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REVIEW ARTICLE

Managing rheumatic diseases during COVID-19

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Abstract

Rheumatology practice, during Coronavirus Disease 2019 (COVID-19) pandemic, has faced multifaceted challenges. Rheumatologists routinely prescribe immunosuppressant medications to their patients with multisystem autoimmune rheumatic diseases who are concerned about the increased risk of acquiring COVID-19 infection and are anxious to know if they should continue or hold these medications. Rheumatologists are often inundated by calls from their patients and physician colleagues caring for COVID-19 patients in hospitals, about how to manage the immunosuppression. Physicians face the challenging task of keeping up with the most up-to-date information on COVID-19. There are uncertainties about the mode of spread, clinical features, management options as well as long-term complications of COVID-19. Data are rapidly evolving and different studies on treatment options are showing contradictory results. It is known that viral illnesses can trigger a flare-up of underlying rheumatic disease that was previously in remission. To further complicate the scenario, some of the immunosuppressants have shown to have antiviral properties. This has created dilemma in the light of current COVID-19 crisis, as whether to continue or stop the immunosuppressive agents which could be essential to prevent complications of the rheumatic diseases including organ failure but also there is concern about acquiring COVID-19 or developing serious infection. Until we get an effective vaccine, immunosuppressant management for rheumatic diseases as well as other autoimmune diseases and transplants will pose difficult questions. This article is an attempt to review and understand COVID-19 and its impact on the immune system with special emphasis on managing medications used for autoimmune rheumatic diseases. We have provided general guidance about decision making, in regards to the immunosuppressive agents used in rheumatology practice with an understanding that this may change in near future.

Keywords Autoimmune · COVID-19 · DMARD · Immunosuppressive · Medications · Rheumatic

Introduction

After severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the third major viral outbreak in 21st century. SARS-CoV-2 originated in Wuhan Province in China in December 2019 and its state media reported the first known mortality on January 11, 2020. World Health Organization (WHO) declared COVID-19 as Public Health Emergency of International Concern on January 30, 2020 [1] and as global pandemic on March 11, 2020 [2]. So far almost 11 million positive cases and more than half a million deaths have been reported worldwide with approximately 129 thousand deaths noted in the USA alone [3].

SARS-CoV-2, a single-stranded ribonucleic acid (RNA) beta-coronavirus of the Ortho Coronaviridae subfamily is thought to have originated from bats, as it has almost 96% genetic similarity to bat coronavirus genetic structure [4, 5]. Two forms of the virus have been identified—S type (~ 30%) and L type (70%), with the latter being more infectious and aggressive than the former, original strain [6]. COVID-19 mainly affects upper and lower respiratory tract, but also can also cause several other symptoms such as thromboembolism, neurological, and gastrointestinal disturbances. Most common reason for death is respiratory failure followed by sepsis and secondary infection [7].

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There is no satisfactory antiviral against COVID-19; however, remdesivir, lopinavir/ritonavir (with and without interferon beta-1b and ribavirin) [8], and hydroxychloroquine (HCQ) are being used and various clinical trials are underway. Remdesivir has shown some promise in vitro [9]. There are also anecdotal reports showing the ability of lopinavir-ritonavir to decrease viral load and improve outcomes [10]. There was tremendous interest about HCQ initially due to existing scientific evidence of in vitro activity against SARS-CoV-2 [11, 12], but enthusiasm is fading away after results from more recent studies [13]. Also, agents like vitamin C [14] and histamine-2 (H2) receptor antagonist-famotidine are being studied [15]. To treat the cytokine storm caused by infection, anti-cytokine therapies including tocilizumab, anakinra, and JAK inhibitors like baricitinib are being tried. In an ongoing landmark trial [RECOVERY] from the UK, dexamethasone was reported to be lifesaving. (ClinicalTrials.gov Identifier: NCT04381936).

Approximately 4.5% to 5.3% (14.7 to 23.5 million) of the United States (US) population have one or more autoimmune diseases of which 40% (2% of population) have autoimmune rheumatic disease [16]. Various trials are underway to determine whether rheumatic medications can potentially be used as preventative therapy, post-exposure prophylaxis and to counteract cytokine storm seen in critically ill COVID-19 patients.

The scientific and research community is interested in the potential role of interleukin (IL)-6 inhibitor like tocilizumab, IL-1 inhibitor–like anakinra, and janus kinase (JAK) inhibitor–like baricitinib in preventing cytokine storm besides investigating preventative and/or post-exposure use of antimalarials like HCQ and chloroquine (CQ).

To better understand the existing conundrum, we extensively reviewed recently published articles and guidelines issued by various societies. We also streamlined the data and attempted to come up with provisional recommendations for managing of rheumatic medications in COVID-19 infected patients.

Pathophysiology of COVID-19

The SARS-CoV-2 virus enters respiratory tract, infecting cells via angiotensin-converting enzyme (ACE)-2 receptors [17]. These receptors are expressed by the cells in the heart, lungs, blood vessels, kidneys, liver, and gastrointestinal tract [18]. It replicates in either ribosomes or the endoplasmic reticulum. During this replication process, RNA proteolysis leads to production of polypeptides, nonstructural proteins, and RNA-dependent RNA polymerase (RdRp). The RNA translation process is followed by reassembly of its outer structural products. Finally, viral multiplication occurs and viral particles get out of infected cells via exocytosis to re-infect other cells (see Fig. 1).

Subsequently, the host mounts an immune response using both the innate and adaptive defense mechanisms. Macrophages, dendritic cells, and natural killer cells play an important role. Memory and regulatory T cells produced during the process preserve their memory in case of future attacks and regulate overactive immune response respectively. Cytokines that are released during the process of trying to eliminate virus cause inflammation (see Fig. 2). In COVID-19, initial inflammatory response is seen as increased levels of tumor necrosis factor (TNF)-alpha, IL-1 beta (both short lasting for 1–2 days), and IL-6 (longer lasting) [19]. Lymphocytes are the main target cells in COVID-19. Age-dependent T- and B-cell function defect along with excess production of type 2 cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) causes uncontrolled viral replication and increased inflammatory response [20]. Low peripheral CD4 and CD8 T-cell count is observed along with hyperactive CD8 T cells. These hyperactive CD8 T cells contain more cytotoxic granules that stain positive for perforins and/or granulysin [21]. IL-6 has been implicated in the consolidation phase of organizing pneumonia and also in prolonging QT interval, leading to torsade de pointes [22, 23].

Coagulopathy in COVID-19 infection manifest as either low grade DIC (thrombocytopenia, increased d-dimer, prolonged PT), or localized pulmonary thrombotic microangiopathy (increased LDH and ferritin) [24]. Some patients with rheumatic diseases like adult-onset Still's disease (AOSD) and systemic lupus erythematosus (SLE) [25, 26] also show unregulated systemic hyperinflammation, presenting as macrophage activation syndrome (MAS). MAS is a subset of hemophagocytic lymphohistiocytosis (HLH) leading to rapid evolution of multiple organ failure and this is similar to the hyperinflammation seen in the setting of COVID-19 infection [20].

An exaggerated host immune response leads to cytokine storm which then leads to multiple organ dysfunction. It is not clear why only some patients develop cytokine storm; however, host genetic risk is suspected as a causation or propagation of these complications [27].

Clinical features, diagnosis, risk/prognosis, and treatment

Mild COVID-19 is characterized by fever, dry or mildly productive cough, and fatigue. Features of critical illness include respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, septic shock, and heart failure [7]. COVID-19 pneumonia can range from mild to severe [28]. An early study reported fever, dyspnea, and dry cough as common presenting symptoms, similar to SARS-CoV-1 and MERS-CoV; however, very few with SARS-CoV-2 had upper respiratory symptoms (rhinorrhea and sore throat) and intestinal symptoms (diarrhea) which is common with other coronavirus infections [20]. Data from > 70,000 patients released by

Chinese CDC reported that 81% had mild, 14% had severe, and 5% had critical illness disease [29]. In a small prospective cohort study of 12 patients in Hamburg, Germany, autopsy showed deep vein thrombosis (DVT) in 58% (7 out of 12) patients even though it was not suspected antemortem, while pulmonary embolism (PE) was directly related to death in 33% (4 out of 12) patients [30].

The severity of disease has not shown to be associated to viral load [31]. COVID-19 diagnosis can be confirmed by doing real-time reverse-transcription polymerase chain reaction (RT-PCR) assay or high-throughput sequencing from nasal and pharyngeal swab specimen [28]. Though chest-computed tomography (CT) manifestations vary among different patients, with COVID-19, bilateral consolidation with ground glass opacities are typical CT manifestations [22].

American College of Rheumatology (ACR) formed COVID-19 clinical task force on March 26, 2020 with aim to provide clinical guidance to rheumatologists. This task force did not identify rheumatic diseases as a risk factor that predicted poor outcome in patients with COVID-19 [32]. Risk factors that predict poor outcomes in those with COVID-19 include older age (> 65 years), obesity, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease (CKD), and cardiovascular disease (CVD) [33]. Biomarkers that predict poor outcomes include lymphopenia, elevated levels of c-reactive protein (CRP), D-dimer, IL-6, and LDH [34].

The mortality rate with COVID-19 is thought to be around 3.7% [35], compared to < 1% from influenza. Case fatality rate of this virus, from data available so far, is estimated to be around 1% which puts it between the range of 0.6% (seen with the 1957 influenza pandemic) and 2% (seen with the 1918 influenza pandemic) [36]. Chinese CDC data from a large study showed average case fatality being 2.3% but as high as 49% in those with critical illness [37].

With the exception of few case reports and some preliminary data from ongoing studies, there is no definitive evidence of effectiveness of any of the current agents that are being used (mostly on compassionate basis) to treat any coronavirus including SARS-CoV-2 [38, 39]. The United States Food and Drug Administration (USFDA) has approved three medications (HCQ sulfate, CQ phosphate, and remdesivir) for Emergency Use Authorization (EUA) for COVID-19 [40]. HCQ and CQ are already FDA-approved drugs and were available to be prescribed outside EUA indications [40]. Adenosine analogue remdesivir had shown promise in vitro effect in a SARS-CoV-2 control group. On May 1, 2020, the FDA authorized emergency use of remdesivir in adults and children hospitalized with severe disease (low oxygen saturation requiring either oxygen or mechanical ventilation) due to COVID-19. Remdesivir is not FDA-approved and hence access is limited to compassionate use programs, expanded access programs, and clinical studies [41]. As the initial uncertainty about availability and distribution of remdesivir was addressed, its price was fixed by the manufacturer for transparency [42].

In a small study, convalescent plasma with neutralizing antibodies resulted in improvement in the clinical status of 5 patients with COVID-19 and ARDS [43]. Another comparatively larger study of 39 critically ill-hospitalized patients with COVID-19 from New York showed improved survival in those that received convalescent plasma, with more benefit seen in non-intubated patients compared to those on mechanical ventilation [44].

Since there is an established role of low molecular weight heparin (LMWH) in critically ill patients for DVT/PE prophylaxis, all patients with COVID-19 who are hospitalized should receive it in absence of contraindication as coagulopathy is noted in sizeable number of patients [24].

COVID-19 and medications used for systemic autoimmune rheumatic diseases

Rheumatologists deal with a wide variety of systemic immune-mediated disorders with complex manifestations and use agents ranging from nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids to potent immunosuppressive agents such as cyclophosphamide. These medications help suppress tissue inflammation, thereby preventing tissue/organ damage in autoimmune diseases. Immunosuppressive agents can suppress cytokine storm, a feature observed in both, systemic autoimmune diseases and viral illnesses. However, it can sometimes cause serious harm when used during viral infection possibly due to factors like secondary bacterial infections [45, 46].

Small, anecdotal studies have proposed that being on certain immunomodulatory regimens might have possibly conferred protection to rheumatologic patients against severe SARS-CoV-2 manifestations [47, 48]. However, there is a relative scarcity of studies that gives guidance regarding the use of immunosuppressant medications during COVID-19 infection.

An early survey study done in Milan, Italy, by Favalli EG et al. showed that it is beneficial to continue all rheumatic medications in someone who has not had COVID-19 exposure, as it helps with disease stabilization and prevent flare-ups [47]. The study by Venerito V et al. concluded that patients with uncontrolled rheumatoid arthritis (RA) and SLE have a higher risk of acquiring infection than being on immunosuppressive regimen while the disease is in remission [48]. Disease flares and use of corticosteroids during disease flares may further increase the risk of infection. A cross-sectional study showed that > 90% patients followed their

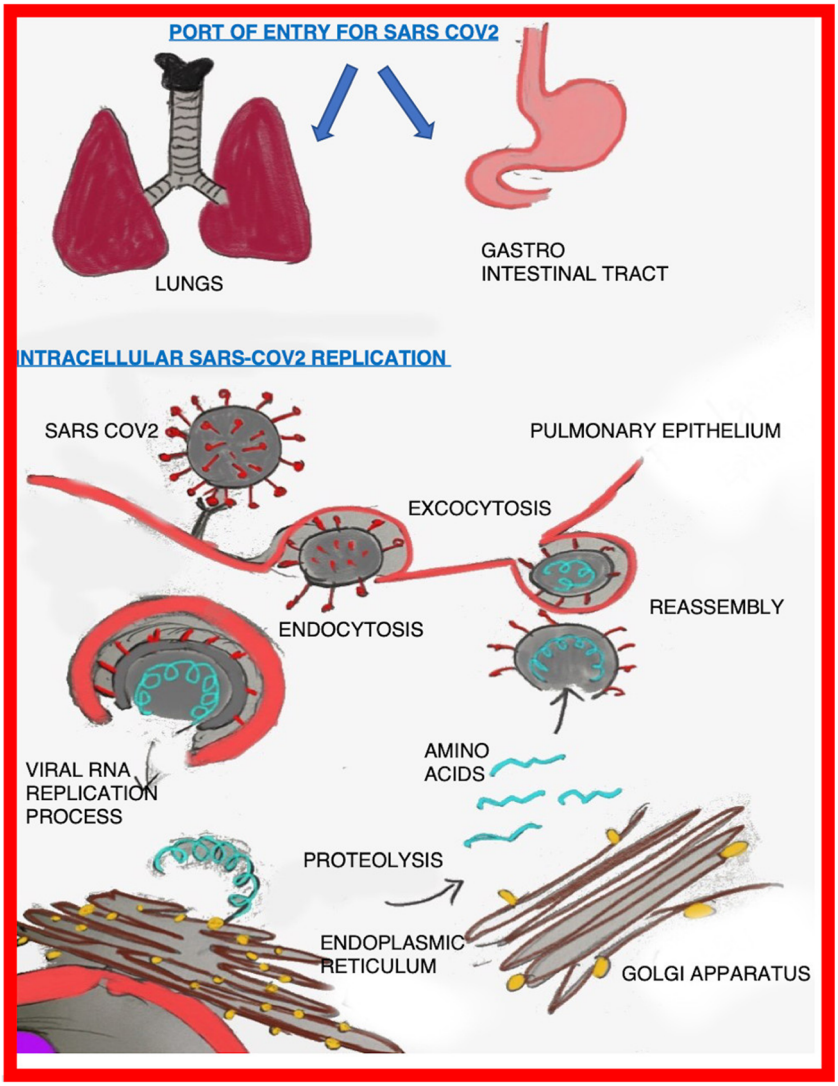

Fig. 1 SARS-CoV2 port of entry is mostly at lungs and GI tract. As the virus infects the epithelium it gets endocytosed and the virus goes through proteolysis releasing its RNA (ribonucleic acid) at EPR (endoplasmic reticulum). With proteolysis, RNA is turned into amino-acids and gets reassembled with structural proteins at Golgi apparatus. After reassembly in cells, it gets exocytosed by cells at pulmonary/gastric epithelium. These reassembled viruses are ready to infect neighboring cells

rheumatologists' recommendation and continued immunosuppressive therapy, irrespective of their treatment regimen [49].

It is unclear whether continuing NSAIDs is beneficial due to its antipyretic and anti-inflammatory effect in less severe COVID-19 cases. Some advocate acetaminophen use, although it can complicate liver injury as seen in few cases [50, 51].

Preliminary data from an ongoing large multi-center open-label randomized trial (RECOVERY (randomized evaluation of COVID-19 therapy)) at University of Oxford, UK, suggested mortality benefit with dexamethasone in those who required supplemental oxygen or mechanical ventilation but not in those who did not require supplemental oxygen (ClinicalTrials.gov Identifier: NCT04381936). In a case series from Italy, younger patients in epidemic areas, who were on corticosteroids for cancer chemotherapy and had a history of solid organ transplant did escape severe COVID-19 [52]. A small hospital cohort study reported methylprednisone use in COVID-19-related ARDS led to a shorter intensive care unit (ICU) stay [53] and improved survival rates [34]. Corticosteroids are associated with a risk of bacterial and opportunistic infections [54] along with a possible reactivation of herpes zoster [55, 56]. A case series from China showed up to 50% of deaths associated with COVID-19 were linked to secondary bacterial infections [7]. American College of Rheumatology (ACR) COVID-19 taskforce recommended against the abrupt withdrawal of corticosteroids due to hypothalamic pituitary adrenal (HPA) axis suppression [32]. We conditionally recommend that corticosteroids be used in the smallest possible dose in patients on chronic steroids.

When used as monotherapy, conventional synthetic (cs)DMARDs are associated with minimal risk of serious infection. HCQ and CQ showed antiviral activity in vitro [9, 11, 12]; however, to date, there is no definitive evidence reported

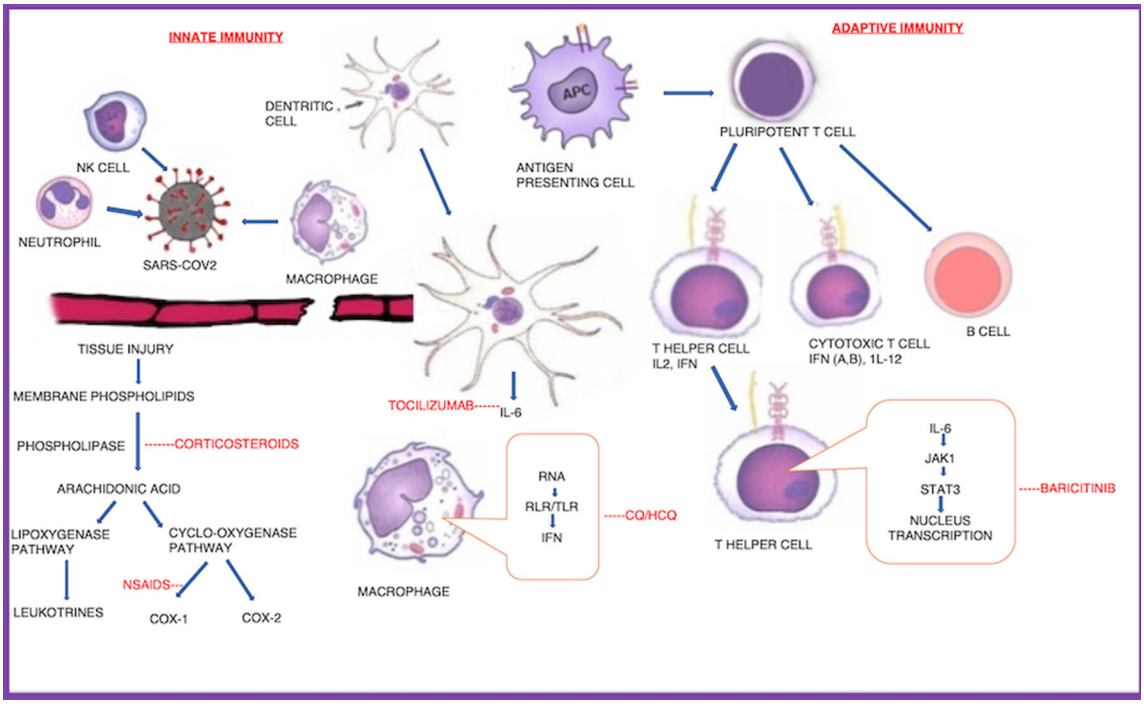

Fig. 2 Immune Response to SARS-CoV2 & pharmacodynamics of rheumatology medications. This figure depicts (1) body's immune response to SARS-CoV2 and (2) rheumatology meds (commonly prescribed) working at different levels. Cells—NK cells (null killer cells); APC, antigen presenting cell; enzyme/cytokines, COX-1, COX-2 = cyclo-oxygenase 1, 2; IL-2, 6, 12 = interleukin 2, 6, 12; IFN, interferon A&B; medications—CQ/HCQ, chloroquine/hydroxychloroquine; NSAIDS, nonsteroidal anti-inflammatory drugs; TLR/RLR, Toll-like receptor/retinoic acid inducible gene–like receptor (within macrophage); JAK/STAT pathway, Janus kinase/signal transducer and activation of transcription (depicted within T-helper cell). Immune response—Virus infection triggers innate immune response at site of infection (left side of figure); whereas the adaptive immune response (right side of dendrites/macrophage) occurs at lymphatic system. Each figure depicts various cells and its secretion. SARS-CoV2 infection triggers both innate and adaptive immunity. With innate immune response, the tissue injury/host infected cell is recognized by neutrophils, NK (null killer cells), macrophages, dendritic cells. Innate immunity focus on preventing instant spread of infection by recruiting more neutrophils, macrophages and NK cells. Dendritic and macrophage cell conveys message to antigen presenting cells, which in turn recruits pluripotent T cell. This pluripotent T cell secretes IL-12 (interleukin-12) and in turn gets differentiated into T-helper (CD4), cytotoxic T cell (CD8) and B cell. T-helper secrets IL-2 (interleukin-2) and IFN (interferon), whereas cytotoxic secrete IFN A, B (interferon A, B) and IL-12 (interleukin-12). Pharmacodynamics—red color–dotted lines indicate inhibition action of medications at specific site in a cell. Corticosteroids—inhibits phospholipase and thereby inhibiting leukotrienes, cycle-oxygenase production leading to less inflammation. NSAIDS—inhibits COX-2/ specific ones COX-1. CQ/HCQ (chloroquine/hydroxychloroquine)—inhibits Toll receptor/RLR receptors at intracellular level within macrophage, leading to decreased IFN production. Baricitinib—inhibits JAK/STAT pathway within T-helper cells, leading to further deactivation of adaptive immunity. Toclizumab—inhibits Interleukin-6 production by dendritic cells further delaying recruitment and inflammation

that it is effective for prevention and post-exposure prophylaxis. Gauderet et al. suggested that HCQ is beneficial in the treatment of COVID-19 [57]. However, the study was noted to have significant statistical limitations with small sample size as well as poor randomization and methodology [58]. Poor interpretation with over-simplification of one study by social media and lay press led to the active propagation of HCQ and CQ as "potential remedy of COVID-19." In certain countries, HCQ was propagated by authorities for prevention and post-exposure prophylaxis [59]. Divergence for using HCQ in COVID-19 led to its temporary shortage, which affected patients with RA and SLE [60]. HCQ and CQ are relatively safe medications and can be continued in patients having COVID-19; caution is advised about increased myocardial toxicity [61] and QT prolongation when used with agents like azithromycin [62].

Targeted synthetic (ts)DMARD like JAK inhibitors and biologic (b)DMARD have a higher risk of serious bacterial and opportunistic infection [63–65] compared to csDMARD. There is also an increased risk of herpes zoster reactivation with JAK inhibitors [66, 67]. Baricitinib, a tsDMARD inhibiting JAK has shown to limit SARS-CoV-2 penetration in pulmonary epithelial cells [68]. Less protein-binding properties with minimal CYP interaction favors baricitinib to be combined with ritonavir and remdesivir [69]. However, a potential downside of baricitinib is that it can impair innate immunity by reducing interferon's response which is deemed critical to control viral replication [68]. In a case report, IL-6 inhibitor—tocilizumab possibly prevented development of severe COVID-19 complications in someone who had been taking it for scleroderma associated interstitial lung disease (ILD) [70]. Tocilizumab is currently being commonly used in

critically ill patients with COVID-19 and has been associated with good outcomes [71, 72].

In a small number of hospitalized patients with COVID-19, anakinra prevented cytokine storm, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis [73]. A phase 3 multi-center, randomized, double-blind, placebo-controlled study is currently underway to evaluate safety and efficacy of colchicine in adults with COVID-19 infection and at least 1 high risk criteria (ClinicalTrials.gov ID: NCT04322682) [74]. Mycophenolate mofetil (MMF) is associated with improved survival rates after MERS-CoV [75] and cyclosporine prevents in vitro replication of coronavirus [76]; however, their impact on SARS-CoV-2 infection risk is not fully understood.

For simplification, we classify FIVE broad categories of medications that most of them fall under—NSAIDs, corticosteroids, DMARDs (csDMARD, tsDMARD, and bDMARD), immunosuppressive agents, and miscellaneous anti-inflammatory agents like colchicine.

For better understanding, we categorize the patients with rheumatic illnesses as the following: no history of exposure, patients with exposure but not currently positive, patients exposed with confirmed infection, patients admitted in hospital including those in ICU, and those discharged from hospital after recovery (post-COVID-19).

We thoroughly reviewed the articles, guidelines, and recommendations so far published and created best practice guidance as shown in Table 1:

Areas of uncertainty

The major cause of mortality in COVID-19 patients is excessive cytokine production which leads to unregulated inflammatory response. It is unclear whether there is any specific area in an immune response that can be inhibited without preventing the hosts' defense [77]. Although IgM and IgG antibodies are detected within a few days to weeks in most COVID-19 patients, it is not known why some patients with COVID-19 infection do not develop these antibodies [78–80]. As of now, there is no known confirmed case of human reinfection of SARS-CoV-2 [81], although viral PCR can remain positive for a long time even after the resolution of infection. Serologic assays that detect SARS-CoV-2 antibodies are increasingly becoming available, although it is not prudent to say currently that these subjects are immune against getting reinfected [81]. Except for a small animal study [82] that favors recovery and possible immunity to reinfection from SARS-CoV-2, there is currently paucity of data about it. In children, Kawasaki-like syndrome, which is provisionally called

Table 1 Rheumatic medications in different COVID-19 scenarios

COVID exposure/rheumatoid meds	Not exposed	Suspected exposure	Tested positive	Hospital/ICU admitted	Post-COVID-19
NSAID	+	~	~	x	+
Corticosteroid	+	~	~	+	+
DMARD (cs)					
Chloroquine (CQ)	+	+	+	+*	+
Hydroxychloroquine (HCQ)	+	+	+	+*	+
Methotrexate (MTX)	+	?	x	x	+
Sulfasalazine (SSZ)	+	+	x*	x	+
Leflunomide (LEF)	+	?	x	x	+
DMARD (ts) (JAK inhibitors)	+	x	x	x	+
DMARD (b)					
IL-6 mediated	+	+	+	+/~	+
Non IL-6 mediated	+	x	x	x	+
Colchicine	+	?	?	?	+
Immunosuppressive (azathioprine, cyclosporine, MMF, tacrolimus)	+	x	x	x	+

+ = continue

x = discontinue

~ = decision based on case to case scenario

? = inadequate data

x* = side effects of SSZ (hepatitis, cytopenia) can be confused with SARS-CoV-2

+* = Closely monitor for myocardial injury and QT prolongation

pediatric inflammatory multisystem syndrome (PIMS-TS), is temporally associated with SARS-CoV-2 [83].

Conclusion

COVID-19 has posed important challenges to the management of autoimmune rheumatic diseases. We have attempted to address the dilemma faced by medical community about the commonly used immunosuppressive medications during COVID-19 crisis using the best available current evidence.

Although it appears that almost all DMARDs can be continued in patients not exposed to COVID-19 and restarted after recovering from the infection, the level of evidence, at least at this point, is limited to few observational studies only, and prospective larger studies are needed to provide the definitive recommendations.

We are optimistic that while adhering to measures that has proven effective to prevent virus spread (frequent hand washing, wearing PPE like face masks and goggles, and social distancing), scientific community will continue its vigorous effort to mitigate this crisis.

Compliance with ethical standards

Disclosures/Conflict of interest Amit P. Ladani—none
Muruga Loganathan—none
Abhijeet Danve—Advisory boards and honoraria: Janssen; Research Grants: Novartis

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