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American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 2

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Due to the rapidly expanding information and evolving evidence related to COVID-19, which may lead to modification of some guidance statements over time, it is anticipated that updated versions of this article will be published, with the version number included in the title. Readers should ensure that they are consulting the most current version.

Guidance developed and/or endorsed by the American College of Rheumatology (ACR) is intended to inform particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to this guidance to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. Guidance statements are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidance developed or endorsed by the ACR is subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Objective. To provide guidance to rheumatology providers on the management of adult rheumatic disease in the context of the coronavirus disease 2019 (COVID-19) pandemic.

Methods. A task force, including 10 rheumatologists and 4 infectious disease specialists from North America, was convened. Clinical questions were collated, and an evidence report was rapidly generated and disseminated. Questions and drafted statements were reviewed and assessed using a modified Delphi process. This included asynchronous anonymous voting by e-mail and webinars with the entire panel. Task force members voted on agreement with draft statements using a 1–9-point numerical scoring system, and consensus was determined to be low, moderate, or high based on the dispersion of votes. For approval, median votes were required to meet predefined levels of agreement (median values of 7–9, 4–6, and 1–3 defined as agreement, uncertainty, or disagreement, respectively) with either moderate or high levels of consensus.

Results. To date, the task force has approved 80 guidance statements: 36 with moderate and 44 with high consensus. These were combined, resulting in 27 final guidance statements.

Conclusion. These guidance statements are provided to promote optimal care during the current pandemic. However, given the low level of available evidence and the rapidly evolving literature, this guidance is presented as a "living document," and future updates are anticipated.

INTRODUCTION

Since its initial outbreak in Wuhan, China, coronavirus disease 2019 (COVID-19) has rapidly evolved into a worldwide pandemic (1). Caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), COVID-19 has impacted millions of lives and has contributed to a growing number of deaths worldwide. The pandemic poses a substantial challenge for both rheumatology providers and patients since serious infection is a well-recognized cause of morbidity and mortality across a number of rheumatic diseases. Therefore, there is an urgent need to address important questions regarding COVID-19 risk and prevention as well as the safety surrounding the administration of rheumatic disease treatments.

The American College of Rheumatology (ACR) convened the COVID-19 Clinical Task Force on March 26, 2020, charged by ACR leadership to rapidly provide guidance to rheumatology providers relevant to the management of rheumatic disease in adult patients during the pandemic. Clinical guidance generated from this effort is intended to aid in the care of individual patients, but it is not meant to supplant clinical decision-making. Modifications to treatment plans, particularly in patients with complex conditions, are highly disease-, patient-, geography-, and time-specific and, therefore, must be individualized as part of a shared decision-making process. Although substantial attention has been given to the use of rheumatology treatments (e.g., hydroxychloroquine [HCQ], chloroquine [CQ], interleukin-6 [IL-6] receptor inhibition) in the prevention and management of COVID-19 and associated inflammatory sequelae of infection, the guidance provided in this report is limited to the management of rheumatic disease and does not address the management of COVID-19 and/or its complications. Furthermore, the guidance herein is presented as a "living" document, recognizing that evidence is evolving rapidly and the ACR anticipates the need for updates of this guidance as such evidence becomes available.

METHODS

Clinical questions. A task force leadership group (TRM, KGS, LF, SRJ) generated initial questions and clinical scenarios to address. Initial questions were informed by review of "Frequently Asked Questions" posted by rheumatology patients on patient-facing web sites hosted by the national Arthritis Foundation (2), CreakyJoints (3), and the Global Healthy Living Foundation (4). Questions were categorized into 4 overlapping domains: 1) risk assessment and prevention, 2) use of rheumatic disease treatments in patients at risk for exposure, 3) rheumatic disease treatment immediately following known SARS–CoV-2 exposure (e.g., community-related exposure as defined by the Centers for Disease Control and Prevention [CDC]), and 4) management of rheumatic disease in the context of COVID-19. The task force agreed that the perspective of the guidance should be that of managing clinicians and their individual patients but that some attention should be directed to a societal perspective, when relevant, around potential issues of availability of specific antirheumatic therapies being considered for treatment of COVID-19. Following an initial task force webinar on March 26, 2020, 4 separate subgroups were formed to address and refine questions in each domain. The task force included 14 members from North America and comprised 10 rheumatologists and 4 infectious disease

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Table 1. Timeline in ACR COVID-19 clinical guidance development*

Date(s)	Milestone
2019	
December	Initial cases of novel coronavirus pneumonia identified in Wuhan, China
2020	
January 21	First (travel-related) case of COVID-19 in US (Washington state)
March 11	COVID-19 declared pandemic by World Health Organization
March 26	ACR COVID-19 Clinical Task Force convened—initial webinar
March 26–30	Task force subgroups refine clinical questions and gather evidence
March 31	Evidence report disseminated to task force members
April 1–3	Initial task force vote on statements/questions
April 4	Results of round one voting reviewed, discussed via webinar
April 5–6	Draft statements generated for additional consideration
April 7–8	Second round of task force voting
April 8	Final statements reviewed and refined via webinar
April 9–10	Approved statements concatenated into 25 recommendations and draft guidance document generated
April 11	Guidance document approved by ACR Board of Directors
April 13	Draft guidance posted on ACR web site

* ACR = American College of Rheumatology; COVID-19 = coronavirus disease 2019.

specialists with broad expertise in relevant clinical areas and representing different geographic regions, rheumatic disease specialty areas, and clinical practice settings.

Evidence review. In addition to refining clinical questions addressed, each subgroup was tasked with gathering evidence that addressed questions within the assigned domains. This nonsystematic evidence review included PubMed searches supplemented by postings from the CDC, US Food and Drug Administration (FDA), and other electronic media sources. Questions and relevant evidence were collated into a single document, which was disseminated by e-mail to the entire task force for review 2 days prior to initial voting.

Initial voting. Following the evidence review, an initial round of voting was conducted anonymously by e-mail using a modified Delphi approach as part of the RAND/University of California at Los Angeles (UCLA) appropriateness method (5). The RAND/UCLA appropriateness method has been shown to be highly reproducible (6) and to have content, construct, and predictive validity (7–9). All votes were weighted equally. Task force members were asked to report their level of agreement with 3 general statements in addition to providing graded yes/no responses to 90 clinical questions. Voting was completed using a numerical rating scale of 1–9 for all items. For the 3 general statements, ratings of 9 corresponded to "complete agreement," 5 corresponded to "uncertain," and 1 corresponded to "complete disagreement." Median vote ratings of 1–3, 4–6, and 7–9 were defined a priori and interpreted as disagreement, uncertainty, and agreement, respectively. For yes/no questions, a voting score of 9 indicated that a positive response was expected "to result in a highly favorable benefit to risk ratio" whereas a voting score of 1 strongly favored a negative response and a voting score of 5 corresponded to uncertainty. For questions, median vote ratings of 1–3, 4–6, and 7–9 were interpreted as no, uncertain, and yes responses, respectively. Panel consensus was also assessed and noted to be "low" when ≥4 votes fell into the 1–3 rating range with ≥4 votes simultaneously falling into the 7–9 rating range. Consensus was deemed to be "high" when all 14 votes fell within a single tertile, with all other combinations considered to reflect "moderate" levels of consensus.

Review of initial voting results and generation of draft guidance statements. Results from the first round of voting were reviewed and discussed as part of a task force webinar on April 4, 2020 (Table 1). Discussion was focused on

Table 2. General guidance for patients with rheumatic disease*

Guidance statement	Level of task force consensus
The risk of poor outcomes from COVID-19 appears to be related primarily to general risk factors such as age and comorbidity.	High
Patients should be counseled on general preventive measures, e.g., social distancing and hand hygiene.	High
As part of a shared decision-making process between patients and rheumatology providers, select measures to reduce health care encounters and potential exposure to SARS–CoV-2 (beyond general preventive measures) may be reasonable, e.g., reduced frequency of laboratory monitoring, optimal use of telehealth, increased dosing intervals between intravenous medications.	Moderate to high
If indicated, glucocorticoids should be used at the lowest dose possible to control rheumatic disease, regardless of exposure or infection status.	Moderate to high
Glucocorticoids should not be abruptly stopped, regardless of exposure or infection status.	High
If indicated, ACE inhibitors or ARBs should be continued in full doses or initiated.	Moderate to high

* COVID-19 = coronavirus disease 2019; SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

questions and/or statements with median votes reflecting uncertainty and with low or moderate consensus. Panelists were given the opportunity to comment on all of the items presented in the initial voting process. Informed by voting results and discussion, the task force leadership group drafted guidance statements for further consideration.

Second round of voting and guidance approval. Draft statements were sent to task force members and agreement was assessed by e-mail, again using an anonymous voting process as detailed above. Guidance statements receiving a median vote rating of 7–9 with moderate or high consensus were approved as recommendations (10). Results from the second round of voting were presented to the task force during a third webinar on April 8, 2020, and minor revisions to statements were made through an iterative process until consensus was achieved. To minimize redundancy and overlap, the approved statements were combined to generate final guidance statements with the agreement of task force members ascertained via e-mail. The ACR Board of Directors approved these recommendations on April 11, 2020. A similar approach was used for changes and/or additions made to the guidance document that followed its initial approval.

RESULTS

Of the 81 guidance statements considered in round 2 voting, 77 received median vote ratings of 7, 8, or 9 and were also associated with moderate consensus (n = 36) or high consensus (n = 41), the predefined threshold for approval (Supplementary Tables 1–6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41437/abstract). There were 2 draft statements receiving a median vote rating of <7 (Supplementary Tables 5 and 6) and 2 additional statements with a median vote rating of ≥7 that were accompanied by low consensus (Supplementary Tables 2 and 3b). The process resulted in 25 final guidance statements that were posted online by the ACR in draft form on April 13, 2020. These include guidance on 1) general considerations relevant to risk assessment, prevention, and the use of glucocorticoids, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) (Table 2), 2) ongoing treatment of patients with stable rheumatic disease in the absence of infection or SARS–CoV-2 exposure and considerations specific to systemic lupus erythematosus (SLE) (Table 3), 3) treatment of newly diagnosed or active rheumatic disease in the absence of infection or SARS–CoV-2 exposure (Table 4), 4) treatment of rheumatic disease after SARS–CoV-2 exposure (Table 5), and 5) rheumatic disease treatment in the context of documented or presumptive COVID-19 (Table 5).

Following approval and publication of these initial 25 guidance statements, the task force approved 3 additional statements (Supplementary Table 7, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41437/abstract). Two of these statements were combined, leading to a total of 27 guidance statements.

Evidence supporting the final recommendations was universally of very low quality: either indirect and/or limited to case series or retrospective cohort studies of COVID-19 patients with limited or no information on underlying rheumatic disease status. Available evidence is summarized below, organized by risk assessment, infection prevention, and rheumatic disease treatments.

Risk assessment. To our knowledge, there is currently no evidence identifying risk factors for poor outcome with COVID-19 that are specific to rheumatic disease. Based on preliminary retrospective cohort studies (11–14), risk factors for poor outcome with COVID-19 include older age (e.g., >65 years) and select comorbidities such as chronic lung disease, hypertension,

Table 3. Guidance for ongoing treatment of patients with stable rheumatic disease in the absence of infection or known SARS–CoV-2 exposure and in patients with SLE*

Guidance statement	Level of task force consensus
Ongoing treatment in patients with stable rheumatic disease	
HCQ/CQ, SSZ, MTX, LEF, immunosuppressants (e.g., tacrolimus, CSA, MMF, AZA), biologics, JAK inhibitors, and NSAIDs may be continued. (This includes patients with GCA with an indication, in whom IL-6 receptor inhibitors should be continued, if available.)	Moderate to high
Denosumab may still be given, extending dosing intervals to no longer than every 8 months, if necessary to minimize health care encounters.	Moderate
For patients with a history of vital organ–threatening rheumatic disease, immunosuppressants should not be dose-reduced.	Moderate
Treatment of SLE	
For patients with newly diagnosed disease, HCQ/CQ should be started at full dose, when available.	High
For pregnant women with SLE, HCQ/CQ should be continued at the same dose, when available.	High
If indicated, belimumab may be initiated.	Moderate

* SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; SLE = systemic lupus erythematosus; HCQ = hydroxychloroquine; CQ = chloroquine; SSZ = sulfasalazine; MTX = methotrexate; LEF = leflunomide; CSA = cyclosporin A; MMF = mycophenolate mofetil; AZA = azathioprine; NSAIDs = nonsteroidal antiinflammatory drugs; GCA = giant cell arteritis; IL-6 = interleukin-6.

Table 4. Guidance for the treatment of newly diagnosed or active rheumatic disease in the absence of infection or known SARS–CoV-2 exposure*

Guidance statement	Level of task force consensus
Inflammatory arthritis	
For patients whose disease is well-controlled with HCQ/CQ, this DMARD should be continued when available; when unable to access (including in patients with active or newly diagnosed disease), switching to a different conventional synthetic DMARD (either as monotherapy or as part of combination therapy) should be considered.	Moderate to high
For patients whose disease is well-controlled with an IL-6 receptor inhibitor, this DMARD should be continued when available; when unable to access the agent, switching to a different biologic should be considered.†	Moderate
For patients with moderate-to-high disease activity despite optimal conventional synthetic DMARDs, biologics may be started.†	High
For patients with active or newly diagnosed inflammatory arthritis, conventional synthetic DMARDs may be started or switched.	Moderate
If indicated, low-dose glucocorticoids (≤10 mg prednisone equivalent/day) or NSAIDs may be started.	Moderate to high
Other rheumatic diseases	
For patients with systemic inflammatory or vital organ–threatening disease (e.g., lupus nephritis or vasculitis), high-dose glucocorticoids or immunosuppressants (e.g., tacrolimus, CSA, MMF, AZA) may be initiated.	Moderate
In the context of a drug shortage due to COVID-19, new HCQ/CQ prescriptions for non–FDA-approved indications should be avoided.	High

* SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; HCQ = hydroxychloroquine; CQ = chloroquine; DMARD = disease-modifying antirheumatic drug; IL-6 = interleukin-6; NSAIDs = nonsteroidal antiinflammatory drugs; CSA = cyclosporin A; MMF = mycophenolate mofetil; AZA = azathioprine; FDA = US Food and Drug Administration.
† The panel noted uncertainty with regard to JAK inhibition in this situation.

cardiovascular disease, chronic kidney disease, obesity, and diabetes mellitus, conditions that are frequently overrepresented among patients with rheumatic disease (15–18). Data linking specific rheumatologic treatments to COVID-19 or its complications are either lacking or, when available, conflicting, and are discussed in detail below.

In addition to older age and comorbidity, a number of laboratory measures have been preliminarily associated with poor

Table 5. Guidance for the treatment of rheumatic disease following known SARS–CoV-2 exposure and in the context of active or presumptive COVID-19*

Guidance statement	Level of task force consensus
Following SARS–CoV-2 exposure	
HCQ/CQ, SSZ, and NSAIDs may be continued.	Moderate to high
Immunosuppressants (e.g., tacrolimus, CSA, MMF, AZA), non–IL-6 biologics, and JAK inhibitors should be stopped temporarily, pending a negative test result for COVID-19 or after 2 weeks of symptom-free observation.†	Moderate
In select circumstances, as part of a shared decision-making process, IL-6 receptor inhibitors may be continued.	Moderate
Documented or presumptive COVID-19	
Regardless of COVID-19 severity, HCQ/CQ may be continued, but SSZ, MTX, LEF, immunosuppressants, non–IL-6 biologics, and JAK inhibitors should be stopped or withheld.	Moderate to high
For patients with severe respiratory symptoms, NSAIDs should be stopped.‡	Moderate
In select circumstances, as part of a shared decision-making process, IL-6 receptor inhibitors may be continued.	Moderate
Reiniating treatment following COVID-19	
For patients with uncomplicated COVID-19 infections (characterized by mild or no pneumonia and treated in the ambulatory setting or via self-quarantine), consideration may be given to restarting rheumatic disease treatments (e.g., DMARDs, immunosuppressants, biologics, and JAK inhibitors) within 7–14 days of symptom resolution. For patients who have a positive PCR test result for SARS–CoV-2 but are (and remain) asymptomatic, consideration may be given to restarting rheumatic disease treatments (e.g., DMARDs, immunosuppressants, biologics, and JAK inhibitors) 10–17 days after the PCR result is reported as positive.	High
Decisions regarding the timing of reinitiating rheumatic disease therapies in patients recovering from more severe COVID-19–related illness should be made on a case-by-case basis.	High

* SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; HCQ = hydroxychloroquine; CQ = chloroquine; SSZ = sulfasalazine; NSAIDs = nonsteroidal antiinflammatory drugs; CSA = cyclosporin A; MMF = mycophenolate mofetil; AZA = azathioprine; IL-6 = interleukin-6; MTX = methotrexate; LEF = leflunomide; DMARDs = disease-modifying antirheumatic drugs; PCR = polymerase chain reaction.
† The panel noted uncertainty with regard to temporarily stopping MTX or LEF in this situation.
‡ The panel demonstrated low consensus with regard to stopping NSAIDs in the absence of severe symptoms.

outcomes from COVID-19 (11,12). Examined in retrospective cohorts of hospitalized patients, biomarkers predictive of poor outcomes have included lymphopenia (particularly, low CD4+ T cell numbers) and elevations in circulating levels of lactate dehydrogenase, C-reactive protein, IL-6, and D-dimer, among others (19–22). Whether lymphopenia portends "preexisting" risk or is a consequence of more severe infection in hospitalized patients is unclear. Defining the precise role different biomarkers might play in predicting COVID-19 outcomes in the context of rheumatic disease will require further study.

General infection prevention. Preventive measures focused on mitigating infection risk and the impact of COVID-19 have been widely publicized by the CDC (23,24) and other public health agencies. The task force acknowledged the importance of these measures, recommending that rheumatic disease patients be provided with guidance around their routine adoption. These focus primarily on optimal hand hygiene, social distancing, and wearing a mask in public when social distancing is not possible, among others. As social distancing has emerged as a focal point in public health strategies aimed at preventing SARS–CoV-2 infection, this may have implications for the delivery of rheumatology care, with efforts to reduce health care encounters as a means of preventing virus spread and preserving the health care workforce (25). The task force acknowledged several relevant strategies that could be applied in the context of rheumatology care, including, but not limited to, optimal use of telehealth, reducing the frequency of routine laboratory surveillance when the associated risk of not testing is deemed to be low, using lower-volume laboratories not located within larger health care facilities, or delaying the initiation or redosing of infusion-based treatments when the risk of disease flare is low. The task force endorsed potential temporary delays in performing intravenous administration of zoledronic acid or subcutaneous administration of denosumab (generally given at a health care setting) as two examples (Supplementary Table 4, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41437/abstract), recommending that dosing intervals with denosumab not exceed 8 months due to concerns regarding increased vertebral fracture risk following denosumab withdrawal (26).

The task force recognized the importance of social distancing for all patients, including in the workplace when feasible. This may be particularly important for vulnerable patients at increased risk of poor COVID-19 outcomes (e.g., older patients with multimorbidity) and those at increased risk of SARS–CoV-2 exposure (e.g., health care workers). Workplace accommodations, including appropriate personal protective equipment (PPE), to minimize the spread of infection should be made available, and additional accommodations in the absence of PPE may be needed.

Rheumatic disease treatments. *ACE inhibitors and ARBs*. Recognizing that ACE2 serves as the cellular receptor for SARS–CoV-2 (27), theoretical concerns have been raised regarding therapies known to increase ACE2 expression (a recognized effect of ACE inhibitors and ARBs) (28). Following acute lung injury, ACE2 levels are down-regulated in local tissue, which may lead to excessive activation of the renin–angiotensin–aldosterone system and worsen underlying pneumonia. This has led to the opposing conjecture that ACE inhibitors or ARBs could be beneficial in the context of active infection (29). To date, however, there are insufficient clinical data to support the notion of either detrimental or beneficial effects of these drugs with respect to COVID-19. The American Heart Association, Heart Failure Society of America, and American College of Cardiology have recommended continuation of ACE inhibitors or ARBs for all patients who have been prescribed these agents, with careful deliberation preceding any change in these treatments (30). A recent cohort study demonstrated that among patients with hypertension hospitalized with COVID-19, the use of ACE inhibitors or ARBs was associated with significantly improved survival (31). The task force recommended continued use of ACE inhibitors and ARBs per standard of care in rheumatic disease patients who are most likely to benefit from these agents, such as those with a history or risk of scleroderma renal crisis or those with SLE and hypertension (32,33).

Nonsteroidal antiinflammatory drugs (NSAIDs). Although speculation was raised early in the pandemic with regard to NSAID use and possible associations with worse COVID-19 outcomes (34,35), these concerns have yet to be substantiated. The task force endorsed the continued use of these agents and prescription of these medications, when indicated, for newly diagnosed rheumatic disease with the exception that NSAIDs be stopped in those with severe manifestations of COVID-19, such as kidney, cardiac, or gastrointestinal injury, which portend a poor prognosis (36–38). The task force demonstrated low consensus specific to whether NSAIDs should be stopped in the setting of less severe COVID-19, where the use of such agents might provide therapeutic antipyretic and/or antiinflammatory benefit. Others have proposed acetaminophen (or paracetamol) as an alternative to NSAIDs in this situation (39), although appropriate caution is needed as there has been evidence of liver injury accompanying COVID-19 in a proportion of cases (40).

Glucocorticoids. The data related to the effects of glucocorticoid treatment in patients infected with SARS–CoV-2 are mixed. Recognizing potential risks associated with the immunosuppressive effects of glucocorticoids, emerging data suggest that their antiinflammatory properties could theoretically mitigate the impact of COVID-19, particularly during the late phases of infection characterized by hyperinflammation and cytokine storm (11,41). Case series suggest that younger patients with a history of solid organ transplantation and those undergoing cancer

chemotherapy living in epidemic areas of Italy, many of whom were receiving glucocorticoids, have not developed severe COVID-19 complications (42). In small hospital-based cohorts, treatment of COVID-19–related acute respiratory distress syndrome with methylprednisolone was associated with improved survival (11) and shorter intensive care unit (ICU) stays (41).

These very limited data suggesting a glucocorticoid benefit in COVID-19 are balanced by indirect data from other viral infections suggesting that there is no meaningful benefit, or even that there may be harm. There are no clinical data, for instance, suggesting benefit from glucocorticoids in the treatment of airway infections related to respiratory syncytial virus, influenza, SARS–CoV-1, or Middle East respiratory syndrome (MERS; caused by a separate coronavirus) (43). Furthermore, in one study of patients with SARS–CoV-1 pneumonia, the use of glucocorticoids was associated with worse outcomes (44). Likewise, glucocorticoid treatment in influenza pneumonia has been associated with significantly worse outcomes including higher mortality, more secondary bacterial infections, and increased length of ICU stay (45). In addition to being associated with reactivation of herpes zoster (46,47), glucocorticoid treatment is associated with a dose-dependent risk of serious bacterial and opportunistic infections (48). This latter concern may be particularly salient, as it was demonstrated in at least one Chinese case series that up to one-half of all COVID-19–related deaths were attributable to secondary bacterial infection (49).

Acknowledging controversies in the available evidence, the task force endorsed continued standard-of-care glucocorticoid administration, avoidance of abrupt treatment withdrawal (given the possibility of hypothalamic–pituitary–adrenal axis suppression [50]), and use of the lowest effective doses to control underlying rheumatic disease manifestations. The panel further endorsed the use of low-dose glucocorticoids when clinically indicated and acknowledged that higher doses in the context of severe, vital organ–threatening disease may be necessary even following SARS–CoV-2 exposure.

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Risks of serious infection with HCQ, CQ, sulfasalazine (SSZ), leflunomide (LEF), and methotrexate (MTX) are relatively small, particularly when given as monotherapies (51,52). This fact informed the task force's recommendation to continue or initiate these therapies, when needed, in the absence of infection or known SARS–CoV-2 exposure. The task force recommended that either HCQ or SSZ could be continued post–SARS–CoV-2 exposure (expressing uncertainty regarding MTX and LEF in this situation) but recommended temporarily withholding SSZ, LEF, and MTX in the setting of active infection. This latter recommendation specific to SSZ stemmed primarily from concerns that adverse effects from this agent (e.g., gastrointestinal upset, diarrhea, hepatitis, cytopenias, and rarely, pneumonitis) could be confused with signs of COVID-19 infection or could be detrimental, and that temporarily withholding this treatment would be unlikely to result in significant rheumatic disease flares.

Despite lack of support from rigorously conducted clinical trials (53–57), HCQ and CQ have been widely used in the treatment of COVID-19. As a result, supply chain issues for both agents have been reported (58). Recognizing the possibility that antimalarial therapy may not be available for all patients, the task force recommended that other csDMARDs could be used in place of HCQ/CQ in the context of inflammatory arthritis. The task force also recommended that in the setting of concerns regarding drug availability, new prescriptions of HCQ/CQ should be limited to patients with FDA-approved indications. The task force achieved strong levels of agreement and high consensus with regard to the continued use of HCQ/CQ in the management of SLE, when possible. It has been shown that therapeutic drug levels (>500 ng/ml in blood) can be achieved with optimal HCQ dosing strategies and that circulating drug concentrations below this threshold are associated with higher disease activity and increased flare risk in SLE (59,60). In addition to being associated with improved pregnancy outcomes in women with SLE (61), continued use of HCQ in SLE decreases the risk of flare and reduces the risk of longer-term morbidity and mortality (62,63).

Noting this relatively favorable risk/benefit profile, the task force endorsed the continued use of HCQ/CQ, if available, including in the setting of SARS–CoV-2 infection. The panel acknowledged, however, the need for surveillance accompanying HCQ/CQ administration in hospitalized patients, based on rare reports of cardiotoxicity. Cardiotoxicity risk may be heightened in the context of myocardial injury (reported with COVID-19 [64]) and/or coadministration of other drugs, such as azithromycin, that are known to prolong the QT interval (65,66).

Biologics, immunosuppressants, and JAK inhibitors. Biologics and JAK inhibitors have been associated with an increased risk of serious infection compared to conventional DMARDs (67–73). Most reports to date have focused on the risk of bacterial and opportunistic infections. Less attention has been directed to viral, and particularly viral respiratory, infections. An exception is the increased risk of herpes zoster observed with JAK inhibition (74–76). Although mechanisms linking these agents to the reactivation of herpes zoster are unclear, dampening of innate antiviral effects of type I and type II interferons has been suggested to play a role (77).

Conducted primarily in the context of rheumatoid arthritis, studies examining tapering or discontinuation of biologics or JAK inhibitors suggest that a large proportion of patients experience rheumatic disease flare (78–81). This is relevant because underlying inflammation or disease activity has been implicated as a risk factor for infection (82,83), a risk that may be heightened further in the context of "rescue" glucocorticoids. Although biologic therapies are associated with an increased risk of hospitalization due to serious infection, at least one report in rheumatoid arthritis has suggested that they are associated with a reduced risk of sepsis or fatal outcome, as compared to nonbiologic DMARDs, among patients developing serious infection with

these therapies (84). These data provide support for the task force's recommendation to continue all immunosuppressants (e.g., tacrolimus, cyclosporin A [CSA], mycophenolate mofetil [MMF], or azathioprine), biologics, and JAK inhibitors in patients with stable rheumatic disease in the absence of COVID-19 or SARS–CoV-2 exposure. For patients with inflammatory arthritis in whom optimal csDMARD therapy has been unsuccessful, or those treated with an IL-6 receptor inhibitor facing a potential drug shortage (25), the task force recommended consideration of a biologic treatment but expressed uncertainty with regard to the safety of JAK inhibition in either situation. This uncertainty centered on a reported dampening of innate antiviral pathways with JAK inhibition (76).

In contrast, emerging data suggest that some immunosuppressants, biologics, and/or JAK inhibitors could theoretically mitigate the severe impact of COVID-19, favoring their continued use or initiation in the management of rheumatic disease (85). MMF, for instance, has been associated with improved survival following MERS-CoV infection (86), while CSA inhibits coronavirus replication in vitro (87,88). Baracitinib, a JAK inhibitor, interferes with cellular endocytosis and could theoretically impair cellular entry of SARS–CoV-2 (43,89). Whether this property impacts infection risk is unknown. Indeed, National Institutes of Health guidelines have recommended against the use of JAK inhibitors in the treatment of COVID-19 given their "broad immunosuppressive effect" (90). In a small, uncontrolled cohort study of 21 patients with COVID-19 (none with rheumatic disease and all with severe/critical respiratory involvement), tocilizumab administration was associated with marked clinical improvement (91). Recognizing that hyperinflammation and cytokine storm appear to play a central role in severe manifestations of COVID-19 (92), select cytokine inhibitors (along with glucocorticoids and other targeted small molecules) have been proposed as potential treatments, with many of these agents under active investigation in randomized controlled trials (RCTs) (93–97).

In the absence of robust RCT data to support their continued use, the task force recommended temporarily withholding or stopping all non–IL-6 biologics, immunosuppressants (e.g., tacrolimus, CSA, MMF, and azathioprine), and JAK inhibitors in the context of documented or presumptive COVID-19, as well as after known SAR–CoV-2 exposure. The panel did not, however, define the precise duration for which these treatments would need to be withheld given current uncertainties about the parameters that might be used to define such a window. The task force also endorsed the notion that, in select circumstances, IL-6 receptor inhibition could be continued in the setting of SARS–CoV-2 infection or following exposure, although corresponding votes achieved only the minimal threshold for approval (both with median vote ratings of 7 and moderate consensus). In discussions relevant to IL-6 receptor inhibition, the panel emphasized the need for shared decision-making between patients and inpatient care teams and endorsed participation in research protocols.

Reinitiating therapies after COVID-19. Following publication of the initial guidance document, the task force approved 3 additional statements specific to reinitiating rheumatic disease treatments withheld following a diagnosis of COVID-19 (Supplementary Table 7, http://onlinelibrary.wiley.com/doi/10.1002/art.41437/abstract), which were combined to form 2 additional guidance statements (Table 5). Evidence supporting these is limited. In a small study of 9 patients with uncomplicated COVID-19 (none with rheumatic disease) (98), infectious SARS–CoV-2 (isolation of live virus) was not detected in nasopharyngeal samples from any patient after 8 days of symptoms (99). Moreover, 2 weeks post–symptom onset (often coinciding with symptom resolution in uncomplicated COVID-19), all patients had detectable antibodies to SARS–CoV-2. Some data suggest that the presence of detectable antibodies may provide longer-term protection (99–101). Although evidence supporting the approach is limited, a symptom-free period of at least 3 days has been used as a clinical surrogate for the development of protective adaptive immune responses following COVID-19.

The task force did not endorse routine polymerase chain reaction (PCR) viral testing or SARS–CoV-2 antibody testing to guide the reinitiation of rheumatic disease treatments. PCR results in select patients have remained positive for periods approaching 30 days (99), well after patients are considered infectious. Requiring a negative PCR result before reinitiating treatment could therefore lead to unnecessarily long delays and result in higher risk of rheumatic disease flare.

With the understanding that individuals developing COVID-19 may be infectious for days before symptom onset, longer delays in reinitiating treatment may be warranted in patients who test positive but remain asymptomatic. In patients with severe COVID-19 (~20% of cases), characterized by pneumonia and sometimes requiring hospitalization, symptom duration can exceed 2 weeks. In such cases, the task force believed decisions regarding reinitiation of rheumatic disease treatment should be made on a case-by-case basis.

DISCUSSION

This ACR guidance document serves as a tool for rheumatology providers to promote optimal care for patients with complex rheumatic disease conditions in the context of the ongoing COVID-19 pandemic. The guidance provided is not intended to be proscriptive nor should it be used to limit treatment options available for patients with rheumatic disease in our current health care climate.

Although the evidence report generated as part of this effort drew on a considerable number of sources, resulting guidance is supported only by very low-quality evidence. In nearly all cases, the evidence identified was indirect and included reports focused on either different infectious etiologies or retrospective cohorts of patients with COVID-19 without consideration of underlying

rheumatic disease state. As a result, all of the guidance provided should be considered "conditional" (102,103). However, the literature in this area is rapidly evolving. A PubMed search limited to the time frame from January 1 through March 31 of 2020 resulted in >2,500 citations using the search term "COVID-19." The same search covering the first half of April resulted in >2,100 citations. As available literature focused on COVID-19 in rheumatic disease populations expands, we anticipate that current knowledge gaps will be addressed.

There are several strengths to this effort that are noteworthy. Responding to the urgency of need, the task force generated guidance over a compressed time frame, while simultaneously leveraging a well-established method of consensus building (modified Delphi in the context of the RAND/UCLA appropriateness method). The panel charged with guidance development included both rheumatologists and infectious disease specialists with broad expertise in relevant clinical areas and representing different regions, disease interests, and practice environments.

We acknowledge limitations in this effort as well. Although the document touches on a broad range of topics, the guidance generated is not comprehensive and does not follow the rigorous guideline methodology routinely used by the ACR when formal clinical practice guidelines are generated. Although this document addresses the administration of many different rheumatology treatments, it does not provide guidance on other medications used in rheumatology practice (e.g., tyrosine kinase inhibitors or prostacyclins). Other questions remain. For example, when choosing a new therapy, how should currently available biologics or targeted small molecule therapies be prioritized? What is the impact of COVID-19 on disease activity or function, in both the short- and the long-term? Are rheumatology treatments safe with the coadministration of emerging COVID-19 treatments?

As these and other questions are addressed and new information becomes available, this guidance document will need to be revisited, expanded, and perhaps, in some cases, amended. The ACR is committed to maintaining this as a "living document," allowing needed modifications throughout the pandemic in order to facilitate optimal outcomes in patients with rheumatic disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mikuls had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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