Rheumatology and COVID-19 at 1 year: facing the unknowns

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This issue of the Annals of the Rheumatic Diseases includes the freshly minted European Alliance of Associations for Rheumatology (EULAR) points to consider in the pathophysiology and use of immunomodulatory therapies in COVID-19. This publication adds to the formidable extant literature on COVID-19, which is of particular interest to rheumatology as the field has become an important stakeholder in the investigation of immune-based therapies targeting the inflammatory phase of SARS-CoV-2 infection. From the outset, we believe these authors recognised that their mission to provide real-time analysis in a timely and reflective manner was a Sisyphean task, as at the time of this writing, over 113,635 publications have been posted on PubMed and MedRxiv alone, largely in the past 12 months (search date 14 February 2021). To their credit, the systematic review process in the accompanying literature search included a ‘hand search’ of the ever increasing grey literature consisting of the torrent of press releases on new drugs and therapies. These types of sources in the COVID-19 field are of particular importance as they are often amplified by social media, creating what some may refer to as ‘epistemic chaos’, and posing an increasing threat to the iterative method of science (eg, the early embrace of hydroxychloroquine). Thus, these points to consider should be viewed as ephemeral and will need ongoing curation to maximise their value in the months ahead.

To poise ourselves to best meet this challenge, we thought it logical to not focus on what has already happened but rather to attempt to selectively gaze ahead and consider some key areas of interest to the field of rheumatology which will likely impact our profession and our patients.

UNKNOWN NUMBER 1: COVID-19 VACCINES AND RHEUMATOLOGY

We now have strong efficacy data reported for three different vaccine constructs: 90%-95% for mRNA vaccines from Pfizer and Moderna, 89% for a protein-conjugate vaccine from Novavax and somewhat lesser efficacy for the adenoviral vaccines that have recently reported. Interestingly, the adenoviral-based Astrazeneca vaccine reportedly 62% efficacy in Brazil, but markedly higher efficacy in England (90%), where mistakenly a half-dose was used as the primary vaccination followed by the correct full dose. The adenoviral-based Jannsen vaccine reported 72% efficacy in a one-dose trial; data from their phase III trial using two doses are still pending. We know that these vaccines provide neutralising antibody titres and measures of cell-mediated immunity equal to or greater than that found in convalescent plasma of those with prior wild-type infection. We hope this implies more robust protection and for longer time periods than does natural infection, and there are data to support longer-term durability of vaccine-induced immunity responses. Interestingly, while second cases among individuals have been reported and in some cases had worse outcomes, the incidence of second cases in the 6-9 months after infection appears to be small, with as few as <1% being reinfected as documented in a large public health study in England.

So what does this mean for those with immune-mediated inflammatory diseases? Most of our understanding of vaccine responses in rheumatic disease and the influence of disease-modifying antirheumatic drugs (DMARDs) on those responses has been generated by a small number of studies involving influenza, pneumococcal and tetanus vaccines, and less commonly others. In general, rituximab is well known to severely diminish the humoral response to vaccination. Both methotrexate and JAK inhibitors have been shown to decrease response to influenza or pneumococcal polysaccharide vaccinations. Tumour necrosis factor blockers and interleukin (IL)-17 blockers have been shown to have little or no effect on these vaccines. Very little data exist for abatacept, but likely responses are diminished. From an efficacy standpoint, it is likely that some of these DMARDs will diminish COVID-19 vaccine immunogenicity, raising the need to study these practical questions as soon as possible. From a safety standpoint, phase III trials have not raised any serious safety concerns, and the postmarketing period is remarkably devoid of serious adverse events despite widespread scrutiny and millions of individuals having been vaccinated. The safety of these vaccines remains to be seen in rheumatology patients, however. No vaccines currently available (or expected to be available in the near future) are live replicating vaccines, including the adenoviral vaccines, and therefore are not contraindicated in immunosuppressed patients. The potential for COVID-19 vaccines to induce disease flare or potentially new autoimmune and/or auto-inflammatory complications remains unquantified. This is of particular relevance as the impact of downstream effects of innate interferon responses generated particularly by the mRNA vaccines remains unknown. Thus, efforts such as the EULAR COVAX database (https://www.eular.org/eular_covid19_database.cfm) where rheumatology providers can report untoward effects from COVID-19 vaccines are vitally important.

The wildcards of vaccine acceptance and the evolution of new virus variants make the future impossible to predict, but our strategy at present is easy to articulate: we should vaccinate as many willing people as quickly as possible no matter the vaccine type. The rise of new variants that are less susceptible to vaccine-induced (and natural) immunity has been demonstrated already in the context of phase III trials for at least two vaccines in development, reminding us that this is likely not a ‘one and done’ situation. This virus has become endemic and commitment to long-term development and maintenance of effective vaccines will remain important for governments and industry alike. As a rheumatology community, we will need to continue to invest in the research that will guide our ability to best protect our patients.

UNKNOWN NUMBER 2: AUTOIMMUNITY AND COVID-19

The intersection of COVID-19 and autoimmunity is complex and bidirectional. For patients with pre-existing clinical or subclinical autoimmune/autoinflammatory diseases, there is potential for their
Bidirectional effects of COVID-19 on autoimmune/autoinflammatory diseases.

**Figure 1** Bidirectional effects of COVID-19 on autoimmune/autoinflammatory diseases. MIS-A, multisystem inflammatory syndrome in adults; MIS-C, multisystem inflammatory syndrome in children.

**Box 1 Possible aetiopathogenetic mechanisms of long COVID-19**

1. End organ damage as sequelae of severe COVID-19.
2. Effects of persistent and possible occult viral infection.
3. Exacerbation of underlying comorbidities, including clinically occult autoimmune and autoinflammatory disease states.
4. De novo autoimmune or autoinflammatory disease from persistent immune activation or autoimmunity.
5. Unknown mechanisms.

> Can be based on more than one mechanism in a given patient.
(absolute risk reduction 4% at 28 days) when given to hospitalised patients with severe COVID-19. This has been the largest trial of IL-6 inhibition to date and gives us pause in our effort to critically appraise where IL-6 inhibition will now fit in the treatment of severe COVID-19.25 Reasons for the somewhat surprising data may include the power of its sheer size (ie, over 2000 patients on active IL-6 inhibition), the fact that 82% also received glucocorticoids (now a standard of care for serious disease) and improvements in general care of patients with serious disease. Moving ahead, we now await results of numerous other agents targeting multiple pathways both singly and combination protocols. Perhaps instead of finding a dramatic drug, we will ultimately whittle away at COVID-19 morbidity and mortality by iterative steps.

As the Nobel Laureate Niels Bohr once said ‘Prediction is very difficult, especially if it’s about the future!’ but in COVID-19 that is exactly what we must do. These are but a few of the many pressing issues for the field of rheumatology to consider. We know there will be many more, so stay tuned.

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