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EXPERT COMMENTS

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# Care for patients with rheumatic diseases during COVID-19 pandemic: A position statement from APLAR

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## 1 | INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China in December 2019. This disease now affects the whole world. Patients with rheumatic diseases are at higher risk of respiratory infections including influenza and pneumococcal pneumonia, which is attributed to the underlying disease, comorbidities and immunosuppressive therapy,[1] but to date we lack good information about the virus SARS-CoV-2. Nonetheless, immunosuppressive treatments are essential to control disease activity and prevent functional deterioration in these patients. Rheumatologists need to be vigilant in preventing rheumatic disease patients from contracting the disease during this pandemic, especially patients with chronic lung problems (eg scleroderma with lung fibrosis) and chronic kidney disease (eg lupus nephritis) and those on high-dose glucocorticoids and immunosuppressants (Appendix 1).

In the desperate search to find effective treatments for COVID-19, drugs largely used by rheumatologists have entered the spotlight, including the caution against use of non-steroidal anti-inflammatory drugs (NSAIDs), the potential of antimalarials and biologic disease-modifying anti-rheumatic drugs (bDMARDs), for example anti-interleukin-6 (IL-6) and targeted synthetic DMARDS (tsDMARDs) Janus-activated kinase (JAK) inhibitors to manage cytokine storm syndrome (CSS)/cytokine release syndrome associated with COVID-19. Here, we try to provide guidance regarding clinical decision-making both for patients with COVID-19 and those with rheumatic diseases, and strategies to mitigate further harm to these patients.

## 2 | METHODS

An Asia-Pacific League Against Rheumatism (APLAR) COVID-19 task force comprising rheumatologists from 9 Asia-Pacific countries

was convened on 31 March, 2020. A set of guidance statements was developed and refined based on best available evidence up to 26 April, 2020 and expert opinion. Given the overall limited nature of the data, a systematic review was not performed. The final guidance statements integrate both the task force members' assessment of the evidence quality and the ratio of risk and benefit from the treatment or action. We assert that the key guiding principle should be to "first do no harm," especially given the unknown efficacy of proposed DMARDs and biologics and their established potential harms. This guidance document has been reviewed and endorsed by the APLAR executive committee and the APLAR scientific committee chairpersons.

## 3 | HOW CAN WE MINIMIZE THE RISK OF RHEUMATIC DISEASE PATIENTS FROM EXPOSURE TO COVID-19?

In the absence of a vaccine or a therapeutic agent, a "mitigation approach", including "social distancing", frequent hand washing and quarantining strategies are the primary interventions to hamper the spread of infection.[2] Another approach, known as "suppression strategies" includes strict lockdown measures – social distancing in entire populations, the closure of schools and community spaces, aggressive case finding and contact tracing, have succeeded in maintaining low case counts of COVID-19. During this extraordinary time, the rheumatology community faces unprecedented challenges as care could be postponed/delayed or handled through virtual care to minimize contact exposure and to practice social distancing.

Comorbid conditions are common in patients with COVID-19.[3] Smoking can cause an increase in the release of IL-6 in bronchial epithelial cells,[4] and upregulate angiotensin-converting enzyme-2 (ACE2) receptors, the known receptor for SARS-CoV.[5] This is particularly relevant as some of the Asia-Pacific countries, for example China, has a high male smoking rate.[6] Globally the quality of evaluation, monitoring and treatment of comorbidities in rheumatic disease patients is variable with considerable scope for improvement.[7] Rheumatologists should be vigilant in assessing and managing comorbidities not only to improve morbidity and mortality, but hopefully to minimize risk of COVID-19 in rheumatic disease patients.

## 4 | NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

In patients with acute respiratory tract infections, short-term use of NSAIDs are associated with increased risk of cardiovascular events and nephrotoxicity,[8-10] higher rates of complications, and delays in the prescription of effective antibiotic treatment.[11] Despite the lack of evidence relating specifically to people with COVID-19, regular NSAID use should not be recommended as the first line option for managing the symptoms of COVID-19.[12] Nonetheless, arthritis patients taking NSAIDs for symptomatic relief should continue their treatment as needed.

## 5 | USE OF IMMUNOSUPPRESSANTS AND RISK OF COVID-19 INFECTION

Epidemiologic studies have identified advanced age, male gender and presence of comorbidities (hypertension, obesity, diabetes, coronary heart disease, chronic obstructive lung disease and chronic kidney disease) as poor prognostic factors for COVID-19.[13] Despite the lack of data on the true prevalence and risk of COVID-19 in rheumatic disease patients, immunosuppressed status (the use of chemotherapy or conditions requiring immunosuppressive treatment) was not reported to be a risk factor and risk for adverse outcome. One patient with systemic sclerosis-associated interstitial lung disease (SSC-ILD) on tocilizumab and 7 patients on bDMARDs or tsDMARDs who developed COVID-19 recovered uneventfully.[14-16] Nonetheless, at least 2 patients on rituximab[17] developed respiratory failure and 1 of them died despite treatment with tocilizumab.[18] In order to gather real-world data to inform treatment strategies and better characterize individuals at increased risk of infection, the COVID-19 Global Rheumatology Alliance has successfully developed online portals and case report forms to enable healthcare providers around the world to enter information on individuals with rheumatic disease who have been diagnosed with COVID-19, with clinical data of the first 110 patients published.[19] For now, patients with stable rheumatic diseases should continue their treatment. In case of infection (including COVID-19), treatment of infection gains precedence and immunosuppressive treatment may be de-escalated or temporarily withheld in consultation with the treating rheumatologist (Appendix 1).

### 5.1 | Glucocorticoid therapy

Acute lung injury and acute respiratory distress syndrome (ARDS) are partly caused by host immune responses. Severe COVID-19-associated pneumonia patients may exhibit features of systemic hyper-inflammation or CSS. COVID-19 infection with CSS typically occurs in subjects with ARDS and historically, non-survival in ARDS was linked to sustained IL-6 and IL-1 elevation.[20] Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance. The effectiveness of adjunctive glucocorticoid therapy in the management of COVID-19 infected patients remains controversial.[21,22] Until results from ongoing randomized-controlled trials are available, the World Health Organization (WHO) has advised against routine use of systemic corticosteroids for treatment of viral pneumonia outside of clinical trials unless they were indicated for other reasons (eg septic shock) (Appendix 2). In rheumatic disease patients on long-term steroids, it is very important to remind them not to stop their prednisone even if they develop symptoms suggestive of COVID-19 (Appendix 1). For patients with active

rheumatic disease, after excluding concurrent active infection, the prednisone dose could be increased carefully according to the severity of the organ manifestation, in spite of the risk of COVID-19.

### 5.2 | Conventional synthetic disease-modifying anti-rheumatic drugs

Preclinical and limited clinical data suggested that hydroxychloroquine (HCQ) and chloroquine (CLQ) have antiviral activities against SARS-CoV-2.[23-25] In contrast, a small but randomized study from China in patients with mild to moderate COVID-19 treated with HCQ or placebo found no difference in recovery rates,[26] and French investigators failed to confirm antiviral activity or clinical benefit of the HCQ and azithromycin combination in 11 hospitalized patients with severe COVID-19.[27] In a French series of 17 systemic lupus erythematosus (SLE) patients with COVID-19 on long-term HCQ, 11 (65%) and 5 (29%) developed respiratory failure and ARDS respectively despite having blood HCQ concentrations within the therapeutic range for the management of SLE.[28] Whether blood HCQ concentrations may be effective for the antiviral activity against SARS-CoV-2 remained uncertain. Nonetheless, data from this study suggest that HCQ may not be able to prevent severe COVID-19 in these patients. The US Food and Drug Administration (FDA) cautioned against use of HCQ or CLQ for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems (Appendix 2). The APLAR task force agreed there are insufficient clinical data to recommend either for or against HCQ or CLQ for COVID-19, and clinicians should monitor patients for adverse effects, especially prolonged QTc interval. Health authorities should ensure adequate supply of these drugs since the HCQ shortage not only will limit availability to patients with COVID-19 if efficacy is truly established but also represents a real risk to patients with rheumatic diseases.

On the other hand, rheumatologists should remind patients to continue HCQ and not to taper the dosage even if they develop symptoms suggestive of COVID-19 and reassurance should be given that this drug should not increase their risk of infection.

### 5.3 | Biologic disease-modifying anti-rheumatic drugs

Once hospitalized, for some patients with COVID-19, death can occur within a few days, many with ARDS, and some with multiorgan dysfunction syndrome.[14] In those critically ill patients, there are both clinical signs and symptoms, as well as laboratory abnormalities, that suggest a CSS is occurring in response to the viral infection. According to data from the Chinese cohorts, patients with severe disease and requiring intensive care often show leucopenia, lymphopenia, significantly higher levels of C-reactive protein (CRP), IL-6, IL-10, and tumor necrosis factor-α (TNF-α).[29] In this setting, biologic drugs selectively blocking inflammatory cytokines, such as TNF-α inhibitors, anti-IL-6, anti-IL-1 and JAK inhibitors are currently employed in the treatment of severe cases of COVID-19 in an experimental manner or undergoing clinical trials (Appendix 2).

Tocilizumab, has been shown effective in treating CSS, a common complication of chimeric antigen receptor-T cell therapy used for treating refractory acute lymphoblastic leukemia[30] and may be effective in Chinese COVID-19 patients with severe and critical disease.[31] Anti-IL-6R antibody is currently included in the treatment recommendation for Chinese COVID-19 patients (Appendix 2). These concepts have led to interests in JAK inhibitors, for example baricitinib, as potential treatments for CSS complicated with severe COVID-19.

ACE2 is a cell-surface protein widely existing on cells in the heart, kidney, blood vessels, especially alveolar epithelial cells. SARS-CoV-2 was believed to invade and enter lung cells through ACE2-mediated endocytosis. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and can be helpful in preventing virus infections. Baricitinib, apart from being a JAK inhibitor, is also an AAK1 inhibitor. Baricitinib was thought to be a possible candidate for treatment of COVID-19, considering its relative safety and high affinity.[32] On the other hand, JAK–STAT (signal transducer and activator of transcription) signal blocking by baricitinib produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection, and therefore may not be a suitable treatment.[33] While we are waiting for the results from the control trials to resolve this controversy, rheumatologists should be particularly cautious of serious infectious events on the use of this agent, in particular viral infection, for example herpes zoster.

## 6 | CONCLUSIONS

Rheumatologists worldwide are trying new strategies to optimize care for rheumatic disease patients during this unprecedented COVID-19 pandemic. Concerted efforts from healthcare providers in different healthcare systems are required to continue clinical assessments and ensure adequate supply of immunosuppressive therapy. Worsening of rheumatic disease may induce a systemic inflammatory state which may represent an adjunctive risk factor for major susceptibility to viral infection. On the other hand, rheumatologists are cautiously enthusiastic that a variety of immune-modulating drugs and targeted cytokine inhibitors available for rheumatic disease patients may also benefit patients as prophylaxis for COVID-19 or with COVID-19-induced CSS. Because of insufficient data, APLAR could not recommend any specific treatments for patients with COVID-19. Nevertheless, rheumatologists/immunologists are expert in the use of these agents and we should be to the forefront in advising around their application, noting risks and benefits are not yet clear and should not be taken for granted in

COVID-19. We emphasize the ongoing importance of critical review of emerging literature to inform current and future treatment decisions. International registries have been created to collect data on rheumatic patients with COVID-19. Ultimately, time and these registries will tell what the right decision is regarding maintaining current therapy for patients with rheumatic diseases. The APLAR task force will respond quickly and efficiently to place the evidence base behind our recommendations and update them should new findings emerge from clinical trials.

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## APPENDIX 1

**Key recommendations for managing patients with rheumatic diseases during the COVID-19 epidemic**

### Potential risk factors for SARS-COV-2 infection in patients with rheumatic diseases

- On immunosuppressive agents
- Chronic kidney disease, eg lupus nephritis
- With lung involvement, eg interstitial lung disease
- Elderly patients
- Frequently visiting medical clinic
- With underlying health conditions, such as smoking, obesity, hypertension and diabetes
- Pregnancy

### Medication for patients with rheumatic diseases[a]

- Continue current treatment if disease is stable, and contact your doctor for suitable medicine if disease has flared
- Use of hydroxychloroquine (HCQ) and sulphasalazine (SLZ) should be continued and should not increase the risk of infection
- Use of other conventional synthetic disease-modifying drugs (csDMARDs, eg methotrexate, leflunomide) and immunosuppressants (eg cyclophosphamide, azathioprine, mycophenolate mofetil, tacrolimus) should be continued
- Corticosteroid use can be continued
- A new prescription of immunosuppressant or increase in dose of an ongoing immunosuppressant would need to be carefully discussed in epidemic areas
- Use of all biologic DMARDs should be continued if possible
- If infliximab infusion is not accessible, switching to other anti-tumor necrosis factor injection at home is encouraged
- Targeted synthetic DMARDs (Janus-activated kinase [JAK] inhibitors) including tofacitinib/baricitinib/upadacitinib can be continued

### Surgery

- Postpone elective surgery, eg joint replacement surgery
- Screening for COVID-19 (symptoms suggestive of COVID-19, complete blood count, nasopharyngeal swab and chest X-ray or chest computed tomography according to local recommendation) before emergency surgery

### Patients with rheumatic disease and fever

- Contact your rheumatologist about potential option to visit fever outpatient clinic with personal protection provisions if temperature continues over 38°C
- Patients must not suddenly stop prednisolone
- Suspend the use of immunosuppressants and biological agents after consultation with your rheumatologist, and follow appropriate local guidance for suspected COVID-19 if COVID-19 cannot be ruled out
- Patients can continue HCQ and SLZ if they are infected with COVID-19.

[a]Concerning glucocorticoids, immunosuppressants, csDAMRDs, bDMARDs and JAK inhibitors, the balance of safety and efficacy in viral infection as well as pulmonary inflammation remains unclear.

## APPENDIX 2

**Useful links for physicians regarding COVID-19**

### The following links would help rheumatologists understand the recent perspectives on COVID-19

Taylor & Francis: https://taylorandfrancis.com/coronavirus/

Elsevier: https://www.elsevier.com/connect/coronavirus-information-center

Wiley: https://novel-coronavirus.onlinelibrary.wiley.com/

Springer Nature: https://www.springernature.com/jp/researchers/campaigns/coronavirus/coronavirus-further-articles

Oxford University Press: https://academic.oup.com/journals/pages/coronavirus?cc=us&lang=en&

*BMJ*: https://www.bmj.com/coronavirus

*New England Journal of Medicine*: https://www.nejm.org/coronavirus

*The Lancet*: https://www.thelancet.com/coronavirus

## The following links are from national or international organizations to help rheumatologists and patients to manage their diseases during COVID-19

European League Against Rheumatism (EULAR) guidance for patients on COVID 19: https://www.eular.org/eular_guidance_for_patients_covid19_outbreak.cfm

American College of Rheumatology (ACR): https://www.rheumatology.org/announcements

World Health Organization (WHO): Coronavirus disease (COVID-19) outbreak

*German Society for Rheumatology - Patient section.* (German only): Deutsche Gesellschaft für Rheumatologie - Patienten Bereich

British Society for Rheumatology guidance for rheumatologists:

https://www.rheumatology.org.uk/news-policy/details/covid19-coronavirus-update-members

Shielding policy in UK: https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

National Rheumatoid Arthritis Society: Coronavirus: What we know so far. https://www.nras.org.uk/coronavirus.

Medical Council of India: Telemedicine Practice Guidelines - Ministry of Health and Family

**www.mohfw.gov.in›pdf›Telemedicine**

## Management of patients with COVID-19

WHO clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

National Institute of Health treatment guideline

https://covid19treatmentguidelines.nih.gov/introduction/

US Food and Drug Administration (FDA) cautions against the use of antimalarial agents outside hospital setting or clinical trial: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

Treatment recommendation for Chinese COVID-19 patients: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

The Australasian Society of Clinical Immunology and Allergy (ASCIA) positional statement: https://www.allergy.org.au/hp/papers

## Research on DMARDs related to COVID-19

Clinicaltrial.gov: https://clinicaltrials.gov/ct2/results?cond=COVID-19

Hydroxychloroquine as post-exposure prophylaxis: https://clinicaltrials.gov/ct2/show/NCT04308668

Hydroxychloroquine for the Treatment of Patients with Mild to ModerateCOVID-19toPreventProgressiontoSevereInfectionorDeath: https://clinicaltrials.gov/ct2/show/NCT04323631?cond=COVID-19&draw=4&rank=21 Tocilizumab: https://clinicaltrials.gov/ct2/show/NCT04317092?cond=COVID-19&draw=2&rank=10

Sarilumab: https://clinicaltrials.gov/ct2/show/NCT04315298?cond=COVID-19&draw=3&rank=12

Baricitinib: https://www.clinicaltrials.gov/ct2/show/NCT04320277

https://clinicaltrials.gov/ct2/show/NCT04321993?cond=COVID-19&draw=2&rank=18

## Rheumatology patient registry

The COVID-19 Global Rheumatology Alliance: https://rheum-covid.org/

EULAR: https://www.eular.org/eular_covid19_database.cfm