



# Implications of COVID-19 in pediatric rheumatology

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## Abstract

COVID-19 (coronavirus disease 2019) pandemic caused by SARS-CoV-2, is a global public health issue threatening millions of lives worldwide. Although the infection is mild in most of the affected individuals, it may cause severe clinical manifestations such as acute respiratory distress syndrome or cytokine storm leading to death. Children are affected less, and most experience a milder disease. As rheumatologists, we deal with the uncontrolled response of the immune system, and most of the drugs we use are either immune modulators or immunosuppressants. Thus, the rheumatologists participate in the multidisciplinary management of COVID-19 patients. On the other hand, our patients with rheumatic diseases constitute a vulnerable group in this pandemic. In this review, a systematic literature search was conducted utilizing MEDLINE/PubMed and Scopus databases, and 231 COVID-19 patients with rheumatic diseases have been identified. Only one of these patients was a child. Among these, 9 (3.9%) died due to COVID-19. In light of the current data, the aspects of COVID-19 resembling rheumatic diseases, the possible reasons for why children are affected less severely, the hypothetical role of available vaccines in preventing COVID-19, the unique position of patients with rheumatic diseases in this pandemic, and the use of anti-rheumatic drugs in COVID-19 treatment are discussed.

**Keywords** COVID-19 · COVID-19 virus · SARS-CoV-2 · Rheumatic disease · Systemic lupus erythematosus · Familial Mediterranean fever

## Introduction

In late December 2019, a severe coronavirus outbreak emerged in China. It was caused by a novel virus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) from *coronaviridae* family [1, 2]. The infection quickly spread over the world. The World Health Organization (WHO) officially named this infection as COVID-19 (coronavirus disease 2019) on February 11th, 2020, and declared COVID-19 a pandemic on March 11th, 2020. There are 4,088,848 confirmed cases and 283,153 deaths ascribed to

COVID-19 worldwide as of May 12th, 2020 (source: WHO Situation Report 113). It has a mortality rate around 7%; however, this could be an overestimation since not everyone is being tested for COVID-19. The main route of transmission is person-to-person via respiratory droplets [3, 4]. Primary prevention strategies such as quarantine, social distancing, and hand hygiene are the main methods to prevent the infection since there has been no vaccine or specific antiviral treatment yet.

SARS-CoV-2 has considerable genetic resemblance (around 80%) with SARS-CoV virus, which was the causative organism of the 2002 SARS (severe acute respiratory syndrome) epidemic [5, 6]. SARS-CoV-2 has spike proteins on its surface, and using these proteins, it binds to target human cells. The receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) mainly expressed on epithelial cells, renal proximal tubular cells, enterocytes, and endothelial cells [5, 7]. After attachment to ACE2, the virus is endocytosed into the cell and interacts with toll-like receptors (TLRs) inside the endosome. This interaction promotes a type I interferon (IFN) response and increases the expression

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of other proinflammatory cytokines through nuclear factor  $\kappa$ B (NF- $\kappa$ B) [8, 9].

There are two main reactions of the immune system to this virus: an initial innate immune response through type I IFNs (described above) and a secondary adaptive immune response, which may lead to cytokine storm. The initial IFN response aims to contain and clear the virus effectively, and an early peak seems crucial for this effective control [10]. The resolution of IFN activity generated during an innate immune response is required for recovery [11]. After the initial IFN response, macrophages are activated through their IFN- $\alpha/\beta$  receptors and produce chemoattractants and proinflammatory cytokines [12]. Another reaction to the virus is the presentation of spike protein antigens to T cells by antigen-presenting cells, which results in the activation of B cells and the production of anti-spike immunoglobulins. When these immunoglobulins bind to spike proteins of the viruses, coated viruses could be internalized into macrophages through Fc receptors [13]. These macrophages release proinflammatory cytokines, which may contribute to the cytokine storm in the adaptive phase [13, 14]. The cellular/tissue damage in COVID-19 probably occurs in two ways: (1) direct damage by the virus through viral replication and (2) the harmful effects of the exaggerated immune response resulting in a cytokine storm, which means the uncontrolled and excessive release of proinflammatory cytokines [15]. Mice and non-human primate studies showed that a disproportionate immune response rather than the virus titer was related to death in SARS-CoV infection [16, 17]. The infection is mild in most of the affected individuals while it could cause a severe clinical situation, mainly characterized by acute respiratory distress syndrome (ARDS) and cytokine storm that can lead to mortality [18]. Cytokine storm is the result of uncontrolled immune activation which leads to hyperinflammation and multi-organ disease [19]. Although everyone is susceptible to being infected by this novel virus, COVID-19 affects a specific group of individuals with more severe disease. The main risk groups are elderly patients, smokers, and individuals with chronic diseases such as diabetes mellitus or hypertension [20–22].

As the pandemic ensues, we observe that children are affected less and most experience a mild form of the disease in case of infection [4, 23]. In the cohort study, including 72,314 COVID-19 patients, Wu et al. reported that only 2% of the cases were below 19 years of age [24]. We assume that the immunosuppressant patients constituted a primary risk group for COVID-19. However, the current data have not conferred immunosuppression as a specific risk factor for severe or fatal disease consistent with the epidemiologic data from the previous coronavirus epidemics, namely SARS and MERS (Middle East respiratory syndrome) [25].

The drugs that are currently being used and tested in COVID-19 treatment are mostly the ones used by patients

with rheumatic diseases. Thus, the rheumatologists participate in the multidisciplinary management of COVID-19 patients, as well. On the other hand, immunosuppressants put patients with rheumatic diseases in a vulnerable group in this pandemic. Thus, making effective and accurate decisions about management strategies regarding these patients is critical, and these should be based on the currently available scientific evidence as much as possible.

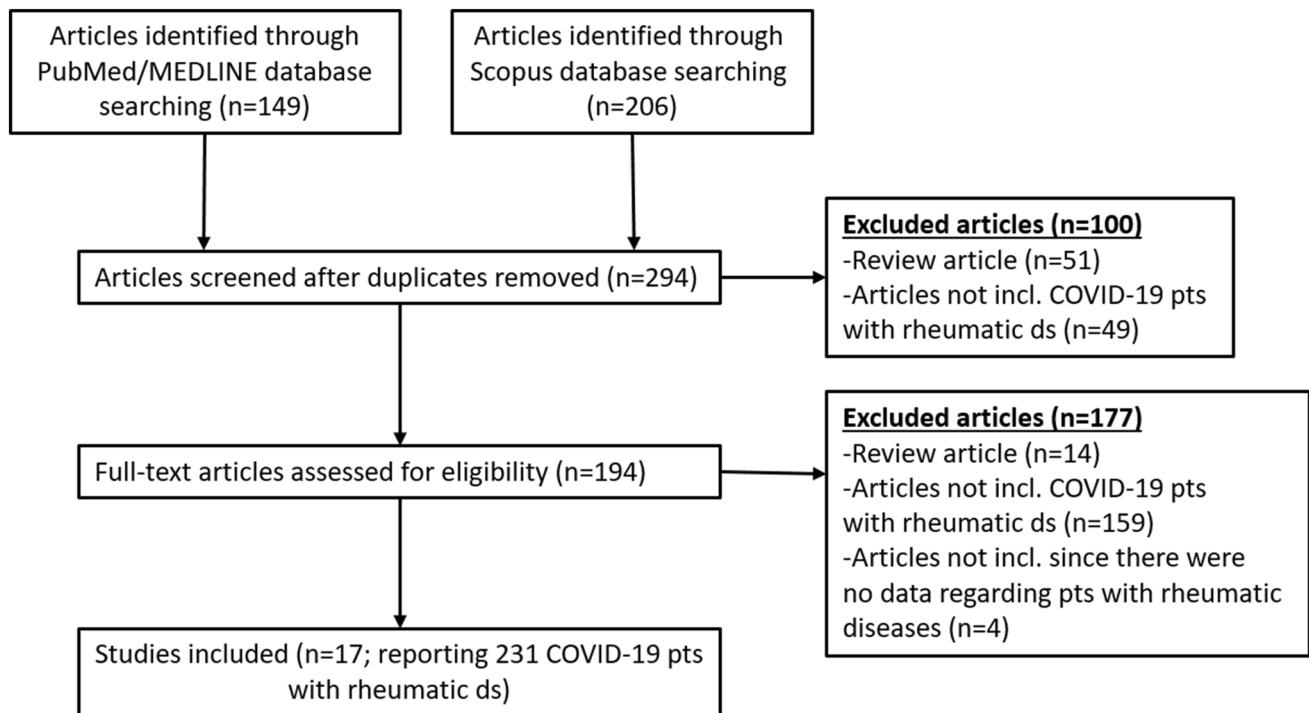
This review aims to provide an overview of COVID-19 pandemic from pediatric rheumatologist's perspective. The aspects of COVID-19 resembling rheumatic diseases, the possible reasons for why children are affected less severely, the hypothetical role of other available vaccines in preventing COVID-19, the unique position of patients with rheumatic diseases in this pandemic, the COVID-19 patients with rheumatic diseases in the literature, and COVID-19 treatment with the drugs used for rheumatic diseases are discussed. Also, a systematic literature search was conducted to identify COVID-19 patients with rheumatic diseases.

## Search strategy

The Scopus and MEDLINE/PubMed databases were searched (from November 1st, 2019 to May 11th, 2020) by entering the following keywords; “coronavirus disease 2019”, “COVID-19”, “SARS-CoV-2”, “rheumatology”, and “rheumatic disease” according to the published guidance on narrative reviews [26]. The complete list of the search terms used for determining articles, including COVID-19 patients with rheumatic diseases, has been provided in the Supplementary Table 1. Case reports, original research articles, editorials, and review articles with a focus on COVID-19 were analyzed. The following parameters were noted from the studies including COVID-19 patients with an underlying rheumatic disease: age, sex, underlying rheumatic disease, age at diagnosis of the rheumatic disease, features associated with rheumatic disease, other comorbidities, the previous and current treatment of rheumatic disease, COVID-19-related symptoms, the method for COVID-19 diagnosis, COVID-19 treatment and outcome, and features regarding cessation and re-initiation of immunosuppressive therapies. The search was restricted to English articles.

## COVID-19 patients with rheumatic diseases in the literature

Seventeen articles describing 231 COVID-19 patients with rheumatic diseases were found during the literature search (Fig. 1) [27–43]. Among these patients, there was only one pediatric patient who was a 6-month-old infant with Kawasaki disease and COVID-19 [31]. The characteristics of



**Fig. 1** The schematic overview of the studies on COVID-19 (coronavirus disease 2019) in patients with rheumatic diseases included in the literature research (pts, patients)

the patients are presented in Table 1. 77.5% of the patients were female ( $n = 179$ ). The most common underlying rheumatic diseases were systemic lupus erythematosus (SLE) ( $n = 117$ ) and rheumatoid arthritis (RA) ( $n = 45$ ). Nine out of 231 (3.9%) patients died. Of note, König et al. did not report outcomes with regard to mortality in their COVID-19 cohort, including 80 SLE patients [41].

In addition to these articles presented in the table, four articles reported COVID-19 patients with rheumatic diseases [44–47]. These articles were not included since there were no details about these reported patients. Garg et al. presented age-stratified COVID-19-associated hospitalization rates of U.S. patients [44]. And in their report, there were three (out of 180) patients who were mentioned to have “rheumatic/autoimmune disease”. One of these patients was in the age range of 18–49 years, while two were  $\geq 65$  years of age. Xu et al. mentioned that there were gout patients in their COVID-19 cohort, including 187 patients [47]. In their patient experience survey study, Sirotych et al. reported that 465 patients with rheumatic diseases had a diagnosis of COVID-19 based on symptoms or physician diagnosis with positive laboratory tests [46]. However, no further details were provided about these patients, including their underlying rheumatic diseases. In the cohort of 1317 SARS-CoV-2 positive patients, Gendelman et al. reported that three were on chronic hydroxychloroquine (HCQ) and seven were on chronic colchicine

treatment [45]. But they did not mention the underlying diseases in these patients.

### Why are children less affected?

Currently, the exact reason why children experience a milder disease remains unknown. Several factors could contribute to this situation; however, the specific effects of these factors with regard to COVID-19 have not been studied yet:

1. Children travel less than adults which may be protective [48].
2. Smoking is not an issue in childhood, and the respiratory tracts of children have been exposed to air pollution for a shorter time compared to adults [48].
3. Common comorbidities of adulthood, like type 2 diabetes mellitus or hypertension, are not so frequent among children [9].
4. The upper respiratory tracts of children are usually colonized with a variety of microorganisms which may compete with SARS-CoV-2 [49–51].
5. In children, the innate immune response is more robust while the adaptive immune system is less educated and immature compared to adults [9, 52]. This may result in a sufficient clearance of the virus and a lack of an exaggerated adaptive response.

**Table 1** The characteristics of COVID-19 (coronavirus disease 2019) patients who had an underlying rheumatic disease

First author [ref. no]	Gianfrancesco [13]	Konig [26]	Mathian [17]	Guilpain [14]	Jones [16]	Song [20]	Mihai [18]	Monti [19]	Han [15]	Favalli [12]	Damiani [21]	Dousa [22]	Duret [23]	Moutouopoulos [27]	Tomelleri [28]	Emmi [24]	Favalli [25]
# of cases	110	80	17	1	1	1	1	4	1	1	3	1	1	1	4	1	3
Age	>65 yrs <sup>a</sup> (n=20)	<65 yrs (n=69)	53.5 yrs (median)	52 yrs	6 mos <sup>a</sup>	61 yrs	57 yrs	58 yrs (mean)	47 yrs	32 yrs	42, 55, 72 yrs	39 yrs	60 yrs	70 yrs	33, 38 yrs (TA <sup>b</sup> ) 79 yrs (GCA <sup>b</sup> )	68 yrs	40, 56, 68 yrs
Sex	F <sup>a</sup> (79/110)	F (72/80)	F (13/17)	F	F	F	F	F	F	F	F (2/3)	F	M	F	F (2/4)	F	F (1/3)
Underlying RD <sup>a</sup>	RA <sup>a</sup> (n=40)	SLE	SLE	GPA <sup>a</sup>	Kawasaki disease	RA	SSc <sup>b</sup>	RA (n=3) SpA (n=1)	SLE	SSc	PsA	RA	SpA	CAPS <sup>a</sup>	TA (n=2) GCA (n=2)	SJS	Sarcoidosis (n=1) SpA (n=1) PsA (n=1)
Age at dx <sup>a</sup> of RD	NI	NI	Ds duration: 8.7 yrs (median)	20 yrs	6 mos	58 yrs	54 yrs	NI	<31 yrs	NI	NI	NI	NI	NI	Ds duration: 99–111 mos (TA) 5–13 mos (GCA)	NI	NI
Features ass. with RD	NI	NI	Arthritis (n=14) Skin-mucosa (n=10) Nephritis (n=9) Serositis (n=9) Cytopenia (n=6) Neuropsychiatric (n=4)	ENT <sup>a</sup> , orbital, lung, joint, involve-ment, ANCA <sup>a</sup> (+)	Fever, rash, conjunctivitis, dry, cracked lips, swollen hands	NI	ILD <sup>a</sup> , polyarthritis, anti-Scl70 (+)	NI	NI	Pulmonary involvement	NI	NI	Fever, urticarial rash, myalgia, arthralgia/arthritis especially after cold exposure	NI	NI	NI	NLRP3 mutation

**Table 1** (continued)

First author [ref. no]	Gianfrancesco [13]	Konig [26]	Mathian [17]	Guilpain [14]	Jones [16]	Song [20]	Mihai [18]	Monti [19]	Han [15]	Favalli [12]	Damiani [21]	Dousa [22]	Duret [23]	Moutso-poulos [27]	Tomelleri [28]	Emmi [24]	Favalli [25]	
Other comorbidities	Ht <sup>a</sup> (n=31) Lung ds (n=22) Cardiovascular ds (n=12) Morbid obesity (n=9) DM (n=9)	NI	Overweight (n=2) Obesity (n=10) Chronic kidney ds (n=8) CVD <sup>a</sup> (n=3) CHD <sup>a</sup> (n=2) Ht (n=6) Malign tumor (n=1) Chronic obst. lung ds (n=2) Current smoker (n=2) Ex smoker (n=5)	Overweight (n=2) Ht	None	NI	Obesity Type 2 DM <sup>a</sup> Ex smoker (n=2)	Ht (n=1) Current smoker (n=1)	NI	NI	Ht (n=2) DM (n=1)	CMP <sup>a</sup>	NI	NI	Ht (n=2) Smoker (n=1) CAD/CKD <sup>a</sup> (n=1)	NI	NI	NI
Previous tx of RD	Biologic DMARD <sup>a,c</sup> (n=49) csDMARD <sup>a</sup> (n=69) JAK <sup>a</sup> inhibitor (n=5) NSAIDs <sup>a</sup> (n=28) Gc <sup>a</sup> (n=27) Others (n=5)	NI	HQ <sup>a</sup> Gc Immunosupp Cyclophosphamide Anti-TNF <sup>a</sup> agents MMF <sup>a</sup> MTX <sup>a</sup> Lef <sup>a</sup> Rituximab Gc	Cyclophosphamide Anti-TNF <sup>a</sup> agents MMF <sup>a</sup> MTX <sup>a</sup> Lef <sup>a</sup> Rituximab Gc	-	NI	TOC <sup>a</sup>	NI	Gc	NI	ADA <sup>a</sup> (n=3)	HQ ETA MTX	NI	Ana <sup>a</sup>	NI	NI	NI	NI
Current tx of RD	Biologic DMARD (n=51) <sup>d</sup> (n=49) csDMARD (n=69) JAK inhibitor (n=5) NSAIDs (n=5) Gc (n=27) Others (n=5)	HQ/CQ (n=51) <sup>d</sup> Gc (n=14) Immunosupp. (n=7) ACEI/ARB <sup>b</sup> (n=6) OAC <sup>a</sup> (n=5)	HQ (n=17) Gc (n=14) Immunosupp. (n=7) ACEI/ARB <sup>b</sup> (n=6) OAC <sup>a</sup> (n=5)	Rituximab (maintenance tx; 500 mg/dose) Prednisone (1.5 mg/day)	IVIg <sup>a</sup> (2 g/kg) High dose ASA MPS <sup>a</sup> Meloxicam Famotidine Folic acid	Lef HQ MPS <sup>a</sup> Meloxicam Famotidine Folic acid	TOC (5 weekly) ETA <sup>a</sup> (n=2) ABA <sup>a</sup> (n=1) TOF <sup>a</sup> (n=1) MTX (n=2) Lef (n=1) HQ (n=1) Gc (n=1) (n=1)	ETA <sup>a</sup> (n=2) ABA <sup>a</sup> (n=1) TOF <sup>a</sup> (n=1) MTX (n=2) Lef (n=1) HQ (n=1) Gc (n=1) (n=1)	Gc	HQ Rituximab	ADA (n=3)	HQ ETA MTX	Car <sup>a</sup>	Gc (n=4) MTX (n=2) IFX <sup>a</sup> (n=1) ADA (n=1)	Gc HQ	ADA (n=1) IFX (n=1) SEC <sup>a</sup> (n=1)	NI	

Table 1 (continued)

First author [ref. no]	Gianfrancesco [13]	Konig [26]	Mathian [17]	Guilpain [14]	Jones [16]	Song [20]	Mihai [18]	Monti [19]	Han [15]	Favalli [12]	Damiani [21]	Doussa [22]	Duret [23]	Moutopoulos [27]	Tomelleri [28]	Emmi [24]	Favalli [25]
COVID-19 related sxx <sup>a</sup>	Fever Cough Shortness of breath Myalgia Sore throat	NI	Fever Cough Sputum Shortness of breath Tachypnea Myalgia Confusion	Fever Myalgia Dry cough Headache	Asymptomatic	Fever Myalgia Dry cough Sore throat	Headache Malaise	Fever Myalgia Dry cough Sputum Rhinor-rhea Fatigue Arthral-gia Anosmia Dysgeu-sia Headache Diarrhea	Cough Nasal congestion Rhinor-rhea	NI	Fever Anosmia Ageusia Asthenia Cough	Fever Sore throat Rinorrhea Diarrhea Cough Dyspnea General-ized body pain Headache Myalgia Fatigue Nausea	Fever Cough Myalgia Diarrhea	Fever Malaise Cough Dyspnea	Fever Cough Dyspnea	Fever Fatigue Cough Dyspnea	NI
COVID-19 related pneumonia	NI	Yes (n = 13)	Yes (n = 13)	Yes	No	Yes	No	Chest X-Rays normal	Yes	Yes	Yes (n = 1)	No	No	No	Yes (n = 4)	Yes	NI
Need for O <sub>2</sub> support	NI	Yes (n = 42)	Yes (n = 11)	Yes	No	No	No	Yes (n = 1)	NI	Yes	No	No	No	No	No	NI <sup>e</sup>	Yes (n = 1)
Need for mechanic ventilation	NI	Yes (n = 30)	Yes (n = 5)	Yes	No	No	No	NI	NI	Yes	No	No	No	No	No	NI <sup>e</sup>	No
Method for COVID-19 dx	NI	RT-PCR <sup>a</sup>	RT-PCR <sup>a</sup>	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR IgG and IgM (+)	RT-PCR RT-PCR (-) RT-PCR IgG and IgM (+)	RT-PCR NI	RT-PCR NI	RT-PCR	RT-PCR NI	RT-PCR NI	RT-PCR	RT-PCR	RT-PCR
COVID-19 tx	NI	HQ (n = 17) Ab <sup>b</sup> (n = 9) TOC (n = 1) Gc maintenance (n = 12) ECMO (n = 2)	HQ (n = 17) Ab <sup>b</sup> (n = 9) TOC (n = 1) Gc maintenance (n = 12) ECMO (n = 2)	Lopinavir/ritonavir HQ	Quarantine at home	Lopinavir/ritonavir HQ (contd.)	Quarantine at home	Antiviral and HQ (n = 1)	Antiviral TOC IFN <sup>α</sup> nebul (n = 4) 1 ab course	Antiviral TOC	Only paracetamol (n = 2) Lopinavir/ritonavir & paracetamol (n = 1)	HQ (contd.) IV paracetamol	IV paracetamol	No tx No tx HQ (n = 2)	No tx HQ (n = 2)	Antiviral TOC	NI
Last dose of the biologic drug before the onset of COVID-19 sxx	NI	NI	NI	1 day before	NA	NA	4 weeks before	NI	NA	NI	NI	NA	2 days before	10 days before	NI	NA	NI
Immunosupp. tx discontinued after COVID-19 dx	NI	Immunosupp. tx discontinued after Gc & HQ contd. <sup>a</sup>	Immunosupp. tx discontinued after Gc & HQ contd. <sup>a</sup>	NI	NA	Lef&MPS discontinued with-contd	Yes	Yes (tem-NI porary withdrawal)	NA	NA <sup>a</sup>	ADA suspended (n = 1)	NA	NI	NI	NI	NI	NI

**Table 1** (continued)

First author [ref. no]	Gianfrancesco [13]	König [26]	Mathian [17]	Gulipain [14]	Jones [16]	Song [20]	Mihai [18]	Monti [19]	Han [15]	Favalli [12]	Damiani [21]	Dousa [22]	Duret [23]	Moutsopoulos [27]	Tomelleri [28]	Emmi [24]	Favalli [25]
Time for re-initiation of immun-suppl. tx	NI	NI	NI	NI	NA	Left: 2 days after 4 days after (-) RT-PCR (-) RT-PCR	Stable after 4 days after (-) RT-PCR	NI	NI	NA	NI	NA	NI	NI	NI	NI	NI
Current situation regarding RD	NI	Clinical SLEDAI <sup>a</sup> =0 (n=16) Active tenosynovitis (n=1)	NI	Stable after relapse on Echo: normal September 2019	Stable	Stable	Stable	Stable	Stable	-	NI	NI	NI	Stable	NI	NI	NI
Outcome of COVID-19	Died (n=6)	NI	Not hospitalized (n=3) Died (n=2/14) Remained in hospital (n=7/14) Discharged (n=5/14)	Recovered; RT-PCR (-) twice	Recovered, RT-PCR (-)	Recovered, RT-PCR (-)	Recovered, RT-PCR (-)	Recovered, RT-PCR (-)	Recovered, RT-PCR (-)	Died	Recovered	Recovered	Recovered	Recovered	Recovered	Improved with tx	Recovered

<sup>a</sup>Ab antibiotic, ABA abatacept, ACEI angiotensin-converting enzyme inhibitor, ADA adalimumab, ANA anakinra, anti-dsDNA anti-double stranded DNA, ARB antitensin receptor blocker, ASA acetylsalicylic acid, ASS associated, CAD coronary artery disease, Can canakinumab, CAPS cryopyrin-associated periodic syndrome, CKD chronic kidney disease, CMP cardiomyopathy, contd. continued, COVID-19 coronavirus disease 2019, CHD coronary heart disease, cs DMARD conventional synthetic disease modifying antirheumatic drug, CVD cerebrovascular disease, DM diabetes mellitus, ds disease, dx diagnosis, ENT ear nose throat, ETA etanercept, F female, Gc glucocorticoid, GCA giant cell arteritis, GPA granulomatous polyangiitis, ht hypertension, HQ hydroxychloroquine, IFN interferon, IFX infliximab, ILD interstitial lung disease, immunosupp. immunosuppressive, IVIG intravenous immunoglobulin, JAK janus kinase, Lef leflunomide, MMF mycophenolate mofetil, MPS methylprednisolone, MTX methotrexate, mos months, NA not applicable, NI not indicated, NSAID nonsteroidal antiinflammatory drugs, OAC oral anticoagulant, PR3-ANCA proteinase 3 antineutrophilic cytoplasmic antibody, PsA psoriatic arthritis, RA rheumatoid arthritis, RD rheumatic disease, RT-PCR reverse transcriptase polymerase chain reaction, RTX rituximab, SEC secukinumab, SjS Sjögren's syndrome, SLE systemic lupus erythematosus, SLEDAI SLE disease activity index, Spa spondyloarthropathy, SSc systemic sclerosis, sxx symptoms, TA takayasu arteritis, TNF tumor necrosis factor, TOC tocilizumab, TOF tofacitinib, tx treatment, yrs years  
<sup>b</sup>Others included inflammatory myopathy, ocular inflammation, other inflammatory arthritis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, osteoporosis, psoriasis, isolated pulmonary capillaritis, gout, and autoinflammatory disease

<sup>c</sup>Biological DMARDs included abatacept, belimumab, CD20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12 and IL-23 inhibitors, IL-17 inhibitors, and tumor necrosis factor inhibitors

<sup>d</sup>Other therapies are not indicated. The authors indicated that 30% of all patients were on only HQ/CQ

<sup>e</sup>Need for O<sub>2</sub> support or mechanic ventilation was not mentioned but the authors indicated that the patient had acute respiratory distress syndrome

6. ACE2 expression patterns in children could be different than adults [53].
7. Last, some childhood vaccines may provide a protective effect against COVID-19 (discussed in detail below).

All of these factors could have a combined overall effect. However, we should keep in mind that children are not immune to COVID-19, and although rarely, the disease could be severe and complicated in children, as well [54]. And although the pandemic itself seems to affect children less severely, it endangers the mass vaccination programs of WHO against polio and measles [55]. This could result in epidemics of preventable infectious diseases, especially among children.

Another point that deserves mention here is neonates of COVID-19-positive mothers. Although anecdotal reports exist, there is no direct evidence about the vertical transmission of SARS-CoV-2 from mother to child [56]. Chen et al. detected no virus in amniotic fluid, umbilical cord blood, and breast milk samples from mothers with COVID-19 and pharynx swabs of neonates born to mothers with COVID-19 [57].

Analyzing differences between different risk groups may provide critical clues about the disease pathogenesis. And, we may develop new strategies to fight against this novel foe.

### Do existing childhood vaccines protect against COVID-19?

COVID-19 seems to affect different countries with varying severity. Several epidemiological and observational studies are performed, and the results show that differences in childhood vaccination policies may partially describe the difference in COVID-19 severity. However, nearly all of these articles are non-peer reviewed, and the results were derived from indirect analyzes of epidemiologic data. Thus, these studies are vulnerable to selection bias, and uncontrolled confounding factors might have significantly deviated the results. Some of these confounding factors are population age, ethnicity, testing rates for COVID-19 infection, the stage of the pandemic in each country, income levels, and major policy decisions (such as quarantine and providing self-protecting equipment like masks). Another limiting factor is that it is not possible to dissect the effect of one specific vaccine such as BCG (Bacillus Calmette-Guerin) with these kinds of studies since the associations may also be caused by another vaccine mediating the protective effect. Thus, the results of these observational and epidemiologic studies should be evaluated with caution considering all the mentioned points.

These studies mainly put forward two vaccines as candidates for reducing the damage caused by COVID-19: BCG

and MMR (measles, mumps, rubella). It is noteworthy that the below discussed protective effects of childhood vaccines against COVID-19 are currently hypothetical, and no scientific proof has been published yet.

### BCG vaccine

Bacillus Calmette-Guerin (BCG) is a live attenuated vaccine. It is derived from an isolate of *Mycobacterium bovis* and used as a vaccine for tuberculosis [58]. The epidemiologic analyzes showed that the incidence of COVID-19 and the death rate were significantly lower in countries with BCG vaccination programs compared to those without such a program [59]. It is not possible to draw reliable conclusions as of yet. However, previous studies, including randomized controlled trials, have suggested a “nonspecific protection against infections” induced by the BCG vaccine [60]. Since *Mycobacterium* is a bacterium while SARS-CoV-2 is a virus, it is unlikely that a protective effect comes from cross-protection based on similar molecular structures. Previous studies have shown two possible mechanisms that explain the nonspecific protection provided by the BCG vaccine [61]: heterologous immunity and trained immunity. Heterologous immunity means that CD4 and CD8 memory cells (produced by the BCG vaccine in this situation) could be activated in an antigen-independent manner [62–65]. This activation could be caused by cytokine stimulation by a secondary infection. It is known that the BCG vaccine induces histone modifications and epigenetic changes in human monocytes at the promoter sites of genes encoding for proinflammatory cytokines such as interleukin 6 (IL-6) and TNF- $\alpha$  (tumor necrosis factor) [66]. This causes a more active innate immune response after re-stimulation (trained immunity) [58, 61, 66], which may contribute to the effective clearance of the virus in case of COVID-19. Arts et al. have recently shown that BCG vaccination reduced the level of viremia after yellow fever vaccination, and this effect was correlated with the induction of cytokine response [61]. Another possible pathway may be through the activation of the IFN-gamma pathway. Two studies (NCT04328441, NCT04327206) are underway to test the nonspecific protective effect of BCG vaccine in COVID-19.

### Measles, Mumps and Rubella (MMR) vaccine

Indirect epidemiologic analyses also suggest a protective role for the MMR vaccine against COVID-19 [67]. Bianchi et al. demonstrated that a considerable proportion of individuals did not show a protective immunoglobulin G (IgG) titer against measles in the 10 years after vaccination [68]. Shanker et al. hypothesized that age-related decline in immunogenicity of the measles vaccine could be an explanation for COVID-19 being mainly an adult



disease if the measles vaccine provides cross-resistance to COVID-19 [69]. Franklin et al. demonstrated that IgG titers against rubella increased in SARS-CoV-2 infection in some cases, which might suggest a structural homology between rubella and SARS-CoV-2 [67]. They reported that there was 29% amino acid sequence homology existing between macro-domains of SARS-CoV-2 and rubella virus and 20% homology between fusion protein of measles virus and spike protein of SARS-CoV-2. This report is the only evidence supporting these data; however, this is a not-peer reviewed article, and it remains unknown whether this resemblance is enough to cause a cross-reactive immune defense.

It will take time for researchers to develop an effective vaccine against COVID-19. Thus, it is wise to analyze the cross-resistance from other vaccines that are already being used. However, these studies should be designed carefully to control confounding factors. Considering all available data, it is too early to conclude on a protective effect from any vaccine at the moment. Another point is that it is not possible to predict how fast the immune system will develop a response that will protect against COVID-19 (if this exists) after another vaccine such as BCG or MMR vaccines. At the moment, childhood vaccinations should be applied according to the routine vaccination schedules of each country. The recommendations about new vaccination plans could arise with accumulating evidence on cross-protectiveness of other vaccines for COVID-19.

## The features of COVID-19 that mimic rheumatic diseases

The main characteristics of COVID-19, such as leukopenia, thrombocytopenia, myocarditis, and interstitial pneumonia, could also be observed in rheumatic diseases such as SLE and systemic sclerosis [18, 70, 71]. However, the clinically significant features are mainly from the inflammatory characteristics that mimic our diseases in both clinical features and pathogenesis. Having common pathways in the pathogenesis highlights some of the drugs that rheumatologists use as candidates for COVID-19 treatment.

Pediatric rheumatologists are very familiar with this entity since a significant portion of some common rheumatic diseases such as systemic juvenile idiopathic arthritis (JIA), SLE, and Kawasaki disease present this complication [72]. This secondary hemophagocytosis is called macrophage activation syndrome (MAS) in pediatric rheumatology practice. Thus, the experience of rheumatologists was important when we realized that the severe end of the COVID-19 clinical spectrum was a multisystem hyperinflammatory syndrome progressing to a cytokine storm with shock. This situation resembles secondary hemophagocytic lymphohistiocytosis (HLH) or MAS. Having said that, we

should be aware that COVID-19-associated cytokine storm is *not identical* to MAS. It shares certain common features such as high ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), low platelet, and lymphocyte counts [73]. But they also differ in some aspects. For instance, a decrease in the erythrocyte sedimentation rate (ESR) is commonly observed in MAS [74]. However, this does not seem to be a mandatory feature of COVID-19-associated cytokine storm [73, 75].

Moreover, Zhang et al. reported that patients with severe COVID-19 had persistently very high ESR [15]. Other interesting data come from autopsy findings of SARS-CoV-infected patients, demonstrating that secondary lymphoid tissues were destroyed [76]. This may explain the absence of splenomegaly as a significant feature of COVID-19-associated cytokine storm, although it is included as a criterion for diagnosing HLH [77]. There are scarce autopsy data regarding COVID-19. In one report of autopsy findings in two patients, Barton et al. reported that there was splenomegaly in one patient while they detected remote splenectomy in the other [78]. Menter et al. shared the autopsy findings of 21 COVID-19 patients, and they mentioned that they did not observe extensive depletion of lymphoid cells [79]. Increasing reports about the laboratory values and histopathological features of critically ill COVID-19 patients will provide more clues about the similarities and differences between COVID-19-associated cytokine storm and secondary HLH/MAS. However, we believe that the experience of pediatric rheumatologists contributed to the management of these severe COVID-19 patients: anti-IL-1 and anti-IL-6 strategies have been employed in the cytokine storm of COVID-19 patients in most intensive care units [19].

Another similar feature to rheumatic diseases is immune complex vasculitis, which could be observed secondary to occlusion of blood vessels with immune complexes, including spike proteins and anti-spike immunoglobulins [9, 15]. This may represent yet another form of immune complex vasculitis, such as the Hepatitis B-related polyarteritis nodosa (PAN) with immune complexes containing the HBsAg.

Skin lesions are increasingly reported features of COVID-19, and some of these are very similar to the findings of rheumatic diseases. Bouaziz et al. reported violaceous macules, livedoid rash, purpura (necrotic and non-necrotic), which are similar to skin manifestations of systemic vasculitis such as severe IgA vasculitis (Henoch-Schönlein purpura) and PAN [80]. They also mentioned chill blain-like lesions in their patients similar to the ones observed in interferonopathies like Aicardi-Goutieres syndrome and SAVI (STING-associated vasculitis with onset in infancy) [81]. Interestingly, chill-blain-like lesions were also found in children and adolescents who were otherwise asymptomatic with regard to COVID-19 [82]. This may well be

because of the high IFN levels induced by the virus. On the other hand, one wonders whether background levels of high IFN would protect against COVID-19 in the children with autoinflammatory interferonopathies such as SAVI or Aicardi Goutières syndrome. Acro-ischemia was reported in COVID-19 patients, as well [83, 84]. This feature is also observed in severe vasculopathies such as deficiency of adenosine deaminase 2 [85, 86]. These vascular lesions could be due to immune complex vasculitis or disseminated intravascular coagulation. Positive antiphospholipid antibodies may also contribute to the pathogenesis as recently reported [87]. We need more histopathologic data to understand the exact pathogenesis of these features.

Another surprising feature of COVID-19 was the development of a Kawasaki-like disease in children. Very recently, Riphagen et al. have reported hyperinflammatory shock in eight children with similar features to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock syndrome [88]. Seven of these patients required mechanical ventilation for cardiovascular stabilization, although no significant respiratory involvement was observed. The initial tests for COVID-19 were negative in all. One of these children died after 6 days, and SARS-CoV-2 was detected post-mortem. Another child was tested positive for SARS-CoV-2 after discharge. And, the authors mentioned that positive antibodies were detected afterward in seven children. The coronary arteries were severely dilated in one. C-reactive protein, procalcitonin, ferritin, triglycerides, and D-dimers were elevated in all. Of note, the ferritin level was highest in the child who died (4220 µg/L while the range was 277–1023 µg/L in the rest of the series). The laboratory features observed in this clinical situation are very similar to those seen in Kawasaki disease shock syndrome. Li et al. previously demonstrated higher levels of CRP, procalcitonin, triglycerides, and D-dimers in patients with Kawasaki disease shock syndrome compared to patients with only Kawasaki disease [89].

Finally, COVID-19 has been reported to present with large vessel stroke in young patients [90].

### Considerations regarding patients with different rheumatic diseases: unanswered scientific questions

There are still no data about the infection rate and course of COVID-19 in patients with rheumatic diseases, as mentioned above. Although the rheumatology practice mainly focuses on the immunosuppression caused by the disease itself or treatment of the disease, a variety of immune dysregulation besides immune suppression exists in different rheumatic diseases.

One group is autoinflammatory recurrent fever syndromes such as familial Mediterranean fever (FMF) or cryopyrin-associated periodic syndrome (CAPS). As we know, pyrin and NLRP3 inflammasomes are overactivated in FMF and CAPS, respectively [91, 92]. *MEFV* mutations (associated with FMF) were thought to provide an advantage against some infections such as tuberculosis or plague in the Mediterranean basin in the past [93]. The findings of the NIH (National Institute of Health) group suggested the idea that individuals carrying an *MEFV* mutation might have a selective advantage against the plague [94]. What will be the effect in COVID-19? Will these patients eliminate SARS-CoV-2 more efficiently? Or will the overactive inflammasome contribute further to the exaggerated immune response that complicate the disease? We do not know the answers at the moment.

CAPS also raises interesting questions. Activation of the NLRP3 inflammasome by SARS-CoV was observed previously [95, 96]. Another microorganism that activates NLRP3 is *Streptococcus pneumoniae* [97]. Previously, Walker et al. observed that pneumococcal vaccines could trigger a severe local and systemic inflammatory reaction in CAPS patients [98]. They hypothesized that further trigger by pneumococcal polysaccharides to an already over-activated NLRP3 inflammasome might have caused these reactions. This raised concern about the use of these vaccines in CAPS patients. Could the same concern be valid in case of COVID-19? Since CAPS is a rare disease, the current data do not let us answer this question either. Another confounding factor is that FMF and CAPS patients are mainly on colchicine and anti-IL-1 therapies, which are currently being tested in COVID-19 treatment. To date, there is only one report of COVID-19 in a patient with CAPS (who was on anti-IL-1 treatment) who experienced a mild disease course and recovered in a couple of days without any treatment [42].

Previous data suggest that mutations in the main causative genes of primary HLH (such as gene encoding for perforin) were also associated with secondary HLH/MAS [99]. There are also other mutations in other genes such as *NLRC4* associated with rare monogenic autoinflammatory diseases causing a tendency to recurrent MAS. *NLRC4*-related disease is characterized by early-onset recurrent fever, enterocolitis, and repeated episodes of MAS [100]. Patients carrying variants of these genes may also be more prone to cytokine storm associated with COVID-19. Future data about the course of COVID-19 in the setting of rare monogenic autoinflammatory diseases will provide further insights about the disease pathogenesis.

SLE is the prototype of the autoimmune diseases. And, the main risk factor seems like the immunosuppressive therapies we use in SLE treatment. However, Sawalha et al. reported that epigenetic dysregulation in SLE resulted in *ACE2* overexpression, and this might cause a specific

tendency to COVID-19 in this patient group [101]. Another debate in the literature focused on the hypothetical prophylactic effect of HCQ, which is used by a majority of SLE patients (discussed below).

Another issue is that most of the debate is on the patients we are already treating with an established diagnosis of a rheumatic disease. In a considerable amount of these patients, there is some degree of disease control, which means a balance between immune dysregulation (autoimmunity/autoinflammation) and immunosuppression/immune modulation (the therapies). The patients with rheumatic diseases who are not diagnosed/treated yet could form another specific vulnerable group for COVID-19.

Last, immunosuppression is a known risk factor for infections. Although it did not emerge as a risk factor during the previous coronavirus epidemics (SARS and MERS) and the situation remains unknown in the current COVID-19 pandemic [102], we still do not have enough evidence. It would be safe to consider these patients risky while taking precautions but not discontinuing immunosuppressive therapies since these are important for disease control. Moreover, active disease is a significant risk factor for an increased rate of infections [103, 104].

Data gathering through international rheumatology COVID-19 registries will provide answers to some questions in our minds. But it is essential not to make any early conclusions about resistance or tendency to COVID-19 regarding a specific rheumatic disease or treatment before solid scientific evidence is obtained.

## Treatment of COVID-19 and special considerations for patients with rheumatic diseases

The hallmarks of COVID-19 treatment are currently antiviral drugs, drugs interfering with viral entry, and immunosuppressive drugs (mainly the ones targeting cytokines). Here, we will primarily focus on drugs that are used in rheumatology practice. Since an early strong immune response is required for the effective clearance of the virus while the following exaggerated adaptive immune response should be tuned, the timing and the duration of immunosuppressive therapies are very critical.

### Antiviral drugs

Currently, there is no specific antiviral drug against SARS-CoV-2. However, several broad-spectrum antivirals such as remdesivir and lopinavir/ritonavir have been proposed to be tested in COVID-19 treatment.

Remdesivir is a nucleotide analog and was effective against SARS-CoV, MERS-CoV, and bat CoV strains [105]. Grein et al. reported clinical improvement in 36 (68%) out of 53 patients with severe COVID-19 who received at least one dose of remdesivir [106]. And, the mortality rate in this group was lower than the general mortality rate in severe COVID-19 (13% versus > 50%, respectively). However, in a recent, randomized, double-blind, placebo-controlled study (158 patients in remdesivir group versus 79 in the placebo group), Wang et al. reported that remdesivir was not associated with statistically significant clinical benefits although adequately tolerated by the patients [107]. There are ongoing clinical trials on remdesivir use in COVID-19 (e.g., NCT04280705, NCT04315948).

Lopinavir, a protease inhibitor, has also been tested in COVID-19 treatment. It is used combined with ritonavir, which inhibits CYP-3A-mediated metabolism of lopinavir. Previous reports showed that lopinavir/ritonavir had improved clinical outcomes in SARS and MERS patients [108]. In a recent, randomized-controlled trial in hospitalized adult COVID-19 patients (99 patients in lopinavir/ritonavir group versus 100 in standard care group), Cao et al. reported that no benefit was associated with lopinavir/ritonavir treatment beyond standard care [109]. Ongoing trials will provide further data regarding the efficacy and safety of lopinavir/ritonavir in COVID-19 treatment (e.g., ChiCTR2000029609; NCT04261907).

### NSAIDs (nonsteroidal anti-inflammatory drugs)

NSAIDs (nonsteroidal anti-inflammatory drugs) are commonly used in rheumatology practice. Actually, they may be of benefit to the musculoskeletal symptoms of COVID-19 [110]. In pediatric rheumatology practice, NSAIDs are the primary therapeutic options, especially in the treatment of oligoarticular JIA. Ibuprofen has been reported to increase ACE2 expression [111]. And anecdotal reports exist on a severe disease course in patients using NSAIDs [112]. However, there is no current evidence for a specific causal association between NSAID use and a more severe disease course in COVID-19 [110, 113]. Previous studies have also suggested an association between NSAID use and higher rates of complications after respiratory tract infections [114, 115]. Currently it is not possible to draw solid, evidence-based conclusion on NSAID use over all.

### Glucocorticoids

Glucocorticoids repress the transcription of proinflammatory genes [116]. They may be used in the management of sepsis and septic shock at small doses and short term [117]. Some studies show beneficial effects of glucocorticoids in the treatment of coronavirus (SARS and MERS) pneumonia

[118–120]. On the other hand, some studies reported more adverse effects with the use of corticosteroids in coronavirus infection [121]. And most recently, Tsai et al. have demonstrated that an early corticosteroid treatment was associated with significantly increased hospital mortality in adult patients with influenza-associated ARDS [122]. Regarding COVID-19, Wu et al. demonstrated that methylprednisolone treatment appeared to decrease the risk of death among patients with acute respiratory distress syndrome [123]. In their retrospective cohort study including 46 COVID-19 patients, Wang et al. observed that early, low-dose, and short-term application of methylprednisolone was associated with better clinical outcomes while they did not show any significant difference with regard to mortality rate [124]. However, it is not possible to conclude on a positive effect since the data are scarce. At the moment, WHO recommends against routine glucocorticoid use in COVID-19 treatment. Randomized controlled trials planned to analyze the effectiveness/safety of glucocorticoid therapy in COVID-19 patients (ChiCTR2000029386, NCT042273321, NCT042244591) will provide better evidence and may enlighten the role of glucocorticoids in COVID-19.

## Hydroxychloroquine

Hydroxychloroquine (HCQ), an antimalarial agent, is the mainstay of treatment, especially in SLE [125]. Being a weak base, HCQ accumulates in acidic environments such as lysosomes and endosomes. And, by increasing the pH in endosomes, HCQ interferes with TLR–virus interaction [126]. It also interferes with glycosylation of ACE2 and maturation process of viral proteins [15, 126]. As a result, it may prevent viral entry and subsequent stimulation of pro-inflammatory pathways. Considering these mechanisms, it appeared as a candidate for both prophylaxis and treatment in COVID-19. To assess its prophylactic use, Shah et al. systematically reviewed the literature and determined five studies (three in-vitro studies and two clinical opinions) [127]. Unfortunately, it is not possible to conclude on a prophylactic effect of HCQ based on these data. In the same lines, Gendelman et al. did not observe a protective effect of chronic HCQ use in their retrospective study, including 1317 COVID-19 patients [45]. Thus, there is not enough evidence supporting prophylactic use of HCQ, and further studies with a randomized controlled design are required.

In an open-label non-randomized clinical trial in a small patient group (20 patients and 16 controls), Gautret et al. showed that HCQ treatment was significantly associated with viral load reduction with more efficient results when azithromycin was added [128]. Studies are underway to obtain a better level of evidence (e.g., NCT04307693, NCT04323631).

Currently, HCQ is used in the treatment of COVID-19 in most countries and for prophylaxis in some. However, considering the lack of evidence supporting its prophylactic use and the risk of short supplies for patients who need this drug, prophylactic treatment should not be recommended at this stage. Monti et al. reported that 51 out of 80 (64%) COVID-19 patients with SLE were taking HCQ/chloroquine (CQ) before infection with SARS-CoV-2 [34]. Moreover, the frequency of hospitalization did not differ with regard to HCQ/CQ use [34].

HCQ is also associated with certain side-effects. Retinal toxicity is not a significant concern since it is mainly associated with its long-term use [129]. However, HCQ use has previously been associated with QT interval prolongation [130]. Besides, azithromycin, which has been used in combination with HCQ in COVID-19 treatment, is also a drug that can cause QT prolongation [131]. Thus, these drugs should be used with caution in the treatment of COVID-19. Of note, Saleh et al. reported that they did not observe *torsade de pointes* or arrhythmogenic death in their large cohort of COVID-19 patients treated with CQ ( $n = 10$ ) or HCQ ( $n = 191$ ) [132]. But they mentioned that QTc interval was significantly longer in the combination group (CQ/HCQ + azithromycin) compared to the monotherapy group (CQ/HCQ only).

## JAK (janus kinase) inhibitors

JAK (janus kinase) inhibitors are not used in pediatric rheumatology patients as extensively as they are used in adult rheumatology. But these drugs are currently used in the treatment of JIA and autoinflammatory interferonopathies [133, 134]. JAK inhibitors have been suggested to interfere with viral entry by inhibiting AAK1, which is a key regulator of SARS-CoV-2 endocytosis (detailed above) [5]. They may also be beneficial by inhibiting the proinflammatory effects of IFNs in the exaggerated immune response phase. Baricitinib is a selective JAK1 and JAK2 inhibitor [135], and it may exert an antiviral effect at the doses used for treatment in RA [136], emerging as a potential treatment option in COVID-19. JAK inhibitors may be beneficial at the severe end of the spectrum, where IFN response contributes to the cytokine storm. Cameron et al. demonstrated a prominent IFN- $\alpha$  and IFN- $\gamma$  signaling in deceased SARS patients compared to a low IFN- $\alpha/\gamma$  signaling in patients discharged from hospital [11]. However, the window of opportunity at the early phase is very narrow and difficult to determine since the patient will be asymptomatic at this phase, and the viral entry will be shortly followed with a strong IFN response which is critical for viral clearance.

IFNs act through JAK/STAT pathway to increase the expression of IFN response genes, and type I IFNs are the primary defense against viral infections [137]. JAK

inhibitors interfere with antiviral immune response, and increased risk of herpes zoster and simplex infections were previously reported with JAK inhibitor use [138]. Since the effective containment and clearance of the virus depends on an effective and abrupt type I IFN response, initiation of JAK inhibitors at the early phase of COVID-19 could interfere with the immune defense. Thus, the jury is out for the benefit of these drugs in COVID-19.

### Drugs targeting cytokines

A cytokine storm similar to secondary HLH/MAS occurs in some patients with COVID-19. Huang et al. have demonstrated that serum levels of several proinflammatory cytokines, including IL-1, IL-6, and TNF- $\alpha$  increased in the hyperinflammatory phase of COVID-19 [2]. These data called for the use of drugs targeting cytokines (mainly anti-IL-6, anti-IL-1, and anti-TNF) as candidates for severe COVID-19 treatment.

Zhou et al. observed that IL-6 levels were higher in deceased COVID-19 patients than the survivors [21]. Other studies also reported elevation of IL-6 levels in patients with severe COVID-19 [123, 139]. Tocilizumab (IL-6 receptor monoclonal antibody) use was associated with significant clinical improvement in several observational studies [140–142]; however, there were no matched controls treated without tocilizumab in these studies. In their retrospective case–control study (20 patients treated with tocilizumab versus 25 patients treated without tocilizumab), Klopfenstein et al. reported that death and/or intensive care unit admissions were higher among patients treated without tocilizumab than those treated with tocilizumab (72% versus 25%, respectively) [143]. Sciascia et al. performed a pilot, prospective single-arm study ( $n = 100$ ), and they reported an improvement in respiratory and laboratory parameters with tocilizumab treatment [144]. Moreover, there are a few case reports on the successful use of tocilizumab in the treatment of severe childhood COVID-19 [145, 146]. Based on these data, anti-IL-6 treatment is currently the most studied drug in the treatment of COVID-19-associated cytokine storm (NCT04322773, NCT04317092, NCT04320615, NCT04306705, NCT04324073, NCT04315298, ChiCTR2000029765, ChiCTR2000030796).

Anti-IL-1 drugs are also among the most promising therapies in cytokine storm associated with COVID-19. In a recent retrospective cohort study, Cavalli et al. evaluated anakinra treatment in COVID-19 [147]. They compared the outcome between 16 patients who were on only standard treatment (HCQ and lopinavir/ritonavir) in addition to mechanic ventilation and 29 patients who were taking high-dose intravenous (IV) anakinra in addition to the standard treatment and mechanic ventilation. Both overall survival and mechanic ventilation-free survival were more frequent

in the high-dose anakinra group than the standard treatment group (90% versus 56% and 72% versus 56%, respectively). There are ongoing trials of anakinra in COVID-19 that will probably provide a higher level of evidence for the efficacy of this treatment (NCT04324021, NCT04330638). Anti-IL-1 treatment has indeed been suggested by some pediatric rheumatologists to be the first-line treatment [73].

There are also ongoing trials for anti-TNF use in COVID-19 (ChiCTR2000030089, ChiCTR2000030580). A combination of different biologic agents may also be considered in selected, very severe cases.

### Other drugs

In severe cases of secondary HLH/MAS, anti-IFN- $\gamma$  treatment is a critical therapeutic option. There is also an ongoing trial of omapalumab (anti-IFN- $\gamma$  monoclonal antibody) and anakinra in COVID-19 (NCT04324021).

There are also other registered trials planned to test the efficacy of leflunomid, ecluzimab, and ruxolitinib [148]. The readers are referred to the review by Lythgoe et al. summarizing all ongoing trials for the management of COVID-19 pandemic [148].

In addition to this trial, it is worth mentioning an open-label, phase II trial for colchicine use in COVID-19 treatment [149].

### Convalescent plasma treatment

Convalescent plasma treatment has emerged as a promising option for the control of severe COVID-19 in the absence of specific antivirals. It is a strategy of passive immunization based on utilizing the hyperimmune IgG antibodies produced by individuals after recovering from COVID-19 [150]. In several case series, clinical improvement and reduction in the viral load have been reported [151–155]. However, there were no matched controls in these studies. Thus, the ongoing clinical trials will probably provide a higher level of evidence and data about the efficacy and safety of convalescent plasma therapy in COVID-19. We should also be cautious considering the potential severe reactions associated with convalescent plasma use such as anaphylactic reactions or transfusion-related acute lung injury [150].

### Considerations for patients with rheumatic diseases regarding their treatment

At the moment, all international rheumatology societies, including ACR (American College of Rheumatology), EULAR (European League Against Rheumatism), and PReS (Pediatric Rheumatology European Society) recommend continuation of immunosuppressive treatment

in patients with rheumatic diseases. Previous studies on SLE and RA patients provided data on the increased rate of infections in cases of high disease activity [103, 104]. Thus, the primary aim should be an effective disease control in our patients with rheumatic diseases.

A considerable amount of rheumatology patients are on drugs that are currently being tested for prophylaxis or treatment of COVID-19. And it is difficult to predict the effects of being already on these treatments on infection rate and severity.

As discussed above, there is a concern for more severe disease in patients using NSAIDs. To be on the safe side, NSAIDs may not be proposed as a primary treatment of rheumatic diseases or may be discontinued if they are not the primary drugs for disease control during COVID-19 pandemic. And for pain control, acetaminophen could be selected over NSAIDs.

Since HCQ is an immunomodulatory rather than immunosuppressive drug, and it probably interferes with viral entry, it might have a protective effect for patients treated with HCQ. However, SLE patients should not be considered resistant to COVID-19. Recently, there are increasing reports of COVID-19 patients with SLE [28, 30, 32, 41]. Mathian et al. have reported the clinical picture of the course of COVID-19 in SLE patients treated with HCQ [32]. The authors concluded that HCQ does not seem to prevent COVID-19, at least its severe forms, in patients with SLE since most of the SLE patients in this study received long-term treatment with HCQ, having blood concentrations of the drug within the therapeutic range. The findings of Konig et al. were in the same lines, as mentioned above [41].

The data about glucocorticoid use are also complex and challenging to interpret. As pediatric rheumatologists, we are always aiming to decrease glucocorticoid use and to keep the glucocorticoid dose as low as possible to control disease activity. Probably, following the same principle will be logical until we get more evidence.

Most of the other drugs such as JAK inhibitors, anti-IL-1, anti-IL-6, and anti-TNF agents are immunosuppressives, and these might interfere with the effective clearance of the virus at early phases of the disease. Thus, being on these drugs at the early phase of infection could be a disadvantage for rheumatology patients. On the other hand, these drugs might prevent the development of a cytokine storm, making a milder disease course possible. Currently, there is not enough data about COVID-19 disease course in patients with rheumatic diseases that are treated with biologic drugs (Table 1). In a survey study from Italy, Filocamo et al. reported that there was no confirmed COVID-19 case among 123 pediatric patients on biologic DMARDs for chronic rheumatic diseases [156]. Current guidelines recommend continuing all

immunosuppressive therapies providing disease control, and proper patient education against the virus.

During active COVID-19, the immunosuppressive therapy was discontinued in most rheumatology patients [29, 32–35]. Another important topic is when to re-initiate these therapies. In the case reports Song et al. [35] and Mihai et al. [33], the immunosuppressive therapies were re-initiated 2–4 days after a negative test result for COVID-19. In their expert opinion article, Sarzi-Puttini et al. suggested that these drugs should be re-initiated only after two negative swabs [157].

Last but not least, how will our decisions be affected while initiating treatment for the patients that are newly diagnosed with a rheumatic disease during COVID-19 pandemic? If possible, it may be recommended to test for SARS-CoV-2 before initiating biologics as we do for tuberculosis. However, the exact response to this question remains unknown currently. This issue will also be a hot topic when the pandemic is over since we currently do not know about the possibility of latent disease in COVID-19.

Gupta et al. performed a survey among rheumatologists in India to assess the attitudes of physicians while initiating anti-rheumatic therapies during COVID-19 pandemic [158]. They observed that almost 60% of the respondents preferred an earlier taper of glucocorticoids during inactive disease. 66.5% of the respondents were more inclined to initiate HQ in patients with borderline indications. And, almost half reduced the usage of biologic drugs.

## Conclusion

COVID-19 pandemic has a high mortality rate and a poorer outcome, particularly in elderly patients and individuals with comorbidities. There are very limited data about the infection rate and disease course in patients with rheumatic diseases and almost no data regarding pediatric rheumatology patients. We should continue the medicines that control the disease activity in pediatric rheumatology patients since uncontrolled disease and high disease activity place patients to a higher risk group with regard to infections. Having said that one needs to decide on treatment on an individual basis, considering personal risk factors. It is critical not to reach early conclusions about the prophylactic effects of the drugs we currently use in pediatric rheumatology practice. And although the disease mostly has a mild course in children, children are not immune to COVID-19, and different clinical manifestations such as Kawasaki-like disease are being related to SARS-CoV-2 infection. We should use the accumulating current scientific evidence and common sense while making decisions about the treatment of our patients and follow the primary prevention principles such as hand hygiene and social distancing.

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## Compliance with ethical standards

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