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COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases

Developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force

This summary was initially approved by the ACR Board of Directors on February 8, 2021 and updated on March 4, 2021. A full paper (Version 1) is pending publication in Arthritis & Rheumatology.

New recommendations regarding mycophenolate, methotrexate, acetaminophen, and NSAID timing considerations+ were added to this summary on April 28, 2021 and are being added to the full paper (Version 2), which will be submitted to Arthritis & Rheumatology for publication.

Purpose

The purpose of this document is to provide guidance to rheumatology providers on the use of the COVID-19 vaccine and the associated management of rheumatic and musculoskeletal disease patients around the time of vaccination against SARS-CoV-2. These statements were based upon a dearth of high-quality data and are not intended to replace clinical judgment. Modifications made to treatment plans, particularly in complex rheumatic disease patients, are highly disease-, patient-, geography-, and time-specific and, therefore, must be individualized as part of a shared decision-making process. This guidance is provided as part of a 'living document,' recognizing rapidly evolving evidence and the anticipated need for frequent updates as such evidence becomes available.

Methods

The North American Task Force panel, consisting of 9 rheumatologists, 2 infectious disease specialists, and 2 public health experts with current or past employment at the Centers for Disease Control (CDC), convened multiple times in December 2020 and January 2021. The Task Force proposed a variety of clinical questions related to COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases (RMD), divided itself into subgroups (i.e., teams), and assigned the clinical questions to the various teams by topic (e.g., vaccine effectiveness, safety). Each team was charged to generate an evidence review covering that topic; the evidence reviews were combined into an evidence summary document that was collated and disseminated to the entire Task Force. The Task Force reviewed the clinical questions and associated proposed vaccine guidance statements that were evaluated using a well-established method of consensus building (modified Delphi process). This process included two rounds of asynchronous anonymous rating by email and two live webinars including the entire Task Force. Panel members rated their agreement with draft statements using a numeric scoring system, and consensus was determined to be either "moderate" (M) or "high" (H), based on the dispersion in the rating results. To be approved as guidance, median ratings were required to correlate to pre-defined levels of agreement (with median values interpreted as "agreement," "uncertainty" or "disagreement") with either moderate or high levels of consensus. For this summary document, several rating statements that were initially separate were combined to facilitate clarity and conciseness.

Results and Conclusion

General considerations related to COVID-19 vaccination in rheumatic and musculoskeletal disease patients are shown in Table 1. Statements more specific to patient groups, as well as general disease- and timing-related considerations, are presented in Table 2. No evidence was found to support a concern regarding the use or timing of immunomodulatory therapies in relation to vaccine safety. Therefore, guidance regarding immunomodulatory medication and vaccination timing (Table 3) was given considering the intent to optimize vaccine response. An important set of guiding principles, foundational assumptions and limitations are mentioned in the Supplemental Table. The ACR is committed to updating this guidance as a 'living document' as new evidence emerges.

Recommendations

Table 1: General Considerations Related to COVID-19 Vaccination in Rheumatic and Musculoskeletal Disease Patients

	Guidance Statement	Level of Task Force consensus
	The rheumatology healthcare provider is responsible for engaging the RMD patient in a discussion to assess COVID-19 vaccination status and engage in a shared decision-making process to discuss receiving the COVID-19 vaccine.	Strong-Moderate
	Acknowledging heterogeneity due to disease- and treatment-related factors, and after considering the influence of age and sex, AIIRD patients are at higher risk for hospitalized COVID-19 and worse outcomes compared to the general population.	Moderate
	Based on their risk for COVID-19, AIIRD patients should be prioritized for vaccination before the non-prioritized general population of similar age and sex.	Moderate
	Beyond known allergies to vaccine components, there are no known additional contraindications to COVID-19 vaccination for AIIRD patients.	Moderate
	The expected response to COVID-19 vaccination for many AIIRD patients on systemic immunomodulatory therapies is likely to be blunted in its magnitude and duration compared to the general population.	Moderate
	A theoretical risk exists for AIIRD flare or disease worsening following COVID-19 vaccination. However, the benefit of COVID-19 vaccination for RMD patients outweighs the potential risk for new onset autoimmunity.	Moderate

RMD = rheumatic and musculoskeletal disease; AIIRD=autoimmune and inflammatory rheumatic disease

Table 2: Recommendations for Use of the COVID-19 Vaccine in RMD Patients

Guidance Statement	Level of Task Force consensus
RMD and AIIRD patients should receive COVID-19 vaccination, consistent with the age restriction of the EUA and/or FDA approval.*	Moderate
RMD patients without an AIIRD who are on immunomodulatory therapy should be vaccinated in a similar fashion as described in this guidance for AIIRD patients receiving those same treatments.	Moderate
Based on the data for the mRNA COVID-19 vaccines available in the U.S., there is no preference for one COVID-19 vaccine over another. Therefore, AIIRD patients should receive either vaccine available to them.**	Moderate
For a multi-dose vaccine, AIIRD patients should receive the second dose of the same vaccine, even if there are non-serious adverse events associated with receipt of the first dose, consistent with timing described in CDC guidelines.	Strong
Healthcare providers should not routinely order any lab testing (e.g., antibody tests for IgM and/or IgG to spike or nucleocapsid proteins) to assess immunity to COVID-19 post-vaccination, nor to assess the need for vaccination in a yet-unvaccinated person.	Strong
Following COVID-19 vaccination, RMD patients should continue to follow all public health guidelines regarding physical distancing and other preventive measures.	Strong
Household members and other frequent, close contacts of AIIRD patients should undergo COVID-19 vaccination when available to them to facilitate a 'cocooning effect' that may help protect the AIIRD patient. No priority for early vaccination is recommended for household members.	Moderate
While vaccination would ideally occur in the setting of well-controlled AIIRD, except for those patients with life-threatening illness (e.g., in the ICU for any reason), COVID vaccination should occur as soon as possible for those for whom it is being recommended, irrespective of disease activity and severity.	Strong-Moderate
RMD = rheumatic and musculoskeletal disease; AIIRD=autoimmune and inflammatory rheumatic disease; EUA = emergency use authorization; FDA = Food and Drug Administration; mRNA = messenger RNA; CDC = Centers for Disease Control; ICU = Intensive Care Unit	

*age ≥16 as of January 2021

** Given the safety concerns raised by the FDA and CDC in the early weeks of April 2021, the decision to rate the preference for mRNA vs. adenoviral vector vaccines was held in abeyance by the task force. Further deliberations will occur as new information becomes available.

Table 3: Guidance Related to the Use and Timing of Vaccination and Immunomodulatory Therapies in Relation to COVID-19 Vaccination Administration in RMD Patients*

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination*	Level of Task Force Consensus
Hydroxychloroquine; apremilast; IVIG; glucocorticoids, prednisone-equivalent dose <20mg/day	No modifications to either immunomodulatory therapy or vaccination timing	Strong-Moderate
Sulfasalazine; Leflunomide;; Azathioprine; Cyclophosphamide (oral); TNFi; IL-6R; IL-1; IL-17; IL-12/23; IL-23; Belimumab; oral calcineurin inhibitors; Glucocorticoids, prednisone-equivalent dose ≥ 20mg/day**	No modifications to either immunomodulatory therapy or vaccination timing	Moderate
Mycophenolate	Assuming that disease is stable, hold for 1 week following each vaccination	Moderate
Methotrexate	Hold MTX for 1 week after each of the 2mRNA vaccine doses, for those with well-controlled disease; no modifications to vaccination timing	Moderate
Methotrexate	Hold MTX for 2 weeks after single-dose COVID vaccination, for those with well-controlled disease	Moderate
JAKi	Hold JAKi for 1 week after each vaccine dose; no modification to vaccination timing	Moderate
Abatacept SQ	Hold SQ abatacept both one week prior to and one week after the first COVID-19 vaccine dose (only); no interruption around the second vaccine dose	Moderate
Abatacept IV	Time vaccine administration so that the first vaccination will occur four weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by one week (i.e., a 5-week gap in total); no medication adjustment for the second vaccine dose	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Rituximab	Assuming that patient's COVID-19 risk is low or is able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated approximately 4 weeks prior to next scheduled rituximab cycle; after vaccination, delay RTX 2-4 weeks after final vaccine dose, if disease activity allows	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, hold for 24 hours prior to vaccination (no restrictions on use post vaccination to treat symptoms)	Moderate

RMD = rheumatic and musculoskeletal disease; IVIG = intravenous immunoglobulin; TNFi = tumor necrosis factor inhibitor; IL = interleukin; JAKi = janus kinase inhibitor; CYC = cyclophosphamide; RTX = rituximab; IV = intravenous; SQ = subcutaneous; NSAID = non-steroidal anti-inflammatory drugs

**guidance to 'hold' a therapy was made based on the assumption that the patient had well-enough controlled disease to allow for a temporary interruption; if not, decision-making should be determined on a case-by-case basis, considering the circumstances involved*

***consensus was not reached for vaccination timing in patients receiving prednisone-equivalent doses ≥ 20mg/day; see full guidance document, when published, for additional details*

IL-6R = sarilumab; tocilizumab; IL-1R = anakinra, canakinumab; IL-17 = ixekizumab, secukinumab; IL-12/23 = ustekinumab; IL-23 = guselkumab, rizankizumab; JAKi = baricitinib, tofacitinib, upadacitinib

Supplemental Table: Foundational Principles, Assumptions, and Considerations for the Guidance Statements

ACR guidance statements are not intended to supersede the judgement of rheumatology care providers nor override the values and perspectives of their patients. Guidance was based on weak and/or indirect evidence and required substantial extrapolation by an expert task force. All statements, therefore, should be considered conditional or provisional. The ACR is committed to updating this guidance document as new evidence emerges.
The rheumatology community lacks important knowledge on how to best maximize vaccine-related benefits. RMD patients exhibit high variability with respect to their underlying health condition, disease severity, treatments, degree of multimorbidity, and relationship with their specialist provider. These considerations must be considered when individualizing care.
There is no direct evidence about mRNA COVID-19 vaccine safety and efficacy in RMD patients. Regardless, there is no reason to expect vaccine harms will trump expected COVID-19 vaccine benefits in RMD patients.
The future COVID landscape is uncertain with respect to vaccine effectiveness and safety, uptake, durability, mitigating societal behavior, and emerging viral strain variants. Clinicians nevertheless must act with their best judgement despite this highly uncertain and rapidly changing landscape.
The risk of deferring vaccination and thus failing to mitigate COVID-19 risk should be weighed against a possible blunted response to the vaccine if given under suboptimal circumstances. As a practical matter, this tension must be resolved in the context of imperfect prediction as to whether those circumstances may be transient, and a paucity of scientific evidence.
Both individual and societal considerations related to a limited vaccine supply should be considered in issuing vaccine guidance and making policy decisions. Given that context, simplicity should be the touchstone: to avoid confusion, improve implementation, and maintain scientific credibility.
In the future, the ability to give an additional vaccine booster (if proven necessary or beneficial) will no longer be constrained by limited supplies. Any vaccination strategy is a reasonable starting point, and decisions about implementation details reduce to allocation of scarce vaccine resources.
RMD = rheumatic and musculoskeletal disease; mRNA = messenger RNA

[+] **Appendix Table 1: History of Updates to ACR COVID Vaccine Guidance Statements, and Locations in Manuscript Tables and Prose Where Guidance Was Amended**	
Provided guidance to hold acetaminophen and NSAIDs for 24 hours prior to vaccination, assuming disease is stable	Table 5
Modified guidance for mycophenolate to hold for 1 week after each vaccine dose	Table 5
Modified guidance for methotrexate to hold for 1 week after each of the 2 mRNA vaccine doses, and for 2 weeks after single-dose COVID vaccine	Table 5
Citations added describing the attenuation of SARS-CoV-2 vaccine response observed in patients receiving mycophenolate, methotrexate, janus kinase inhibitors, and other immunomodulatory therapies	Prose accompanying Table 5

Updated April 28, 2021