Clinical course of COVID-19 in children with rheumatic disease under biologic therapy

Sirs,

Since the beginning of the COVID-19 pandemic Turkey, more than two million people have been infected and more than 20,000 people died. Although children are infected less frequently and generally have milder symptoms of COVID-19, the number of patients with a more severe clinical course as multisystem inflammatory syndrome in children (MIS-C) is increasing significantly (1). Comorbidities and immunosuppression are known as the risk factors for the worse course of COVID-19 infection (2). However, it has not been shown exactly how biological disease-modifying anti-rheumatic drug (bDMARD)s, used frequently in our paediatric rheumatology practice, and the underlying rheumatological diseases affect the clinical course of COVID-19. These treatments are work by targeting the pathways on the immune system by cytokine blockade, thus this can result in immune dysregulation in the body. Emerge of serious infections have been reported in adults and children treated with bDMARDs (3). Here, we aimed to reveal the outcome of COVID-19 infection in our patients with paediatric rheumatic disease and treated with bDMARDs.

Our Paediatric Rheumatology clinic, Umraniye Training and Research Hospital is one of the largest tertiary paediatric rheumatology centres in Istanbul, Turkey. 436 children are currently using biological treatments for different rheumatological diseases in our clinic. During the period between April 1, 2020, and December 1, 2020, the patients who received bDMARDs were evaluated at the regular outpatient clinic follow-up or by telemedicine with a maximum of three-month intervals. Clinical and demographic characteristics, COVID-19 data, and outcomes of these patients were retrospectively collected. Informed consent was obtained from all patients and their legal guardians for the use of personal and clinical data.

Out of the 436 patients treated with bDMARDs, 39 children were infected with COVID-19. The diagnosis was confirmed in 37 patients by RT-PCR (nasal pharyngeal swab) and in two by an antibody test. All patients were under biological treatment when they were diagnosed with COVID-19 or MIS-C. When the patient was diagnosed with COVID-19, depending on the severity of the COVID-19 symptoms and the type of bDMARD being administered, the use of bDMARDs were ceased according to the ACR and PReS recommendations on a patient basis (4, 5).

Twenty-two (56.4%) patients were female (17 male, %43.6) and the median age of patients were 12.3 years (min-max:1.2-20.9).The primary diagnosis of patients were as follows; 20 juvenile idiopathic arthritis (JIA) (six were systemic subtype), 12 systemic autoinflammatory disease (SAID)s (seven were familial Mediterranean fever, two were hyperimmunoglobulin D syndrome, one were cryopyrin-associated periodic syndrome, one were idiopathic recurrent pericarditis and one were undefined subtype), three vasculitis (two were deficiency of adenosine deaminase-2 (DADA-2) and one were polyarteritis nodosa), three chronic recurrent multifocal osteomyelitis (CRMO) and one Sjögren's syndrome. Four patients had also additional comorbid diseases (hypertension, Crohn's disease, hereditary spherocytosis, and chronic renal failure, in individual patients) (Table I). Prior to COVID-19 infection, 13 patients (33.3%) were using canakinumab, seven were on infliximab(18%), five were on adalimumab (12.8%), four were on etanercept (10.2%), four were on tocilizumab (10.2%), three were on anakinra (7.7%), two were on rituximab (5.1%), and one was on tofacitinib (2.6%). Additionally, 14 patients were using conventional DMARD (11 methotrexate, two leflunomide, and one salazopyrin), 12 were colchicine, two were mycophenolate mofetil and one was cyclosporine. Six patients were also receiving ≤0.5mg/kg/day dosage steroid treatment (Table I). Of the 39 patients, 21 had at least one COVID-19-related symptom (fever, cough, diarrhoea, myalgia, anosmia, and/or rash), while 18 patients were asymptomatic. Asymptomatic patients were diagnosed after screening tests performed due to their contact with a person diagnosed with COVID-19. There were COVID-19 positive patients in the families of our 30 patients. Five of our patients had contact with COVID-19 positive case outside of their family. No laboratory or imaging tests were performed for asymptomatic patients and they were followed up without treatment at home isolation. Laboratory tests revealed that fourteen patients had elevated acute phase reactants, six had elevated D-dimer levels, three had lymphopenia (<1000/mm^3), and three

Table I. Demographic and clinical characteristics of patients.

Characteristics	Number of patients (n), percentage (%), or median (minimum-maximum)
Gender (female/male)	22/17, (56.4%/43.6%)
Age (year)	12.3 (1.2-20.9)
Primary rheumatic disease	
Systemic onset JIA	6 (15.3%)
Other JIA	14 (35.9%)
FMF	7 (17.9%)
HIDS	2 (5.1%)
CAPS	1 (2.5%)
IRP	1 (2.5%)
Undefined SAID	1 (2.5%)
DADA-2	2 (5.1%)
PAN	1 (2.5%)
CRMO	3 (7.7%)
Sjögren's syndrome	1 (2.5%)
Comorbid diseases	
Chronic renal failure	1 (2.5%)
Crohn's disease	1 (2.5%)
Hereditary spherocytosis	1 (2.5%)
Hypertension	1 (2.5%)
Biologic DMARDs	
Etanercept	4 (10.2%)
Infliximab	7 (17.9%)
Adalimumab	5 (12.8%)
Tocilizumab	4 (10.2%)
Canakinumab	13 (33.3%)
Anakinra	3 (7.7%)
Rituximab	2 (5.1%)
Tofacitinib	1 (2.5%)
Concomitant conventional DMARD or immunosuppressive treatments	
Methotrexate	11 (28.2%)
Leflunomide	2 (5.1%)
Salazopyrin	1 (2.5%)
Mycophenolate mofetil	2 (5.1%)
Cyclosporine	1 (2.5%)
Colchicine	12 (30.7%)
Corticosteroid (≤ 0.5mg/kg/day)	6 (15.3%)
COVID-19-related symptom	
Fever	17 (43.6%)
Cough	15 (38.5%)
Diarrhoea	2 (5.1%)
Myalgia	6 (15.3%)
Anosmia	1 (2.5%)
Rash	1 (2.5%)
Asymptomatic	18 (46.1%)
Laboratory and radiologic results	
Elevated acute phase reactants	14 (35.9%)
Elevated D-dimer	6 (15.3%)
Lymphopenia (<1000/mm^3)	3 (7.7%)
Hyperferritinaemia	3 (7.7%)
COVID-19 compatible CT findings	2 (22%)*
Outcome	
Hospitalisation	20 (51.3%)
Paediatric intensive care unit admission	1 (2.5%)
Presence of MIS-C	5 (12.8%)
Presence of myocardial dysfunction	1 (2.5%)
Mortality	1 (2.5%)

*It shows the proportion among the total number of individual that examined with CT.

CAPS: cryopyrin-associated periodic syndrome; CRMO: chronic recurrent-multifocal osteomyelitis; CT: computed tomography; DADA-2: deficiency of adenosine-deaminase-2; DMARD: disease-modifying anti-rheumatic drug; FMF: familial Mediterranean fever; IRP: idiopathic recurrent pericarditis; JIA: juvenile idiopathic arthritis; HIDS: hyperimmunoglobulin-D syndrome; MIS-C: multisystem inflammatory syndrome in children; PAN: polyarteritis nodosa; SAID: systemic autoinflammatory disease.

had hyperferritinaemia. Viral pneumonia compatible findings were detected in three of nine patients who underwent computed tomography.

Hospitalisation was required in 20 patients (51.3%) at median of 7-days (min-max: 3-17) and paediatric intensive care unit admission in one. Five patients developed MIS-C and one of these patients was followed up in the paediatric intensive care unit. When we look at the distribution of underlying systemic disease and treatments in patients with MIS-C, one patient had CRMO with etanercept treatment, one had DADA-2 and was on infliximab, one had undefined SAID and was on tocilizumab, and two had systemic JIA and being treated with anakinra or canakinumab. Myocardial dysfunction was developed in one patient and he died despite corticosteroid, intravenous immunoglobulin, anti-interleukin-1, plasma exchange, and extracorporeal membrane oxygenation treatments. This patient had a previous case of macrophage activation syndrome (MAS) attack and was diagnosed with systemic JIA. Some differences were observed between the MIS-C and the previous MAS course. Clinically, he had conjunctivitis, resistant fever despite to all treatments, and cardiac decompensation in MIS-C course. Additionally in laboratory tests, he had lymphopenia and increased ferritin level (> 40,000 U/L) that did not respond to treatments. The other four patients fully recovered with no remaining morbidity. All demographic and clinical data of the patients are shown in the table.

There is a limited number of studies in the literature on the clinical course of COVID-19 infection in patients with paediatric rheumatic disease who received bDMARDs. To the best of our knowledge, our study is the largest series of children with rheumatic disease in the literature who received bDMARDs and diagnosed with COVID-19 infection. Most of the reported data on adult patients suggested, there was no worsening or only insignificantly increased risk in the course of COVID-19 infection in patients treated with bDMARDs (6, 7). On the contrary, Gianfrancesco *et al*. reported, 107 patients under bDMARDs had lower rates of hospitalisation than those who did not receive these treatments (8). No severe COVID-19 course has also been reported in children with rheumatic diseases (9). COVID-19 infection related symptoms were not observed in nearly half (46%) of our 39 patients who were under bDMARD treatment. MIS-C was shown in five patients, and most of them did not develop any long-term complications. One patient, who died due to MIS-C, had a previous diagnosis of systemic JIA and MAS, and a heterozygous pathogenic mutation in the perforin gene. This patient, who had poor prognostic risk factors, died after myocardial dysfunction that developed based on recalcitrant hyperinflammation. Except for this patient, no COVID-19 related complications were seen in our paediatric cohort treated with bDMARD.

Considering the literature data and the results of our study, it is not possible to say that currently used bDMARDs worsen the course of COVID-19 infection. In patients with underlying risk factors for hyperinflammation, as in one of our patients, COVID-19 may cause mortality regardless of the use of bDMARDs. Whether bDMARDs affect the severity of the disease or not, it is still not true to say that these drugs are protective. Since the cessation of bDMARDs for COVID-risk may cause exacerbation of the primary rheumatic disease, continuing with current treatments seems an appropriate approach. In a patient treated with bDMARD during the active COVID-19 infection period, it may be considered to interrupt the biological treatment on a patient basis by the current biological agent, primary disease status, and clinical findings of COVID-19 infection, according to ACR and PReS recommendations (4, 5).

Acknowledgement

We are grateful to the patients and their families for their cooperation.

Key message

COVID-19 infection does not appear to have a more severe course in rheumatic children under biological therapy.

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Competing interests: none declared.

Clin Exp Rheumatol 2021; 39 (Suppl. 128): S36-37.

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