the hospitalized patients. Correspondingly, we showed that steroid usage, the presence of fever, and dyspnea were more common among the hospitalized patients. However, we could not demonstrate any differences between hospitalized patients and ambulatory patients in terms of rheumatic disease diagnosis or the type of antirheumatic drugs received or comorbidities. In addition, we found that patients treated with rituximab and tofacitinib were hospitalized for a longer time. Most recently, a nationwide registry of biologics in pediatric rheumatology from Germany presented the outcomes of 76 patients with a rheumatic disease and laboratory-confirmed SARS-CoV-2 infection [16]. Among these patients, 76% patients were treated

with DMARDs, 41% with biologic drugs, and 11% with systemic corticosteroids. They concluded that children with rheumatic diseases under various medications had a milder course of SARS-CoV-2 infection with favorable outcomes. On the same lines, they did not demonstrate any association between the underlying disease activity and the course of COVID-19 [16].

The primary disease may deteriorate further during the SARS-CoV-2 infection. Disease flare was reported by previous reports in children infected with SARS-CoV-2 who were receiving bDMARD [6, 13]. However, we could not demonstrate disease flare after COVID-19 or an additional late complication after post-COVID-19 during follow-up.

During the SARS-CoV-2 infection, aberrant immune response plays a central role, especially in severe cases, and it is well-known that, during childhood, both the morbidity and mortality of COVID-19 are commonly related to MIS-C rather than to primary SARS-CoV-2 infection. Villacis-Nunez et al. [7] did not describe an MIS-C patient in their cohort of 55 pediatric patients with rheumatic diseases. Interestingly, five of the 113 cases developed MIS-C after asymptomatic COVID-19. All of them required hospitalization and two of them died. While this association has not been elucidated, the pattern of immune reaction in primary rheumatic disease may influence the response to SARS-CoV-2.

The retrospective design of this study and the small number of patients limited our results, but the multicenter design strengthened our study. As the ethnicity and socioeconomic status may influence the course of infectious diseases, our results are quite important with clinical characteristics and the outcomes of patients from a developing country infected with SARS-CoV-2 while receiving a bDMARD. Moreover, the small sample size did not allow more detailed statistical analysis and presented the risk factors for hospitalization and severe course completely.

Conclusion

In patients with underlying comorbidities, COVID-19 may have a severe course, regardless of the use of bDMARD. However, in the present study, we could not demonstrate whether the course of COVID-19 or the primary disease worsened in patients receiving bDMARDs. Further multicenter, international studies are believed to demonstrate the risk factors for a severe course of COVID-19 among patients with rheumatic diseases.

Author contributions BS conceptualized and designed the study, drafted the initial manuscript, and had full access to all the data in the study. All authors conducted the data analyses, drafted the initial manuscript, and had full access to all the data in the study. All authors reviewed and revised the manuscript and approved the final version of the manuscript.

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Declarations

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