RHEUMATOLOGY

Editorial

The Avalanche of Antirheumatic therapy and COVID-19 vaccinations

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Conflicts of interest

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This Editorial refers to 'COVID-19 vaccination and antirheumatic therapy', by Jack Arnold, Kevin Winthrop and Paul Emery.

At the time of writing, there are three vaccines for COVID-19 authorised for emergency use in the UK by the Medicines and Healthcare Products Regulatory Agency, three for use in the US by the Food and Drugs administration, and four for use in the European Union by the European Medicines Agency. The Pfizer-BioNtech and Moderna vaccines are nucleoside-modified messenger RNA (mRNA) vaccines that use viral mRNA to provide the genetic code to allow host cells to produce the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral spike protein.[1,2]The Oxford-AstraZeneca vaccine uses a replication deficient chimpanzee adenovirus vector to deliver the DNA sequence that codes for the SARS-CoV-2 viral spike protein to allow host cells to produce the viral spike protein.[3]

Mounting an optimal immune response to COVID-19 vaccines requires effective activation and function from both T and B lymphocytes.[4,5]Patients on immunosuppressive therapy may mount an unsatisfactory immune response following vaccination which could reduce vaccine effectiveness.

In this issue of the Journal, Arnold *et al*[6] have reviewed the existing data on the effect of antirheumatic therapies on vaccine responses such as influenza, pneumococcal and hepatitis B vaccines in patients with inflammatory arthritis. The purpose of their review is to formulate a pragmatic strategy for the management of immunosuppressive therapies in the context of COVID-19 vaccination.

The scarcity of supportive literature on the effect of biologics and various immunosuppressive therapies on COVID -19 vaccinations has been the main driver for the review. The authors have elegantly summarized the existing evidence on various vaccine efficacies alongside disease-modifying anti-rheumatic drugs (DMARDs) and various biologic

therapies; most of the data were extrapolated from published literature on influenza, pneumococcal, tetanus and Zostavax vaccines which might not be entirely applicable to COVID-19 vaccinations. There are still unknowns with regards to long term immune responses particularly in the context of DMARDs and various antirheumatic therapy following COVID-19 vaccinations. The therapeutic considerations are to avoid vaccination during a disease flare, ideally steroid taper to <10 mg prednisolone prior to vaccination, consider holding off methotrexate for two weeks post-vaccination, and avoiding vaccinating ideally for six months, post-rituximab. If there is insufficient time to alter or amend DMARDs/biologic treatment, then the recommendation is to vaccinate and reassess vaccine response at a later date. The basis of the advice about rituximab is that B-cell depleting therapy may impair humoral responses to the influenza and pneumococcal vaccines. There was also preliminary data suggesting worse outcomes particularly in rituximab-treated COVID-19 patients. Conversely, anti-TNF therapy is associated with decreased odds of hospitalisation due to COVID-19.[7]

Arnold *et al*[6] have focused on the effect of antirheumatic therapies on humoral immunity with less emphasis of cellular mediated immunity in the context of vaccines responses. T cells play a pivotal role in generating an effective antibody response and long term memory.[8] Whilst they acknowledged that most prior vaccine response studies largely investigated antibody titres post-vaccination[9], effective vaccine candidates, particularly for viruses such as SARS CoV2, would also benefit from inducing effective cellular mediated immunity. Furthermore, facilitating an optimal cytotoxic T cell effect is essential particularly when antibody responses fail to completely block viral infection or transmision[8] which has been the case with pathogens that are highly variable and/or cause persistent and latent infections such as human immunodeficiency virus, hepatitis C virus, and Mycobacterium tuberculosis.[8,10]

Thus, monitoring antibody levels alone as a marker of vaccine response may not accurately ascertain efficacy and protection.

Moreover, the pathogenic mechanisms of various rheumatic disorders and their impact on the immune system require special consideration.[11] The heterogeneity of these disorders and multifactorial interactions between different components of the immune systems and antirheumatic therapies may result in diverse clinical phenotypes and prognosis.[7] It is extremely difficult to apply the same approach to all patients with rheumatological disorders e.g. patients with systemic lupus erythematosus compared to rheumatoid arthritis or other connective tissue diseases.[11] The detailed advice with respect to individual drugs is welcome, the authors do stress that modification of therapy should not delay matters - the priority is to proceed with vaccination. Pending data on vaccine outcome in patients with or without pre-vaccine medication will also be important. Exploring the risks and benefits of treatments with patients to promote shared decision making and obtain informed consent is essential whilst the situation with COVID-19 pandemic and guidance is evolving with time.

Unanswered questions

Further understanding of the immune response to COVID-19 vaccines in the context of various antirheumatic medications is vital in formulating a logistic strategy for individuals with autoimmune and inflammatory disorders. More data is needed to understand the immune biomarkers for protection against COVID-19 vaccinations. Antibodies generally speaking are potential correlates of protection, although the protective role of cellular immunity and duration of both neutralising antibodies and cellular responses and the correlates of protection remain to be defined. The effectiveness of the current COVID-19 vaccines against prevailing variants of SARS-CoV-2 is reassuring. However, strict surveillance to identify new variants

of concern is required in order to change our mind-set from a reactive to a more proactive and predictable approach.

REFERENCES

1. Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. Immunity. 2020; 52:583-9.
2. Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov 2018;17:261-279.
3. van Doremalen N, Lambe T, Spencer A, et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature 2020;586:578–582.
4. Ewer KJ, Barrett JR, Belij-Rammerstorfe S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med 2021;27:270-8.
5. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 2020;586:594–9.
6. Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. Rheumatology (Oxford). 2021 Mar 12:keab223. doi: 10.1093/rheumatology/keab223.
7. Scherlinger M, Lutz J, Galli G, Richez C, Gottenberg JE, Sibilia J, Arnaud L, Blanco P, Schaeverbeke T, Chatelus E, Truchetet ME. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments. Semin Arthritis Rheum. 2021 Feb;51(1):36-42.
8. Sallusto, F.; Lanzavecchia, A.; Araki, K.; Ahmed, R. From Vaccines to Memory and Back. Immunity 2010, 33, 451–463.

9. Ben Nessib D, Fazaa A, Miladi S, Sellami M, Ouenniche K, Souabni L, et al. Do immunosuppressive agents hamper the vaccination response in patients with rheumatic diseases? A review of the literature. Therapies [Internet]. 2020; Available from: https://doi.org/10.1016/j.therap.2020.08.002
10. Skeiky YA, Sadoff JC. Advances in tuberculosis vaccine strategies. Nat Rev Microbiol. 2006 Jun;4(6):469-76. doi: 10.1038/nrmicro1419. PMID: 16710326.
11. Soy M, Keser G, Atagunduz P, Mutlu MY, Gunduz A, Koybaşi G, Bes C. A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: a non-systematic review. Clin Rheumatol. 2021 Mar 22.