SARAA Guidance for vaccination against COVID-19 infection in patients with rheumatic and musculoskeletal disease(RMD)

This working document contains information that is appropriate based on evidence available to us currently. Recommendations may change, and this guidance will be updated as new information emerges from ongoing research.

Rheumatic and musculoskeletal diseases (RMDs) refer to a group of disorders affecting the musculoskeletal system (joints, muscles, bones, cartilage) often accompanied by systemic multiorgan disease. This term encompasses connective tissue disorders and all other autoimmune inflammatory rheumatic disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, inflammatory myositis etc.)

A] General considerations related to COVID-19 vaccination in patients with RMD

- Patients with RMDs may be at increased risk of severe COVID-19 infection and worse outcomes as compared to the general population. Factors associated with this include: the older age of presentation of RMDs, the disease itself, treatments used, as well as associated comorbidities.

- All patients with RMDs should be vaccinated against COVID-19, in line with local vaccination guidelines, barring known contraindications (i.e. known allergy to vaccine components). Although South Africa's initial vaccination strategy prioritised patients with comorbidities, including immunosuppressed patients, this has since changed to a simplified age-based system, to expediate the vaccination roll-out process. Therefore, it is incumbent on the patient and the rheumatology practitioner to ensure that patients with RMDs vaccinate as soon as possible based on South Africa's phased roll-out.

- The rheumatology practitioner is responsible for engaging the patient in a shared decision-making process to discuss receiving the COVID-19 vaccine. Ideally the patient should have low or no disease activity at the time of vaccination, however this is not always possible. The risk of severe COVID-19 infection, supports the importance of vaccination in moderate and severe disease states as well. Timing should be discussed with the rheumatology practitioner.

- In addition to the COVID-19 vaccine, patients with RMDs should get their annual flu vaccine. The flu vaccine and COVID-19 vaccines should be timed at least 2 weeks apart.

- Patients should continue to practice social distancing, hand hygiene and other preventive measures after receiving their vaccination.

- All close contacts of patients with RMDs should be encouraged to vaccinate once able to, in order to protect the at-risk patient.

B] Safety and efficacy concerns related to COVID-19 vaccination in patients with RMD

- All currently registered vaccines: Pfizer/BioNTech COVId-19 and Moderna (mRNA vaccines), Johnson & Johnson COVID-19 Vaccine Janssen and Oxford/AstraZeneca ChadOx (adenovirus vector vaccines) are **non-live** vaccines, and as such are safe for use in immunosuppressed individuals, including those patients with RMD on immunosuppressing therapies. At present, only the Johnson and Johnson (JnJ) and Pfizer/BioNTech vaccines have been issued in South Africa.

- The immune response to the vaccine may be reduced (both in magnitude and duration) in immunosuppressed RMD a patients compared to the general population. This is not based on current COVID-19 vaccine trial data, but rather extrapolated from data related to the flu vaccine in immunosuppressed patients. The immune response seems to be especially affected in patients on Rituximab.

- There is a hypothetical risk of flares of underlying RMD following vaccination. This has not been shown with COVID-19 vaccines but is based on data from other vaccinations. Nevertheless, the benefits of the vaccine far outweigh the rare possibility of an immune-mediated disease flare.

- Other recognized adverse reactions include rare reports of anaphylaxis with the Pfizer/BioNTech vaccine and thromboembolic events with the JnJ vaccine. Patients with a history of rapid onset of anaphylaxis to multiple drugs or unexplained anaphylaxis, or known allergies to components of the Pfizer vaccine, should receive an alternate vaccine. Vaccine induced immune thrombocytopenia and thrombosis (VITT), a condition seen with the JnJ vaccine, is extremely rare and should not deter patients from taking this vaccine,

regardless of the presence of known risk factors for thrombosis or a prior history of thrombotic events. The risk of thrombosis from COVID-19 infection is far greater than that from the vaccine.

C] Considerations regarding the use of background immunomodulatory therapies prior to COVID-19 vaccination in patients with RMD

- Advice regarding the timing of vaccination and alterations in background treatment are not based on any documented research but rather specialist opinion, derived from knowledge of RMDs and an understanding of the likely immune response to vaccination.

- Patients with RMD should not preemptively discontinue their treatment. This may lead to worsening of disease activity and unnecessary hospitalisations, increasing the risk of exposure to COVID-19.

- If ***possible*** to delay commencement of immunosuppressive treatment, consider a 2 week delay after completing the full vaccination schedule prior to the introduction of immunosuppression, to allow best vaccine-induced immune response. This should be a shared decision based on risks of COVID-19 infection and associated with the underlying condition.

- Many of the medications used for RMDs can be continued safely without consideration for specific timing of vaccine dosing. These include:

    - chloroquine or hydroxychloroquine,
    - intravenous immunoglobin (IVIG),
    - low-moderate doses of corticosteroids (equivalent to prednisone < 20mg/day)
    - ***conditionally*** high dose corticosteroids (equivalent *to* prednisone $\geq$ 20mg/day)*
    - sulphasalazine
    - leflunomide
    - azathioprine
    - calcineurin inhibitors
    - Some biologics: any TNF inhibitors; tocilizumab; secukinumab; ustekinumab

    In patients on high dose corticosteroids for control of their disease activity, **where possible, without generating major delays, time vaccination at the lowest possible dose to ensure best immune response to the vaccine.*

- Consider withholding acetaminophen (paracetamol) and NSAIDs 24 hours prior to vaccine dose (can be used safely after the dose to manage side effects e.g. pain at inoculation site).

- **Methotrexate** (MTX) has been shown to blunt the host immune response to COVID-19 infection and thus it is appropriate to withhold MTX 1 week following each mRNA vaccine dose or 2 weeks after single-dose vaccines.

- **Mycophenolate mofetil and JAK inhibitors** (Tofacitinib, Baricitinib, Upadacitinib) – hold for 1 week following each vaccine dose. No modifications to vaccination timing.

- Intravenous administration of **cyclophosphamide** should ideally be timed 1 week after each vaccine dose where possible.

- **Abatacept** (**subcutaneous**) - hold injection 1 week prior and 1 week following first vaccine dose. No interruption required for the second vaccine dose.

- **Abatacept (intravenous)** – time the first vaccine dose 4 weeks after abatacept infusion, then wait 1 week prior to giving the next abatacept infusion. No further adjustments are needed for the second vaccine dose.

- **Rituximab** and other B-cell depleting therapy can significantly dampen the host immune response to vaccine. As such the following considerations should be made:

    - If an unvaccinated patient needs to initiate a new biologic DMARD, consider an alternative to rituximab if available and appropriate e.g. for refractory RA.

    - Similarly, with delays in vaccine availability, and accessibility, consider switching to an appropriate alternate treatment where disease state allows (i.e. stable disease).

    - Rituximab should not be delayed if needed for a life- or organ-threatening disease state, and vaccine should be administered when available. There is no evidence to suggest how long after a pulse of rituximab a patient should delay COVID-19 vaccine, however consensus suggests ideally 4-8 weeks where possible.

    - **In stable patients receiving maintenance rituximab, schedule vaccination so that the vaccine series is initiated approximately 4 weeks prior to next scheduled rituximab cycle. Ideally, complete full dose schedule of vaccination approximately 2 weeks prior to the next rituximab infusion.**

D] Useful links and Resources:

1. **Vanderbilt University: Common COVID Vaccine Questions Answered.**
   https://www.vumc.org/coronavirus/common-covid-vaccine-questions?tabOrder=.%2Findex.html%2C.Findex.htmlCfaqsClinks%2Cfaqs%2Clinks&referrerPageUrl=https%3A%2F%2Fwww.vumc.org%2Fcoronavirus%2Fcovid-19-vaccines&verticalUrl=faqs.html

2. **The NICD COVID Vaccine page**
   https://www.nicd.ac.za/diseases-a-z-index/covid-19/what-you-need-to-know-about-vaccines-in-general/

3. **American College of Rheumatology vaccine guidance**
   https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf

E] Key References:

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

Hyrich, K.L., Machado, P.M. Rheumatic disease and COVID-19: epidemiology and outcomes. *Nat Rev Rheumatol* **17,** 71–72 (2021). https://doi.org/10.1038/s41584-020-00562-2

Tiphaine Lenfant, Yuxuan Jin, Elizabeth Kirchner, Rula A Hajj-Ali, Leonard H Calabrese, Cassandra Calabrese, Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients, *Rheumatology*, 2021

Arthritis and Musculoskeletal Alliance: Principles for COVID-19 Vaccination in musculoskeletal and rheumatology for clinicians (Version 7, 9 June 2021)
http://arma.uk.net/covid-19-vaccination-and-msk/

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