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CLINICAL LETTER

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Optimal biologics for juvenile idiopathic arthritis in an infection with SARS-CoV-2 α-variant

To the Editor,

The worldwide pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still raging and continues to have a serious impact on global health care and the economy across nations. The risk of severe COVID-19 is of concern for patients with rheumatic diseases (RMDs) using disease-modifying anti-rheumatic drugs (DMARDs) including biologics.[1] COVID-19 appears to show a milder clinical course in children than in adults, but multisystem inflammatory syndrome in children (MIS-C) occurs as a life-threatening complication due to unknown causes.[2] The emergence of newly identified mutant SARS-CoV-2 lineages, reported in the UK (B.1.1.7), South Africa (B.1.351), Brazil (P.1), and India (B.1.617.1–3), is a grave menace, which is worsening the continued pandemic.[3] However, limited information is available about the management of RMDs in childhood. We herein report a patient with juvenile idiopathic arthritis (JIA) who was infected by an α-variant of SARS-CoV-2 called lineage B.1.1.7 while under tocilizumab treatment.

The patient was a 7 years-old girl who was diagnosed as having systematic JIA at 2 years of age. She achieved remission without macrophage activation syndrome (MAS) for 5 years after the introduction of tocilizumab (8 mg/kg) every 4 weeks and methotrexate (MTX, 7 mg/m^2) weekly. She developed fever and cough three days after her father was diagnosed to have SARS-CoV-2 lineage B.1.1.7 according to a reverse transcription-polymerase chain reaction (RT-PCR) test. The patient presented with a fever of up to 38.0°C for two days, and then, a positive RT-PCR result prompted the girl to be hospitalized at our institution for care and isolation. On admission, she was afebrile and free from respiratory symptoms or desaturation. Chest X-rays showed no abnormality. Laboratory tests were unremarkable as follows: leukocytes, 3.9 × 10^9/L (reference range [rr], 3.3–8.6 × 10^9/L); neutrophils, 1.7 × 10^9/L (rr, 1.5–8.0 × 10^9/L); lymphocytes, 1.6 × 10^9/L (rr, 1.5–7.0 × 10^9/L); hemoglobin, 13.3 g/dl (rr, 11.5–14.4 g/dl); platelet count, 22.3 × 10^9/L (rr, 18–51 × 10^9/L); C-reactive protein, 0.01 mg/dl (rr, <0.14 mg/dl); lactate dehydrogenase, 259 U/L (rr, 175–320 U/L); fibrinogen, 218 mg/dl (rr, 200–400 mg/dl); prothrombin time, 11.1 s (rr, 10.0–13.5 s); D-dimer, <0.5 mg/L (rr, <0.5 mg/L); ferritin, 24.1 ng/ml (rr, 6.2–138.0 ng/ml); and matrix metalloproteinase-3, <10 ng/ml (rr, <10 ng/ml). The serum cytokine levels at the diagnosis of COVID-19 showed slightly elevated levels of TNF-α (26.4 pg/ml; rr, <10 pg/ml), IL-6 (64.1 pg/ml; rr, <10 pg/ml), and IL-8 (41.6 pg/ml; rr, <10 pg/ml). The patient was carefully observed while receiving concomitant oral MTX on scheduled days without antiviral drugs or oxygen therapy. Tocilizumab was postponed for 2 days from the scheduled day, and then administered for 5 days after the resolution of fever. She was uneventfully discharged from the hospital on Day 10 of illness under the sustained remission of JIA, CHAQ-DI of 0. A serum cytokine analysis at discharge showed undetectable levels of TNF-α and IL-8 (<10 pg/ml) and a decreased level of IL-6 (20.7 pg/ml). The activity of primary disease has been stably controlled during and after this episode of COVID-19 without altering the management of JIA.

Our review of all publications and sentinel sources using PubMed, and Google Scholar for citations published after the outbreak of COVID-19 from December 2019 to July 2021, identified six JIA patients diagnosed with COVID-19 during the treatment course of biologic DMARDs (Table 1).[4–6] They all received TNF-α blockers or an anti-IL-1β antibody. This is the first report of infection of SARS-CoV-2 with the lineage B.1.1.7 in a JIA patient receiving tocilizumab therapy. Six of the seven patients including the present girl infected with B.1.1.7 under tocilizumab therapy had a favorable course without complications. Only one patient (case 3) who continued oral prednisolone during the early treatment phase of JIA under canakinumab therapy required oxygen therapy for pneumonia. Of the two patients (case 2: oligoarticular type and case 5: polyarticular type) who discontinued anti-TNF-α treatment, the former patient had a flare-up of the primary disease. Our findings revealed that COVID-19 was curable without serious complications in JIA controlled under biologics, but not steroid therapy. These results support the hypothesis that uncontrolled JIA and its baseline inflammatory state are a risk factor for severe COVID-19, even in children, or that immunosuppression associated with prolonged corticosteroid treatment acts as another risk factor for severe disease.

The current consensus on COVID-19 in children is that immunosuppressive therapy does not significantly increase the risk in pediatric patients with RMDs.[7] Several lines of cohort study indicated that adult or pediatric patients with RMDs under biologic DMARDs have no increased risk of severe COVID-19. Demier et al.[3] reported that 6 of 39 patients with RMDs under biologic therapies with corticosteroids contracted non-severe COVID-19. All of them received low-dose corticosteroids (<0.5 mg/kg/day). These findings support that patients in whom JIA is stably controlled by biologics without/with low-dose prednisolone show favorable outcomes. Opoka-Winiarska et al.[8]

TABLE 1 Summary of the clinical and laboratory findings in all reported pediatric patients with JIA who developed COVID-19 during biologic therapies

Case	1	2	3	4	5	6	7
Time since JIA diagnosis	5 years	11.5 years	2 mo	10 years	2.8 years	NA	NA
SARS-CoV–2 lineage	B.1.1.7	Not tested	preexisting	preexisting	NA	NA	NA
Age at the onset of COVID–19 infection	7 years	12 years	4 years	15 years	12 years	NA	NA
Sex	F	F	F	F	F	NA	NA
JIA subtypes	Systemic	Oligoarticular	Systematic	Oligoarticular	Polyarticular	NA	NA
Biologics: targets (drugs)	Anti-IL–6 receptor (tocilizumab)	Anti-TNF-α (golimumab)	Anti-IL–1β (canakinumab)	Anti-TNF-α (infliximab)	Anti-TNF-α (etanercept)	Anti-TNF-α (etanercept)	Anti-TNF-α (adalimumab)
DMARDs	MTX	MTX	No	MTX	HCQ	No	No
Glucocorticoids	No	No	PSL(1 mg/kg/day)	No	No	No	No
Disease status before COVID–19	Remission	Remission	NA	NA	Remission	NA	NA
Initial symptoms	Fever	Asymptomatic*	Fever, cough	Fever, sore throat	Dry cough	Cough, anosmia	Cough, anosmia
Chest imaging findings	Normal	NA	Lobar consolidation, pleural effusion	Normal	NA	Normal	NA
CRP (mg/dl)	0.01	NA	34.1	0.03	NA	NA	NA
Treatment	No	NA	Lopinavir, ritonavir, oxygen therapy	No	NA	AZM, oseltamivir	HCQ
Interruption of biologics	No	Yes	NA	NA	Yes	NA	NA
Disease status after COVID–19	Remission	Disease flare	NA	NA	Remission	NA	NA
Country origin	Japan	Italy	Spain	Spain	Italy	Turkey	Turkey
References	Our case	Marino, 2020	Calvo, 2021	Calvo, 2021	Marino, 2020	Yildiz, 2020	Yildiz, 2020

Abbreviations: AZM, Azithromycin; CHAQ, Childhood Health Assessment Questionnaire; DI, Disability index; DMARDs, Disease-modifying anti-rheumatic drugs; HCQ, Hydroxychloroquine; JIA, Juvenile rheumatoid arthritis; mos, Months; MTX, Methotrexate; NA, Not available; PSL, Prednisolone; y, Years.

*A PCR test was performed because the patient's sister had been previously diagnosed to have COVID-19.

reported that eight JIA patients on immunosuppressive therapy with no history of infection had anti-SARS-CoV-2 antibodies, although 62 JIA patients did not have a higher seroprevalence of anti-SARS-CoV-2 antibodies than 32 healthy children. In this setting, a more asymptomatic or less symptomatic infection of SARS-CoV-2 may occur in pediatric patients with RMDs than we expected.

Pediatric rheumatologists have recently recognized that MIS-C associated with severe COVID-19 had pathophysiological similarities to hyperinflammatory disorders such as MAS in JIA patients.[2] Anti-cytokine therapy with biologics or corticosteroids is challenging for pediatric patients with severe COVID-19 including MIS-C. Tocilizumab, as administered in the present patient, has been considered as a promising immunomodulatory agent for the control of cytokine storms in severe COVID-19. Several clinical trials suggest that the administration of tocilizumab may be beneficial for the outcomes of severe COVID-19 pneumonia, although it remains unclear which biologic agent is best indicated in mild cases or in children.[9] The present patient showed a mild clinical course without a cytokine storm during tocilizumab therapy. On the contrary, only one prednisolone user (case 3) under canakinumab therapy experienced severe complications of COVID-19 (Table 1). One patient with systemic JIA in the pediatric RMD cohort in Turkey died from MIS-C or the flare-up of MAS without severe COVID-19, despite multi-immunomodulatory therapies, including corticosteroids, biologics, or intravenous immunoglobulins.[3] As mentioned in the American College of Rheumatology Guidance, a limited type of biologics should be continued, and glucocorticoids, with efforts made to reduce the dose as much as possible for controlling an underlying disease. The further accumulation of cases with biologics or glucocorticoids is required to elucidate the pathophysiology of severe COVID-19 in JIA patients.

SARS-CoV-2 lineage B.1.1.7 has rapidly spread worldwide and shown greater transmissibility than previous lineages. This variant B.1.1.7 has shown an increased mortality rate of COVID-19 among elderly populations, but not younger individuals.[10] The risk of B.1.1.7 in COVID-19 has not yet been identified among patients with RMDs. The present patient only developed fever without severe hypercytokinemia during the infection of B.1.1.7. Further investigations are needed to determine the responsible factors for the outcome of COVID-19 in JIA patients concerning the virus strains and loads, age, ethnicity, primary disease activity, and optimal biologic agents. In conclusion, our findings suggest that biologic agents including tocilizumab can be safely used in controlled JIA patients after exposure to SARS-CoV-2 lineages. Some immunomodulatory target therapies may concurrently protect against the reactivation of JIA and the excessive inflammation associated with COVID-19.

KEYWORDS

COVID-19, juvenile idiopathic arthritis, tocilizumab

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CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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