CRA Recommendation on Three Doses of mRNA Vaccine for Preventing COVID-19

Version 1.0, November 23, 2021

The Canadian Rheumatology Association guideline panel suggests using a third dose of mRNA COVID-19 vaccination [BNT 162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)] in persons aged 18 and older with autoimmune rheumatic disease.

(Conditional recommendation, very low certainty of the evidence about effects.)

Remarks:

- This recommendation is based on evidence for mRNA-1273 (Moderna).
- The recommendation needs to be viewed in the context of any guidance or restrictions for vaccine use set by national or provincial bodies, that may change over time. This includes guidance in people who have had a mixed initial vaccine series (2 different vaccines).

Primary justification:

- The panel judged that for the majority of patients the potential benefits outweigh the potential harms in people with autoimmune rheumatic diseases, although this may vary considerably by person, based on their medications, age, other comorbidities. The recommendation was graded as conditional because of very low certainty of the evidence about effects in the population of interest.

Primary implementation consideration for policy makers and providers:

- Persons with autoimmune rheumatic diseases should be able to access a third vaccine dose if desired, and not be required to take additional steps to obtain their vaccination.

View the Evidence-to-Decision Framework (EtD)

Justification

The CRA panel decided on a conditional recommendation for a third dose of mRNA COVID-19 vaccination in persons aged 18 and older with autoimmune rheumatic disease. The panel balanced the
very low certainty in the moderate benefits of a third dose (prevention of symptomatic infection) against the very low certainty of evidence for trivial harms. The panel discussed that the expected benefits are likely to vary considerably in individuals by current medications, age, and other comorbidities, but the expected harms are likely to be trivial. The decision to receive a third dose should be an individual discussion between a patient and their healthcare provider.

Subgroup considerations

The benefits of a third dose will likely vary considerably between individuals. Subgroups of patients in whom serological protection has been shown to be lower would be expected to have the greatest potential benefit from a third dose. Evidence is being accumulated on clinical outcomes and serological responses to COVID vaccination in patients with ARDs in a living systematic review (Whittle SL, Hazlewood GS et al. 2021), and will inform updates to this guideline.

As of October 2021, the evidence supports the following:

- People taking rituximab: Studies have consistently shown lower immunogenicity from the initial 2 doses of COVID-19 vaccination in people taking rituximab, which is consistent with other vaccines (Papp, Haraoui et al. 2019). Third doses should ideally be administered $\geqslant 4-5$ months after the last dose and at least 4 weeks prior to the subsequent dose of rituximab.
- People taking other DMARDs: There was a modest, but consistent reduction in serological response to COVID-19 vaccination in people with immune mediated inflammatory diseases across the six pooled case-control studies (see ‘desirable effects’ section of EtD). The evidence is less certain when analyzed by medication subgroups. In data from other (non-COVID) vaccines, methotrexate, mycophenolate mofetil, tofacitinib and prednisone ($\geqslant 10$ mg/day) have been shown to attenuate vaccine-induced responses (Papp, Haraoui et al. 2019). A single small study with abatacept and influenza vaccine also showed decreased immunogenicity (Ribeiro, Laurindo et al. 2013). It is likely that some medications (hydroxychloroquine, sulfasalazine) have little effect on serological response.

Implementation considerations

- As access to third doses is determined by provincial health authorities, it will be essential to ensure people with ARDs do not face unnecessary additional barriers. People with ARDs should not be required to obtain a physician letter as proof of an informed decision discussion.
- People with ARDs may have mobility limitations and appropriate access to vaccine clinics should be ensured.
Monitoring and evaluation

- Monitoring of vaccine uptake should occur in people with ARDs, including populations at risk of inequity. Low uptake may point to barriers to access or hesitancy.
- The frequency of serious adverse events, disease flares, and COVID-19 infection/serious outcomes should be followed in patients with ARDs who do and do not receive the vaccine.
- People with ARDs should be encouraged to track their immunization history using an online Canadian vaccination tracker, developed with funding support from the Public Health Agency of Canada (www.canimmunize.ca).

Research priorities

- Randomized controlled trial evidence for the effect of a third dose in ARDs as compared with placebo
- Observational evidence on the frequency of harms (in particular serious adverse events/serious disease flares) in people with ARD
- Evidence comparing the frequency of serious adverse events and autoimmune adverse events in people with ARDs to those without ARD
- Evidence on the benefits (both clinical outcomes and serological studies) in people with ARDs on different medications, including in pediatric populations
- Evidence on patient values and preferences for the benefits and harms across different patient populations
- Understanding vaccine hesitancy and barriers to vaccine access faced by persons with ARDs
- Understanding vaccine benefits and harms in populations at risk for inequities.

REFERENCES


25. Hazlewood, G. S., A. Loyola-Sanchez, V. Bykerk, P. M. Hull, D. Marshall, T. Pham, C. E. Barber, C. Barnabe, A. Sirois, J. Pope, O. Schieur, D. Richards, L. Proulx and S. J. Bartlett
(2021). "Patient and Rheumatologist Perspectives on Tapering DMARDs in Rheumatoid Arthritis: A Qualitative Study." Rheumatology (Oxford) [submitted].


