The impact of SARS-CoV-2 infection in children with rheumatic/autoinflammatory diseases on immunosuppressive treatment: a single centre experience

Sir,

In general, children comprise a small proportion of COVID-19 cases or deaths, since they appear to be mildly affected by the novel SARS-CoV-2 virus. Contrary to adults, susceptibility of paediatric patients with chronic conditions, including rheumatic diseases, remains largely unclear. A US cohort with 8540 adults reported a substantial mortality risk (5.6%) among patients with autoimmune and inflammatory rheumatic diseases (AIRD) (1), while a meta-analysis indicated a higher risk of SARS-Cov2 infection, though not a more severe disease outcome among rheumatic patients (2).

Data on the risks or benefits of immunosuppressive therapies are scarce as well (3, 4). The American College of Rheumatology recommends temporal withholding of biological/conventional disease-modifying antirheumatic drugs (bDMARDs/cDMARDs), only for symptomatic COVID-19 rheumatic patients (5). However, their role in paediatric COVID-19 course as well as that of AIRD activity at the time of COVID-19 acquisition, the role/dosage of steroids and the synchronous use of multiple DMRADs, have not yet been fully addressed (6). Controversies exist on whether these agents attenuate the adaptive response to SARS-Cov2, responsible for the devastating cytokine storm, or they contribute to the already aberrant immune response and thus increase the attributable risk of these patients to the virus. In a recent cohort including 8 children with rheumatic disease, Calvo *et al*. highlighted the impact of uncontrolled disease activity on the course of COVID-19 (4). Yildiz *et al*. did not report any severe complications or sequelae among children receiving DMARDs who acquired SARS-Cov2 infection (7).

In this study, we intended to describe the characteristics of paediatric patients with AIRD and SARS-Cov2 infection, to access the potential effect of SARS-Cov2 infection in the course of the rheumatic/autoinflammatory diseases as well as the role of DMARDs on the outcome of COVID-19. A cross-sectional study consisting of a telephone interview, followed by a review of health records was performed between May 2020 and March 2021, in our centre. A hospital physician interviewed parents of all the enrolled patients inquiring about main disease characteristics, current DMARD use/duration, COVID-19 main symptoms, if any, source of transmission and duration as well as the need of hospitalisation. Out of 453 enrolled patients with AIRD, who were currently on bDMARDs/cDMARDs, 16 (3.5%) had a nasopharyngeal polymerase chain reaction (PCR) positive for SARS-CoV-2 (wild type). All patients were surveyed longitudinally for possible adverse outcomes (clinical or laboratory disease relapse) by the Immunology and Rheumatology Unit, Second Department of Peadiatrics, "P. & A. Kyriakou" Children's Hospital, University of Athens, Greece. All children were closely monitored with serial molecular testing until confirming three negative RT-PCR tests in them and their families.

Demographic and clinical characteristics of the 16 above-mentioned cases (male/female ratio = 1, median age = 10.5 years old, interquartile range = 5-14.8 years) are summarised in Table I. The underlying AIRD was polyarticular juvenile idiopathic arthritis in 44% of cases, followed by extended oligoarticular arthritis (25%). The primary AIRD was in remission at the time of SARS-Cov2 infection in all cases. None of the patients had any of the severe comorbidities affect-

Table I. Characteristics of children with rheumatic diseases on immunomodulatory treatment and COVID-19 between May 2020 and March 2021

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex (M/F)	F	F	M	F	M	F	M	F
Age (years)	9	16	14	15	14	5	6	14
Main disease	eoJIA	SLE	ERA	eoJIA	PJIA	eoJIA	FMF	PJIA
Disease duration	2 years	6 years	6 years	2 years	7 years	3 years	2 years	5 years
Disease status	RM	RM	RM	RM	RM	RM	RM	RM
Ongoing DMARD	ETN	BEL	ADA	ADA	TCZ	ADA	CAN	TCZ
DMARD Duration	1 year	18 mo	3 mo	18 mo	4 years	2 years	1 year	4 years
Concomitant therapy	(-)	HCQ	(-)	MTX	MTX	MTX	Colchicine	(-)
Comorbidities	(-)	HT	(-)	(-)	Asthma HT	(-)	(-)	AD
Influenza vaccine	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
RT-PCR SARS-CoV-2	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
COVID -19 symptoms	(-)	Sore throat, malaise, cough, abd.ache	(-)	(-)	(-)	(-)	Fever, malaise, sore throat, cough, abd.ache	Fever Malaise Cough
COVID- 19 symptoms duration	(-)	3 days	(-)	(-)	(-)	(-)	7 days	2 days.

	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
Sex (M/F)	M	M	M	F	F	M	F	?
Age (years)	9	7	4	12	5	15	16	3.5
Main disease	AS	eoJIA	PJIA	PJIA	PJIA	PsA	PJIA	PJIA
Disease duration	2 years	5 years	1 year	3 years	9 mo	4 years	4 years	9 mo
Disease status	RM	RM	RM	RM	RM	RM	RM	RM
Ongoing DMARD	ADA	ETN	TCZ	TCZ	TCZ	ANR	TCZ	TCZ
DMARD Duration	16 mo	9 mo	1 year	2 years	6 mo	9 mo	3 years	7.5 mo
Concomitant therapy	(-)	(-)	(-)	MTX	(-)	MTX	(-)	(-)
Comorbidities	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Influenza vaccine	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
RT-PCR SARS-CoV-2	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
COVID -19 symptoms	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
COVID- 19 symptoms duration	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)

ing COVID-19 outcome (8). Thirteen children (81%) were asymptomatic, while predominant symptoms were malaise (100%), cough (100%), sore throat (67%) and fever (67%). Interestingly, no in-school transmission was documented. No critical illness, shift to cytokine dysregulation necessitating hospitalisation or flares of the underlying AIRD were recorded. All patients successfully recovered after a median of 3 days and were followed until having three serial negative PCR.

The b/cDMARDs were not administered during the acute illness. Tocilizumab was the most prevalent bDMARD (44%), followed by adalimumab (25%) and etanercept (12.5). Six patients (38%) were also receiving cDMRADs (5 patients on methotrexate, 1 patient on hydroxychloroquine). None of the participants was on systemic corticosteroids. The three symptomatic patients were on belimumab, canakinumab and tocilizumab, respectively.

The study was approved by the hospital's Ethics Committee and patient's data were anonymised.

Written informed consent was obtained from parents/guardians of all children prior to the study.

In conclusion, in our small cohort of children with AIRD, SARS-CoV-2 infection did not exceed detrimental effects on their health status nor did it trigger a relapse of the underlying AIRD. Although no causal interpretations should be made, our findings may suggest a protective role of bDMARDs (especially IL-6 receptor antagonists) (3, 6), regarding evolution of COVID-19, when routinely used by children with AIRD. Nevertheless, this perspective could be limited in the settings of a stable chronic course without flares/relapses. Comorbidities also need to be taken into account as they influence the risk of hospital admission and the outcome of patients with AIRD (8, 9). Larger multicentre studies are required to assess the effect of COVID-19 in this group of patients, especially in view of the novel mutations, which seem to exceed a different disease burden in children (10).

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