Editorial

The COVID-19 Vaccine Landscape: What a Rheumatologist Needs to Know

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In January 2020, a new strain of coronavirus was described. Less than 3 months later, a pandemic was declared. Within 9 months, the first vaccine received emergency authorization. Keeping up with the infodemic has been arduous, due to the unparalleled pace of scientific study. Here, we summarize the work toward a vaccine, framing the progress in a manner relevant to physicians managing patients on immune modulation.

The SARS-CoV-2 vaccines

SARS-CoV-2 is a positive sense single-stranded RNA virus. Like other coronaviruses, it has 4 structural components: spike, envelope, membrane, and nucleocapsid proteins. The spike protein facilitates binding and fusion to host cells, making it an attractive vaccine antigen. There have been 3 approaches in developing a SARS-CoV-2 vaccine: (1) attaching the spike protein to a nonreplicating viral vector; (2) using messenger RNA (mRNA) technology to induce host spike protein synthesis; and (3) delivery of spike protein with an adjuvant.

The AstraZeneca vaccine takes the first approach, using a replication-deficient chimpanzee adenovirus vector containing the spike gene. Once inside a cell, the vector uses the cell’s existing molecular machinery to transcribe DNA to mRNA and produce the spike protein. Replication-deficient viral vector-based vaccines have been used safely in immunosuppressed individuals. The second approach is employed by Pfizer-BioNTech and Moderna, who have produced the first vaccines to be licensed using synthetic mRNA technology. mRNA is within a lipid droplet, protecting it from enzymatic breakdown and enabling cell entry. The mRNA strand induces spike protein synthesis without entering the cell’s nucleus or affecting genetic material. Finally, Novavax have developed a protein-based vaccine, currently in submission for licensing. Manufactured from moth cells infected with baculovirus, it contains a modified spike gene, producing the spike protein. This is harvested and assembled into nanoparticles. It is combined with an immunity-priming adjuvant (matrix M1), enhancing vaccine response. The spike protein is taken up by cells and presented on their surface.

Vaccine efficacy

Phase III vaccine trials have demonstrated high efficacy: >90% with Pfizer-BioNTech and Moderna; 70% with AstraZeneca. Direct comparisons are problematic due to differences in coronavirus disease 2019 (COVID-19) case ascertainment between studies. Importantly, the AstraZeneca vaccine did not identify patients in the vaccine arm with severe COVID-19 who required hospitalization.3

Patients receiving immunosuppression are considered clinically extremely vulnerable (CEV). Many have spent the pandemic “shielding.” National recommendations by vaccination and immunization committees advise that the vaccination program prioritize CEV individuals.2,3,4

There are currently no data on the immune response to the SARS-CoV-2 vaccines in patients receiving immunosuppression. Published trials have excluded immunosuppressed patients, and most listed autoimmune conditions in their exclusion criteria (Table 1). It is possible that individuals receiving immunosuppressive therapy may mount less robust immune responses to the SARS-CoV-2 vaccines, as is observed with other vaccines in this patient population, subject to the type and dose of immunosuppression. For example, a 30-40% reduction in IgG response is observed with the influenza vaccination in patients on methotrexate (MTX).3 However, trial data have demonstrated comparatively high titers of neutralizing antibody against SARS-CoV-2...

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post vaccination in immunocompetent individuals compared to that following natural infection. It is therefore likely that immunosuppressed patients will mount clinically meaningful neutralizing antibody titers, even if they are numerically lower than immunocompetent individuals. Research in this area is anticipated to be published imminently.

It is tempting to consider measuring serological response to determine vaccine immunogenicity. Some commercial COVID-19 antibody assays measure immune response to the nucleocapsid, and not the spike, protein. These tests would remain negative post vaccination. It is also unclear if antibody titers are the best surrogate of vaccine efficacy. Measures of T cell response may be superior.

Reports of new SARS-CoV-2 variants are concerning, as mutations could theoretically evade the vaccine-induced antibody response. Pfizer and Moderna have tested serum from immunized patients and demonstrated effective neutralization to the UK strain (B.1.1.7) but reduced capacity against the South African (B.1.351) variant. The true effect of mutation events will be clarified by the proportion of fully vaccinated patients subsequently hospitalized with a variant strain.

Extending the dosing schedule
The UK SARS-CoV-2 vaccination program has delayed the second dose, a decision not replicated in other countries to date and one that has generated much skepticism from the medical community. This is based on prioritizing first doses to as many people as possible. Understanding the effect of this delay requires consideration of reasons for sequential vaccine dosing: (1) to increase the initial immune response; and (2) to strengthen response durability. The initial immune response to licensed SARS-CoV-2 vaccines is strong, but uncertainties remain about the duration of protection offered.

The AstraZeneca trial included longer spacing between doses: 59% of UK and 19% of Brazilian trial participants received the second dose 9–12+ weeks after the first. Vaccine efficacy after the second dose was higher in patients with > 6 weeks between doses (65% vs 53%). This is seen with routine vaccinations where increased duration between doses is advantageous in strengthening IgG durability.

There is limited evidence on protection offered by a single SARS-CoV-2 vaccine dose. Pfizer-BioNTech report vaccine efficacy of 52% after the first dose until the second dose (3-week spacing), rising to > 90% after the second dose. This does not imply that the first dose is 52% effective, as the immunological response would be expected to strengthen irrespective of the second dose. There are simply no data on single-dose efficacy beyond 21 days. Public Health England’s exploratory analysis (full data not publicly available) of the AstraZeneca trial participants receiving 1 standard dose reports 73% efficacy.

There is justification for dose spacing from a public health perspective. Given that the UK was following a similar trajectory to other European countries, we may have been facing a third wave of COVID-19 infection. The UK vaccination program immunized 15 million people with their first dose by mid-February, targeting at-risk groups, accounting for 88% of all COVID-19 deaths. Delaying the second dose will be a trade-off between stronger earlier individual immunity and moving toward population herd immunity.

As it stands, international organizations (Centers for Disease Control and Prevention, WHO) have iterated that the vaccine efficacy after the second dose is likely robust, and that any potential waning is not a reason to delay the second dose for those who are to receive it. Thus, the goal remains to allow the greatest number of people to receive the vaccine, given the potential for severe illness or death in those who are unvaccinated.
Control and Prevention, World Health Organization) and regulatory bodies (U.S. Food and Drug Administration [FDA], European Medicines Agency [EMA]) have advised vaccination schedules should be followed as designed in vaccine trials. While the rest of the world watches, time will tell if the UK decision was wise.

The question surrounding immunsuppression

In immunosuppressed patients, the rationale for spacing doses is complex. The blunting of initial immune response and timing of vaccinations around disease-modifying antirheumatic drug (DMARD) treatment require consideration. Current guidelines advise routine vaccines are administered during quiescent disease and before planned immunosuppression. Given the unpredictable natural history of autoimmune diseases in terms of flare, it is not practical to risk delaying vaccination to await disease control. For patients commencing planned immunosuppressive treatment, UK national recommendations advise that SARS-CoV-2 vaccines are offered at least 2 weeks before therapy, when their immune system is better able to respond, and that the second dose is administered before starting treatment. This likely necessitates offering the second dose at the recommended minimum spacing (3–4 weeks after the first dose).4

For patients already on immune modulation, the literature on routine vaccinations could be extrapolated. However, responses differ across vaccinations. Synthetic and biological DMARDs demonstrate immunogenicity with the influenza vaccine, but changes in serologic response are seen with the pneumococcal vaccine. Rituximab clearly suppresses humoral responses to both vaccines13,14 and is anticipated to exert a similar effect on the SARS-CoV-2 vaccines. The general advice to vaccinate at least 6 months after administration and 4 weeks before the next course of B cell–depleting therapy may not be possible with the SARS-CoV-2 vaccines, especially if using longer dosing intervals. Current routine vaccination guidelines suggest that immunization may be considered under B cell–depleting therapy, taking into consideration a potential suboptimal response to the vaccine. This may be a pragmatic decision, made on an individual basis. For some patients, there may be justification to interrupt conventional synthetic DMARD therapy. This is demonstrated in influenza vaccine randomized controlled trials where IgG responses were greater when MTX was discontinued for 2 weeks post vaccination.5,15 The benefit of interrupting treatment may be offset by disease flare.16 Destabilizing disease control during the pandemic might pose greater risk.

Safety

There are limited data on SARS-CoV-2 vaccine safety in our patient population. Acute side-effects in healthy volunteers include fever, myalgia, headache, nausea, fatigue, and injection site reactions. These may be more pronounced after the second dose. Risk of allergy is higher with the Pfizer-BioNTech vaccine (1:100,000 vs 1:1,000,000 with most vaccines).17 This may relate to the polyethylene glycol (PEG) ingredient, also in the Moderna vaccine. Similar PEG allergy is reported with certolizumab pegol. The FDA, European Medicines Evaluation Agency, and Medicines and Healthcare products Regulatory Agency advise individuals with severe allergy/anaphylaxis to any vaccine component to avoid vaccination. Longer-term effects have not yet been defined. There is a theoretical risk that the vaccine may trigger autoimmunity by molecular mimicry, with antibodies to spike proteins cross-reacting with structurally similar host proteins.18 The vaccines may also drive inflammation by their potent type I interferon response.19 These are yet to be described, and current literature on existing vaccinations in our patients is reassuring, with no changes in disease activity and only mild adverse events,14 although studies were underpowered for safety and were unable to detect rare events. The safety of the SARS-CoV-2 vaccines will remain under immense scrutiny in the coming months. Reports of central venous sinus thrombosis combined with thrombocytopenia occurring in the days following vaccination have been described and are currently under investigation by the EMA.20 Estimates of risk and benefit clearly favor vaccination and the narrative from healthcare professionals to patients and the general public will be crucial in maintaining trust.

Conclusion

If you have read to the end of this editorial, we hope you have taken away our key messages. The benefits of SARS-CoV-2 vaccines outweigh the risks for our patients. Even if vaccination produces a smaller IgG response, it likely still confers protection. At present there is no rationale to choose one vaccine over another. A universal decision on DMARD interruption has not been made and there may be clinicians who make personalized decisions for their patients. Future research needs to address the question of vaccine effectiveness (not solely immunogenicity) in patients with autoimmune rheumatic diseases.

REFERENCES