SARS-CoV-2 and the rheumatology patient: the last 12 months and a boost in the future

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EDITORIAL

It is a rare opportunity to enter the backside (hopefully) of a pandemic. Not since the Spanish influenza has the world experienced such a level of contagion. While we averted a worldwide crisis 20 years ago with the first SARS virus infection, SARS-CoV-2 with its unique ability to transmit easily among asymptomatic persons has altered our 21st-century appreciation and respect for viral diseases. From a scientific standpoint, we believe the scientific collaboration and innovation of the last 12 months have been unprecedented. The pandemic united rheumatologists and infectious disease physicians in an effort to develop both therapeutics and vaccines. While some of our patients appear to be partially protected with the currently available vaccines, we must continue our efforts at understanding optimal ways to manage Disease Modifying Anti-Rheumatic Drug (DMARD) therapy and vaccination in light of COVID-19. Providing a booster dose of vaccine to those with suboptimal vaccine responses, particularly those at greatest risk due to immune compromise, must urgently be pursued and evaluated.

In this themed issue of the *Annals of the Rheumatic Diseases*, focused on COVID-19 and SARS-CoV-2 vaccination in rheumatology, a number of papers have been assembled, which advance our understanding in this area and should allow for optimising the approach to this pandemic in the near future.^{1–20} To date, our understanding of COVID-19 risk in rheumatology comes primarily from observational registry-based cohorts. A clear signal has emerged in that patients receiving B-cell depletion therapy or

high-dose glucocorticoids at baseline are at higher risk of more severe COVID-19 outcomes if infected.¹⁴ In addition, and most recently, the global alliance data suggest an increased risk for Janus kinase (JAK) inhibitors as well, although less statistically sophisticated analysis from inflammatory bowel disease registries does not suggest an increased risk for tofacitinib.²¹ Similarly, the findings of these studies are affected by channelling bias/confounding by indication (eg, those with higher disease activity are more likely to be using these agents), and it is clear that many rheumatology patients who perceive themselves at higher risk are more likely to practise avoidance behaviour to minimise the risk of infection.²² Despite the difficulty in controlling for these factors within these studies, there is strong biologic plausibility as to why these drug classes could diminish antiviral host defences. The development of a neutralising antibody response is clearly important in recovery from an initial infection and protection from subsequent infection.^{23–25} Furthermore, interferon signalling is an essential host response to a number of viral infections, including SARS-CoV-2.²⁶

THERAPEUTICS

The rheumatological therapeutic armamentarium took centre stage from the beginning of the pandemic, with an effort to repurpose existing drugs for both antiviral and anti-inflammatory purposes. Despite the ‘Trumped-up’ early results of hydroxychloroquine studies, randomised controlled trials (RCTs) provided no evidence of efficacy. Despite initial observational studies suggesting efficacy,²⁷ the eventual triumph of interleukin 6 inhibition after multiple negative RCTs was notable,²⁸ whereby a small magnitude of effect could only be ‘significant’ with an RCT of unusually large proportions. The Recovery trial enrolled >4000 hospitalised hypoxic patients with COVID-19 randomised to tocilizumab or standard of care and observed a decrease in mortality from 33% to 29% (corresponding to a number needed to treat of 25)²⁹; this

was consistent across other similar RCTs when subjected to meta-analysis (OR for survival, 0.83 (0.74–0.92)),³⁰ but taken as individual ‘pivotal’ clinical trials, these studies were deemed ‘negative’, lacking the statistical power to detect a relatively small magnitude of effect. The evolution of study end points and inclusion criteria across these studies is beyond the scope of this editorial, but suffice it to say, trials eventually settled on the prevention of severe disease (ie, a combined outcome of mechanical ventilation and death) as a primary outcome measure. To date, monoclonal antibodies provide our best antiviral approach (more below), and more recently, from a drug class of initial concern (JAK inhibition) in potentially diminishing host antiviral response, baricitinib has been shown to shorten time to clinical recovery when used with remdesivir and to reduce mortality when used in combination with dexamethasone.^{31 32} In addition, tofacitinib was more recently shown to do much the same.³³ Thank you Rheumatologists for leading the way!

VACCINATION

While we lack well-defined ‘immune correlates of protection’, experimental studies in non-human primates suggest the importance of both cell-mediated and humoral vaccine responses. Use of monoclonal antibodies in infected naïve macaques was protective in dose-dependent fashion following infectious challenge. Antibodies limited both the risk of infection and the extent/length of disease among those infected. Regarding T-cell immunity, when comparing previously infected macaques, those that were experimentally depleted of CD8 + T lymphocytes (n=5) were easily reinfected on challenge compared with macaques with intact cell-mediated immunity (n=5) that did not develop infection.³⁴ These data lay the foundation for our observations in human RCTs of monoclonal antibody therapy against SARS-CoV-2—data from pivotal phase III vaccination studies, as well as observational studies of breakthrough infections among those previously vaccinated; taken together, these data inform strategies as to how to best to manage the rheumatology patient in this pandemic era.

We now have human data that recapitulate those from the experimental macaque studies. Prophylactic use of anti-SARS-CoV-2 monoclonal antibodies among uninfected humans shows the ability to prevent infection.³⁵ Furthermore, among those infected who have

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not yet mounted an antibody response, neutralising antibodies have proven able to prevent progression of infection from mild to severe disease.^{35 36} The development of these antibodies started with high-dose products, but eventually proved that lower doses were equivalent in antiviral capacity. These data suggest that some threshold level is necessary to provide protection; however, this threshold remains undefined and might differ depending on whether cell-mediated immune responses are present. The data from phase III vaccine studies attest to a correlation of high vaccine efficacy with both robust humoral and T-cell responses.³⁷ Importantly, diminished efficacy against some variants correlates with in vitro reductions in vaccine-induced neutralising capacity against these variants.^{38 39} Finally, while little published data exist on 'breakthrough' infections to date, early reports suggest immunocompromised patients are disproportionately affected. Up to 40% of a large cohort (n=152) of breakthrough infections in recipients of the Pfizer messenger RNA (mRNA) vaccine in Israel were immunocompromised, and B-cell depletion therapy was an important identified risk factor.⁴⁰

To date, studies from rheumatic diseases, transplant, glomerular diseases and multiple sclerosis have consistently identified a large percentage of vaccinated individuals who have no measurable humoral responses after vaccination.⁴¹ B-cell depletion therapy, mycophenolate, tacrolimus and high-dose corticosteroids have all been associated with a lack of seroconversion.^{6 42 43} Interestingly, some data suggest that patients using rituximab still develop cell-mediated immunity despite a lack of humoral response.⁴⁴ Methotrexate has been shown to strongly diminish the development of cytotoxic CD8 + responses, documented to be important in SARS-CoV-2 protection at least among macaques.^{8 34} There are data suggesting JAK inhibitors and tumour necrosis factor blockers also diminish responses, but to much lesser degrees.⁴²

BOOST OR NOT TO BOOST

As we write, the American College of Immunisation Practices is meeting to consider this very issue. The demonstrable efficacy of exogenous monoclonal antibodies clearly speaks to the importance of protective neutralising antibody responses so that, in our mind, patients with an undetectable antibody response after vaccination will not likely have the same protection as those with positive titres.

While the level of sufficient or 'protective' titre is unknown, it is hard to believe that an absence of titre does not equate to diminished protection, even if vaccine-induced cell-mediated immune responses are developed. Accordingly, for those individuals receiving B-cell depletion and other therapies strongly associated with a lack of seroconversion, it seems reasonable to evaluate postvaccination titres, recognising such serological assessments are not necessary for otherwise healthy individuals. It is also important to recognise that there is wide variability in the reliability of existing licensed assessments. If antibodies are absent, however, then a booster dose of vaccine will increase the likelihood of their development and ultimately might increase protection.⁴⁵ For all other DMARD recipients, while levels of postvaccination titres might be somewhat diminished, it is unclear whether this is problematic and whether a booster of vaccine would be required or even helpful. In fact, the first study in immunosuppressed non-responders to mRNA vaccination has been completed, in which a randomised comparison of inducible humoral and cellular immune answers to a third booster vaccination with mRNA vaccine versus single switch boost using a vector vaccine was done, and results are awaited eagerly (clinical trial registration number: 2021-002348-57). In the meantime, our patients who are likely to develop inadequate vaccine responses should live like it was 2020, with masking and avoidance in mind, and sceptics need to be reminded the greatest risk of inadequate immune response occurs with a failure to get vaccinated! We should continue to pursue studies to evaluate the effect of holding certain DMARDs to determine whether this assists with the building or maintenance of vaccine-induced immune responses associated with both primary and booster immunisations alike. Finally, we should reassure our patients that the vaccines in use are safe, not associated with underlying disease flare to date and much more enjoyable to receive than COVID-19 itself.^{7 11 14 15 46}

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