22 NOV 2021

CONSENSUS STATEMENT

COVID-19 VACCINATION

FOR PEOPLE WITH RHEUMATIC DISEASE - RECOMMENDATIONS FOR ENHANCED PRIMARY SERIES (THIRD DOSE)

CHAPTER OF RHEUMATOLOGISTS

COLLEGE OF PHYSICIANS, SINGAPORE

ACADEMY OF MEDICINE SINGAPORE

CHAPTER OF RHEUMATOLOGISTS
COLLEGE OF PHYSICIANS, SINGAPORE

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Recommendations

1. We *strongly* recommend that PRD on immunomodulatory drugs, who have received 2 doses of the mRNA vaccine against COVID-19, be offered a 3rd dose of the mRNA vaccine as part of an enhanced primary series.

2. For PRD, we *conditionally* recommend that the 3rd dose of mRNA vaccine against COVID-19 be given at least 4 weeks after the 2nd dose, or as soon as possible thereafter.

BACKGROUND

The COVID-19 pandemic remains a worldwide problem and threat to human life and livelihood in 2021. The Ministry of Health, Singapore (MOH) Expert Committee on COVID-19 Vaccination (EC19V) has recommended a third dose of mRNA vaccine as part of an enhanced primary series in immunocompromised patients.[1] People with rheumatic diseases (PRD) and/or patients on immunosuppressive therapy have impaired immunogenicity from the vaccine, as seen by lower rates of seroconversion compared to the general population.[2,3] Additionally, they are at increased risk of post-vaccine breakthrough COVID-19 infection[4,5] and poor outcomes such as mechanical ventilation and death.[6-8] Conversely, the risk of flare of rheumatic disease after COVID-19 vaccination remains unclear. Immune-mediated adverse reactions, such as myocarditis, have been reported.[9]

We conducted a systematic review to summarize the published literature describing the efficacy and safety of a third dose of mRNA COVID-19 vaccination in PRD. Consensus recommendations were developed using a Delphi method and based on the available evidence by the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore.

TARGET AUDIENCE

Healthcare professionals involved in the care of PRD.

METHODS

An expert panel was convened by the Chapter Chair. A core-working group reviewed the literature and formulated draft recommendations for rating by an invited task force panel, which included experts in adult and paediatric Rheumatology and Infectious Diseases.

The core-working group conducted systematic literature reviews to answer five research questions (see below). Other academic bodies' recommendations for COVID-19 vaccination in PRD and/or immunocompromising conditions were also considered. GRADE methodology for assessing quality of evidence and assigning strength of recommendations was used.[10] The quality

of evidence and recommendations were presented and discussed to achieve consensus among the task force panel.

GRADE system of assigning strength of recommendations:

• *Strong*: the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not.

• *Weak (conditional)*: the trade-offs are less certain - either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

PRD include, but are not limited to, those diagnosed with:

1. Chronic inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis, spondyloarthritides, juvenile idiopathic arthritis, adult onset Still's disease)
2. Connective tissue diseases (e.g. systemic lupus erythematosus, idiopathic inflammatory myositis, Sjögren syndrome, systemic sclerosis)
3. Primary systemic vasculitides
4. Autoinflammatory diseases

Immunomodulatory drugs considered for this guidance include:

1. Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine)
2. Biologic DMARDs (anti-tumour necrosis factor, tocilizumab, rituximab, abatacept, secukinumab, ixekizumab, anakinra, belimumab)
3. Targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib)
4. Immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin A, tacrolimus)
5. Glucocorticoids (any dose)

Research questions:

1. Do PRD and/or patients on immunosuppressants (IS) have decreased immune response to the COVID-19 mRNA vaccines compared to the general population?
2. Does a third dose of mRNA COVID-19 vaccine lead to enhanced protection of immunocompromised patients against COVID-19 infection/ poor outcomes?
3. In PRD, are COVID-19 mRNA vaccines harmful?
4. In PRD, should the third dose be the same or a different vaccine?
5. What is the best time for administration of the third dose of the vaccine?

There is low level of evidence to show a reduction in rates of infection and severe disease, and a low level of evidence to show increased immunogenicity, as measured by enhanced humoral and cellular response after a third dose of mRNA vaccine against COVID-19 in PRD. In a general population administrative database from Israel, of 1,137,804 people older than 60 years of age, the rate of confirmed infection, and severe illness was lower in the booster group, administered at least 5 months after the standard 2-dose regimen (homologous BNT162b2), than in the non-booster group, by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3) and 19.5 (95% CI, 12.9 to 29.5) respectively.[11] In a double-blind, randomized, controlled trial among 120 organ-

transplant recipients, a third dose of mRNA vaccine (Moderna) given at 2 months after standard regimen, demonstrated both enhanced humoral and T cell response compared to those given placebo injections.[12] There were twelve and two more observational studies that showed an enhanced humoral response, and cellular response respectively, after a third dose of vaccine against COVID-19.[13-24]

Among PRD, the rates of flares of immune diseases after vaccination against COVID-19 were reported from cohort studies mostly without a comparator group. Two cohorts consisting of 1377 and 185 PRD showed lower rates of flares in those with good control of their underlying RD.[25,26] In those who flared, the majority had worsening of pre-existing symptoms and were not severe.[25] Rates of flares of immune diseases after vaccination against COVID-19 from all reviewed cohort studies ranged from 0% to 18.8%, and the rates of severe flares ranging from 0% to 1.2%[3,25-33]

There are insufficient data to inform whether the third mRNA vaccine dose, in PRD, should be homologous (where the third dose is the same vaccine as the initial two doses) or heterologous (where the third dose is different from the initial two doses), hence no recommendation is made. One case series described thirty solid organ transplant recipients with a heterologous prime-boost strategy; however, no comparison between the regimens was made.24 Two randomised controlled trials (RCTs) assessed third dose vaccination strategies in PRD and kidney transplant patients respectively, involving non-mRNA vaccines.[34,35] All three studies only reported immunogenicity data; no clinical efficacy was reported.

There are no comparative studies comparing different dose intervals available in the literature. The US CDC recommends a third dose of mRNA vaccine in immunocompromised patients at least four weeks after the second dose.[36] The median dosing interval in various studies involving PRD or transplant recipients was 30-77 days and ranges from 30 to 94 days after the second dose.[12-17,19-21,23,24]

REFERENCES

1. Booster doses. Ministry of Health, Singapore. Updated 16 Oct 2021. https://www.moh.gov.sg/covid-19/vaccination/faqs---booster-doses.

2. Boekel L, Steenhuis M, Hooijberg F, et al. Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. Lancet Rheumatol 2021;3:e778-e88.

3. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330-8.

4. Chodick G, Tene L, Rotem RS, et al. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. Clin Infect Dis 2021:May 17. Online ahead of print.

5. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States. Clin Infect Dis 2021:Aug 6. Online ahead of print.

6. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin

Microbiol Infect 2021;27:1652-7.

7. D'Silva KM, Jorge A, Cohen A, et al. COVID-19 Outcomes in Patients With Systemic Autoimmune Rheumatic Diseases Compared to the General Population: A US Multicenter, Comparative Cohort Study. Arthritis Rheumatol 2021;73:914-20.

8. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-6.

9. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med 2021;385:1078-90.

10. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

11. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med 2021;385:1393-400.

12. Hall VG, Ferreira VH, Ku T, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med 2021;385:1244-6.

13. Benotmane I, Gautier G, Perrin P, et al. Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. JAMA 2021:326(11): 1063-5.

14. Bensouna I, Caudwell V, Kubab S, et al. SARS-CoV-2 Antibody Response After a Third Dose of the BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis or Peritoneal Dialysis. Am J Kidney Dis 2021:S0272-6386(21)00833-7.

15. Chavarot N, Morel A, Leruez-Ville M, et al. Weak antibody response to three doses of mRNA vaccine in kidney transplant recipients treated with belatacept. Am J Transplant 2021:Aug 24. Epub ahead of print.

16. Connolly CM, Teles M, Frey S, et al. Booster-dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series. Ann Rheum Dis 2021:Sep 7. Epub ahead of print. .

17. Del Bello A, Abravanel F, Marion O, et al. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. Am J Transplant 2021:Jul 31. Online ahead of print.

18. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int 2021;100:702-4.

19. Espi M, Charmetant X, Barba T, et al. Justification, safety, and efficacy of a third dose of mRNA vaccine in maintenance hemodialysis patients: a prospective observational study. medRxiv 2021:2021.07.02.21259913.

20. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med 2021;385:661-2.

21. Longlune N, Nogier MB, Miedouge M, et al. High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant 2021;36:1704-9.

22. Shroff RT, Chalasani P, Wei R, et al. Immune responses to two and three doses of the BNT162b2 mRNA vaccine in adults with solid tumors. Nat Med 2021:Sep 30. Epub ahead of print.

23. Stumpf J, Tonnus W, Paliege A, et al. Cellular and Humoral Immune Responses After 3 Doses of

BNT162b2 mRNA SARS-CoV-2 Vaccine in Kidney Transplant. Transplantation 2021;105:e267-e9.

24. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med 2021;174:1330-2.

25. Connolly CM, Ruddy JA, Boyarsky BJ, et al. Safety of the first dose of mRNA SARS-CoV-2 vaccines in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021:Mar 19. Epub ahead of print.

26. Rotondo C, Cantatore FP, Fornaro M, et al. Preliminary Data on Post Market Safety Profiles of COVID 19 Vaccines in Rheumatic Diseases: Assessments on Various Vaccines in Use, Different Rheumatic Disease Subtypes, and Immunosuppressive Therapies: A Two-Centers Study. Vaccines (Basel) 2021;9:730.

27. Geisen UM, Berner DK, Tran F, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis 2021;80:1306-11.

28. Peet CJ, Papadopoulou C, Sombrito BRM, Wood MR, Lachmann HJ. COVID-19 and autoinflammatory diseases: prevalence and outcomes of infection and early experience of vaccination in patients on biologics. Rheumatol Adv Pract 2021;5:rkab043.

29. Sattui SE, Liew JW, Kennedy K, et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2021;7:e001814.

30. Machado PM, Lawson-Tovey S, Hyrich K, et al. LB0002 COVID-19 Vaccine Safety In Patients With Rheumatic And Musculoskeletal Disease. Ann Rheum Dis 2021;80:199-200.

31. Izmirly PM, Kim MY, Samanovic M, et al. Evaluation of Immune Response and Disease Status in SLE Patients Following SARS-CoV-2 Vaccination. Arthritis Rheumatol 2021:Aug 4. Online ahead of print.

32. Barbhaiya M, Levine JM, Bykerk VP, et al. Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City. Ann Rheum Dis 2021;80:1352-1354.

33. Braun-Moscovici Y, Kaplan M, Braun M, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. Annals of the Rheumatic Diseases 2021;80:1317-21.

34. Bonelli M, Mrak D, Tobudic S, et al. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomized controlled trial. medRxiv 2021:2021.09.05.21263125.

35. Schrezenmeier E, Rincon-Arevalo H, Stefanski AL, et al. B and T Cell Responses after a Third Dose of SARS-CoV-2 Vaccine in Kidney Transplant Recipients. J Am Soc Nephrol 2021:Oct 19. Epub ahead of print.

36. Centres for Disease Control and Prevention. COVID-19 Vaccines for Moderately to Severely Immunocompromised People. Updated on 18th Oct, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

ACKNOWLEDGEMENT

Core Working Group	
(1) Dr Manjari LAHIRI	Chair, Chapter of Rheumatologists Senior Consultant, Division of Rheumatology, Department of Medicine National University Hospital
(2) Dr LEUNG Ying Ying Katy	Board Member, Chapter of Rheumatologists Senior Consultant, Department of Rheumatology & Immunology Singapore General Hospital
(3) Dr XU Chuanhui	Senior Resident Department of Rheumatology, Allergy and Immunology Tan Tock Seng Hospital
(4) Dr Amelia SANTOSA	Board Member, Chapter of Rheumatologists Senior Consultant, Division of Rheumatology, Department of Medicine National University Hospital
(5) Dr Warren FONG	Senior Consultant Department of Rheumatology & Immunology Singapore General Hospital
(6) Dr CHEW Li-Ching	Vice-Chair, Chapter of Rheumatologists Senior Consultant, Department of Rheumatology & Immunology Singapore General Hospital
(7) Dr Melonie Kannamma SRIRANGANATHAN	Board Member, Chapter of Rheumatologists Head and Consultant, Division of Rheumatology, Department of Medicine Changi General Hospital
(8) Dr Stanley ANGKODJOJO	Honorary Secretary, Chapter of Rheumatologists Consultant, Rheumatology Service, Department of General Medicine Sengkang General Hospital

Task Force Panel	
(1) Dr Thaschawee ARKACHAISRI	Head & Senior Consultant Rheumatology and Immunology Service, Department of Paediatric Subspecialties KK Womens' and Children's Hospital
(2) Dr Suresh ERNEST	Head & Senior Consultant Department of Medicine Ng Teng Fong General Hospital
(3) Dr KONG Kok Ooi	Head & Senior Consultant Department of Rheumatology, Allergy & Immunology Tan Tock Seng Hospital
(4) Dr Aisha LATEEF	Board Member, Chapter of Rheumatologists Chief & Senior Consultant, Department of Medicine Woodlands Health
(5) Dr LEE Tau Hong	Vice Chair, Chapter of Infectious Disease Physicians Consultant National Centre for Infectious Disease
(6) Dr LEONG Keng Hong	Rheumatologist Leong Keng Hong Arthritis and Medical Centre
(7) Dr Andrea Hsiu Ling LOW	Head & Senior Consultant Department of Rheumatology & Immunology Singapore General Hospital
(8) Dr Anselm MAK	Senior Consultant Division of Rheumatology, Department of Medicine National University Hospital

PUBLISHED: 22 NOV 2021

Chapter of Rheumatologists
College of Physicians, Singapore
Academy of Medicine, Singapore
81 Kim Keat Road
#11-00 NKF Centre
Singapore 328836