

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

Version 4

Revised October 27, 2021

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](#)), was published in *Arthritis & Rheumatology* on May 24, 2021.**

*New recommendations regarding mycophenolate, methotrexate, acetaminophen, and NSAID timing considerations⁺ were added to this summary on April 28, 2021 and were added to the full paper ([Version 2](#)), which was published in *Arthritis & Rheumatology* on June 15, 2021.***

*Updated recommendations regarding age restrictions, preferences between specific vaccines, and need for continued preventive measures were added to this summary on June 19, 2021 and were added to the full paper ([Version 3](#)), which was published in *Arthritis & Rheumatology* on August 4, 2021.****

*Updated recommendations regarding preference for use of mRNA vaccines, use of a supplemental vaccine dose (i.e., 'booster') and associated temporary interruption of immunomodulatory medications, and the FDA EUA for post-exposure prophylaxis with monoclonal antibody treatment for vaccinated AIIRD patients were added to this summary on August 19, 2021. These recommendations were added to the full paper (Version 4), which will be submitted to *Arthritis & Rheumatology* for publication.*

*Updated recommendations for supplemental (booster) dosing and revised information for holding immunomodulatory medications were added to the version 4 summary on October 27, 2021. These recommendations were added to the full paper (Version 4), 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 based on the statements as they were originally voted upon, unless they were subsequently reconsidered. 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. Statements in **bold** are those that have been revised or added in the most current version of the document. These changes are also summarized in the Appendix Table.

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 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 Primary and Supplemental Dosing 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
For AIIRD patients not yet vaccinated, either of the mRNA vaccines is recommended over the single dose J&J vaccine. There is no recommendation for one mRNA vaccine over another.	Moderate
For a multi-dose vaccine (e.g. the Pfizer or Moderna mRNA vaccine series), 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
For patients who previously completed the 2-dose mRNA series or received the 1-dose J&J COVID-19 vaccine, a supplemental (booster) COVID vaccine dose is recommended at least 28 days after the completion of the vaccine series for AIIRD patients receiving any immunosuppressive or immunomodulatory therapy other than hydroxychloroquine monotherapy.	Moderate
For patients who previously completed the mRNA COVID-19 vaccine series or 1-dose J&J COVID-19 vaccine, and who are receiving a supplemental (booster) dose, an mRNA vaccine supplemental dose of either type (Pfizer or Moderna) is preferred.	Moderate
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
AIIRD patients at high risk for poor outcomes related to COVID should receive monoclonal antibody therapy with REGEN-COV if available, either as prevention (i.e. post-exposure prophylaxis for asymptomatic, recently-exposed patients) or as treatment for newly symptomatic patients.	Moderate
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 = US Food and Drug Administration; mRNA = messenger RNA; CDC = Centers for Disease Control and Prevention; ICU = intensive care unit

† Age ≥12 as of June 7, 2021

‡ Given uncertainties in the interpretation of lab testing following vaccination as it would impact clinical decision-making, the panel reaffirmed this statement in Version 4 of this guidance document.

§ The Task Force discussed the possibility of recommending additional and more sustained public health measures in AIIRD patients. After deliberation, they did not elect to exceed current public health authority guidance given uncertainties about the clinical effectiveness of vaccination in such patients. The appropriateness for continued preventive measures (e.g., masking, physical distancing) should be discussed with patients as their rheumatology providers deem appropriate.

Table 3: Guidance Related to the Use and Timing of Vaccine Dosing and Immunomodulatory Therapy in Relation to COVID-19 Vaccination in RMD Patients

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination	Level of Task Force Consensus
	(applies to both primary vaccination and supplemental [booster] dosing)	
Abatacept IV	Time vaccination so that it occurs one week prior to the next dose of IV abatacept	Moderate
Abatacept SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	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
Belimumab SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitor†	The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Hydroxychloroquine	No modifications to either immunomodulatory therapy or vaccination timing	Strong
Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding‡	Moderate
All other conventional and targeted immunomodulatory or immunosuppressive medications except those listed above§	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate

Note: individual medications that were specifically voted on by the task force are listed on separate rows and were not collapsed, even if the resulting recommendation was similar to others.

* 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

† Examples of specific cytokine inhibitors are as follows: IL-6R = sarilumab; tocilizumab; IL-1R = anakinra, canakinumab; IL-17 = ixekizumab, secukinumab; IL-12/23 = ustekinumab; IL-23 = guselkumab, risankizumab; JAKi = baricitinib, tofacitinib, upadacitinib

‡ Some practitioners measure CD19 B cells as a tool with which to time the booster and subsequent rituximab dosing. For those who elect to dose without such information, or for whom such measurement is not available or feasible, provide the booster 2-4 weeks before next anticipated rituximab dose (e.g., at month 5.0 or 5.5 for patients on an every 6 month rituximab dosing schedule)

§ Includes apremilast; azathioprine; calcineurin inhibitors; cyclophosphamide (oral); IVIG; leflunomide; methotrexate, janus kinase inhibitors [JAKi] (baricitinib, tofacitinib, upadacitinib), mycophenolate; sulfasalazine

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.

Based on evidence published to date, the expected benefits of the COVID-19 vaccine outweigh the potential for vaccine harm in most 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.

RMD = rheumatic and musculoskeletal disease; mRNA = messenger RNA

[†] Appendix Table 1: History of Major Changes to ACR COVID Vaccine Guidance Statements in the Summary Tables (i.e., this online document) and Locations in the Published Manuscript Tables and Prose Where Guidance Was Revised		
Provided guidance to hold acetaminophen and NSAIDs for 24 hours prior to vaccination, assuming disease is stable	Table 5 (Summary Table 3)	Version 2
Modified guidance for mycophenolate to hold for 1 week after each vaccine dose	Table 5 (Summary Table 3)	Version 2
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 (Summary Table 3)	Version 2
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	Version 2
Age restriction lowered to age 12	Footnote to Table 3 (Summary Table 2)	Version 3
Preference for mRNA vs. non-mRNA vaccines	Footnote to Table 3 (Summary Table 2)	Version 3
Need for continued preventive measures	Footnote to Table 3 (Summary Table 2)	Version 3
Preference for two-dose mRNA vaccine over single-dose vaccine in AIIRD patients	(Summary Table 2)	Version 4
Recommendation for booster vaccination in AIIRD patients	(Summary Table 2)	Version 4
Recognition of the FDA Emergency Use Authorization for use of post-exposure prophylaxis with casirivimab and imdevimab (REGEN-COV) for prevention of COVID-19 in AIIRD patients	(Summary Table 2)	Version 4
Recommended temporary interruption of oral calcineurin inhibitors at time of vaccination	(Summary Table 3)	Version 4
Recommendations for temporary treatment interruption of various immunomodulatory therapies at the time of receipt of a vaccine booster dose.	(Summary Table 3)	Version 4
Recommendation for supplemental (booster) dosing for mRNA and J&J vaccine recipients	(Summary Table 2)	Version 4 Revised
Preference for the same type of mRNA supplemental (booster) dose in patients previously completing either the Pfizer or Moderna mRNA vaccine series	(Summary Table 2)	Version 4 Revised
Recommendation for monoclonal antibody therapy with REGEN-COVID as either prevention (i.e., post-exposure prophylaxis) or as treatment for high-risk patients	(Summary Table 2)	Version 4 Revised
Complete revision of immunomodulatory medication recommendations regarding timing in relation to COVID-19 vaccine series and supplemental (booster) dosing.	(Summary Table 3)	Version 4 Revised

Recommendations updated April 28, 2021
Link to Version 1 manuscript added May 24, 2021
Link to Version 2 manuscript added June 15, 2021
Recommendations updated June 19, 2021
Link to Version 3 manuscript added August 4, 2021
Recommendations updated August 19, 2021
Recommendations updated October 27, 2021
Link to version 4 manuscript pending

*** How to cite this article:**

Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 1. *Arthritis Rheumatol* 2021. <https://onlinelibrary.wiley.com/doi/10.1002/art.41734>

**** How to cite this article:**

Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 2. *Arthritis Rheumatol* 2021. <https://onlinelibrary.wiley.com/doi/full/10.1002/art.41877>

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Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 3. *Arthritis Rheumatol* 2021. <https://onlinelibrary.wiley.com/doi/10.1002/art.41928>