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To the Editor

We read with interest the Editorial by Cron and Chatam (1) suggesting a cytokine storm syndrome (CSS) occurring in response to SARS-CoV-2 infection and, consequently, a possible role for targeted approaches to blocking inflammatory cytokines.

Almost 30% of COVID-19 patients develops severe acute respiratory distress syndrome (ARDS) with high mortality rate. (2) In those critically ill patients, there are both clinical signs and symptoms, as well as laboratory abnormalities, that suggest a CSS is occurring in response to the viral infection. (1)

In contrast with adults, pediatric patients with COVID-19 seem to have a milder clinical course and asymptomatic SARS-CoV-2 infections may be frequent. (3) However, albeit rarely, severe infections may occur even in children, with PICU admission or high-flow ventilation. In a recent Spanish cohort, 60% of confirmed infections in children required hospitalization. (4)

COVID-19 pediatric transmission routes include close contact with family members, exposure to epidemic areas, or both . The school community is a place that can rapidly enhance the spread of a highly infectious virus, and Italian children may have been exposed to SARS-CoV-2 infection weeks before the school lockdown decided by the government.

Several concerns have been raised about children with autoimmune or autoinflammatory conditions characterized by an increased infectious risk, due both to the immune dysregulation of the underlying disease or to its immunosuppressive treatment, including glucocorticoids (GCs), conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic disease-modifying drugs (bDMARDs). However, the increasing knowledge about the pathophysiology of SARS-CoV-2 infection is paradoxically supporting the beneficial role of some well-known anti-rheumatic drugs for the management of severe COVID-19. (5) Preliminary experience has shown that adult patients with chronic arthritis treated with bDMARDs or cDMARDs do not seem to be at increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with the general population. (6) Moreover, in another recent report on patients with Inflammatory Bowel Disease

(IBD) treated with cDMARDS and or bDMARDS none of them was affected by a complicated SARS-CoV-2 related pneumonia. (7)

Pediatric rheumatologists are certainly involved in decisions related to chronic care and management during this difficult period, (8), but to the best of our knowledge there are no published data yet related to the risk of severe complications from SARS-CoV-2 infection in children affected with rheumatic diseases .

In order to investigate the impact of COVID-19 on pediatric patients with rheumatic diseases treated with bDMARDs, with or without cDMARDS, a questionnaire was prepared and administered in our pediatric rheumatology clinics in Milan, Lombardy, the most affected region in Italy. The survey evaluated patients' health conditions, direct exposure to subjects known to be affected by COVID-19, modifications of ongoing DMARDs treatment and potential flares of underlying disease during the early weeks of Italian COVID-19 outbreak. All patients had provided their informed consent for the use of personal and clinical data for scientific purposes, and no patient refused to participate.

Between 25th February and 14th April 2020, we collected data from children treated with bDMARDs and followed in the ASST Pini and Fondazione IRCCS Ca' Granda Policlinico hospitals in Milan. The survey was administered face-to-face to all patients during outpatient clinic visits, or by telephone in those who missed a scheduled visit during the period under review. The final study population included 123 pediatric patients (83F, 62 %, median age 13 years, range 4-20) on bDMARDs for chronic rheumatic diseases (89 with juvenile idiopathic arthrtis, 5 with chronic uveitis, 5 with autoinflammatory disease, 24 with others chronic rheumatic diseases). As shown in **Table 1**, none of them were confirmed cases of COVID-19. Eight children presented mild respiratory symptoms, three of them were family members of adults suspected for COVID-19 infection. In our region diagnostic swabs are not routinely performed, and a case is considered probable in the context of epidemic area and compatible clinical signs and symptoms (fever, cough, dyspnea). No patient stopped ongoing therapy or needed hospitalization. All contacted patients

declared that they had adopted a preventive strategy against COVID-19 based on social distancing and use of personal protective equipment, even if this usually happened only after the beginning of the outbreak.

Our results do not allow any conclusions on the incidence rate of SARS-CoV-2 infection in children with rheumatic diseases, nor on the overall outcome of immunocompromised patients affected by COVID-19. However, according to the above mentioned observations on adult rheumatology patients (6), our preliminary experience supports the idea that patients with chronic diseases treated with bDMARDs do not seem to be at increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with the general population. Keeping the disease under control may therefore be extremely important even during the epidemic, since it is known that disease activity may be a risk factor for superimposed infections.

Table 1.

Disease	
Juvenile Idiopathic Arthritis (JIA)	89 (72.3)
Oligoarticular	60 (48.8)
Poliarticular (Rheumatoid Factor negative)	14 (11.4)
Poliarticular (Rheumatoid Factor positive)	0
Enthesitis Related Arthritis	4 (3.3)
Systemic JIA	7 (5.7)
Psoriatic	4 (3.3)
Autoinflammatory diseases	5 (4.1)
Cronic uveitis	5 (4.1)
Recurrent pericarditis	2 (1.6)
Others	22 (17.9)
Female	83 (62.4)
Median desease duration *	6 (3-10)
bDMARDS	
Anti TNF	95 (77.2)
Etanercept	38 (30.9)
Adalimumab	53 (43.1)
Infliximab	4 (3.3)
Anakinra	7 (5.7)
Tocilizumab	7 (7.7)
Canakinumab	2 (1.6)
Baricitinib	1 (0.8)
Other	11 (8.9)
Concomitant cDMARDS	
Methotrexate	77 (62.7)
Colchicine	3 (2.4)
Cyclosporine	1 (0.8)
Mycophenolate mofetil	1 (0.8)
Systemic steroids	6 (4.9)
Confirmed COVID – 19 infection	0
Suspected COVID – 19 infection	0
Children with mild respiratory symptoms	8 (3 of them family members of adults suspected for COVID-19)

Principal characteristics of 123 pediatric patients with chronic rheumatic diseases on bDMARDS. Values are expressed in numbers (%). * median (1°-3° quartile)

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