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REVIEWS AND RECOMMENDATIONS

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Updated APLAR consensus statements on care for patients with rheumatic diseases during the COVID-19 pandemic

Lai-Shan Tam[1] | Yoshiya Tanaka[2] | Rohini Handa[3] | Zhanguo Li[4] | Jose Paulo Lorenzo[5] | Worawit Louthrenoo[6] | Catherine Hill[7] | Kevin Pile[8] | Philip C. Robinson[9] | Leonila F. Dans[10] | Li Yang Hsu[11] | Sang-Min Lee[12] | Jiacai Cho[13] | A. T. M. Tanveer Hasan[14] | Babur Salim[15] | Saba Samreen[15] | Syahrul Sazliyana Shaharir[16] | Priscilla Wong[1] | Jeffrey Chau[17] | Debashish Danda[18] | Syed Atiqul Haq[19]

[1]Division of Rheumatology, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

[2]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

[3]Apollo Indraprastha Hospitals, New Delhi, India

[4]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China

[5]Section of Rheumatology, Department of Medicine, Makati Medical Center, Makati City, Philippines

[6]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

[7]Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, SA, Australia

[8]Rheumatology Unit, Campbelltown Hospital, Western Sydney University, Sydney, NSW, Australia

[9]Faculty of Medicine, University of Queensland School of Medicine, Brisbane, QLD, Australia

[10]Department of Pediatrics and Department of Clinical Epidemiology, University of the Philippines–Philippine General Hospital, Manila, Philippines

[11]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[12]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

[13]Division of Rheumatology, Department of Medicine, National University Hospital, Singapore

[14]Department of Rheumatology, Enam Medical College & Hospital, Dhaka, Bangladesh

[15]Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi, Pakistan

[16]Division of Rheumatology, Department of Internal Medicine, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia

[17]Hong Kong Psoriatic Arthritis Association, Hong Kong, Hong Kong

[18]Department of Clinical Immunology & Rheumatology, Christian Medical College & Hospital, Vellore, India

[19]Department of Rheumatology, BSM Medical University, Dhaka, Bangladesh

Correspondence
Syed Atiqul Haq, Department of Rheumatology, BSM Medical University, Dhaka, Bangladesh.
Email: haqsyedatiqul@gmail.com

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Abstract

Aim: To update previous guidance of the Asia Pacific League of Associations for Rheumatology (APLAR) on the management of patients with rheumatic and musculoskeletal diseases (RMD) during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Research questions were formulated focusing on diagnosis and treatment of adult patients with RMD within the context of the pandemic, including the management of RMD in patients who developed COVID-19. MEDLINE was searched for eligible studies to address the questions, and the APLAR COVID-19 task force convened 2 meetings through video conferencing to discuss its findings and integrate

best available evidence with expert opinion. Consensus statements were finalized using the modified Delphi process.

Results: Agreement was obtained around key aspects of screening for or diagnosis of COVID-19; management of patients with RMD without confirmed COVID-19; and management of patients with RMD with confirmed COVID-19. The task force achieved consensus on 25 statements covering the potential risk of acquiring COVID-19 in RMD patients, advice on RMD medication adjustment and continuation, the roles of telemedicine and vaccination, and the impact of the pandemic on quality of life and on treatment adherence.

Conclusions: Available evidence primarily from descriptive research supported new recommendations for aspects of RMD care not covered in the previous document, particularly with regard to risk factors for complicated COVID-19 in RMD patients, modifications to RMD treatment regimens in the context of the pandemic, and COVID-19 vaccination in patients with RMD.

KEYWORDS

APLAR guidance, Asia Pacific, consensus, rheumatic disease, SARS-CoV-2

1 | INTRODUCTION

In May 2020, the Asia Pacific League of Associations for Rheumatology (APLAR) published a position statement on the care of patients with rheumatic and musculoskeletal diseases (RMD) during the coronavirus disease 2019 (COVID-19) pandemic.[1] The document was borne from the urgency to provide a preliminary rheumatology management guide for Asia Pacific practitioners as the rapid spread of COVID-19 generated challenges unique to the treatment of rheumatic disease.

The lack of data from quantitative research on COVID-19 before the May publication of the APLAR statement, especially data that centers on patients with RMD, precluded our guideline working group, the APLAR COVID-19 task force, from providing specific recommendations. Since then, new information from both quantitative and qualitative research has emerged from globally conducted dynamic research efforts. We aimed to review all available new and pertinent evidence, and to update our preliminary statement by developing consensus recommendations for the management of patients with RMD during the COVID-19 pandemic.

This document presents our findings and the resultant 25 consensus statements. The recommendations together aim to provide a much-needed practical guide to clinical decision-making of the healthcare practitioner caring for RMD patients during this time. They do not include recommendations on the specific management of COVID-19 infection.

2 | METHODS

The APLAR COVID-19 task force consisted of 21 members including specialists in the fields of rheumatology, pulmonology, and infectious disease, and a patient representative. Most members are internationally recognized rheumatologists with many years of clinical and scientific experience, who fulfill or have fulfilled official positions in the APLAR organization. Task force leaders compiled a list of key RMD topics and formulated questions that reflected clinically relevant issues in RMD management in the context of COVID-19, namely: (a) screening for or diagnosis of COVID-19 in patients with RMD; (b) the management of patients with RMD but with no COVID-19; and (c) the management of patients with RMD and COVID-19 (Table 1). To address the questions, eligible studies involving adult patients were identified in the archives of MEDLINE (through PubMed) published from December 2019 to August 2020. Medical subject headings (MeSH) for "rheumatic diseases" and "COVID-19" were used in the search strategy, along with the appropriate MeSH terms for the concepts of prevention, diagnosis, screening, and treatment. For drug therapy, the following key words and their related terms were included in the search: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). With the understanding that controlled trials may have not yet been completed, searches were not limited to randomized controlled trials but also included other study types such as non-controlled trials, cohort studies, other comparative studies, case series, and case reports. Other consensus documents and abstracts were also retrieved and reviewed. Searches were also not limited to the English language to broaden the yield of studies from across the globe.

The members were grouped according to the identified core RMD topics and their corresponding research questions. Each group was instructed to review the evidence, then draft relevant consensus

TABLE 1 Research questions

Screening for/diagnosis of COVID-19
1. Do patients with RMD have a higher risk of COVID-19 compared to the general population?
2. How can COVID-19 risk be mitigated in patients with RMD?
3. Should patients with RMD be screened for COVID-19 differently than the general population?
Management of RMD patients without COVID-19
4. In newly diagnosed patients, should treatment be initiated differently during this pandemic period compared with prior to the pandemic?
5. What is the evidence on continuing/de-escalating/discontinuing treatment in patients with RMD who are close contacts of individuals with SARS-CoV-2 infection?
6. What has been the effect of the pandemic on treatment adherence?
7. What is the role of telemedicine in the management of patients with RMD in the setting of COVID-19?
8. Which vaccines should be recommended for patients with RMD during the pandemic period?
Management of RMD patients with COVID-19
9. What are the rheumatic manifestations of COVID-19?
10. Is the clinical presentation of COVID-19 in patients with RMD different from that in patients without RMD?
11. Can patients with RMD continue their medication once diagnosed with COVID-19?
12. What is the evidence for de-escalating/discontinuing treatment in patients with RMD with COVID-19?
13. What is the evidence on glucocorticoids in the treatment of COVID-19?
14. What is the evidence on continuing/re-initiating treatment in patients with RMD post-COVID-19?
15. What is the effect of COVID-19 on the quality of life of patients with RMD post-COVID-19?

Abbreviations: COVID-19, coronavirus disease 2019; RMD, rheumatic and musculoskeletal disease.

statements, all for presentation and discussion during pre-planned video conferences.

The first meeting was held on 10 October 2020 to discuss, refine, and vote on the statements. The quality of evidence supporting each statement was evaluated using the evidence-assessment frameworks prescribed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[2,3] Using the modified Delphi approach to achieve expert group consensus, the meeting attendees provided feedback on the evidence presentation and the proposed statements. An online poll launched during the meeting allowed them to indicate their levels of agreement with the proposed statements by choosing among 5 options: 1, accept completely; 2, accept with some reservations; 3, accept with major reservations; 4, reject with reservations; and 5, reject completely. The draft statement was endorsed as a final consensus recommendation when the combined percentages for the responses of "accept completely" and "accept with some reservations" totaled ≥80% of votes among the attendees. The group agreed on a strength of recommendation where applicable, that is, for statements recommending a course of action.

Discussion of the research questions, their associated evidence, and proposed statements continued during the second meeting, which was held on 1 November 2020. Further clarifications on unresolved matters during the first meeting were carried over to the second meeting. The panel members were encouraged to review additional references that emerged during the interval between the 2 meetings. Grading of the statements and online voting proceeded for the remainder of topics and their draft statements. Consensus was again established at ≥80% agreement. Some proposed statements were considered at the time to have insufficient supporting evidence. These "expert opinion" statements were made available to the task force members online for final review and voting after the second meeting.

3 | RESULTS

The task force achieved consensus on 25 statements (Table 2). Nine of the statements were deemed "expert opinion" statements, given the paucity of supporting evidence on these topics.

3.1 | Screening for and diagnosis of COVID-19

3.1.1 | Risk of COVID-19 in RMD patients

C1. Patients with immune-mediated RMD may be at a higher risk of COVID-19 and of respiratory failure than the general population. (90% agreement, grade of evidence very low, strength-of-recommendation assessment not applicable).

C2. Those potentially at high risk include patients on glucocorticoids (≥10 mg prednisolone/d). (100% agreement, grade of evidence moderate, strength-of-recommendation assessment not applicable).

C3. Patients with RMD should be strongly advised to follow all preventive measures as stipulated by the healthcare authorities in their countries, as for patients without RMD. (94% agreement, grade of evidence low, strong recommendation).

In a meta-regression of 65 observational studies, patients with RMD had the highest rates of hospitalization (0.54; 95% CI 0.46-0.63) and mortality (0.113; 95% CI 0.098-0.13) due to COVID-19 among patients with autoimmune diseases.[4] Meanwhile, descriptive studies suggest that RMD and RMD-related factors may be associated with a more severe course of COVID-19. A higher risk of respiratory failure was shown in RMD patients when matched against non-rheumatic patients from a Wuhan, China cohort study (patients with respiratory failure: 38% of RMD patients vs 10% of those without RMD; $\chi^2 = 13$, $P < .001$).[5] A higher risk of mechanical ventilation was also seen for RMD patients in a Boston, Massachusetts cohort (multivariable odds ratio [OR] 3.11, 95% CI 1.07-9.05), but a follow-up

that extended the study period from 4 to 6 months showed similar risk between rheumatic and non-rheumatic patients (adjusted hazard ratio [HR] 1.51, 95% CI 0.93-2.44).[6,7] The presence of comorbidities, older age, and use of prednisone ≥10 mg/d have been suggested as risk factors for poor outcomes in SARS-CoV-2-infected RMD patients.[8-11] Also, according to primary care data from the UK, patients with the diagnosis of rheumatoid arthritis, systemic lupus erythematosus, or psoriasis, analyzed as a group, were more likely to die from COVID-19-related causes compared to patients without those conditions (adjusted HR 1.19; 95% CI 1.11-1.27).[12]

Initially, shielding, or strict quarantine and minimizing non-essential contact even with other household members, was recommended for certain high-risk RMD patients.[13] However, shielding may even be less important than self-education and adherence to general preventive measures.[14] RMD patients should thus be advised to follow locally stipulated guidance for transmission prevention as advised for the general population.

3.1.2 | Diagnosing COVID-19 in RMD patients

C4. There is no evidence to support a different diagnostic strategy for COVID-19 in patients with RMD from that of non-RMD patients. (100% agreement, expert opinion, strength-of-recommendation assessment not applicable).

C5. Patients with RMD should be tested as soon as they develop any symptoms of COVID-19 because of the potential increased risk of poorer outcomes. (100% agreement, expert opinion, strong recommendation).

The task force aimed to address whether the approach to test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with RMD should be modified from the current testing protocol for non-rheumatic patients. No evidence currently supports a different strategy. Despite this, owing to the risks for complicated COVID-19 discussed earlier, it is recommended that timely testing be performed, that is, upon symptom onset.

3.2 | Management of RMD patients without COVID-19

3.2.1 | Initiation of RMD therapies in patients with newly diagnosed RMD

C6. In the absence of contrary evidence, patients with newly diagnosed RMD without COVID-19 should be treated as per standard of care during the pandemic. (100% agreement, expert opinion, strong recommendation).

C7. Therapeutic options alternative to rituximab, sulfasalazine, and cyclophosphamide may be considered on a case-by-case basis. (82% agreement, grade of evidence very low, weak recommendation).

No publications have, as yet, reported on whether starting rheumatologic treatment during the pandemic influenced the clinical course or condition of a patient newly diagnosed with RMD. Therefore, it is recommended that management of newly diagnosed RMD without COVID-19 should be as indicated for each specific RMD, using established, guideline-based therapies.

Underpinning the decision to start RMD treatment during the pandemic is the risk of contracting COVID-19, which may be increased by use of immune-modulating medication. This may stem from a known risk of other infections with use of some DMARDs.[15] Furthermore, immunosuppression with some agents, including rituximab (RTX), sulfasalazine (SSZ) and cyclophosphamide (CYC), may have a role in altering the immune response to infection. The true risk of infection associated with RMD therapies is still uncertain, but caution stemming from a registry-reported risk of COVID-19-related death with RTX, SSZ, and CYC[16] prompted our group's proposal to use good but safer alternatives, if available. Our votes were almost equally divided between accepting statement C7 completely and accepting with some reservations. Nevertheless, the members agreed that the decision to use alternatives should always be individualized. It was considered that the high risk for COVID-19 exposure in endemic areas may be a contributing and confounding factor to the development of COVID-19; thus, starting treatment with alternative options in these locations may be appropriate. On the other hand, to manage acute, critical conditions such as vasculitis and myositis, established therapies may be more beneficial than alternatives. The urgency to control disease in these critical conditions will need to be prioritized over the potential risk of acquiring SARS-CoV-2 infection.

3.2.2 | Modification of RMD treatment of patients who are close contacts of SARS-CoV-2 -infected individuals

C8. For patients with RMD who do not have COVID-19 symptoms and do not have documented COVID-19, but who have had close contact with a highly suspected or documented COVID-19 case, the recommendations for RMD medications vary depending on risk. (84% agreement, expert opinion, weak recommendation).

C9. For asymptomatic RMD patients without documented infection, antirheumatic medications, if stopped after exposure, may be resumed once a negative test has been certified, or after approximately 2 weeks of symptom-free observation from the day of exposure, if a test was not performed. (84% agreement, expert opinion, weak recommendation).

Exposure to SARS-CoV-2 through close contact implies a risk of contracting the infection, raising the question of modifying treatment even in the absence of confirmed COVID-19. “Close contact” is described by the Centers for Disease Control and Prevention (CDC) as being within 6 feet of the infected individual for a total of 15 minutes over 24 hours.[17] Some groups recommend modifying

TABLE 2 Summary of consensus statements

Consensus statements	Grade of evidence	Agreement	Strength of recommendation
C1. Patients with immune-mediated RMD may be at a higher risk of COVID-19 and of respiratory failure than the general population.	Very low	90%	Not applicable
C2. Those potentially at high risk include patients on glucocorticoids (≥10 mg prednisolone/d).	Moderate	100%	Not applicable
C3. Patients with RMD should be strongly advised to follow all preventive measures as stipulated by the healthcare authorities in their countries, as for patients without RMD.	Low	94%	Strong
C4. There is no evidence to support a different diagnostic strategy for COVID-19 in patients with RMD from that of non-RMD patients.	Expert opinion	100%	Not applicable
C5. Patients with RMD should be tested as soon as they develop any symptoms of COVID-19 because of the potential increased risk of poorer outcomes.	Expert opinion	100%	Strong
C6. In the absence of contrary evidence, patients with newly diagnosed RMD without COVID-19 should be treated as per standard of care during the pandemic.	Expert opinion	100%	Strong
C7. Therapeutic options alternative to rituximab, sulfasalazine, and cyclophosphamide may be considered on a case-by-case basis.	Very low	82%	Weak
C8. For patients with RMD who do not have COVID-19 symptoms and do not have documented COVID-19, but who have had close contact with a highly suspected or documented COVID-19 case, the recommendations for RMD medications vary depending on risk.	Expert opinion	84%	Weak
C9. For asymptomatic RMD patients without documented infection, if stopped after exposure, antirheumatic medications may be resumed once a negative test has been certified, or after approximately 2 wk of symptom-free observation from the day of exposure, if a test was not performed.	Expert opinion	84%	Weak
C10. Rheumatologists should explore the perceptions of patients and address their concerns to ensure treatment adherence during the COVID-19 pandemic.	Moderate	100%	Strong
C11. The use of telemedicine should be strongly encouraged, especially in areas of high community transmission levels, for follow-up of appropriate patients with RMD if implementing such an intervention is feasible and accepted by patients.	Moderate	100%	Strong
C12. It is recommended that patients with RMD receive an approved SARS-CoV-2 vaccine as soon as it becomes available to them.	Expert opinion	100%	Strong
C13. RMD patients with normal or altered immunocompetence should receive vaccination based on current country, regional and/or international guidelines for vaccinations.	Expert opinion	100%	Strong
C14. Immunization schedules of RMD patients should be maintained while adhering strictly to the safety protocols of COVID-19 prevention.	Expert opinion	100%	Strong
C15. Clinical manifestations mimicking RMDs, laboratory reports of positive antinuclear antibodies, antiphospholipid antibodies, and lupus anti-coagulant have been reported with COVID-19 patients. These patients should be followed for the possibility of persistent intermediate- to long-term immune dysregulation.	Expert opinion	95%	Strong
C16. The clinical presentation of COVID-19 in patients with RMD is similar to that in patients without RMD. Nonetheless, RMD patients who experience worsening of respiratory symptoms should immediately seek further healthcare advice of an expert in treating COVID-19 (eg, pulmonologist, infectious diseases specialist, or general internist) according to local recommendations.	Low	100%	Strong
C17. HCQ, NSAIDs, and ACEi/ARBs may be continued but should be individualized based on disease condition.	Moderate	100%	Strong
C18. The clinician should consider stopping or withholding csDMARDs (other than HCQ), tsDMARDs, and bDMARDs, on a case-by-case basis.	Moderate	94%	Weak
C19. RMD patients with COVID-19 should be treated according to the standard of care.	Low	92%	Strong
C20. Glucocorticoids should be used at the lowest possible dose to control RMD and should not be abruptly stopped.	High	94%	Strong
C21. Immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus) should be discontinued in patients with COVID-19.	Low	82%	Strong

(Continues)

TABLE 2 (Continued)

Consensus statements	Grade of evidence	Agreement	Strength of recommendation
C22. In general, RMD treatments may be re-introduced at least 2 wk after recovery from acute COVID-19. They may need to be individualized based on the clinical scenario and the physician's judgment.	Low	100%	Weak
C23. For asymptomatic individuals, RMD treatment may be re-introduced approximately 10 d after diagnosis of COVID-19.	Low	100%	Weak
C24. SARS-CoV-2 infection has a negative impact on the QoL of RMD patients, particularly the mental health component.	Expert opinion	95%	Not applicable
C25. Social isolation or shielding has a negative impact on the QoL (both mental and physical) of RMD patients during the COVID-19 pandemic.	Expert opinion	90%	Not applicable

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; bDMARDs, biologic disease-modifying antirheumatic drugs (DMARDs); COVID-19, coronavirus disease 2019; csDMARDs, conventional synthetic DMARDs; HCQ, hydroxychloroquine; NSAIDs, non-steroidal anti-inflammatory drugs; QoL, quality of life; RMD, rheumatic and musculoskeletal disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tsDMARDs, targeted synthetic DMARDs.

treatment based on the patient's confirmation of COVID-19 status and clinical condition, thus requiring that patients be tested for SARS-CoV-2 upon known exposure. The European League Against Rheumatism (EULAR) guidelines recommend testing even if the patient does not have COVID-19 symptoms, while the German Society of Rheumatology advises this only for symptomatic persons.[18,19] We suggest that the decision to test for SARS-CoV-2 in these close contacts should be based on local protocols.

Votes were divided among the responses for acceptance and rejection for C8 and C9, which seems to indicate that the topic of withholding RMD medication in unconfirmed COVID-19 remains debatable; nevertheless, consensus was reached for these statements. A change in administration of RMD therapies may be determined by the patient's risk of poor outcomes with use of specific agents during a presumed COVID-19 infection.

The association of specific RMD therapies with poor COVID-19 outcomes is described in detail for COVID-19-afflicted individuals in a later part of this document. For asymptomatic RMD patients with no COVID-19 but who are close contacts, we recommend that, pending testing results, antimalarials and NSAIDs may be continued, which is aligned with the American College of Rheumatology (ACR) guidelines.[20] SSZ may be continued at the discretion of local COVID-19 experts and according to guidance from APLAR rheumatology member national organizations. In agreement with similar guidance from ACR and EULAR, we recommend that immunosuppressants (eg, CYP, azathioprine [AZA], mycophenolate mofetil [MMF], tacrolimus, Janus kinase inhibitors [JAKi]), and all biologics, especially RTX, should be stopped or avoided except when necessary in managing critical RMD conditions. Glucocorticoids should be used at the lowest possible dose to control RMD. Finally, methotrexate (MTX) should be discontinued unless considered indispensable for a specific RMD by the treating rheumatologist.

With the confirmation of a negative SARS-CoV-2 test, asymptomatic individuals may resume RMD medications that were suspended. Recognizing that testing may not be easily available or accessible in some countries, resumption of RMD medication is recommended after approximately 2 weeks from contact if the patient with no confirmatory test remains asymptomatic.

3.2.3 | Impact of COVID-19 on treatment adherence

C10. Rheumatologists should explore the perceptions of patients and address their concerns to ensure treatment adherence during the COVID-19 pandemic. (100% agreement, grade of evidence moderate, strong recommendation).

Surveys reported on patient feedback about their RMD medications during the early part of the pandemic. These were conducted by rheumatologic treatment centers in the US, Germany, Greece, Italy, Mexico, Iran, and Saudi Arabia through email or telephone interviews. Rates of non-adherence (self-change or self-discontinuation of regimen) ranged 2.2%-15%. Possible reasons for non-adherence included: lack of availability of medications; inability to travel to the dispensing facility; fear of contracting COVID-19; perception of worsening RMD activity; and fear of immunosuppression.[21-26] An Australian survey found that patients were worried that RMD medications may increase their risk of contracting COVID-19 or increase COVID-19 severity, and the concern for contracting COVID-19 was increased when RMD regimens with combination csDMARDs or bDMARDS/tsDMARDs were used.[27]

From the reasons cited above for non-adherence, it appears that perceptions about the immune-modulating effects of rheumatologic drugs influenced patients' understanding of their susceptibility to contracting COVID-19 and to having a complicated course if infected. Physicians are encouraged to elicit feedback from their patients and help them address any challenges to continuing their current treatment regimen.

3.2.4 | Role of telemedicine in RMD management during the COVID-19 pandemic

C11. The use of telemedicine should be strongly encouraged, especially in areas of high community transmission levels, for follow-up of appropriate patients with RMD if implementing such an intervention is feasible and accepted by patients. (100% agreement, grade of evidence moderate, strong recommendation).

Before the pandemic, telemedicine for consultation, disease activity monitoring, and delivery of self-management programs for RMD were reported to have high feasibility and patient satisfaction rates.[28] During the pandemic, a rheumatology unit in Italy recently reported on its experience of using telemedicine, thus demonstrating its feasibility. In the unit, outpatient consultations, except for urgent cases, were conducted as tele-consults. Assessments of disease activity were carried out through questionnaires, and considering the changes brought about by the pandemic, patients were also asked about infection symptoms and psychological well-being. Medications were accordingly adjusted.[29] Survey respondents in Hong Kong indicated a high acceptance of use of telemedicine for follow-up. They agreed that disease activity assessment through telemedicine is accurate and that telemedicine reduces the risk for infection during the pandemic.[30]

More descriptive studies on telemedicine are expected given the adjustments made by both practitioners and patients during the pandemic. Future research evaluating the effectiveness of telemedicine for rheumatology care is much desired. In the context of the COVID-19 pandemic, telemedicine can minimize potential exposure to COVID-19 in stable RMD patients.[18,20] We recognize this is particularly important in areas with high community transmission; follow-up through telemedicine can provide treatment guidance safely while helping to ensure treatment continuity.

3.2.5 | Vaccination

C12. It is recommended that patients with RMD receive an approved SARS-CoV-2 vaccine as soon as it becomes available to them. (100% agreement, expert opinion, strong recommendation).
C13. RMD patients with normal or altered immunocompetence should receive vaccination based on current country, regional and/or international guidelines. (100% agreement, expert opinion, strong recommendation).
C14. Immunization schedules of patients with RMD should be maintained while adhering strictly to the safety protocols of COVID-19 prevention. (100% agreement, expert opinion, strong recommendation).

SARS-CoV-2 vaccines have been in development since the start of the pandemic and several vaccine candidates are in Phase 3 evaluation.[31] In the US and EU, messenger RNA (mRNA) SARS-CoV-2 vaccines have been granted emergency use authorization by the US Food and Drug Administration and European Medicines Agency, respectively, and the initial vaccination phase has begun for healthcare personnel and residents of long-term healthcare facilities in the US as recommended by the Advisory Committee on Immunization Practices.[32-36] While no data are currently available on the safety of mRNA or other SARS-CoV-2 vaccines in patients with RMD or who are otherwise immunocompromised, based on vaccine clinical trial results, there is no reason to expect that these vaccines are any less safe in these patient subgroups than in the general population.[37] Moreover, while there is a theoretical possibility that these vaccines are less effective in those taking immunosuppressant medications, there are, as yet, no data to support this. In the context of the ongoing COVID-19 pandemic, it is recommended that patients with RMD receive a SARS-CoV-2 vaccine approved for use by their national health authority, as soon as it becomes available to them; however, they must be counseled about the paucity of safety and efficacy data on these vaccines in the RMD population.

There are no live vaccines currently available for COVID-19. Should one become available, it should generally be avoided in immunocompromised persons with RMD until such time that vaccine data on safety and efficacy have been reviewed. A revised recommendation should then be considered based on its merits.

If disease activity allows, immunosuppressive therapy should be initiated in patients with newly diagnosed RMD at least 2 weeks after the completion of SARS-CoV-2 vaccination with the minimum recommended interval between 2 successive vaccine doses, in order to allow the immune system to mount an adequate immune response to the vaccine and also to minimize the delay in the administration of immunosuppressive therapy.[38] Given prior evidence of improved immunogenicity of the influenza vaccine upon temporary discontinuation of MTX for 2 weeks post-vaccination without an increase in rheumatoid arthritis disease activity, a similar strategy may be considered for MTX in patients with well-controlled rheumatoid arthritis receiving a SARS-CoV-2 vaccine.[39,40]

Because of physical distancing requirements, important preventive services such as routine vaccination may be delayed.[41] The CDC and World Health Organization (WHO) underscore the need to maintain the recommended schedule of routinely administered vaccines for all individuals during the pandemic.[41,42] For persons with suspected or confirmed COVID-19, the CDC recommends deferment until completion of isolation (for suspected cases, and for asymptomatic individuals) or after recovery from acute illness (for symptomatic cases).[42] Vaccine administration should be safely undertaken while following protocols to prevent the spread of COVID-19.[41,42] Appointments should be scheduled to ensure that all required vaccinations can be given, including catch-up doses, to minimize unnecessary healthcare visits and potential exposure to SARS-CoV-2.[42]

At this time no published studies can provide information on whether specific routine vaccines should be recommended for patients with RMD during the pandemic. C13 and C14 are based on the current advice of maintaining and updating the appropriate vaccination schedule, with precautions for immunocompromised individuals and patients with autoimmune inflammatory RMD.[18,43,44]

3.3 | Management of RMD patients with COVID-19

3.3.1 | Clinical manifestations of COVID-19 in RMD patients

C15. Clinical manifestations mimicking RMD, laboratory reports of positive antinuclear antibodies, antiphospholipid antibodies, and lupus anti-coagulant have been reported with COVID-19 patients. These patients should be followed for the possibility of persistent intermediate- to long-term immune dysregulation. (95% agreement, expert opinion, strong recommendation).

C16. The clinical presentation of COVID-19 in patients with RMD is similar to that in patients without RMD. Nonetheless, RMD patients who experience worsening of respiratory symptoms should immediately seek further healthcare advice of an expert in treating COVID-19 (eg, pulmonologist, infectious diseases specialist, or general internist) according to local recommendations. (100% agreement, grade of evidence low, strong recommendation).

Acute SARS-CoV-2 infection triggers hyperinflammatory and autoimmune processes that manifest similarly to RMD, including a cytokine release syndrome seen in critical patients with SARS-CoV-2 infection.[45,46] Musculoskeletal, skin, and central nervous system manifestations similar to those in RMD have been reported. Specific examples include: arthralgias, myalgias, and myositis; "COVID toes" or pseudo-chilblains, transient urticarial or maculopapular rash, livedoid or necrotic lesions, punctiform or diffuse purpura, and erythema elevatum diutinum-like rash; and large-vessel stroke in the young.[47-49] Features of giant cell arteritis such as headache, cough, fever, and fatigue can also be mimicked by COVID-19.[50] After the acute phase, post-viral autoimmune manifestations in the form of Guillain-Barré syndrome and Kawasaki-like disease have also been reported.[51-53]

Furthermore, laboratory results positive for antinuclear antibodies, antiphospholipid antibodies, lupus anti-coagulant assay, and increased levels of D-dimer associated with RMDs, erythrocyte sedimentation rate, and C-reactive protein have been documented with COVID-19.[50,54] In patients with established RMD, the identification of RMD-like COVID-19 manifestations should prompt close monitoring for immune dysregulation.[45]

The clinical presentation of COVID-19 among RMD patients is generally similar to its presentation in non-rheumatic patients. Fever, cough, sore throat, and dyspnea manifest in the same manner.[6,55,56] Laboratory parameters were also found to be similar, except for higher white blood cell count at presentation and lower peak ferritin levels in RMD patients.[6,56] Because RMD patients are more likely to develop complicated COVID-19, worsening of respiratory symptoms should prompt a consult with an expert in treating COVID-19.

3.3.2 | Modification of RMD treatment in patients with COVID-19

C17. Hydroxychloroquine (HCQ), NSAIDs, and angiotensin-converting enzyme inhibitors (ACEi) / angiotensin receptor blockers (ARBs) may be continued but should be individualized based on disease condition. (100% agreement, grade of evidence moderate, strong recommendation).

C18. The clinician should consider stopping or withholding csDMARDs (other than HCQ), tsDMARDs, and bDMARDs, on a case-by-case basis. (94% agreement, grade of evidence moderate, weak recommendation).

C19. RMD patients with COVID-19 should be treated according to the standard of care. (92% agreement, grade of evidence low, strong recommendation).

C20. Glucocorticoids should be used at the lowest possible dose to control RMD and should not be abruptly stopped. (94% agreement, grade of evidence high, strong recommendation).

C21. Immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus) should be discontinued in patients with COVID-19. (82% agreement, grade of evidence low, strong recommendation).

High-quality studies to directly address adjustment (de-escalation, discontinuation, re-initiation) of RMD medication regimens upon confirmed COVID-19 diagnosis are lacking. The risk of developing COVID-19 complications with these regimens is also uncertain. Our recommendations are mainly based on guidance from regulatory bodies and other specialty organizations, extrapolations from studies that included patients who developed other infections while using RMD therapies, and information from registries and case series. Votes garnered for this topic were divided between complete acceptance and acceptance with some reservations despite achieving consensus. Generally, our task force agreed that modifying current RMD therapies should be individualized, and potential benefits and risks should be discussed with patients and family.

NSAIDs, ACEi and ARBs, and HCQ may be continued but with consideration of the patient's clinical condition. No association was found between NSAID use in non-SARS-CoV-2 viral respiratory infections and poor clinical outcomes.[57,58] Recently, a retrospective cohort study in primary care did not find an increased risk in COVID-19-related mortality among osteoarthritis patients treated with NSAIDs versus comparator drugs (paracetamol plus codeine/hydrocodeine).[59]

The WHO presented low-certainty evidence that patients on long-term ACEi/ARB therapy are not at a higher risk of poor outcomes from COVID-19.[60] In addition, the only randomized trial data to date did not show clinical benefit with discontinuing long-term ACEi/ARB treatment for hospitalized, COVID-19-positive patients. The BRACE CORONA trial was a phase 4, randomized study evaluating 2 approaches in hospitalized patients with confirmed COVID-19 taking long-term ACEi/ARB: temporarily stopping the ACEi/ARB for 30 days versus continuing ACEi/ARB. The study found no significant difference in the number of days alive and out of hospital, the primary outcome, between approaches.[61]

Chloroquine and HCQ were initially thought to be useful in COVID-19 because they have been shown to inhibit SARS-CoV-2 in vitro; however, to date there is no convincing evidence of clinical

efficacy for either agent.[62] Their use in the treatment of COVID-19 per se is beyond the scope of this document. In the management of RMD, observational studies, primarily of registry data, did not show an association between HCQ use and poor outcomes from COVID-19,[11,55,63,64] except that a case series suggested a link with higher hospitalization rate. [65] One retrospective study suggested overall reduced mortality with HCQ use.[66]

Similar to the list of agents to consider for a treatment pause upon known COVID-19 exposure, our group suggests temporarily discontinuing csDMARDs (other than HCQ, such as SSZ, MTX, leflunomide), tsDMARDs (eg, JAKi, other than baricitinib), and bDMARDs (eg, tumor necrosis factor inhibitors [TNFi], rituximab, tocilizumab) upon diagnosis of COVID-19. RMD patients already on baricitinib may be maintained on it, and ideally paired with remdesivir in the context of COVID-19 treatment – a randomized controlled trial showed that baricitinib plus remdesivir was superior to remdesivir in improving outcomes in confirmed COVID-19;[67] however, use of baricitinib in an RMD patient with COVID-19 should be within the context of approved COVID-19 management guidelines in the clinician's country. Case series, case reports, and observational studies showed mixed results: while some immune-modulating therapies were not associated with poor outcomes, others were linked to a more severe COVID-19 course, particularly rituximab and SSZ.[13,68-76] The results of the meta-analysis by Akiyama et al. should also be considered: meta-regression analysis according to RMD therapeutics revealed that studies with a greater percentage of patients using csDMARDs and the bDMARD/tsDMARD–csDMARD combination had a higher rate of hospitalization or death from COVID-19.[4] Use of bDMARD/tsDMARD monotherapy, particularly TNFi monotherapy, was associated with lower COVID-19 hospitalization or mortality rates.[4] TNFi use appears to be protective in some studies,[77,78] but this benefit needs to be replicated in further studies before a specific recommendation can be proposed. For treatment of SARS-CoV-2 infection in hospitalized patients, the use of interleukin (IL)-6 inhibitor tocilizumab has been evaluated in a randomized controlled trial but did not lead to significantly different clinical outcomes compared with placebo.[79]

Glucocorticoids, specifically dexamethasone, may be useful for severe COVID-19.[80,81] It is expected that glucocorticoids may confer additional benefit in terms of managing COVID-19 in infected RMD patients, but observational data suggest a likelihood toward a more severe course. The meta-analysis by Akiyama et al. showed a trend for higher rates of hospitalization and death with glucocorticoid use.[4] From the registry-based observational studies, glucocorticoid use was associated with poor COVID-19 outcomes, including hospitalization, mortality, intensive care unit admission, and ventilator use.[11,55,63,66,76] In terms of dose, the GRA-19 study showed that prednisone ≥10 mg/d was associated with a higher risk of hospitalization (OR 2.05, 95% CI 1.06-3.96, $P = .03$).[11] Therefore, it is recommended to reduce the dose to <10 mg daily if the underlying RMD disease activity permits. However, in severe or life-threatening autoimmune disease, a higher dose of glucocorticoid may be needed for disease control. Thus, dosage of glucocorticoid for control of the underlying RMD should be determined on a case-by-case basis according to disease activity and patients' COVID-19 status.

As with the use of other RMD therapies, the need to control RMD activity should be weighed against preventing severe COVID-19. Currently, only low-quality evidence suggests a predisposition toward poor COVID-19 outcome with glucocorticoid use; thus, RMD patients should receive standard care, and continue glucocorticoids with the appropriate dose adjustment as indicated to control flares. The use of the lowest possible doses to manage disease activity is considered as good clinical practice.[18,20]

3.3.3 | Restarting RMD medication

C22. In general, RMD treatments may be re-introduced at least 2 weeks after recovery from acute COVID-19. They may need to be individualized based on the clinical scenario and the physician's judgment. (100% agreement, grade of evidence low, weak recommendation).

C23. For asymptomatic individuals, RMD treatment may be re-introduced approximately 10 days after diagnosis of COVID-19. (100% agreement, grade of evidence low, weak recommendation).

The optimal time to resume RMD medication that was discontinued in the context of COVID-19 infection is uncertain. Limited evidence from observational studies on the course of viral shedding and clearance may guide the decision to re-start RMD treatment.

Viral shedding has been noted 2-6 days before symptom onset; up to 10 days after symptom onset in mild COVID-19; and up to a median of 8 days after symptom onset in immunocompromised patients with severe COVID-19 (range of 0-20 days).[82-85] The time frame for viral shedding was not described for mild COVID-19 in immunocompromised individuals, although the CDC suggests that prolonged viral shedding may be present in immunocompromised patients even with mild SARS-CoV-2 infection.[86] Extrapolating the data for RMD patients, and depending on COVID-19 severity, it may be reasonable to wait for at least 2 weeks after symptom onset or after a positive reverse-transcription polymerase chain reaction (RT-PCR) test before re-introducing RMD therapy. Similarly, the ACR guidance recommends a waiting period of 7-14 days after symptom resolution in mild COVID-19, or 10-17 days after a positive RT-PCR test for asymptomatic patients.[20]

This time frame for medication re-start is compatible with the CDC's 10-day wait after symptom onset prior to discontinuing transmission-based precautions (eg, quarantine).[86] Based on viral clearance studies, this interval was proposed as viral load had presumably declined, and transmission likelihood had been reduced. In mild to moderate COVID-19, the CDC suggests waiting 10 days; for severe disease or immunocompromised individuals this wait can be up to 20 days. The CDC further requires that the last fever incident should have occurred at least 24 hours prior, with no anti-pyretic use, and symptoms such as cough should have improved.[86] When

restarting RMD therapy, assessment of the patient's condition can use a similar symptom-based approach as the CDC's approach to de-isolation. In cases of acute conditions, the need to control flares urgently may also affect the timing of re-introduction. SARS-CoV-2 re-testing, if feasible, may be warranted in severely immunocompromised individuals.

3.3.4 | Impact of COVID-19 on the quality of life (QoL) of RMD patients

C24. SARS-CoV-2 infection has a negative impact on the QoL of RMD patients, particularly the mental health component. (95% agreement, expert opinion, strength-of-recommendation assessment not applicable).

C25. Social isolation or shielding has a negative impact on QoL (both mental and physical) of RMD patients during the COVID-19 pandemic. (90% agreement, expert opinion, strength-of-recommendation assessment not applicable).

Surveys have shown lower QoL while coping with the life changes borne from the pandemic among the general populations in Europe.[87] Understandably, lower QoL was also reported after being infected with COVID-19.[88]

The pandemic has also impacted the QoL of RMD patients. Individuals in New York City surveyed during the heightened phase of implementing transmission prevention measures reported worsening of their RMD with the changes to their daily lives regardless of SARS-CoV-2 infection status. Fatigue from multitasking and adherence to isolation measures may have directly contributed to disease flares.[89] Stress from uncertainties in finances, exposure to infection, and changes to RMD medication, among other issues, were indirect contributors.[89] One study which used the Short Form 12-item Health Survey to specifically measure QoL in a UK cohort of RMD patients, showed a worsening of physical and mental functioning during the pandemic. Mental component scores of the survey were significantly lower for the group infected with SARS-CoV-2 compared with those of the non-infected group (mean difference: −3.3; 95% CI −5.2-1.4, $P < .001$). In the non-infected group, those who were in strict isolation had significantly lower mental (−2.1; 95% CI −2.9-1.4, $P < .001$) and physical component scores (−2.2; 95% CI −3.8-2.5, $P < .001$) than those not in isolation.[90]

Mindful of the known negative impact of COVID-19 on patients' QoL, rheumatologists caring for RMD patients during the pandemic should be ready to ask about life changes and mental well-being. They should provide or recommend support for mental and physical functioning, in addition to managing RMD.

4 | CONCLUSIONS

To update the initial APLAR position statement, the COVID-19 task force was mandated to address important concerns in the care of the patient with RMD that arose from the rapid changes to healthcare due to the pandemic. Patients with RMD have also been coping with the challenges of adhering to infection prevention directives while working with their treating rheumatologists to control their disease.

Based on currently available best evidence, our group has updated previous APLAR guidance by:

- noting the potential risk of RMD patients for complicated COVID-19 and listing probable risk factors
- describing the clinical manifestations of COVID-19 that are similar to RMD features
- reviewing the initial findings of potential risks associated with specific RMD therapies and providing some guiding principles for medication adjustment, and
- highlighting the role of vaccination, the role of telemedicine, changes in RMD treatment adherence, and the importance of changes to QoL during the pandemic.

The vibrant research landscape has, to date of this publication, produced a great volume of descriptive research that has helped to provide a better understanding of COVID-19. Importantly, numerous studies have also covered how aspects of RMD management are impacted by the pandemic. However, most of the data from publications summarized here were considered as low-quality to moderate-quality evidence. Our audience should regard this guidance judiciously and continue to monitor for more robust, definitive data from randomized controlled trials and larger, population-based studies; the APLAR COVID-19 task force will do the same, updating this document in 2021 as new evidence becomes available.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

L-S Tam, Y Tanaka, R Handa and SA Haq planned the meeting and prepared the clinical questions. All task force members contributed

to the development of the manuscript by drafting, reviewing, and discussing the statements and supporting evidence, voting to refine and finalize statements, and reading and approving the manuscript.

ORCID

Lai-Shan Tam https://orcid.org/0000-0001-6410-8852
Yoshiya Tanaka https://orcid.org/0000-0002-0807-7139
Rohini Handa https://orcid.org/0000-0001-6685-4170
Zhanguo Li https://orcid.org/0000-0002-2590-6242
Worawit Louthrenoo https://orcid.org/0000-0003-3105-6122
Philip C. Robinson https://orcid.org/0000-0002-3156-3418
Li Yang Hsu https://orcid.org/0000-0002-0396-066X
Jiacai Cho https://orcid.org/0000-0002-4477-3430
A. T. M. Tanveer Hasan https://orcid.org/0000-0002-5332-3319
Syahrul Sazliyana Shaharir https://orcid.org/0000-0002-9068-8114
Debashish Danda https://orcid.org/0000-0002-2121-0942
Syed Atiqul Haq https://orcid.org/0000-0003-4154-7283

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