



Does immunosuppressive treatment entail an additional risk for children with rheumatic diseases? A survey-based study in the era of COVID-19

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Received: 8 June 2020 / Accepted: 24 July 2020 / Published online: 2 August 2020
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Abstract

The aim of the research was to further extend current knowledge of whether severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease 2019 (COVID-19) entails a risk for children with various rheumatic diseases under immunosuppressive treatment. Telephone survey was administered by conducting interviews with the parents from May 1, 2020 to May 20, 2020. A message containing a link to the actual questionnaire was sent to their phones simultaneously. The medical records of the patients were reviewed for gathering information about demographic data, clinical follow-up, and treatments. Patients who were followed-up under immunosuppressive treatment ($n=439$) were attempted to be contacted. The diagnostic distribution of patients ($n=414$) eligible for the study was as follows: juvenile idiopathic arthritis (JIA) ($n=243$, 58.7%), autoinflammatory diseases ($n=109$, 26.3%), connective tissue diseases ($n=51$, 12.3%), and vasculitis ($n=11$, 2.7%). In the entire cohort, the mean age was 12 ± 4.7 years, and 54.1% ($n=224$) were female. Nine patients have attended the hospital for COVID-19 evaluation, 6 of whom were in close contact with confirmed cases. One patient with seronegative polyarticular JIA, previously prescribed methotrexate and receiving leflunomide during pandemic was identified to be diagnosed with COVID-19. None, including the confirmed case, had any severe symptoms. More than half of the patients with household exposure did not require hospitalization as they were asymptomatic. Although circumstances such as compliance in social distancing policy, transmission patterns, attitude following contact may have influenced the results, immunosuppressive treatment does not seem to pose an additional risk in terms of COVID-19.

Keywords Biological therapies · COVID-19 · Dmards · Immunosuppressants · Paediatric rheumatology

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease 2019 (COVID-19), first reported from the Wuhan city of China in December 2019, swept the world in a few months and became a global health emergency

of primary international concern and was announced a pandemic by the World Health Organisation (WHO) [1]. Although the repercussions of the coronavirus continue throughout the world, we are faced with devastating impacts on social life, education, and economy. Unfortunately, it also disrupted the health care system by delaying the treatment plans of patients at the stage of diagnosis and causing hitches in the visits of patients struggling with chronic diseases.

The substantial infectivity, source and transmission ways, age and gender differences (poor outcome in men and elders), broad clinical spectrum, and complex etiopathogenesis of COVID-19 led to tricky questions and debates around the world [2, 3]. The similarities at clinical and molecular levels with previously encountered coronavirus types and the published data from severe acute respiratory syndrome (SARS 2002) and Middle East respiratory syndrome (MERS 2012) outbreaks acted as a guide in the early periods of the

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00296-020-04663-9>) contains supplementary material, which is available to authorized users.

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struggle and created the backbone of the current therapeutic strategy [4]. However, the growing knowledge about the pathogenesis of COVID-19 and associated cytokine storm syndrome, namely multisystem inflammatory syndrome suggests a new treatment approach with targeted therapy to manage the uncontrolled spread of the infection and inflammation [3, 5].

During the COVID-19 pandemic, several drugs already with essential roles in rheumatology practice emerged as promising treatment alternatives with encouraging results. On the other hand, dysregulation of innate immunity and virus–host interactions in the etiopathogenesis serve a major concern for patients in an immunosuppressive state or under immunosuppressive treatment [6, 7]. In the light of this evidence, several questions are raised regarding the management of patients with rheumatic diseases in terms of drug selection, initiation, continuation or withdrawal, appropriate dose adjustments, and likely problems in drug supply [6–10]. Current guidelines have attempted to draw a common path, but several epidemiological studies are undoubtedly needed. This study is set out to determine whether COVID-19, showing a milder course in children, entails a risk for patients with rheumatic diseases concerning immunosuppressive treatment with nonbiologic disease-modifying antirheumatic drugs (nbDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs).

Methods

Study design

In order to find out how the COVID-19 pandemic affects the patients receiving immunosuppressive treatment for rheumatic diseases, telephone survey was administered by conducting interviews with the parents from May 1, 2020 to May 20, 2020. A message containing a link to the actual questionnaire was sent to their phones simultaneously. Only parents were accepted as responders. The medical records of the patients were reviewed for demographic data, clinical follow-up, and treatments.

Subjects and data collection

Patients with rheumatic diseases aged between 0 and 20, under immunosuppressive treatment and followed-up at the Paediatric Rheumatology Department in Istanbul Medical Faculty were classified according to their diagnosis and treatment modalities. Sociodemographic data, disease-related information (disease duration, length of the treatment, current medication, disease status at the last visit, comorbidity, and concomitant drugs) were assessed.

The immunosuppressive antirheumatic drugs were categorized into the following active ingredient groups: nonbiologic DMARDs (methotrexate, leflunomide, mycophenolate mofetil, azathioprine, cyclophosphamide, hydroxychloroquine, sulfasalazine); biologic DMARDs (etanercept, adalimumab, infliximab, tocilizumab, anakinra, canakinumab, abatacept, rituximab); janus kinase (JAK) enzyme inhibitors (tofacitinib). Systemic steroids and intravenous immunoglobulin (IVIG) used within the past six months were stated. Comorbid diseases and drugs were noted. Whether the patients required tuberculosis prophylaxis or treatment, status of Bacillus Calmette–Guerin (BCG) vaccination and presence of scar formation were interrogated and cross-checked with their medical records.

Parents were informed about the research and asked for verbal consent on the phone call. The written consent and signature were obtained via online survey afterwards. Patients with incomplete medical data and those whose parents were unable to communicate via phone or refused to participate in the survey were excluded from the study. Each patient participating in the study approved the use of their information.

Content of the survey

The content of the survey, consisting of open-ended and closed-ended questions, was formulated by the authors of the study (added as a supplementary file 1). A plain and comprehensible language was used. In order to check the relevance, concordance, and consistency of the answers, the survey was conveyed to the participants both in a written format and via one-to-one voice communication over the phone. A pilot test was applied to 10% of the participants. Topics related to the COVID-19 in the survey were:

- A. The query of clinical and demographic information;
- B. Symptoms related to COVID-19 (*interrogated by one by*); fever, non-productive cough, sputum production, sore throat, rhinorrhea, fatigue, arthralgia, myalgia, anosmia or dysgeusia, dyspnea, headache, nausea or vomiting, diarrhea, rash;
- C. History of risk and contact; healthcare worker in the family (household contact), confirmed diagnosis in the family (household contact) or in relatives and neighbours living in the same apartment, history of contact with confirmed cases of COVID-19 (clearly stated);
- D. Attendance at a hospital with a suspicion of COVID-19;
- E. Diagnostic tests or imaging modalities performed for COVID-19; pharyngeal swab COVID-19 nucleic acid test (PCR), chest X-ray, computed tomography (CT) and the findings (also checked from the hospital archive);
- F. The presence of antirheumatic drug interruption during the outbreak; reason and duration of discontinuation;

G. Compliance to social distancing and isolation measures.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows 21.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA) and Microsoft Excel (Redmond, WA). Kolmogorov–Smirnov (KS) normality test was used to analyze the distribution of the variables. Mean values with standard deviations (mean \pm SD) or median (med) with minimum and maximum values (min–max) were given for demonstration of the data according to the distribution. Categorical variables were presented as counts or frequencies.

Ethics

Approval was obtained for the study from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved: May 2020-62,254). Our article has been shared on the ‘research square platform’ as a preprint (<https://doi.org/10.21203/rs.3.rs-36583/v1>).

Results

Demographic and clinical characteristics of the patients

Among 439 patients treated with immunosuppressive drugs, 25 could not be contacted, the response rate was 94.3% ($n=414$). In the entire cohort, the mean age (at the study) was 12 ± 4.7 years, and 54.1% ($n=224$) of the patients were females. The median disease duration was 45 (range: 3–221) months. The diagnostic distribution and subgroups of the study cohort are presented in Table 1. In 14.5% ($n=60$) of the patients, immunosuppressive treatment has been terminated in the past six months. According to their current treatment, 42.3% ($n=175$) of these patients were receiving bDMARDs, 28.7% ($n=119$) were using nbDMARDs, 14.5% ($n=60$) were on both. In the last six months, 18.6% of the patients have received systemic steroids either as a bridging therapy or in combination with other therapies during a flare. Table 2 demonstrates the demographic and clinical characteristics of the patients diagnosed with Juvenile Idiopathic Arthritis (JIA), the majority of the cohort.

The subgroups of autoinflammatory diseases in the cohort were colchicine-resistant familial mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS) hyper immunoglobulin D syndrome (HIDS), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), chronic recurrent multifocal osteomyelitis (CRMO), synovitis acne pustulosis hyperostosis osteitis

Table 1 Diagnostic distribution of the study cohort

Study cohort ($n=414$)	n (%)
Juvenile idiopathic arthritis	243 (58.7)
Oligoarthritis	82 (33.7)
Seronegative polyarthritis	50 (20.6)
Seropositive polyarthritis	12 (4.9)
Psoriatic arthritis	12 (4.9)
Enthesitis-related arthritis	62 (25.5)
Systemic-onset JIA	25 (10.3)
Autoinflammatory diseases	109 (26.3)
Colchicine-resistant FMF	70 (64.2)
CAPS	13 (11.9)
HIDS	7 (6.4)
TRAPS	6 (5.5)
CRMO	8 (7.3)
SAPHO	3 (2.8)
Juvenile sarcoidosis	2 (1.8)
Connective tissue diseases	51 (12.3)
JSLE	21 (41.2)
JSc	16 (31.4)
JDM	11 (21.6)
MCTD	3 (5.9)
Vasculitis	11 (2.7)
Behçet’s disease	8 (72.7)
Takayasu arteritis	2 (18.2)
PAN	1 (9.1)

FMF Familial mediterranean fever, CAPS Cryopyrin-associated periodic syndrome, HIDS Hyper immunoglobulin D syndrome, TRAPS Tumor necrosis factor receptor-associated periodic fever syndrome, CRMO Chronic recurrent multifocal osteomyelitis, SAPHO Synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, JSLE Juvenile systemic lupus erythematosus, JSc Juvenile scleroderma, JDM Juvenile dermatomyositis, MCTD Mixed connective tissue disease, PAN Polyarteritis nodosa

syndrome (SAPHO), juvenile sarcoidosis. Concomitant use of colchicine was noted in 89 (81.7%) patients. Six patients have experienced an inflammatory episode in the past six months. The majority of the patients with connective tissue diseases in the cohort were juvenile systemic lupus erythematosus (JSLE) ($n=21$, 41.2%), and juvenile scleroderma (JSc) ($n=16$, 31.4%). Concomitant use of hydroxychloroquine was noted in 30 (58.8%) patients. Three patients have been treated with six cycles of cyclophosphamide in the past year. Five patients have received intravenous immunoglobulin therapy in the past 6 months. In the group of subjects with vasculitis ($n=11$), concomitant use of colchicine was noted in 10 (90.9%) patients and 4 (36.4%) patients have taken an infusion of cyclophosphamide in the past year. The demographic and clinical manifestations including the type and duration of immunosuppressive treatments of non-JIA patients are demonstrated in Table 3.

Table 2 Demographic and clinical manifestations of patients with juvenile idiopathic arthritis

Age at the study (years), med (min–max)	12.5 (2–20)	
Gender, <i>n</i> (%)		
Female	124 (51)	
Male	119 (49)	
Disease duration (mo), med (min–max)	42 (4–221)	
JADAS-27 at last visit (mean ± SD) (range)	2.2 ± 4.9 (0–20)	
Nonbiologic DMARDs		
Type, <i>n</i> (%); Duration (mo), med (min–max)		
Methotrexate	226 (93)	18 (2–114)
Leflunomide	41 (16.9)	12 (5–60)
Sulfasalazine	53 (21.8)	6 (1–24)
Hydroxychloroquine	3 (1.2)	4 (3–4)
Biologic DMARDs		
Type, <i>n</i> (%); Duration (mo), med (min–max)		
Etanercept	97 (39.9)	14 (2–60)
Adalimumab	54 (22.2)	12 (2–36)
Infliximab	4 (1.6)	11 (3–24)
Tocilizumab	35 (14.4)	14 (3–76)
Anakinra	12 (4.9)	4 (1–8)
Canakinumab	8 (3.3)	24 (6–36)
Abatacept	4 (1.6)	16 (9–18)
JAK inhibitors		
Type, <i>n</i> (%); Duration (mo), med (min–max)		
Tofacitinib	1 (0.4)	3

JADAS Juvenile Arthritis Disease Activity Score-27, DMARDs Disease-modifying antirheumatic drugs, JAK inhibitors Janus kinase enzyme inhibitors

In the entire cohort, 25.4% ($n = 105$) of the patients had comorbid conditions, most common being; uveitis ($n = 34$, 8.2%), proteinuria ($n = 17$, 4.1%), thyroid disease ($n = 5$, 1.2%), inflammatory bowel disease ($n = 4$, 1%). Forty were concomitantly diagnosed with FMF aside from the rheumatic diseases. Angiotensin-converting enzyme (ACE) inhibitors ($n = 16$, 3.9%), thyroid hormone therapy ($n = 3$, 0.8%), antiepileptics ($n = 1$, 0.2%) were the drugs used concurrently. In the entire cohort, 366 patients (88.4%) have been BCG vaccinated, and scar formation was present. Ninety-six patients (23.2%) have received prophylactic tuberculosis therapy.

The survey results

All participants ($n = 414$) completed the survey and answered the questions fully. The most common symptoms were arthralgia ($n = 49$, 11.8%), fever ($n = 20$, 4.8%) and myalgia ($n = 15$, 3.6%), respectively. Table 4 details the survey results. Nine patients attended the hospital for COVID-19 evaluation, 6 of whom were in close contact with confirmed cases (Table 5). One confirmed case of COVID-19 was identified. Medical records of the patient belong to the pandemic period were examined.

During the pandemic, the treatments of 59 patients have been interrupted under the control of their parents, either voluntarily or involuntarily. Parents of 49.2% of the patients declared that the social restrictions, fear, and anxiety or new arrangements in health centres kept them from access to health care. The parents of 16 patients stated that they believed the drugs would pose a risk for COVID-19 and

Table 3 Demographic and clinical manifestations of non-juvenile idiopathic arthritis patients

Cohort ($n = 171$)	Autoinflammatory diseases	Connective tissue diseases	Vasculitis
Age at the study(y), med (min–max)	11 (4–20)	13 (4–20)	16 (11–20)
Female, <i>n</i> (%)	59 (54.1)	39 (76.5)	4 (36.4)
Disease duration (mo), med (min–max)	55 (9–173)	41 (4–101)	41 (3–125)
Nonbiologic DMARDs			
Type, <i>n</i> (%); Duration (mo), med (min–max)			
Methotrexate	13 (11.9); 16 (3–48)	29 (56.9); 20 (2–36)	2 (18.2); 14.5 (9–20)
Mycophenolate mofetil	–	24 (47.1); 14 (2–48)	1 (9.1); 8
Azathioprine	–	14 (27.5); 12 (5–20)	9 (81.8); 10 (2–36)
Biologic DMARDs			
Type, <i>n</i> (%); Duration(mo), med (min–max)			
Etanercept	5 (4.6); 12 (8–48)	–	1 (9.1); 16
Infliximab	1 (0.9); 9	–	2 (18.2); 6.5 (5–8)
Anakinra	81 (74.3); 3 (1–24)	–	–
Canakinumab	84 (77.1); 16 (2–75)	–	–
JAK inhibitors			
Type, <i>n</i> (%); Duration(mo), med (min–max)			
Tofacitinib	–	3 (5.9); 5 (3–10)	–

JIA Juvenile idiopathic arthritis, DMARDs disease-modifying antirheumatic drugs, JAK Inhibitors: janus kinase enzyme inhibitors

Table 4 Telephone survey results related to coronavirus disease 2019

Analyzing survey data of the participants (<i>n</i> = 414)	Results <i>n</i> (%)
COVID-19-related symptoms	
Fever	20 (4.8)
Non-productive cough	8 (1.9)
Sputum production	–
Sore throat	9 (2.2)
Rhinorrhea	3 (0.7)
Fatigue	8 (1.9)
Arthralgia	49 (11.8)
Myalgia	15 (3.6)
Anosmia/dysgeusia	3 (0.7)
Dyspnea	1 (0.2)
Headache	–
Nausea/vomiting	2 (0.5)
Diarrhea	8 (1.9)
Rash	4 (1)
A healthcare worker in the family (household contact)	9 (2.2)
Confirmed diagnosis in the family (household contact)	17 (4.1)
Confirmed diagnosis in relatives or neighbors living in the same apartment	63 (15.2)
History of contact with confirmed cases (clearly stated)	18 (4.3)
Attendance at a hospital with suspicion of COVID-19	9 (2.2)
History of contact	6
Chest X-ray performed for COVID-19	6 (1.4)
History of contact	4
Consistent with COVID-19	1
Computed tomography performed for COVID-19	4 (0.9)
History of contact	3
Consistent with COVID-19	1
Pharyngeal swab COVID-19 nucleic acid test	9 (2.1)
History of contact	6
Positive for COVID-19	1
Treatment interruption during the outbreak (antirheumatic drugs)	59 (14.3)
Reason for discontinuation of treatment	
Inadequate access to health care	29 (49.2%)
Concern about increased risk	16 (27.1%)
Shortage of medication	14 (23.7%)

COVID-19: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease 2019

admitted that the treatment has been interrupted due to their own worries. Fourteen patients particularly using hydroxy-chloroquine for their rheumatic diseases have been found to interrupt their treatment reluctantly, due to the difficulties in procuring the drug since it has been taking part in the treatment of COVID-19.

Case description

The case with COVID-19 was a 14-year-old female diagnosed with seronegative polyarticular JIA in August 2019. Initially, she has received methotrexate approximately for

3 months and due to gastrointestinal adverse reactions, it has been switched to leflunomide.

In the 3rd week of April, her father and uncle have had a diagnosis of COVID-19 requiring hospitalization. On the 4th day of household contact, she has been admitted to the hospital with fever and other suspicious symptoms. The CT of the case is given in Fig. 1. The diagnosis of COVID-19 has been confirmed by a history of contact, consistent clinical features, and a positive PCR test in May 2020. Timeline representation and clinical evolution of the case is given in Fig. 2.

Table 5 Patients suspected of coronavirus disease-2019

Attendance at a hospital (n=9)	Rheumatic disease	Disease duration (mo)	Comorbid diseases	Current treatment	BCG status	Treatment interruption	Symptoms	Contact history	Chest X-ray (n=6)	CT (n=4)	PCR (n=9)	Confirmed diagnosis
15-y M	oJIA + FMF	41	–	Methotrexate, Etanercept, Colchicum	Neg	No	Asymptomatic	Mother	–	–	Neg	No
16-y M	ERA + FMF	85	–	Adalimumab, Colchicum	Pos	No	Fever, arthralgia, myalgia	No	Normal	Normal	Neg	No
11-y M	SoJIA	54	–	Tocilizumab	Pos	No	Asymptomatic	Cousin	Normal	–	Neg	No
16-y F	RF + PoJIA + FMF	90	–	Abatacept, Leflunomide	Pos	No	Cough	No	Normal	–	Neg	No
17-y M	ERA	64	–	Adalimumab	Pos	No	Fever, sore throat	Father	Normal	Normal	Neg	No
14-y F	RF-PoJIA	9	–	Leflunomide	Pos	No	Fever, cough, fatigue, anosmia, dysgeusia	Father, uncle	Suspicious infiltrates	Ground glass opacity + consolidation	Pos	Yes
13-y F	FMF	77	–	Canakinumab	Pos	Yes*	Fever, arthralgia	No	–	–	Neg	No
10-y M	CAPS	89	–	Canakinumab	Pos	No	Arthralgia	Mother	–	–	Neg	No
12-y F	FMF	78	–	Canakinumab	Pos	Yes*	Asymptomatic	Father, brother	Normal	Normal	Neg	No

*Inadequate access to health care. *BCG* Bacillus Calmette-Guérin, *CT* Computed tomography, *PCR* Pharyngeal swab COVID-19 nucleic acid test, *oJIA* Oligoarthritis juvenile idiopathic arthritis, *FMF* Familial Mediterranean fever, *Enthesitis-related arthritis*, *SoJIA* Systemic-onset arthritis, *RF-PoJIA* Rheumatoid factor -positive polyarthritis, *RF-PoJIA* RF-negative polyarthritis, *CAPS* Cryopyrin-associated periodic fever syndrome, *neg* negative, *pos* positive

Discussion

In our cohort, consisting of patients who received nbD-MARDs and bDMARDs for various rheumatic diseases, one patient who had a history of household exposure has been diagnosed with COVID-19. In the pandemic period, none of the patients in our cohort have experienced a severe health status, including the one diagnosed with COVID-19 who recovered with an uncomplicated course.

Similar to the previous coronavirus outbreaks, SARS-CoV-2 infection seems to influence children less prevalently, and the course of the disease appears to be milder compared with adults [11–14]. Although there is no clear-cut

explanation, some relevant speculations have been asserted. Since children are different from adults in several aspects, such as immune defence functions against viruses, they have a distinctive feature of eliminating the viral disease [12, 15]. Differences in the expression and function of ACE-2 receptor, playing a crucial role in the invasion capacity of COVID-19, sets precedent relevance to the issue [12, 14, 16, 17].

The current epidemiological studies show that children primarily contract the disease through household exposure, but rarely vice versa [18–20]. The incubation period may differ in adults and children, making it challenging to identify the primary source [21]. In our case, the virus has been transmitted from father or uncle. The prevalence of the disease in adults seems to be a significant reason for the parents being the index case of the infection in the family. On the other hand, children’s social ecologies and the probability of contact with contamination sources can concretize the difference. In our cohort, COVID-19 has not been detected in household contacts, supporting the claim that children are less likely to become infected. On the contrary, several sources suggest children are just as likely as adults to become infected but are less likely to be symptomatic or develop severe symptoms [12, 18, 22].

Another point is that children do not seek medical attention as they overcome the disease, usually without demonstrating any sign or symptom [13, 22]. Correspondingly, more than half of our patients with household contacts have not been taken to the hospital as they were asymptomatic. When this point was mentioned, all the parents have stated that they strictly adhered to home-based quarantine and social distancing rules. Psychosocial distress, the fear of social stigma, or lack of awareness of the possible

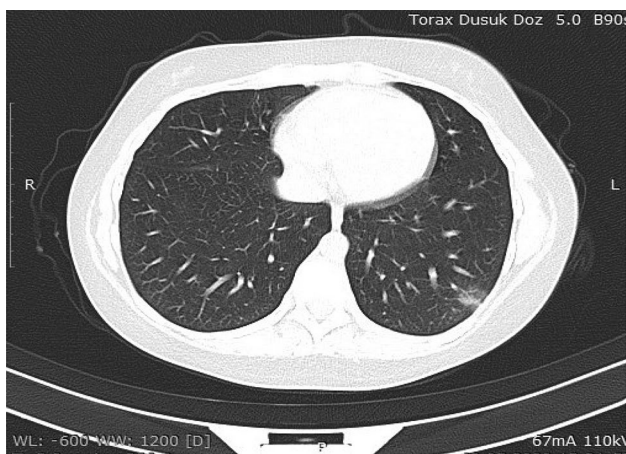


Fig. 1 14-year-old female with confirmed coronavirus disease (COVID-19). CT image shows perivascular distributed ground-glass opacity with superimposed consolidation in the posterobasal segment of the left lung

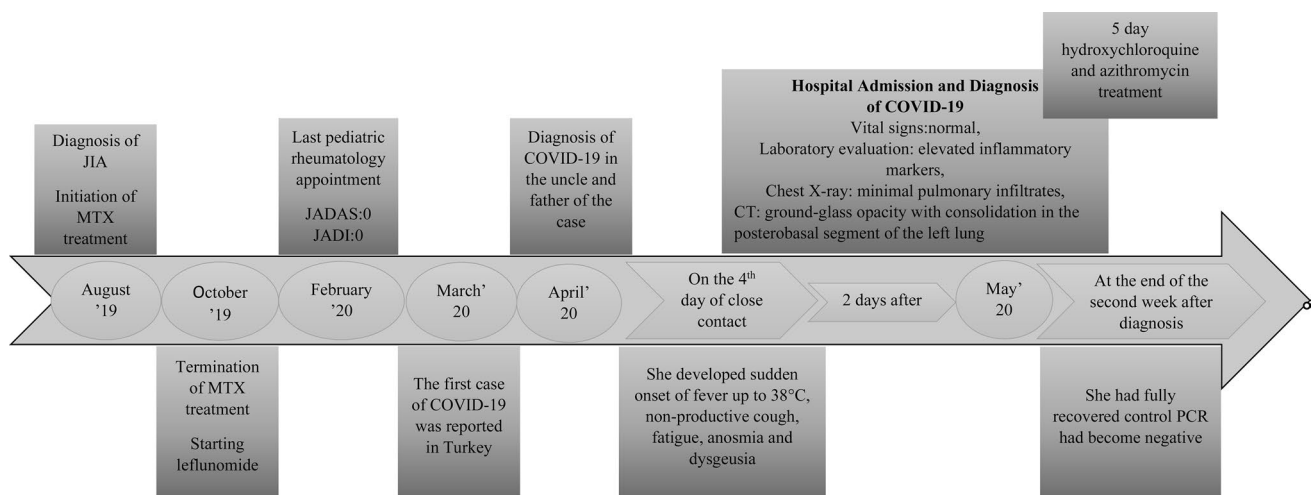


Fig. 2 Timeline depiction of a 14-year-old female with seronegative polyarticular JIA, later diagnosed with COVID-19

consequences of the pandemic may be the other likely reasons kept them from seeking medical help.

Indeed, as still developing organisms, children may be more susceptible to some infections. Especially those with immunocompromised states are vulnerable to various viral or bacterial agents (such as tuberculosis) and may encounter a more severe disease course [23, 24]. Hence, the screening of the patients, particularly those receiving nbDMARDs and bDMARDs, for such common infections is a part of a routine in pediatric rheumatology practice. Novel coronavirus demonstrating high morbidity and mortality worldwide has raised substantial concern for the patients with immune-related conditions and subspecialties as rheumatology dealing with their management [24, 25]. The current evidence suggests not withdrawing the immunosuppressive treatment and no need for additional dose adjustment during the pandemic process unless physician indication or presence of specific symptoms [7, 8, 16, 24–27]. Although the current guidelines relevant to the topic, yet available online, are mostly based on the adult series, they served as an essential guide to elucidate multiple issues yet not resolved in this field [9, 28, 29].

Some preliminary work has been carried out in the early period of the pandemic from jeopardous regions to investigate the association between SARS-CoV-2 and immunosuppressive drugs. In a report from Italy on adult patients with chronic arthritis treated with DMARDs, there was no increased risk of respiratory or life-threatening complications among the confirmed and suspected cases [30]. Considering both the average age of the cohort and the nature of the disease, the result may seem unexpected. Another report presented from one of the most affected regions in Italy notified no confirmed or suspected cases of COVID-19 in 123 children with rheumatic diseases (the majority of JIA) on bDMARDs treatment [31]. The limitation of the report, a methodologically inspiring and pioneering source, is the size and distribution of the sample. In another report from the same region of Italy, among 530 patients, 54 of whom were children, three confirmed cases with mild symptoms were informed, and it was underlined that the compliance of the social distancing might be reflected in the results [32]. In a recent report from Kazakhstan, SARS-CoV-2 infection was not reported among children with rheumatic diseases treated with immunosuppressive antirheumatic drugs [33]. Among the patients in our cohort, 18 were close contacts who have been socially interacted with the confirmed cases, of whom 17 were with household members. Among the patients with a history of contact, three have developed symptoms, and only one has been diagnosed with COVID-19. Because all of the contact children could not be tested, a definite ratio of the diagnosis is hard to be given which is a key problem with most of the literature, still, the infection did not cause any severe symptoms or complications apparently.

In rheumatology practice, questioning the compliance of the patients to the treatment is the principal point in the follow-up of complications and the decision of treatment switch. Given the ongoing concerns about the use of immunosuppressants, we initially interrogated whether they did interrupt the treatment or not. The treatment of 59 (14.3% of the study cohort) patients have been interrupted under the control of the parents due to the circumstances during the pandemic. The conspicuous reason was that patients treated with infusion therapy or who used drugs in subcutaneous form could not provide access to health institutions. Noteworthy was the concern that treatment would increase the risk, as expected. These results underline the importance of patient–doctor communication throughout the patient’s entire treatment process.

Although different centres continue to convey their experiences on the issue, another point is whether the rheumatic diseases have a higher risk of COVID-19 by themselves. On the one hand, it is argued that autoinflammatory recurrent fever syndromes, such as FMF may have a protective role in the pandemic, while on the other hand, it preoccupied that it may worsen the infection by contributing to the exaggerated immune response [15]. Moreover, SLE, a prototype of the autoimmune diseases, is considered to create a predisposition for SARS-CoV-2 and associated with a more complicated disease course due to ACE-2 hypomethylation and overexpression [15]. In a recent study from Turkey, no risk of severe disease or infection in terms of COVID-19 disease was detected in patients diagnosed with autoinflammatory diseases using biologic treatment and/or colchicine therapy [34]. The limited resources available indicate that rheumatic diseases, generally heterogeneous and associated with immune dysregulation, and various immunosuppressive drugs used in their treatment do not pose a risk for COVID-19. Our experiment is in line with the previous results.

As in adults, the most common symptoms are fever and dry cough.[11, 13, 18, 35]. Gastrointestinal symptoms may also accompany mostly in children [7, 20]. Among our patients, musculoskeletal system symptoms have been in the foreground. Since similar complaints are encountered in the course of rheumatic diseases, the hospital attendance rate was low among the patients suffering from arthralgia, myalgia, and fever during the pandemic process and without a history of contact. Therefore rheumatological syndromes and the common clinical manifestations of COVID-19 require the careful approach of rheumatologists [27].

Another link between the field of rheumatology and the current pandemic is the shared drugs commonly used in rheumatology and recently included in the management of COVID-19 [25, 36]. In the light of *in vivo* and *in vitro* studies, antiviral effects of some antirheumatic drugs came to the fore in the process [37–40]. In our patients receiving hydroxychloroquine therapy, we neither encountered an

exacerbation associated with current autoimmune diseases nor a severe impact of the pandemic. However, in other respects, the alliance has caused a shortage of drug supply for rheumatology patients within the early period of the pandemic [41, 42] also for 23.7% of our cohort. Providing control and taking precautions can prevent patients with rheumatic diseases from encountering such circumstances. The only case diagnosed with COVID-19 in our cohort has been using leflunomide, which is another nbDMARDs that have been demonstrated to have antiviral capacity [40, 43]. Nevertheless, leflunomide is not one of the drugs shining in the strategy against COVID-19 [40].

Glucocorticoids and IVIG, which are used in many fields of medicine and are frequently used in rheumatology, are the first remedies for COVID-19, but have failed to take part in routine use [6, 25]. The fact that glucocorticoids may increase virus replication on one hand, and have potent anti-inflammatory effects, on the other hand, led to a contradiction in pandemic and this controversy extends to the management of chronic patients already under glucocorticoid therapy [25, 40]. When we go back over our data, there has been no active usage of steroid or IVIG among the contacted patients.

Given the similarities of the cytokine storm syndromes, biologic DMARDs gained prominence in the era of SARS-CoV-2 [24, 40, 44, 45]. Particularly tocilizumab is an indispensable treatment approach in the management of severe disease [25, 46]. In our cohort, an 11-year-old male patient with sJIA under tocilizumab treatment who had a history of contact with a confirmed case has remained asymptomatic, and the PCR result has been negative. At a large adult cohort from Italy, one of the two cases with COVID-19 was using tocilizumab. In this report, the role of biological agents in acute respiratory distress syndrome was emphasized, and it was pointed out that this patient might lack immune triggers [47]. Even though the experiences of rheumatology patients on tocilizumab therapy have been a guide, it has not yet been possible to consider their place in the risk cluster.

The countries with the inclusion of BCG vaccination in their national vaccination programs were considered to show a lower contagion and mortality rate, suggesting that the vaccine may induce trained immunity for SARS-CoV-2 [48]. Since our country is one of the regions where BCG is routinely administered, the majority of those surveyed (88.4%) have been vaccinated. Besides, the patients are regularly screened for tuberculosis before and throughout biological treatment. There is no definitive proof of causality that justifies the protective role of BCG vaccination [49]. Moreover, one should not overlook the differences in demographic, social and genetic structure of the populations while assessing the link to BCG and COVID-19.

As per the quarantine and social isolation policy, while conducting the study, face-to-face communication with the

patients could not be established and a control group could not be taken as a limitation. Moreover, the relatively low rate of children attending the hospital may influence the frequency of detected cases and thus the results. The consistency in the limited number of the reports presented so far is worth mentioning.

We have presented our experience by in-depth research with a large population consisting of children with various rheumatic diseases under immunosuppressive treatment while the link between antirheumatic drugs and SARS-CoV-2 was on the table. In addition to the comorbid conditions and drugs, questioning the BCG status which is a debate topic in the era of the pandemic has enabled the evaluation of the results from various aspects.

Although circumstances, such as compliance in social distancing rules, transmission patterns, attitude following contact may have influenced the results, various rheumatic diseases in our cohort and immunosuppressive treatment do not seem to pose an additional risk. On the contrary, abrupt withdrawal of these drugs may lead to clinical instability, exacerbation of the underlying disease, and worse consequences. Moreover, one should be alert in terms of triggering disease exacerbations related to COVID-19. On the other hand, it is essential to ensure the families are informed with the right resources and not to lose the doctor–patient communication without disregarding their fears and concerns. What is needed is a cross-national study involving larger populations and assessing the long-term effects and safety profiles of the mentioned drugs.

Author contributions All authors contributed to the study design. N.AA and R.O were responsible for conception of the work. O.K, F.G.D, G.K, F.C, A.T, S.G.K and H.E.S were responsible for collection of data and analysis. All authors were responsible for the interpretation of data. O.K and N.AA participated in the writing and validation of the manuscript. All authors take full responsibility for the integrity of the study and approved the final and revised manuscript.

Funding This study was funded by Scientific Research Projects Coordination Unit of Istanbul University. Project Number: 36852. No other specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Compliance with ethical standard

Conflict of interest Author O.K, Author F.G.D, Author G.K, Author F.C, Author A.T, Author S.G.K, Author H.E.S, Author R.O and Author N.AA declare that they have no conflict of interest including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials. All authors declare that they have no relationship with pharm agencies.

Ethical approval Approval was obtained for the study from the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approved: May 2020-62254). Informed consent was obtained from

the legally authorized representatives of our patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Our article has been shared on the ‘research square platform’ as a preprint (<https://doi.org/10.21203/rs.3.rs-36583/v1>).

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