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Indonesian Rheumatology Association Recommendation for Management of Autoimmune Rheumatic Disease Patients During Covid-19 Pandemic

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ABSTRACT

Background Coronavirus-19 (COVID-19) disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). first reported from Wuhan, the capital of Hubei province, China, in December 2019. Since the occurrence of COVID-19 pandemic, there have been concerns about the risk of SARS-CoV-2 infection and complications in systemic autoimmune-rheumatic patient. Therefore, we intend to make recommendations for the management of autoimmune rheumatic diseases during this pandemic. Indonesian Rheumatology Association (IRA) held an online meeting on May 17th, 2020 and formed a task force that was in charge to make recommendation for management of adult autoimmune rheumatic disease patients during COVID-19 pandemic. This task force consisted of 9 IRA members that held their first online meeting on May 18th, 2020. The draft of the recommendation was reviewed in three online meetings that resulted in final recommendation through consensus from all of task force members. The final draft of recommendation was approved by IRA executive board on July 10th, 2020. Results The management of autoimmune-rheumatic diseases during the COVID-19 pandemic must consider several important factors such as underlying rheumatic-autoimmune disease factors, risk factors for COVID-19 exposure in autommune-rheumatic disease patients and the presence of COVID-19 infection symptoms

1. Introduction

Coronavirus-19 (COVID-19) disease is caused by severe acute respiratory syndrome coronavirus-2

(SARS-CoV-2), a type of beta-coronavirus with an RNA core. The disease was first reported from

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Wuhan, the capital of Hubei province, China, in December 2019¹⁻² and has since spread around the world.3-6 On March 11, 2020 WHO stated COVID-19 as a pandemic. According to the WHO-130 situation report, on June 14, 2020, globally there are 7.690.708 COVID-19 positive case, and caused 427.630 deaths.7 In Indonesia, according to Gugus Tugas Percepatan COVID-19 report, until July 8, 2020 there are 68.079 positive cases and caused 3.359 deaths.8 The highest fatality rate (crude fatality rate/CFR) has been reported in elderly patients and comorbidities, especially in patient with chronic cardiovascular or respiratory disease, diabetes, hypertension, and cancer.9 High CFR has been reported in transplant patients, especially in those with long-term immunosuppressive regimens.¹⁰

Since the occurrence of COVID-19 pandemic, there have been concerns about the risk of SARS-CoV-2 infection and complications in systemic autoimmune-rheumatic patient.11 These patient have a higher risk of infection because they are in a state of decreased immunity due to the use of immunosuppresant medications¹² and on the other hand the immunosuppressants also suppress the immune responses in COVID-19 disease which is responsible for the most severe disease complication eg interstitial pneumonia. 13 It should be noted that as of the writing of this recommendation, there is no study Indonesia about the increased number of autoimmune-rheumatic disease patients contract SARS-CoV-2 infection, nor about morbidity and mortality of autoimmune-rheumatic disease patients that are also infected with SARS-CoV-2.

Certain viral infections are known to trigger various autoimmune rheumatic diseases, for example rheumatoid arthritis, etc. 14 although there is no clear evidence of this happening in SARS-CoV-2 infection. However, recently there have been serial reports of COVID-19 cases of tromboembolism that might correlate with the presence of antiphospholipid antibodies i.e. anticardiolipine and anti- β 2 glycoprotein, 15 and there are also reports of the

emergence of Kawasaki disease in children affected by COVID-19.16

The aforementioned problems will affect the doctor's practice, because most autoimmune rheumatic patients use immunosuppressants as well as corticosteroids. Thus, during this pandemic, there is a dilemma in giving immunosuppressants and corticosteroids in patients who have long or routinely received them, and also in starting treatment in newly diagnosed autoimmune rheumatic disease patients. Therefore, we intend to make recommendations for the management of autoimmune rheumatic diseases during this pandemic.

2.Methods

Indonesian Rheumatology Association (IRA) held an online meeting on May 17th 2020 and formed a task force that was in charge to make recommendation for management of adult autoimmune rheumatic disease patients during COVID-19 pandemic. This task force consisted of 9 IRA members that held their first online meeting on May 18th 2020. In this initial meeting, the task force discussed relevant clinical questions/problems that will be addressed in the recommendation and also gathered clinical evidence that comprised of clinical studies, case reports, reviews, and recommendations from other institutions that address the clinical The of questions/problems. draft the recommendation were reviewed in three online meetings that resulted in final recommendation through consensus from all of task force members.

Clinical questions/problems. Clinical questions/problems that were to be addressed in the recommendation comprised of three main aspects: 1) risk stratification of autoimmune rheumatic disease patient for COVID-19; 2) management of autoimmune rheumatic disease patients in the context of COVID-19 pandemic; and 3) infection prevention and referral system for autoimmune rheumatic disease patients that were exposed to

COVID-19. Thus, the task force formed separate subgroups to address and review each aspects of the recommendation.

Evidence review. Each subgroups is tasked to gather clinical evidence that include clinical studies, case reports, reviews, and recommendations from other institutions relevant to the clinical questions/problems. Evidence review was done non-systematically.

Formulation of recommendation draft. After each subgroups finished drafting their own aspects of recommendation, the task force held online meeting to discuss and compile the recommendation draft. The task force only include points that had universal consensus, that is agreed by all task force member, in the recommendation draft.

Review of recommendation draft. The recommendation draft that was agreed during the task force meeting was then presented in an online meeting with IRA executive board. The draft was evaluated thoroughly until the task force and executive board reached agreement for the final draft of the recommendation.

Final recommendation. The final draft of recommendation was then refined by the task force to generate final recommendation that was approved by IRA executive board on July $10^{\rm th}$ 2020.

RESULTS

The management of autoimmune-rheumatic diseases in the context of COVID-19 pandemic is not yet universally agreed upon. High quality evidence regarding the management of autoimmune-rheumatic diseases in the context of COVID-19 pandemic is scarce, but there is an urgent need for a management protocol to guide clinicians to manage autoimmune-rheumatic diseases during the pandemic. ¹⁷⁻¹⁸

The management of autoimmune-rheumatic diseases during the COVID-19 pandemic must consider several important factors, i.e:

 Underlying rheumatic-autoimmune disease factors that include: type of autoimmunerheumatic disease, diagnosis status of patients (newly diagnosed or established patients), degree of disease activity (remission, low activity and stable disease, moderate disease activity, or high disease activity), pharmacological treatments related to the autoimmune-rheumatic diseases (corticosteroid, conventional DMARD or biologic DMARD, NSAID, and other therapies).

- 2) Risk factors for COVID-19 exposure in autommune-rheumatic disease patients and the presence of COVID-19 infection symptoms. The COVID-19 exposure status in this recommendation is in accordance to Indonesia Ministry of Health guideline:
 - Autoimmune rheumatic disease patients without symptoms of infection and without risk of exposure
 - Autoimmune rheumatic disease patients without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients. These group of patients include:²⁰
 - a. Face-to face/close contact to COVID-19
 probable or confirmed patients in 1
 metre radius and over 15 minutes or
 more.
 - b. Direct physical contact with COVID-19 probable or confirmed patients (such as handshake, holding hands, etc).
 - c. Individuals who give direct care to COVID-19 probable or confirmed patients without the use of standard personal protective equipment.
 - d. Any other situations that indicate contact based on a local risk assessment determined by the local epidemiology tracing team.
 - 3. Autoimmune rheumatic disease patients with symptoms of COVID-19 infection but the infection status is not yet known. These groups of patients might show mild or severe

symptoms if COVID-19 infection in accordance to the definition of COVID-19 suspected or probable case in the Indonesia Ministry of Health guideline.²⁰

Definition of suspected case of COVID 19 is individuals with one or more of the followings:

- a. Individuals with acute respiratory infections and in the last 14 days before symptoms develop have a history of traveling or living in a country / region of Indonesia that reports local transmission.
- b. Individuals with one of the symptoms/signs of acute respiratory infections and in the last 14 days before the onset of symptoms have a history of contact with a confirmed/probable COVID-19 case.
- c. Individuals with severe acute respiratory infections/pneumonia who need hospitalization and no other cause based on a convincing clinical picture.

 The definition of a COVID-19 probable case is a suspected case with severe acute respiratory infections / acute respiratory distress syndrome / death with a convincing clinical picture of COVID-19 and results of RT-PCR laboratory examination is not yet obtained.²⁰
- 4. Autoimmune rheumatic disease patients with confirmed COVID-19 infection

Recommendations for pharmacological management of autoimmune rheumatic disease patients during COVID-19 pandemic

 Autoimmune rheumatic disease patients without symptoms of infection AND without risk of exposure to COVID-19

The recommendation for autoimmune rheumatic disease patients without symptoms of

infection and without risk of exposure to COVID-19 is to continue the rheumatic disease medication, because abrupt withdtrawal of the treatment could trigger flare up of the disease.¹⁹

For autoimune-rheumatic disease patients that are newly diagnosed, stable disease (remission/low disease activity), or active disease (moderate-severe disease activity) without symptoms of infection or without without risk of exposure to COVID-19, the recmommendations are as follows:

- Non steroid anti inflammatory drugs (NSAIDs), ACE inhibitor/angiotensin receptor inhibitor, corticosteroid, hydroxychloroquine (HCQ), chloroquine (CQ), conventional DMARDs (sulfasalazine (SSZ), mesalazine, methotrexate (MTX), leflunomide (LEF), tacrolimus, cyclosporine, mycophenolate mofetil (MMF), mycophenolate acid (MPA), azathioprine (AZA), cyclophosphamide (CYC)), biologic DMARDs, intravenous immunoglobulin (IVIG) could be initiated or continued.²¹
- Screening for COVID-19 with PCR testing is needed before initiating strong immunosuppressant such as CYC or biologic DMARDs, especially for patients in areas with high risk for SARS-CoV-2 infection (R>1, red zone area that is determined by the government, or local transmission area that is determined by the government).²²
- The use of corticosteroid for autoimmunerheumatic diseases should be at the lowest possible dose that could still control the disease activity.²¹ Abrupt termination of longstanding corticosteroid use (prednisolon dose ≥ 5 mg or equivalent for ≥ 4 weeks) is not recommended because of the risk of adrenal insufficiency. ²³⁻²⁴
- Autoimmune rheumatic disease patients that is on immunosuppressant should not reduce their immunosuppressant dose without indication.²¹

- For newly diagnosed patients or patients with active inflammatory conditions, conventional DMARDs could be initiated or escalated. ²¹
- For patients with moderate-severe disease activity failing to respond with conventional DMARDs, biologic DMARDs could be initiated.

Recommendation for autoimmune rheumatic disease patients without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients

For autoimmune rheumatic disease patients without symptoms of infection and with close contact (exposure) to COVID-19 probable or confirmed patients, the main priority is to do diagnostic workup to determine whether the patient is infected with SARS-CoV-2 or not. For those who are not able to do the diagnostic workup or are still waiting for the diagnostic workup result, the recommendations are as follows:

a. Recommendation for newly-diagnosed autoimmune rheumatic disease patients without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients

For newly-diagnosed autoimmune rheumatic disease patients without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients, NSAID, HCQ/CQ, sulfasalazine and mesalazine could be initiated to manage the autoimmune rheumatic disease.25-26 Immunosuppressant drugs (MTX. AZA. cyclosporine, MMF, MPA, tacrolimus, CYC) and biologic DMARDs should not be initiated before the patient is proven negative for COVID-19. The decision to give corticosteroid and the dose of corticosteroid should take into account individual infection risk factor and severity of autoimmunerheumatic disease. The decision to give high dose or pulse dose of corticosteroid in severe or life or organ threatening rheumatic disease should be

assessed individually for each cases.

b. Recommendation for autoimmune rheumatic disease patients with stable disease activity/remission without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients

For autoimmune rheumatic disease patients with stable disease activity/remission without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed cases, NSAID, HCQ/CQ, sulfasalazine and continued. 21,24,26-27 be mesalazine could Immunosuppressant drugs (MTX, AZA, cyclosporine, MMF, MPA, tacrolimus, CYC) and biologic DMARDs should be stopped until the patient is proven negative for COVID-19.19,21,28-30

If the patient is taking corticosteroid, the dose should be tapered down to the smallest dose that could still control the disease activity. Tapering down should be done gradually and corticosteroid should not be stopped abruptly to avoid adrenal crisis and flare of the disease. ²⁷

c. Recommendation for autoimmune rheumatic disease patients with active or progressive disease activity without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients

For autoimmune rheumatic disease patients with active or progressive disease activity without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients, NSAID, HCQ/CQ, sulfasalazine and mesalazine could be initiated to manage the disease.3,6-8. autoimmune rheumatic Immunosuppressant (MTX, AZA, drugs cyclosporine, MMF, MPA, tacrolimus, CYC) and biologic DMARDs should be stopped until the patient is proven negative for COVID-19.21,27,30 The decision to give or to escalate corticosteroid dose should take into account individual infection risk factor and severity of autoimmune-rheumatic disease, assessed individually for each cases.

Recommendation for autoimmune rheumatic disease patients with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19)

For autoimmune rheumatic disease patients with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19), diagnostic workup to confirm the infection status should be a priority. For patients who are still waiting for the diagnostic workup result, the recommendations are as follows:

a. Recommendation for newly-diagnosed autoimmune rheumatic disease patients with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19)

For autoimmune rheumatic disease patients with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19):

- NSAID could be given when indicated as part of the management of the rheumatic disease.
 NSAID should be stopped in patients with severe respiratory, cardiac, gastrointestinal, and kidney symptoms, because of poor prognosis and NSAID could worsen the clinical condition.
- Corticosteroid could be initiated in the smallest effective dose according to the rheumatic disease activity. For autoimmune rheumatic disease patients with severe symptoms of COVID-19, corticosteroid dose should consider individual clinical assesment and the risk-benefit ratio of each cases.
- Conventional DMARD that could be initiated is HCQ. Other conventional DMARD or immunosuppressants could be initiated after the patient is proven negative for COVID-19 and

- other infections have been excluded or treated.
- Anti-IL6 for the management of the rheumatic disease could be given after the patient is proven negative for COVID-19. Anti-IL6 for autoimmune rheumatic disease patients that are suspect or probable cases of COVID-19 and are showing signs of cytokine storm syndrome should follow IRA recommendation.³⁵ Other biologic DMARD could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. ^{19,30}
- IVIG could be initiated if indicated for the management of the autoimmune-rheumatic disease.
- ACE inhibitor and ARB could be given. 36-38
- b. Recommendation for autoimmune rheumatic disease patients with stable disease activity/remission AND with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19)

For autoimmune rheumatic disease patients with stable disease activity/remission AND with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19):

- NSAID could be given when indicated as part
 of the management of the rheumatic disease.
 NSAID should be stopped in patients with
 severe respiratory, cardiac, gastrointestinal,
 and kidney symptoms, because of poor
 prognosis and NSAID could worsen the
 clinical condition. ^{21,31-34}
- Corticosteroid could be given in the smallest effective dose according to the rheumatic disease activity and efforts should be done towards tapering down the steroid dose.
- Conventional DMARD that could be given is HCQ. Other conventional DMARD or immunosuppressants could be given after the patient is proven negative for COVID-19

- and other infections have been excluded or treated. 19,30
- Anti-IL6 for the management of the rheumatic disease could be given after the patient is proven negative for COVID-19. Anti-IL6 for autoimmune rheumatic disease patients that are suspect or probable cases of COVID-19 and are showing signs of cytokine storm syndrome should follow IRA recommendation. Other biologic DMARD could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. 19,30
- ACE inhibitor and ARB could be given.^{36–38}
- c. Recommendation for autoimmune rheumatic disease patients with active or progressive disease activity AND with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19)

For autoimmune rheumatic disease patients with active or progressive disease activity AND with symptoms of COVID-19 infection but the infection status is not yet known (suspect and probable case of COVID-19):

- NSAID could be given when indicated as part of the management of the rheumatic disease. NSAID should be stopped in patients with severe respiratory, cardiac, gastrointestinal, and kidney symptoms, because of poor prognosis and NSAID couldworsen the clinical condition. 21,31-34
- Dose escalation of corticosteroid or initiating high/pulse dose of corticosteroid should consider individual clinical assesment and the risk-benefit ratio of each cases.
- Conventional DMARD that could be given is HCQ. Other conventional DMARD or immunosuppressants could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated.^{19,30}

- Biologic DMARD that could be given is anti IL-6 for the management of the rheumatic disease. Anti-IL6 could be given after the patient is proven negative for COVID-19. The use of anti-IL6 for patients that are showing signs of cytokine storm syndrome should follow IRA recommendation. Pemberian anti IL-6 pada pasien reumatik-autoimun yang menderita COVID-19 dan mengalami badai sitokin mengacu pada rekomendasi yang dikeluarkan oleh IRA.³⁵ Other biologic DMARD could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. ^{19,30}
- IVIG could be initiated if indicated for the management of the autoimmune-rheumatic disease.
- ACE inhibitor and ARB could be given. 36–38
- 4. Recommendation for autoimmune rheumatic disease patients with confirmed COVID-19 infection
 - a. Recommendation for confirmed COVID-19 patients that are newly-diagnosed with autoimmune rheumatic disease

For confirmed COVID-19 patients that are newly-diagnosed with autoimmune rheumatic disease:

- NSAID could be given when indicated as part of the management of the rheumatic disease.
 NSAID should be stopped in patients with severe respiratory, cardiac, gastrointestinal, and kidney symptoms, because of poor prognosis and NSAID could worsen the clinical condition. ^{21,31-34}
- Corticosteroid could be given to patients with asymptomatic or mild-moderate symptoms of COVID-19 in the smallest effective dose according to the rheumatic disease activity.
 For patients with severe infection symptom, corticosteroid dose should consider individual clinical assesment and the riskbenefit ratio of each cases.

- Conventional DMARDs that could be given is HCQ. Other conventional DMARDs or immunosuppressants could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated.^{19,30}
- Biologic DMARD that could be given for the management of the rheumatic disease is anti IL-6, that is given after the patient recovered from COVID-19. Anti-IL6 for patients that are showing signs of cytokine storm syndrome should follow IRA recommendation. Other biologic DMARD could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. 19,30
- IVIG could be initiated if indicated for the management of the autoimmune-rheumatic disease.
- ACE inhibitor and ARB could be given. 36-38

b. Recommendation for confirmed COVID-19 patients with stable/in remission autoimmune rheumatic disease

- NSAID could be given when indicated as part
 of the management of the rheumatic disease.
 NSAID should be stopped in patients with
 severe respiratory, cardiac, gastrointestinal,
 and kidney symptoms, because of poor
 prognosis and NSAID could worsen the
 clinical condition. ^{21,31-34}
- Corticosteroid could be continued and efforts should be done towards tapering down the steroid to the smallest efective dose.
- Conventional DMARD that could be given is HCQ. Other conventional DMARD or immunosuppressants could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated.^{19,30}
- Biologic DMARD that could be given for the management of the rheumatic disease is anti IL-6, that is given after the patient recovered

from COVID-19. The use of anti-IL6 for patients that are showing signs of cytokine storm syndrome should follow IRA recommendation.³⁵ Other biologic DMARDs could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. ^{19,30}

- ACE inhibitor and ARB could be given. 36-38

c. Recommendation for confirmed COVID-19 patients with active/progressive autoimmune rheumatic disease

- NSAID could be given when indicated as part of the management of the rheumatic disease. NSAID should be stopped in patients with severe respiratory, cardiac, gastrointestinal, and kidney symptoms, because of poor prognosis and NSAID could worsen the clinical condition. ^{21,31-34}
- Corticosteroid could be continued and efforts should be done towards tapering down the steroid to the smallest efective dose.
- Dose escalation of corticosteroid or initiating high/pulse dose of corticosteroid for life/organ saving condition should consider individual clinical assessment and the riskbenefit ratio of each cases.
- Conventional DMARDs that could be given is HCQ. Other conventional DMARD or immunosuppressants could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. 19,30
- Biologic DMARD that could be given for the management of the rheumatic disease is anti IL-6, that is given after the patient recovered from COVID-19. The use of anti-IL6 for patients that are showing signs of cytokine storm syndrome should follow IRA recommendation.³⁵ Other biologic DMARDs could be given after the patient is proven negative for COVID-19 and other infections have been excluded or treated. ^{19,30}

- IVIG could be given if indicated for the management of the autoimmune-rheumatic disease.
- ACE inhibitor and ARB could be given. 36-38

Table 1. Recommendation for pharmacological management of autoimmune rheumatic disease patients during COVID-19 pandemic

No	Name of medication	Patients without symptoms of infection AND without risk of exposure to COVID-19			patients without symptoms of infection AND with close contact (exposure) to COVID-19 probable or confirmed patients			Patients with symptoms of COVID-19 infection but the infection status is not yet known (suspected and probable case of COVID-19)			Patients with confirmed COVID-19 infection		
Activity of autoimmune- rheumatic disease		Newly diagnosed	Remission /low disease activity	Moderate- high disease activity	Newly diagnosed	Remission/low disease activity	Moderate- high disease activity	Newly diagnosed	Remission /low disease activity	Moderate- high disease activity	Newly diagnosed	Remisssion/low disease activity	Moderate- high disease activity
1.	NSAID										@		
2.	Cortikosteroid		^	^	\$	^	#	\$	^	#	\$	٨	#
3.	HCQ/CQ												
4.	Methotrexate												
5.	Sulfasalazine												
6.	Mesalazin												
7.	Leflunomide												
8.	MMF												
9.	MPA												
10.	Azathioprin												
11.	Siklosporin												
12.	Siklofosfamid												
13.	Anti TNF-α												
14.	Anti IL-6							+	+	+	+	+	+
15.	Anti IL-17												
16.	Anti IL-12/23												
17.	Rituximab												
18.	IVIG												
19.	Takrolimus												
20.	ACEI/ARB												

Green: medication could be initiated/continued

Yellow: the use of the medicatio should consider risk-benefit ratio on an individual basis of risk assesment

Red: the use of medication should be stopped and could not be resumed/initiated until the patient is proven negative for COVID-19

^ For patients who are receiving steroid, the dose should be in the smallest dose that could still control disease activity

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^{\$} Initiating corticosteroid in newly-diagnosed autoimmune rheumatid disease patients should consider clinical condition and risk-benefit for each case

[#] Escalation dose of corticosteroid (high or pulse dose) could be given with consideration to clinical condition and risk-benefit for each case

[@] The use of NSAID in confirmed case of COVID-19 asymptomatic or mild-moderate symptom is allowed. The use of NSAID in confirmed case of COVID-19 with severe symptoms of respiratory should consider clinical condition and risk-benefit for each case

⁺ The use of anti IL-6 in autoimmune rheumatic disease patients who have COVID-19 and show signs of cytokine storm syndrome should follow IRA recommendation

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