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

Oya Koker · Fatma Gul Demirkan · Gulsah Kayaalp · Figen Cakmak · Ayse Tanatar · Serife Gul Karadag · Hafize Emine Sonmez · Rukiye Omeroglu · Nuray Aktay Ayaz

Received: 8 June 2020 / Accepted: 24 July 2020 / Published online: 2 August 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

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...
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, sulphasalazine); biologic DMARDs (etanercept, adalimumab, infliximab, tocilizumab, anakinra, canakinumab, abatacept, rituximab); janus kinase (JAK) enzyme inhibitors (tocitinitib). 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 ± 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 oesteitis 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 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 (46.2) |
| 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, oesteitis syndrome, JSLE Juvenile systemic lupus erythematosus, JSc Juvenile scleroderma, JDM Juvenile dermatomyositis, MCTD Mixed connective tissue disease, PAN Polyaarteritis nodosa
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 2 | Demographic and clinical manifestations of patients with juvenile idiopathic arthritis |
|---------|-----------------------------------------------------------------------------------|
| **Age at the study (years), med (min–max)** | 12.5 (2–20) |
| **Gender, n (%)** | |
| 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, n (%); 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, n (%); 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, n (%); 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

| 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, n (%)** | 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, n (%); 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, n (%); 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, n (%); 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
admitted that the treatment has been interrupted due to their own worries. Fourteen patients particularly using hydroxychloroquine 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          | _        | No                  |

*Inadequate access to health care. **BCG** Bacillus Calmette-Guerin, **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 syndrome, neg negative, pos positive
Discussion

In our cohort, consisting of patients who received nbDMARDs 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 immuno suppressive 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 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.
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).

References

1. World Health Organization (WHO).org [Internet]. Coronavirus disease (COVID-19) outbreak situation 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed 25 May 2020

2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Med Res 7(1):11. https://doi.org/10.1186/s40779-020-00240-0

3. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzione S, Rizzardini G, Antinori S, Galli M (2020) COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 38(2):337–442.

4. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY (2016) Coronavirus – drug discovery and therapeutic options. Nat Rev Drug Discov 15(5):327–347. https://doi.org/10.1038/nrd.2015.37

5. Cron RQ, Chatham WW (2020) The Rheumatologist’s Role in COVID-19. J Rheumatol 47(5):639–642. https://doi.org/10.3899/jrheum.2003344

6. Ferro F, Elefante E, Puxeddu I, Baldini C, Bartoloni E, Baratè C, Galimberti S, Talarico R, Mosca M, Bombardieri S (2020) COVID-19: the new challenge for rheumatologists First update. Clin Exp Rheumatol 38(3):373–382

7. Sarzi-Puttini P, Marotto D, Antivalle M, Salaffi F, Atzeni F, Maconi G, Monteleone G, Rizzardini G, Antinori S, Galli M, Ardizzione S (2020) How to handle patients with autoimmune rheumatic and inflammatory bowel diseases in the COVID-19 era: An expert opinion. Autoimmunity Rev. https://doi.org/10.1016/j.autrev.2020.102574

8. Haşçak V, Yildiz M, Adrovic A, Barut K, Kasapçopur Ö (2020) Childhood Rheumatic Diseases and COVID-19 Pandemic: An Intriguing Linkage and a New Horizon. Balkan Med J. https://doi.org/10.4274/balkanmedj.galenos.2020.4.43

9. Mikuls TR, Johnson SR, Fraenkel AR, Baden LR, Bermas BL, Chatham W, Cohen S, Costenbader K, Gravallese EM, Kalil AC, Weinblatt ME, Winthrop K, Mudano AS, Turner A, Saag KG (2020) American College of Rheumatology Guidance for the Management of Adult Patients with Rheumatic Disease During the COVID-19 Pandemic. Arthritis Rheumatol (Hoboken, NJ). https://doi.org/10.1002/art.41301

10. Cron RQ, Chatham WW (2020) The question of whether to remain on therapy for chronic rheumatic diseases in the setting of the covid-19 pandemic. J Rheumatol. https://doi.org/10.3899/jrheum.2004924

11. Shen Q, Guo W, Guo T, Li J, He W, Ni S, Ouyang X, Liu J, Xie Y, Tan X, Zhou Z, Peng H (2020) Novel coronavirus infection in children outside of Wuhan. Chinese Pediatric Pulmonol 55(6):1424–1429. https://doi.org/10.1002/ppul.24762

12. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S (2020) Epidemiology of COVID-19 Among Children in China. Pediatrics. https://doi.org/10.1542/peds.2020-0702

13. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D (2020) Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. https://doi.org/10.1016/s1473-3099(20)30198-5

14. Li Y, Guo F, Cao Y, Li L, Guo Y (2020) Insight into COVID-19 for pediatricians. Pediatr Pulmonol 55(5):E1–E4. https://doi.org/10.1002/ppul.24734

15. Batu ED, Özen S (2020) Implications of COVID-19 in pediatric rheumatology. Rheumatol Int 40(8):1193–1213. https://doi.org/10.1007/s00296-020-04612-6

16. Hedrich CM (2020) COVID-19 – Considerations for the paediatric rheumatologist. Clin Immunol (Orlando, Fla) 214:108420. https://doi.org/10.1016/j.clim.2020.108420

17. Lucchino B, Di Franco M, Conti F (2020) COVID-19: an unexpected indication for anti-rheumatic therapies? Rheumatology (Oxford, England) 59(6):1200–1203. https://doi.org/10.1093/rheumatology/kea194

18. Zheng F, Liao C, Fan QH, Chen HB, Zhao XG, Xie ZG, Li XL, Shen Q, Guo W, Guo T, Jiang F, Jiang Z, Tong S, Wu J, Luo X, Wang Z, Zhou YY, Bai Y, Wu XY, Jin RM (2020) Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei China. Curr Med Sci 40(2):275–280. https://doi.org/10.1007/s11596-020-2172-6

19. Chen F, Liu ZS, Zhang FR, Xiong RH, Chen Y, Cheng XF, Wang WY, Ren J (2020) [First case of severe childhood novel coronavirus pneumonia in China. Zhonghua er ke za zhi = Chinese J Pediatrics 58(3):179–182. https://doi.org/10.3790/mao.issn.0578-1310.2020.03.003

20. Choi SH, Kim HW, Kang JM, Kim DH, Cho EY (2020) Epidemiology and clinical features of coronavirus disease 2019 in children. Clin Exp Dermatol 63(4):125–132. https://doi.org/10.3345/ced.2020.00535

21. Cao Q, Chen YC, Chen CL, Chiu CH (2020) SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics. J Formosan Med Assoc Taiwan yi zhi 119(3):670–673. https://doi.org/10.1016/j.jfma.2020.02.009

22. Zimmermann P, Curtis N (2020) Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options In Children. Pediatr Infect Dis J 39(5):355–368. https://doi.org/10.1097/INF.0000000000002660

23. Aygun D, Sahin S, Adrovic A, Barut K, Cokugras H, Camcıoglu Y, Kasapçopur O (2019) The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study. Clin Rheumatol 38(4):1025–1030. https://doi.org/10.1007/s10067-018-4367-9

24. Liccari F, Giani T, Baldini L, Favalli EG, Caporal R, Cimaz R (2020) COVID-19 and what pediatric rheumatologists should know: a review from a highly affected country. Pediatric Rheumatol Online J 18(1):35. https://doi.org/10.1186/s12969-020-00422-z

25. Ceribelli A, Motta F, De Santis M, Ansari AA, Ridgway WM, Gershwin ME, Selmi C (2020) Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. J Autoimmun 109:102442. https://doi.org/10.1016/j.jaut.2020.102442

26. Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I, Talarico R, Mosca M, Bombardieri S (2020) COVID-19: the new challenge for rheumatologists. Clin Exp Rheumatol 38(2):175–180

27. Misra DP, Agarwal V, Gazparyan AY, Zimba O (2020) Rheumatologists’ perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol 39(7):2055–2062. https://doi.org/10.1007/s10067-020-05073-9
28. European League Against Rheumatism (EULAR).org [Internet]. Guidance for patients COVID-19 outbreak 2020. Available from: https://www.eular.org/eular_guidance_for_patientscovid19_outbreak.cfm Accessed 25 May 2020.

29. Paediatric Rheumatology INternational Trials Organisation (PRINTO).org [Internet]. PRES recommendations in the coronavirus era - COVID-19,2020. Available from: https://www.printo.pedia-tric-rheumatology/ Accessed 25 May 2020

30. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C (2020) Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 79(5):667–668. doi.org/10.1136/annrheumdis-2020-217424

31. Filocamo G, Minoia F, Carbogno S, Costi S, Romano M, Cimaz R (2020) Absence of severe complications from SARS-CoV-2 infection in children with rheumatic diseases treated with biologic drugs. J Rheumat. doi.org/10.3899/jrheum.200483

32. Favalli EG, Ingegnoli F, Cimaz R, Caporali R (2020) What is the true incidence of COVID-19 in patients with rheumatic diseases? Ann Rheum Dis. doi.org/10.1136/annrheumdis-2020-217615

33. Mukusheva Z, Assylbekova M, Poddighé D (2020) Management of pediatric rheumatic patients in Kazakhstan during the coronavirus disease 2019 (COVID-19) pandemic. Rheumatol Int 40(8):1351–1352. doi.org/10.1007/s00296-020-04613-5

34. Haslak F, Yildiz M, Adrovic A, Sahin S, Koker O, Aliyeva A, Barut K, Kasapcopur Ö (2020) Management of childhood-onset autoimmune inflammatory diseases during the COVID-19 pandemic. Rheumatol Int. doi.org/10.1007/s00296-020-04645-x

35. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D (2020) Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol 55(5):1169–1174. doi.org/10.1002/ppul.24718

36. Favalli EG, Ingegnoli F, Cimaz R, Caporali R (2020) Dealing with COVID-19 in a Pediatric Rheumatology Unit in Italy. Paediatric Drugs. doi.org/10.1007/s40272-020-00395-2

37. Yao X, Ye F, Peng X, Li Z, Hu D (2020) Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol 55(5):1169–1174. doi.org/10.1002/ppul.24718

38. Haslak F, Yildiz M, Adrovic A, Sahin S, Koker O, Aliyeva A, Barut K, Kasapcopur Ö (2020) Management of childhood-onset autoimmune inflammatory diseases during the COVID-19 pandemic. Rheumatol Int. doi.org/10.1007/s00296-020-04645-x

39. Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Ladadie K, Martinon F, Gras G, Lebon P, Ng LFP, de Lamballerie X, Le Grand R (2018) Paradoxical Effect of Chloroquine Treatment in Enhancing Chikungunya Virus Infection. Viruses. doi.org/10.3390/v10050268

40. Perricone C, Triggianese P, Bartoloni E, Cafauro G, Bonifacio AF, Bursi R, Perricone R, Gerli R (2020) The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. J Autoimmun. doi.org/10.1016/j.jaut.2020.102468

41. Scuccimarri R, Sutton E, Fitzcharles MA (2020) Hydroxychloroquine: A Potential Ethical Dilemma for Rheumatologists during the COVID-19 Pandemic. J Rheumatol. doi.org/10.3899/jrheum.200369

42. Costi S, Caporali R, Cimaz R (2020) Dealing with COVID-19 in a Pediatric Rheumatology Unit in Italy. Paediatric Drugs. doi.org/10.1007/s40272-020-00395-2

43. Silva JT, Pérez-González V, Lopez-Medrano F, Alonso-Moralejo R, Fernández-Ruiz M, San-Juan R, Brañas P, Folgueira MD, Aguado JM, de Pablo-Gafas A (2018) Experience with leflunomide as treatment and as secondary prophylaxis for cytomegalovirus infection in lung transplant recipients: A case series and review of the literature. Clin Transplan. doi.org/10.1111/ctr.13176

44. Georgiev T (2020) Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. Rheumatol Int 40(5):825–826. doi.org/10.1007/s00296-020-04570-z

45. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 395(10229):1033–1034. doi.org/10.1016/s0140-6736(20)30628-0

46. Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, D’Offizi G, Marchioni L, Murachelli C, Ippolito G, Antinori A (2020) National Institute for the Infectious Diseases “L. Spallanzani”, IRCCS Recommendations for COVID-19 clinical management. Infectious Dis Rep 12(1):8543. doi.org/10.4081/idr.2020.8543

47. Conticini E, Bargagli E, Bardelli M, Rana GD, Baldi C, Cameli P, Gentilesci S, Bennett D, Falsetti P, Lanzarone N, Bellisai F, Barreca C, D’Alessandro R, Cantarini L, Frediani B (2020) COVID-19 pneumonia in a large cohort of patients treated with biological and targeted synthetic antirheumatic drugs. Ann Rheum Dis. doi.org/10.1136/annrheumdis-2020-217681

48. Netea MG, Giamaretlos-Bourboulis EJ, Dominguez-Andrés J, Curtis N, van Crevel R, van de Veerdonk FL, Bonten M (2020) Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection. Cell 181(5):969–977. doi.org/10.1016/j.cell.2020.04.042

49. O’Neill LAJ, Netea MG (2020) BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol. doi.org/10.1038/s41577-020-0337-y