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EDITORIAL

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A vaccination update for rheumatologists—SARS-CoV-2, influenza and herpes zoster

1 | INTRODUCTION

Vaccination is currently at the forefront of everyone's mind. The SARS-CoV-2/COVID-19 pandemic has resulted in enormous changes to the way we practice rheumatology.[1] The number of worldwide cases, deaths and long-term health and economic impact from SARS-CoV-2 infection has been sobering. With many countries in lockdown or other forms of societal restrictions, widespread vaccination is critical at protecting people and combating the pandemic.

This paper will summarize the currently available evidence regarding SARS-CoV-2 vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) with a focus on vaccine options in the Asia-Pacific region. (We have included only peer-reviewed publications and excluded conference abstracts or preprint manuscripts). The onset of influenza season in Australia with the widespread availability of adjuvant or high-dose influenza vaccines makes this an opportune time to discuss influenza vaccination and its timing with SARS-CoV-2 vaccination. The recent availability of a recombinant herpes zoster vaccine (RZV, or Shingrix®) in Australia with the concern provoked by administration of the live zoster vaccine (ZVL, or Zostavax®) to immunosuppressed AIIRD patients also means this is a fruitful topic for discussion. As there has been dialog regarding a "travel bubble" between Australia and Singapore, we have included a Singaporean perspective on these issues.

2 | SARS-CoV-2/COVID-19 IN RHEUMATOLOGY PATIENTS

2.1 | Risk of hospitalization and death

Recent data from the COVID-19 Global Rheumatology Alliance physician-reported registry (3729 patients, 390 deaths) suggested that higher likelihood of COVID-19-related death was associated with increased age (66-75 years: odds ratio [OR] 3.00, 95% confidence interval [CI] 2.13 to 4.22; >75 years: 6.18, 4.47-8.53; both compared to those ≤65 years of age), male gender (1.46, 1.11-1.91), hypertension with cardiovascular disease (1.89, 1.31-2.73), chronic lung disease (1.68, 1.26-2.25) and prednisolone-equivalent dosage >10 mg/d (1.69, 1.18-2.41; compared to no glucocorticoid).[2]

Moderate/high disease activity compared to remission/low disease activity was also associated with increased odds of death (1.87, 1.27-2.77). Rituximab (4.04, 2.32-7.03), sulfasalazine (3.60, 1.66-7.78), immunosuppressants (azathioprine, cyclophosphamide, cyclosporin, mycophenolate or tacrolimus; 2.22, 1.43-3.46) and not receiving any disease-modifying anti-rheumatic drug (DMARD; 2.11, 1.48-3.01) were associated with higher odds of death, compared with methotrexate (MTX) monotherapy.[2]

Prednisone dose ≥10 mg/d was associated with higher odds of hospitalization (OR 2.05, 95% CI 1.06-3.96). Reassuringly, conventional synthetic DMARD (csDMARD) alone, or in combination with biologic DMARDs (bDMARDs) or Janus kinase inhibitors (JAKi) was not associated with hospitalization (OR 1.23, 95% CI 0.70-2.17 and OR 0.74, 95% CI 0.37-1.46, respectively). Interestingly, tumor necrosis factor inhibition (TNFi) was associated with a lower odds of hospitalization (OR 0.40, 95% CI 0.19-0.81).[3] Despite initial enthusiasm about the benefits of hydroxychloroquine, this association was not observed (OR 0.94, 95% CI 0.57-1.57).[3]

A North American study used a large multicenter electronic database to identify patients with AIIRD infected with SARS-CoV-2 and compared outcomes to matched patients with SARS-CoV-2, but without AIIRD. Reassuringly, once correction for comorbidities was undertaken, there was no difference in outcomes, except for the higher risk of venous thromboembolism in those with AIIRD (relative risk [RR] 1.60; 95% CI 1.14-2.25).[4]

2.2 | Vaccine hesitancy

Despite SARS-CoV-2 vaccination being critical for dealing with the pandemic and protecting immunosuppressed AIIRD patients, there was more hesitation regarding vaccination among Italian patients compared to healthy controls.[5] However, AIIRD patients were willing to undergo vaccination if informed about risks and benefits by their trusted specialist.[5] While a French web-based survey involving participants from 56 countries found the proportion of patients with AIIRD willing to undergo SARS-CoV-2 vaccination was 54.2% (686/1266), uncertainty was reported in 32.2% (n = 408) and unwillingness to undergo vaccination in 13.6% (n = 172).[6] The most trusted healthcare professional for vaccination advice was their medical specialist.[6] The commonest patient concerns were limited

experience/information regarding the new SARS-CoV-2 vaccines, use of relatively "new" messenger RNA (mRNA) vaccine technology, possible flare of their AIIRD and risk of a local reaction or side effects.[6] There is marked national variation in attitudes to vaccination with differences in acceptance rates ranging from almost 90% in China to less than 55% in Russia.[7]

2.3 | Vaccine safety, immunogenicity and efficacy

As immunocompromised patients were excluded from studies of SARS-CoV-2 mRNA vaccines, there is limited evidence regarding vaccine efficacy in immunosuppressed rheumatology and musculoskeletal (RMD) patients. A non-randomized study of 123 RMD patients found that at a median (interquartile range [IQR]) of 22 (18-26) days after the first vaccine dose (52% BNT162b2, Pfizer-BioNTech; 48% mRNA-1273, Moderna), 74% (95% CI 65%-81%) had a detectable antibody response against the receptor-binding domain of the SARS-CoV-2 spike protein.[8] Those treated with mycophenolate or rituximab were less likely to develop an antibody response. Another study from the same group found that at a median time of 20 days (IQR 17-24 days) after the first vaccine dose, antibody to the anti-S1 or anti–receptor-binding domain, was detectable in only 76 participants (17%; 95% CI 14%-21%).[9] Those treated with anti-metabolite immunosuppressants, such as mycophenolate or azathioprine, were less likely to develop an antibody response than those not on these agents (37% compared to 63%, respectively; adjusted incidence rate ratio [IRR] 0.22; 95% CI 0.15-0.34).[9] However, despite their importance in protection against SARS-CoV-2 infection, post-vaccination cellular immune responses were not assessed in these studies.

A small German study of 42 healthy controls and 26 patients with chronic inflammatory disease (mean age 37.5 and 50.5 years, respectively) treated with a range of bDMARDs found that anti-SARS-CoV-2 antibodies and neutralizing activity using a separate enzyme-linked immunosorbent assay was detectable in all participants following the second dose of mRNA vaccine.[10] Immunoglobulin G (IgG) titers were significantly lower in patients compared with controls (2053 binding antibody units/mL ± 1218 vs 2685 ± 1102). However, post-vaccination cellular immune responses were again not assessed in this study. While vaccination was not associated with disease flares, the short follow-up of 7 days may have been insufficient to study this.[10]

Despite assay differences between studies, there is a strong relationship between levels of neutralizing antibodies and vaccine protective efficacy across different SARS-CoV-2 vaccines.[11] Furthermore, the estimated neutralization level for protection from severe infection is approximately 6-fold lower than that required for protection from a symptomatic infection.[11]

A recent small study from New York found that only 18/25 (72%) patients on MTX for treatment of AIIRD had an adequate humoral response (IgG antibodies against the spike protein) following BNT162b2 (Pfizer-BioNTech) compared to 24/26 (92%) of AIIRD patients not on MTX and 96% (25/26) of normal controls.[12] In the same study, post-vaccination cellular immunity was also impaired in patients on MTX, with a lack of CD8+ T-lymphocyte activation.

A British study compared antibody responses and seroconversion rates in patients with inflammatory bowel disease (n = 865) treated with the TNFi, infliximab compared to those treated with vedolizumab (n = 428), a gut-selective anti-integrin α4β7 monoclonal antibody.[13] Geometric mean (SD) anti-SARS-CoV-2 antibody concentrations were lower in patients treated with infliximab compared to vedolizumab following 1 dose of the BNT162b2 vaccine (Pfizer-BioNTech; 6.0 U/mL, SD 5.9 vs 28.8 U/mL, SD 5.4; $P < .0001$) and 1 dose of the ChAdOx1 nCoV-19 (Oxford/AstraZeneca; 4.7 U/mL, SD 4.9 vs 13.8 U/mL, SD 5.9; $P < .0001$) preparation. Despite this blunting of post-vaccination serologic response, following the second vaccine doses, 85% (17/20) of infliximab-treated patients and 86% (6/7) of vedolizumab-treated patients seroconverted.[13] Unfortunately, vaccine supply delay in the United Kingdom at the time limited the number of study participants who received the second dose of both vaccines.

2.4 | Recommendations from various national rheumatology organizations

While the American College of Rheumatology COVID-19 Vaccine Clinical Guidance Task Force suggested with-holding MTX for 1 week after each dose of the mRNA COVID vaccine and for 2 weeks after single dose COVID vaccination in those with well-controlled disease, this was based on expert consensus opinion rather than firm evidence.[14] While a South Korean study found cessation of MTX 2 weeks before and 2 weeks after seasonal trivalent influenza vaccination in patients with rheumatoid arthritis (RA) resulted in better serologic responses,[15] similar data are not currently available for SARS-CoV-2 vaccines. Nevertheless, the Korean College of Rheumatology advised temporary discontinuation of MTX for 1-2 weeks after each vaccine dose can be considered, but that DMARDs should be continued during vaccination since their with-holding can increase disease activity, which is associated with worse SARS-CoV-2 infection severity and outcomes.[16]

The Singapore Chapter of Rheumatologists recommended that immunomodulatory drugs, other than rituximab, can be continued alongside SARS-CoV-2 vaccination, that is without the need for cessation. For those on rituximab, vaccination should be administered a minimum of 6 months after the last dose, and/or 4 weeks prior to the next dose of rituximab. If possible, vaccination should ideally be performed prior to commencing rituximab.[17]

2.5 | Summary

As csDMARDs, bDMARDs and targeted synthetic DMARDs (tsDMARDs) may reduce serologic responses following SARS-CoV-2 vaccination,[8-10,12,13] it is reasonable to minimize immunosuppression around the time of SARS-CoV-2 vaccination by with-holding these

agents – if possible, so long as joint inflammation is quiescent and risk of underlying disease flare is low. Vaccination urgency will obviously be dependent on the prevailing national healthcare burden of SARS-CoV-2 morbidity and mortality. However, the logistics of with-holding DMARDs can be challenging and given the ambivalence toward vaccination already expressed by many rheumatology patients,[5] every effort should be made to remove vaccination hurdles. Reassuringly, despite the lower post-vaccination serologic titers observed following a TNFi, most patients still seroconverted.[13]

There is currently insufficient data to warrant routine measurement of post-vaccination serologic responses.[14]

Medication adherence in rheumatology patients is a major issue compromising optimal care,[18] so clinicians advising with-holding of DMARDs around the time of vaccination should ensure patients recommence immunosuppression as soon as possible afterwards to avoid disease flares. As population vaccination is a critical strategy to fight this pandemic, and their opinion matters to patients,[5] rheumatologists should encourage all patients to undergo SARS-CoV-2 vaccination as per national guidelines. It would also be prudent to encourage vaccination of household and other close contacts to reduce likelihood of SARS-CoV-2 exposure. In Australia, the Pfizer vaccine has now been approved for use in pregnant women.[19]

2.6 | Useful links for patients

- https://rheumatology.org.au/downloads/20210422%20COVID-19%20Vaccination%20for%20Rheum%20Patients%2022Apr21.pdf
- https://rheum-covid.org/covaripad-summary/
- https://creakyjoints.org.au/covid_19/
- https://www.health.gov.au/resources/publications/atagi-covid-19-vaccination-shared-decision-making-guide-for-people-with-immunocompromise

3 | INFLUENZA

Influenza vaccination in the setting of AIIRD has been recently discussed.[20-22] With onset of influenza season in Australia, quadrivalent seasonal influenza vaccines are recommended for those aged 10-65 years, for example FluQuadri®, Afluria Quad®.[23] However, due to waning age-associated immunity, the adjuvant influenza vaccine, Fluad Quad®, is recommended for those aged ≥65 years.[23]

In Singapore, either the trivalent or quadrivalent influenza vaccines are recommended annually for immunosuppressed individuals.[24]

Reduced serologic responses occur in AIIRD patients following vaccination against seasonal influenza – probably due to therapeutic immunosuppression.[20-22] A Canadian study randomized 279 patients with RA to standard-dose quadrivalent influenza vaccine (SD-QIV) and 139 to a high-dose trivalent preparation (HD-TIV). Those who received HD-TIV were more likely to seroconvert than those who received SD-QIV with OR of 2.99 (95% CI 1.46-6.11) for seroconversion to strain A/H3N2, 1.95 (1.19-3.22) for strain B/Bris, 3.21 (1.57-6.56) for strain A/H1N1 (in 2016-2017), and 2.44 (1.18-5.06) for seroconversion to strain A/H1N1 (in 2017-2018).[25] No flare in RA activity was observed following either vaccine.

A British study using a large community-based database (Clinical Practice Research Datalink) found seasonal influenza vaccination reduced the risk of influenza-like illness (adjusted hazard ratio [aHR] 0.70), hospitalization for pneumonia (aHR 0.61) and chronic obstructive pulmonary disease exacerbations (aHR 0.67), and death due to pneumonia (aHR 0.56) in AIIRD patients.[26] No association was seen in the AIIRD population between influenza vaccination and disease flares or vaccine-related adverse events.[27]

The Australian Technical Advisory Group on Immunisation (ATAGI) does not routinely recommend co-administration of a SARS-CoV-2 vaccine with other vaccines, including influenza. Instead, ATAGI suggests a minimum 7-day interval between administration of a SARS-CoV-2 vaccine and other vaccines, including the influenza vaccine.[28] However, this interval can be shortened in certain circumstances, for example during a significant SARS-CoV-2 or influenza outbreak. The Singapore Ministry of Health recommends a 14-day interval between administration of a SARS-CoV-2 vaccine and other vaccines.[29]

3.1 | Summary

Rheumatologists should encourage all patients to undergo seasonable influenza vaccination as per national guidelines. Influenza vaccination should occur as far as possible from a dose of rituximab - the CD-20 depleting antibody.[30] All immunosuppressed AIIRD patients who receive the seasonal influenza vaccine for the first time should receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter on an ongoing basis.[31,32] Consideration should be given to vaccinating immunosuppressed AIIRD patients with an adjuvant or high-dose seasonal influenza vaccine – if available.[25]

4 | HERPES ZOSTER

The increased risk of herpes zoster (HZ) reactivation in immunosuppressed AIIRD patients, especially in the setting of JAKi use is well-recognized.[33] Since ZVL was included in the Australian National Immunisation Program (NIP) in November 2016 for those 70 years and older, there has been a marked fall in HZ antiviral prescription rates in this age group, by an average of 13.6% per year (95% CI 1.5-24.2).[34] (As ZVL is not included in the Singapore National Vaccination Program, the high cost and concern for vaccine-related disseminated VZV in immunosuppressed AIIRD patients has led to relatively low uptake). While these results indicate incorporation of ZVL onto the Australian NIP was successful in protecting many 70-79-year-olds against HZ, there have been 3 post-vaccination deaths due to disseminated infection from the vaccine strain used in ZVL. Only 1 of

these has occurred in an AIIRD patient on prednisone and hydroxychloroquine, the other 2 were in oncology patients.[35,36] Current recommendations are that live virus vaccines should be avoided in the setting of immunosuppression.[32,37] However, low-to-moderate doses of corticosteroid (dose equivalent to prednisone ≤10 mg/d), leflunomide, salazopyrine and MTX (≤0.4 mg/kg per week) and AZA (≤3 mg/kg per day) are not listed as a contraindication to ZVL.[32]

The recent availability of Shingrix® in Australia, a RZV with greater sustained efficacy than ZVL[38] should simplify vaccination against this troublesome pathogen. Waning age-related immunity following ZVL was not observed with RZV.[39] While local injection site reactions are common, presumably due to the potent adjuvant, most adverse events were of short duration, with no difference in vaccine-related autoimmune disturbances between the vaccine and placebo groups at 3 years of follow-up.[38] While the above is reassuring and use of a recombinant preparation means no risk of disseminated VZV infection post-vaccination, the use of RZV has not been studied in immunosuppressed AIIRD patients. However, studies in AIIRD patients [40] and those with inflammatory bowel disease[41] are ongoing. Currently, cost considerations for RZV in both Australia and Singapore will probably limit uptake in the foreseeable future.

4.1 | Summary

Availability of the recombinant RZV vaccine will simplify zoster vaccination in AIIRD patients as it can be given concurrently with bDMARDS and tsDMARDS. While it will eliminate the risk of disseminated post-vaccination HZ, cost may limit widespread use.

5 | CONCLUSION

The current pandemic has highlighted the importance of vaccination in preventing disease, especially in immunosuppressed AIIRD patients. There is increasing availability and range of vaccines against SARS-CoV-2, influenza and HZ. Their knowledge of immunosuppression and trust placed in them by patients means rheumatologists should take the lead role in vaccination advice for their patients.

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