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Article type : Full Length

American College of Rheumatology Guidance for the Management of Adult Patients with Rheumatic Disease During the COVID-19 Pandemic

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

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Keywords: COVID-19; pandemic; SARS-CoV-2; rheumatic disease; treatment

Conflict of Interest:

TRM: Research support and/or consultant for Pfizer, Bristol Myers Squibb, Horizon Therapeutics

SJ: Research support from Glaxo Smith Kline, Corbus, Roche, Merck, Bayer; research / advisory board for Boehringer Ingelheim; advisory board for Ikaria

LF: None

RJA: None

LRB: Involved in HIV vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Military HIV Research Program (MHRP), Gates Foundation, and the Ragon Institute. Research grants from the NIH, Gates Foundation and Wellcome Trust. Deputy Editor N Eng J Med.

BB: None

WC: Research support from Bristol Myers Squibb, Janssen, and Glaxo Smith Kline

SC: Research support and/or consultant for Amgen, Abbvie, Bristol Myers Squibb, Lilly, Gilead, Genentech, Pfizer, and Roche

KC: Astra Zeneca, Glaxo Smith Kline, Janssen, Lilly, Merck (research support/collaborations)

EMG: Associate Editor, N Eng J Med; Editor of textbook *Rheumatology*

AK: None

MEW: Research grants from Amgen, Bristol Myers Squibb, Crescendo Bioscience, Lilly, and Sanofi; Consultant for Abbvie, Amgen, Bristol Myers Squibb, Canfite, Corrona, Crescendo Bioscience, Glaxo Smith Kline, Gilead, Horizon Therapeutics, Johnson & Johnson, Lilly, Pfizer, Roche/Genentech, Samsung, Scipher, and Set Point; Stock options including Canfite, Inmedix, Lycera, Vorso, Scipher; Royalties: Co-editor of textbook *Rheumatology*

KW: Research grants from Pfizer, Bristol Myers Squibb; Consultant for Bristol Myers Squibb, Abbvie, Lilly, Roche, UCB, Gilead, Pfizer, and Glaxo Smtih Kline

AM: None

AT: Employee, American College of Rheumatology

KGS: Consulting fees from Abbvie, Amgen, Bayer, GSK Behring, Daiichi Sankyo, Gilead, Radius, Roche/Genentech; research support from Amgen and Radius.

Funding: This effort was supported by the American College of Rheumatology

Abstract Word Count: 216

Tables: 5

Text Word Count: 4,140

Innovation and Significance

- Using a well-established method of consensus building, an ACR task force developed guidance for the management of rheumatic disease patients during the COVID-19 pandemic.
- The task force generated 25 final guidance statements, covering areas of risk assessment, general prevention, and medication use.
- ACR guidance is provided as part of a living document, recognizing rapidly evolving literature in this area.

Objective: To provide guidance to rheumatology providers on the management of adult rheumatic disease patients in the context of the COVID-19 pandemic.

Methods: A task force, including 10 rheumatologists and 4 infectious diseases 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 two rounds of asynchronous anonymous voting by email and three webinars with the entire panel. Task force members voted on agreement with draft statements using a 9-point numeric scoring system (1 to 9), and consensus was determined to be "low", "moderate", or "high", based on the dispersion of votes. For approval, median votes were required to meet pre-defined 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: The task force approved 77 initial guidance statements, 36 with moderate and 41 with high consensus. These were combined, resulting in 25 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.

Since its initial outbreak from 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 adult rheumatic disease patients during the pandemic. Clinical guidance generated from this effort is intended to aid in the management of individual patients, but it is not meant to supplant clinical decision-making. Modifications to treatment plans, particularly in complex patients, 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, chloroquine, interleukin [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 (TM, KS, LF, SJ) 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 websites hosted by the national Arthritis Foundation[2], CreakyJoints[3] and the Global Healthy Living Foundation[4]. Questions were categorized into four overlapping domains: 1) risk assessment and prevention; 2) the 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 defined per the Centers for Disease Control [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 the managing clinician and their individual patients but that some attention should be directed to a societal perspective, when relevant around potential issues of availability of specific anti-rheumatic therapies being considered for treatment of COVID-19. Following an initial task force webinar on March 26, 2020, four separate sub-groups were formed to address and refine questions in each domain. The task force included 14 members from North America, comprised of 10 rheumatologists and 4 infectious diseases 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 sub-group was tasked with gathering evidence that addressed questions within the assigned domains. This non-systematic evidence review included PubMed searches supplemented by postings from the CDC, Food and Drug Administration and other electronic media sources. Questions and relevant evidence were collated into a single document, which was disseminated by email to the entire task force for their review two days prior to initial voting.

Initial voting. Following the evidence review, an initial round of voting was conducted anonymously by email 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 provide their level of agreement with three general statements in addition to providing graded yes/no responses to 90 clinical questions. Voting was completed using a 9-point numeric rating scale (1 to 9) for all items. For the three general statements, ratings of 9 corresponded to “complete agreement”, 5 corresponded to “uncertain”, and 1 corresponded to “complete disagreement”. Median votes of 1 to 3, 4 to 6, and 7 to 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 1 strongly favored a negative response and a vote of 5 corresponded to uncertainty. For questions, median votes of 1 to 3, 4 to 6, and 7 to 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 to 3 range with ≥4 votes simultaneously falling into the 7 to 9 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 (See Timeline, **Table 1**). Discussion was focused on questions and/or statements with median votes reflecting uncertainty and where there was a 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 email, again using an anonymous voting process as detailed above. Guidance statements receiving a median vote of 7 to 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 email. The ACR Board of Directors approved these recommendations on April 11, 2020.

Results

Of the 81 guidance statements considered in round two voting, 77 received median votes of 7, 8 or 9 and were also associated with moderate (n = 36) or high (n = 41) consensus, the pre-defined threshold for approval (**Supplemental Tables 1 to 6**). There were two draft statements receiving a median vote <7 (**Supplemental Tables 5 and 6**) and two additional statements with a median vote ≥7 that were accompanied by low consensus (**Supplemental 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 stable patients 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**).

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 without knowledge of 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 of poor outcome with COVID-19 that are specific to rheumatic disease. Based on preliminary retrospective cohort studies[11-14], risk factors of poor outcome with COVID-19 include older age (e.g., >65) and select comorbidity such as chronic lung disease, hypertension, cardiovascular disease (CVD), chronic kidney disease (CKD), obesity and diabetes mellitus, conditions frequently overrepresented in 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 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 cells) and elevations in circulating lactate dehydrogenase (LDH), C-reactive protein (CRP), interleukin (IL)-6, and D-dimer, among others.[19-22] Whether lymphopenia portends 'pre-existing' risk or is a consequence of more severe infection in hospitalized patients is unclear. Defining the precise role that 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 guidance be given to rheumatic disease patients 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 healthcare encounters as a means of preventing

virus spread and preserving the healthcare 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 off-site from larger healthcare facilities; or delaying the initiation or re-dosing of infusion-based treatments when the risk of disease flare is low. The task force endorsed potential temporary delays in the administration of intravenously administered zoledronic acid or subcutaneously administered denosumab (generally given at a health care setting) as two examples (**Supplemental Table 4**), recommending that dosing intervals with denosumab not exceed 8 months due to concerns of 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 an increased risk for 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 for therapies known to increase ACE2 expression (a recognized effect of ACE inhibitors and ARBs).[28] Following acute lung injury, ACE2 levels are downregulated in local tissues, which may lead to excessive activation of the renin-angiotensin-aldosterone system (RAS) 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 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 these agents for all patients who have been prescribed ACE inhibitors or ARBs 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 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]

Non-steroidal Anti-inflammatory Drugs (NSAIDs). Although speculation was raised early in the pandemic with regards to NSAID use and possible associations with worse COVID-19 outcomes, these concerns have yet to be substantiated.[34,35] 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, and gastrointestinal injury, which portend a poor prognosis[36-38]. The task force demonstrated low consensus specific to whether NSAIDs should be stopped with less severe COVID-19, where the use of such agents might provide therapeutic antipyretic and/or anti-inflammatory benefit. Others have proposed acetaminophen (or paracetamol) as an alternative to NSAIDs in this situation[39], although appropriate caution is needed as COVID-19 is accompanied by evidence of liver injury in a proportion of cases.[40]

Glucocorticoids. The data related to the impact of glucocorticoids on patients infected with SARS-CoV-2 are mixed**.** Recognizing potential risks associated with the immunosuppressive effects of glucocorticoids, emerging data suggests that their anti-inflammatory properties could theoretically mitigate the impact of COVID-19, particularly during the late phases of infection characterized by hyperinflammation and cytokine storm.[41,42] Case series suggest that younger patients with a history of solid organ transplant and those undergoing cancer chemotherapy living in epidemic areas of Italy, many of whom were on glucocorticoids, have not developed severe COVID-19 complications.[43] In small hospital-based cohorts, treatment of COVID-19 related acute respiratory distress syndrome (ARDS) with methylprednisolone was associated with improved survival[41] and shorter intensive care unit (ICU) stays.[42]

These very limited data suggesting a glucocorticoid benefit in COVID-19 are balanced by indirect data from other viral infections suggesting no meaningful benefit or even harm. There are no clinical data, for instance, suggesting benefit from glucocorticoids in the treatment of airway infections related to respiratory syncytial virus (RSV), influenza, SARS-CoV-1, or Middle East Respiratory Syndrome (MERS; caused by a separate coronavirus).[44] Furthermore, in one report of patients with SARS-CoV-1 pneumonia, the use of glucocorticoids was associated with worse outcomes.[45] 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.[46] In addition to being associated with reactivation of herpes zoster [47,48], glucocorticoids are associated with a dose-dependent risk of serious bacterial and opportunistic infections.[49] This latter concern may be particularly salient, as at least one Chinese case series has demonstrated that up to one-half of all COVID-19 related deaths were attributable to secondary bacterial infection.[50]

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 [HPA] axis suppression[51]) and the 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 Anti-Rheumatic Drugs (csDMARDs). Serious infection risks with hydroxychloroquine (HCQ), chloroquine (CQ), sulfasalazine (SSZ), leflunomide (LEF), and methotrexate (MTX), are relatively small, particularly when given as monotherapies.[52,53] 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 holding SSZ, LEF and MTX with 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 holding this treatment would be unlikely to result in significant rheumatic disease flares.

Despite lack of support from rigorously conducted clinical trials, HCQ and CQ have been widely used in the treatment of COVID-19.[54-58] As a result, supply chain issues for both agents have been reported.[59] Recognizing the possibility that anti-malarial 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 absence of robust efficacy data[60] and in the setting of concerns regarding drug availability, prescribing HCQ/CQ to patients with newly diagnosed Sjögren's should be avoided. The task force made no

recommendations specific to patients with established Sjögren's taking HCQ/CQ. In contrast, the task force achieved strong levels of agreement and high consensus in 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.[61,62] In addition to being associated with improved pregnancy outcomes in women with SLE,[63] continued use of HCQ in SLE decreases the risk of flare and reduces the risk of longer-term morbidity and mortality.[64,65] Noting this relatively favorable risk-benefit profile, the task force endorsed the continued use of HCQ/CQ, if available, including in the context 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[66]) and/or co-administration of other drugs such as azithromycin that are known to prolong the QT interval.[67,68]

Biologics, Immunosuppressants and Janus Kinase (JAK) inhibitors. Biologics and JAK inhibitors have been associated with an increased risk of serious infection compared to conventional DMARDs.[69-75] 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.[76-78] Although mechanisms linking these agents to the reactivation of herpes zoster are unclear, dampening of innate anti-viral effects of type I and type II interferons has been suggested to play a role.[79]

Examined primarily in the context of rheumatoid arthritis (RA), studies examining tapering or discontinuation of biologics or JAK inhibitors suggest that a large proportion of patients experience rheumatic disease flare.[80-83] This is relevant because underlying inflammation or disease activity has been implicated as a risk factor for infection[84,85], a risk that may be heightened further in the context of "rescue" glucocorticoids. Although biologic therapies are associated with a higher risk of hospitalization due to serious infection, at least one report in RA has suggested that they are associated with a reduced risk of sepsis or fatal outcome as compared to non-biologic DMARDs among patients developing serious infection on these therapies.[86] These data provide support for the task force's recommendation to continue all immunosuppressants (e.g., tacrolimus, cyclosporine, mycophenolate mofetil, 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 failing optimal csDMARD therapy, 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 uncertainly centered on data reporting a dampening of innate anti-viral pathways with JAK inhibition.[78]

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.[87] Mycophenolate mofetil (MMF), for instance, has been associated with improved survival following MERS-CoV infection[88] while cyclosporine inhibits coronavirus replication *in vitro*.[89,90] Baracitinib, a JAK inhibitor, interferes with cellular endocytosis and could theoretically impair cellular entry of SARS-CoV-2.[44,91] Whether this property impacts infection risk is unknown. Indeed, NIH guidelines have recommended against the use of JAK inhibitors in the treatment of COVID-19 given their "broad immunosuppressive effect".[92] 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.[93] Recognizing that hyperinflammation and cytokine storm appear to play a central role in severe manifestations of COVID-19[94], 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).[95-99]

In the absence of robust RCT data to support their continued use, the task force recommended temporarily holding or stopping all non-IL-6 biologics, immunosuppressants (e.g., tacrolimus, cyclosporine, mycophenolate mofetil, and azathioprine), and JAK inhibitors in the context of documented or presumptive COVID-19 as well as following known SARS-CoV-2 exposure. The panel did not, however, define the precise duration for which these treatments would need to be held given current uncertainties about the parameters that might be used to define such a window. The task force also endorsed that, in select circumstances, IL-6 receptor inhibition could be continued in the context of SARS-CoV-2 infection or following exposure, although corresponding votes achieved only the minimal threshold for approval (both with median votes 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.

Discussion

This ACR guidance document serves as a tool for rheumatology providers to promote optimal care for complex rheumatic disease patients in the context of the ongoing COVID-19 pandemic. The recommendations provided are not intended to be proscriptive nor should they be used to limit treatment options available for patients suffering from rheumatic disease in our current healthcare 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".[100,101] However, the literature in this area is rapidly evolving. A PubMed search limited to the timeframe from January 1 through March 31 of 2020 resulted in more than 2,500 citations using the search term "COVID-19". The same search covering the first half of April resulted in over 2,100 citations. As available literature focused on COVID-19 in rheumatic disease populations expands in coming weeks to months, we anticipate that current knowledge gaps will be addressed. Answers to many prevailing questions are likely to come not only from ongoing clinical trials, but also from analyses of large claims databases, the collection of both provider- and patient-level data, efforts currently being supported by the COVID-19 Global Rheumatology Alliance[102] and other groups and, ultimately, well-orchestrated systemic literature reviews and meta-analyses.

There are several strengths to this effort that are noteworthy. Responding to the urgency of 'need', the task force generated guidance over a compressed timeframe, 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 diseases 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. For example, the guidance recommendations herein focus on adult rheumatology patients and do not address the management of pediatric patients (recognizing that younger patient populations appear

to be at a substantially lower risk for poor outcomes related to COVID-19[103]). 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 can medicines that have been held be restarted in patients recovering from COVID-19? When choosing a new therapy, how should currently available biologics or targeted small molecules be prioritized? What is the impact of COVID-19 on disease activity or function, both in the short- and long-term? Are rheumatology treatments safe with the co-administration 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.

Table 1: Timeline in American College of Rheumatology (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 U.S. (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 by 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 by 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 website

*COVID-19 = coronavirus disease 2019

Table 2: General recommendations for patients with rheumatic disease.

Recommendation 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 healthcare encounters and potential exposure to SARS-CoV-2 (beyond general preventive measures) may be reasonable, e.g., reduced frequency of lab 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

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

Recommendation Statement	**Level of Task Force Consensus**
Ongoing Treatment in Stable Patients	
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	
In newly diagnosed disease, HCQ/CQ should be started at full dose, when available.	High
In 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 = cyclosporine; MMF = mycophenolate mofetil; AZA = azathioprine; JAK = Janus kinase; NSAID = non-steroidal anti-inflammatory drug; GCA = giant cell arteritis

Table 4: Recommendations for the treatment of newly diagnosed or active rheumatic disease in the absence of infection or known SARS-CoV-2 exposure

Recommendation Statement	**Level of Task Force Consensus**
Inflammatory Arthritis	
For patients well-controlled on 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 well-controlled on 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 active or newly diagnosed inflammatory arthritis, conventional synthetic DMARDs may be started or switched.	Moderate
If indicated, low-dose glucocorticoids (≤10 mg prednisone equivalent) or NSAIDs may be started.	Moderate to High

Other Rheumatic Diseases	
In 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 patients with newly diagnosed Sjögren's, given the paucity of data proving efficacy, HCQ/CQ should not be started.	Moderate

*SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; HCQ = hydroxychloroquine; CQ = chloroquine; DMARD = disease-modifying anti-rheumatic drug; CSA = cyclosporine; MMF = mycophenolate mofetil; AZA = azathioprine; JAK = Janus kinase

¶The panel noted uncertainty with JAK inhibition in this situation

Table 5: Recommendations for the treatment of rheumatic disease following known SARS-CoV-2 exposure and in the context of active or presumptive COVID-19

Recommendation 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 held.	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

*SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; HCQ = hydroxychloroquine; CQ = chloroquine; SSZ = sulfasalazine; NSAID = non-steroidal anti-inflammatory drug; CSA = cyclosporine; MMF = mycophenolate mofetil; AZA = azathioprine; MTX = methotrexate; LEF = leflunomide;; JAK = Janus kinase

¶The panel noted uncertainty with temporarily stopping MTX or LEF in this situation

§The panel demonstrated low consensus with regards to stopping NSAIDs in the absence of severe symptoms

References:

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Arthritis foundation.https://www.arthritis.org/.
3. GHLF creakyjoints.https://creakyjoints.org/.
4. Global Healthy Living Foundation(GHLF).https://www.ghlf.org/.
5. Brook R. US Agency for Health Care Policy and Research Office of the Forum for Quality and Effectiveness in Health Care clinical practice guideline development: methodology perspectives. In: McCormick K MS, Siegel R, ed. The RAND/UCLA appropriateness method. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1994:p. 59–70.
6. Shekelle PG, Kahan JP, Bernstein SJ, Leape LL, Kamberg CJ, Park RE. The reproducibility of a method to identify the overuse and underuse of medical procedures. The New England journal of medicine 1998;338:1888-95.
7. Shekelle PG, Chassin MR, Park RE. Assessing the predictive validity of the RAND/UCLA appropriateness method criteria for performing carotid endarterectomy. International journal of technology assessment in health care 1998;14:707-27.
8. Hemingway H, Chen R, Junghans C, et al. Appropriateness criteria for coronary angiography in angina: reliability and validity. Annals of internal medicine 2008;149:221-31.
9. Kravitz RL, Laouri M, Kahan JP, et al. Validity of criteria used for detecting underuse of coronary revascularization. JAMA 1995;274:632-8.
10. Shekelle PG, MacLean CH, Morton SC, Wenger NS. Assessing care of vulnerable elders: methods for developing quality indicators. Ann Intern Med 2001;135:647-52.
11. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine 2020.
12. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-62.
13. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020.

14. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama 2020.
15. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheumatol 2015;11:693-704.
16. Bichile T, Petri M. Prevention and management of co-morbidities in SLE. Presse Med 2014;43:e187-95.
17. Mikuls TR. Co-morbidity in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:729-52.
18. Burner TW, Rosenthal AK. Diabetes and rheumatic diseases. Curr Opin Rheumatol 2009;21:50-4.
19. Sarzi-Puttini P, Giorgi V, Sirotti S, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 2020;38:337-42.
20. Liu Z, Long W, Tu M, et al. Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. J Infect 2020.
21. Giwa AL, Desai A, Duca A. Novel 2019 coronavirus SARS-CoV-2 (COVID-19): an overview for emergency clinicians. Pediatr Emerg Med Pract 2020;17:1-24.
22. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020.
23. Centers for Disease Control and Prevention (CDC).How to Protect Yourself & Others. 2020. (Accessed April 8th,2020, at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html.)
24. Centers for Disease Control and Prevention (CDC). What to Do if You Are Sick. 2020. (Accessed April 8th,2020, at https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html.)
25. American College of Rheumatology (ACR).COVID-19 Practice and Advocacy Resources. 2020. (Accessed April 15th ,2020, at https://www.rheumatology.org/Announcements/COVID-19-Practice-and-Advocacy#Telehealth.)
26. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone 2017;105:11-7.
27. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? The Lancet Respiratory Medicine 2020;8:e21.

28. Danser AHJ, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic. Hypertension;0:HYPERTENSIONAHA.120.15082.
29. Younes A, Samad N. Utility of mTOR inhibition in hematologic malignancies. The oncologist 2011;16:730-41.
30. American Heart Association(AHA).Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. 2020. (Accessed April 8th,2020, at https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician.)
31. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020.
32. Tselios K, Koumaras C, Urowitz MB, Gladman DD. Do current arterial hypertension treatment guidelines apply to systemic lupus erythematosus patients? a critical appraisal. Semin Arthritis Rheum 2014;43:521-5.
33. de Vries-Bouwstra JK, Allanore Y, Matucci-Cerinic M, Balbir-Gurman A. Worldwide Expert Agreement on Updated Recommendations for the Treatment of Systemic Sclerosis. J Rheumatol 2020;47:249-54.
34. FitzGerald GA. Misguided drug advice for COVID-19. Science 2020;367:1434.
35. U.S. Food and Drug Administration.FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. (Accessed April 9th,2020, at https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.)
36. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020.
37. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020.
38. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020.
39. National Institute for Health and Care Excellence (NICE).COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community. 2020. (Accessed April 15th,2020, at https://www.nice.org.uk/guidance/ng163.)

40. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428-30.
41. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.
42. Qin X,Qiu S, Yuan Y et al.Clinical Characteristics and Treatment of Patients Infected with COVID-19 in Shishou, China. 2020. (Accessed April 9th,2020, at https://ssrn.com/abstract=3541147.)
43. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transplantation;n/a.
44. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020;395:e30-e1.
45. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol 2004;31:304-9.
46. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 2019;23:99.
47. Pappas DA, Hooper MM, Kremer JM, et al. Herpes Zoster Reactivation in Patients With Rheumatoid Arthritis: Analysis of Disease Characteristics and Disease-Modifying Antirheumatic Drugs. Arthritis Care Res (Hoboken) 2015;67:1671-8.
48. Chen D, Li H, Xie J, Zhan Z, Liang L, Yang X. Herpes zoster in patients with systemic lupus erythematosus: Clinical features, complications and risk factors. Exp Ther Med 2017;14:6222-8.
49. Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am 2016;42:157-76, ix-x.
50. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
51. LaRochelle GE, Jr., LaRochelle AG, Ratner RE, Borenstein DG. Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisone. Am J Med 1993;95:258-64.
52. Ibrahim A, Ahmed M, Conway R, Carey JJ. Risk of Infection with Methotrexate Therapy in Inflammatory Diseases: A Systematic Review and Meta-Analysis. J Clin Med 2018;8.
53. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46:1157-60.

54. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020.
55. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.
56. U.S. Food and Drug Administration (FDA).Coronavirus (COVID-19) Update: Daily Roundup March 30, 2020. 2020. (Accessed April 9th,2020, at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020.)
57. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 2020;30:269-71.
58. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72-3.
59. U.S. Food and Drug Administration (FDA).FDA Drug Shortages. 2020. (Accessed April 15th,2020, at https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Hydroxychloroquine+Sulfate+Tablets&st=c&tab=tabs-4&panels=0.)
60. Gottenberg JE, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. Jama 2014;312:249-58.
61. Mok CC, Penn HJ, Chan KL, Tse SM, Langman LJ, Jannetto PJ. Hydroxychloroquine Serum Concentrations and Flares of Systemic Lupus Erythematosus: A Longitudinal Cohort Analysis. Arthritis Care Res (Hoboken) 2016;68:1295-302.
62. Geraldino-Pardilla L, Perel-Winkler A, Miceli J, et al. Association between hydroxychloroquine levels and disease activity in a predominantly Hispanic systemic lupus erythematosus cohort. Lupus 2019;28:862-7.
63. Peart E, Clowse ME. Systemic lupus erythematosus and pregnancy outcomes: an update and review of the literature. Curr Opin Rheumatol 2014;26:118-23.
64. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 1991;324:150-4.

65. Tsakonas E, Joseph L, Esdaile JM, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus 1998;7:80-5.
66. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. JAMA Cardiol 2020.
67. Sears SP, Getz TW, Austin CO, Palmer WC, Boyd EA, Stancampiano FF. Incidence of Sustained Ventricular Tachycardia in Patients with Prolonged QTc After the Administration of Azithromycin: A Retrospective Study. Drugs - real world outcomes 2016;3:99-105.
68. Choi Y, Lim HS, Chung D, Choi JG, Yoon D. Risk Evaluation of Azithromycin-Induced QT Prolongation in Real-World Practice. Biomed Res Int 2018;2018:1574806.
69. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford) 2013;52:53-61.
70. Tudesq JJ, Cartron G, Riviere S, et al. Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders. Autoimmun Rev 2018;17:115-24.
71. Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015;386:258-65.
72. Singh JA. Infections With Biologics in Rheumatoid Arthritis and Related Conditions: a Scoping Review of Serious or Hospitalized Infections in Observational Studies. Curr Rheumatol Rep 2016;18:61.
73. Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70:1914-20.
74. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. Jama 2011;306:2331-9.
75. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford) 2011;50:124-31.

76. Zhang N, Wilkinson S, Riaz M, Östör AJ, Nisar MK. Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review. Clin Exp Rheumatol 2012;30:962-71.
77. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. Jama 2009;301:737-44.
78. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy. Arthritis Rheumatol 2017;69:1960-8.
79. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13:320.
80. Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013;381:918-29.
81. van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis 2016;75:52-8.
82. Smolen JS, Emery P, Fleischmann R, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet 2014;383:321-32.
83. Takeuchi T, Genovese MC, Haraoui B, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. Ann Rheum Dis 2019;78:171-8.
84. Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:785-91.
85. Pimentel-Quiroz VR, Ugarte-Gil MF, Harvey GB, et al. Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multi-national, Latin American lupus cohort. Lupus 2019;28:1101-10.
86. Richter A, Listing J, Schneider M, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1667-73.
87. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmun Rev 2020:102523.

88. Al Ghamdi M, Alghamdi KM, Ghandoora Y, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC Infect Dis 2016;16:174.
89. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. Viruses 2013;5:1250-60.
90. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol 2011;92:2542-8.
91. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020;20:400-2.
92. National Institutes of Health(NIH).Therapeutic Options for COVID-19 Currently Under Investigation. 2020. (Accessed April 24th,2020, at https://covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/.)
93. Xu X., Han M. ,Li T. et al.Effective treatment of severe COVID-19 patients with Tocilizumab. 2020. (Accessed April 9th,2020, at https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf.)
94. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev 2020:102537.
95. ClinicalTrials.gov.National Library of Medicine(U.S.).Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection.Identifier: NCT04324021. 2020. (Accessed April 15th,2020, at https://clinicaltrials.gov/ct2/show/NCT04324021.)
96. ClinicalTrials.gov.National Library of Medicine(U.S.).Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure (TOCIVID).Identifier: NCT04322773. 2020. (Accessed April 15th,2020, at https://www.clinicaltrials.gov/ct2/show/NCT04322773.)
97. ClinicalTrials.gov.National Library of Medicine(U.S.).Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS).Identifier: NCT04306705. 2020. (Accessed April 15th,2020, at https://clinicaltrials.gov/ct2/show/NCT04306705.)
98. ClinicalTrials.gov.National Library of Medicine(U.S.).Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19.Identifier: NCT04315298. 2020. (Accessed April 15th,2020, at https://clinicaltrials.gov/ct2/show/NCT04315298.)

99. ClinicalTrials.gov.National Library of Medicine(U.S.).Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients.Identifier: NCT04321993. 2020. (Accessed April 15th,2020, at https://clinicaltrials.gov/ct2/show/NCT04321993.)
100. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
101. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
102. Robinson PC, Yazdany J. The COVID-19 Global Rheumatology Alliance: collecting data in a pandemic. Nat Rev Rheumatol 2020.
103. Hasan A, Mehmood N, Fergie J. Coronavirus Disease (COVID-19) and Pediatric Patients: A Review of Epidemiology, Symptomatology, Laboratory and Imaging Results to Guide the Development of a Management Algorithm. Cureus 2020;12:e7485.