SARS-CoV-2 vaccines in patients with SLE

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ABSTRACT

As the Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) vaccines become available to patients with autoimmune diseases and SLE, practitioners will have to inform them about the safety and efficacy of these vaccines. Here we discuss the challenges of applying vaccine data to patients with autoimmune diseases and the evidence available in the literature that may help in the decision process.

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Key messages

What is already known about this subject?
► There have been previous studies on patients with SLE and COVID-19, and patients with SLE and vaccines; however, there is minimal information about patients with lupus and SARS-CoV-2 vaccinations.

What does this study add?
► This paper discusses the challenges of applying vaccine data to patients with autoimmune diseases and reviews the evidence available in the literature.

How might this impact clinical practice or future developments?
► This paper may help practitioners counsel patients with autoimmune diseases who are eligible for vaccination.

The COVID-19 pandemic has affected nearly every corner of the world and changed the face of medicine. Almost a year into the pandemic, there have been over 91 million cases and more than 1970000 deaths globally.[1] During the winter of 2021, there has been a new surge of virulent strains in many parts of the world with no assurances of when lasting relief can be expected. Given these grim statistics, the approval and initial dispersion of the Moderna and Pfizer/BioNTech vaccines are monumental events. There is limited knowledge about the safety and efficacy of the COVID-19 vaccines in patients with SLE. While the overall safety and efficacy of the vaccines are reassuring, reports of immunological adverse reactions to the vaccine may be concerning to people with autoimmune diseases such as SLE.

SLE is characterised by dysregulation in type I interferon pathways.[2 3] Type I interferons are key components of the innate and adaptive immune responses to new pathogens.[4] The critical role of type I interferons in antiviral immunity is well known, including responses to SARS-CoV-2.[5 6] While data are limited, patients with SLE do not seem to be at higher risk of SARS-CoV-2 infections or severe COVID-19 disease compared with the general population.[7–9] However, patients with SLE may be at higher risk of hospitalisation during the COVID-19 disease course.[10 11] In addition, it is possible that COVID-19 leads to increased SLE disease activity.[12 13] COVID-19 has been associated with the development of autoantibodies in the serum of hospitalised patients and features suggestive of severe, uncontrolled autoimmunity appear to be present in those most ill from COVID-19.[14–16]

Patients with SLE in our cohort experienced COVID-19 infections at a rate similar to that of the general population (27/450 or 6%), and 6/27 (22.2%) experienced a disease flare within 22 days after developing symptoms.[17] Of these six flares, five were mild/moderate and one was severe, using SLE Disease Activity Index Flare Index definitions. The symptoms manifested included arthritis, alopecia, rash, pleurisy and serological worsening (low complement components C3/C4 and antibodies to double-stranded DNA (anti-dsDNA)). Although these observations did not seem to indicate a high risk of serious flares, further long-term longitudinal studies are needed to determine the impact of COVID-19 infection on SLE disease activity.

Both Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) vaccines contain RNA that encodes the stabilised prefusion SARS-CoV-2 Spike (S) protein. The RNA enters host cells and produces non-virulent Spike protein that elicits high titres of neutralising antibodies and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.[18–21] The immunogenic protein includes the full-length S protein, with both the receptor-binding subunit (S1) and the membrane

fusion subunit (S2). These are the first mRNA-based antiviral vaccines in human use and, as such, produced some public controversy. Phase I trials found systemic side effects in up to 90% of participants.[18 19] However, the late phase vaccine trials provided reassurance about their safety prior to what is planned to be the largest-scale worldwide vaccine distribution in history.[22 23]

The efficacy rate in preventing COVID-19 infections for the Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) vaccines was 94.1% and 95.0%, respectively. The phase III trials of both vaccines reported low percentages of serious adverse events (below 0.1%).[22 23] Local reactions were common and included tenderness, erythema and swelling at injection sites. Transient systemic reactogenicity such as fever, fatigue, headache, and muscle and joint pain were noted. These effects are generally seen within 24–48 hours following the vaccination and one or more may occur in up to 95% of vaccine recipients.[22 23] Earlier work from Pfizer/BioNTech on a vaccine (BNT162b1) that encodes the secreted trimerised SARS-CoV-2 receptor–binding domain was abandoned because of greater severity of systemic reactions in older adults.[18 24]

Unfortunately, patients treated with immunosuppressants or immune-modifying drugs for >14 days within 6 months of entry were excluded from all phases of Moderna (mRNA-1273) vaccine trials (NCT04470427).[19 23] In the Pfizer/BioNTech (BNT162b2) vaccine trials, individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention were specifically excluded from phase I (NCT04368728), and patients who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, were excluded from phases I–III.[22 24] The applicability of the published data to the safety and efficacy of COVID-19 RNA vaccines in patients with autoimmune disorders is unknown, especially in those patients receiving immunosuppressive treatment.

The dysregulation of the immune systems and concurrent use of immunosuppressive therapies raise theoretical concerns about the efficacy of vaccinations in patients with SLE. To the extent that optimal dosing of immune modulators restores immune set points towards normal, vaccine responses might be enhanced, allowing the development of protective immunity without major immunological side effects. However, since our current knowledge falls short of refined immunological control of the background immune disorder, vaccines could synergise with either incomplete or mistargeted immune modulation to either inhibit effective adaptive immunity or unleash excessive interferon responses. Indeed, as indirectly suggested by the results of a study of influenza vaccine in patients with lupus, greater interferon responses might in turn be associated with decreased neutralising antibodies to vaccinations, along with a greater development of autoantibodies and flares.[25] Thus, treatments targeting the immune system could have the potential to enhance or inhibit vaccine responses, depending on a patient's underlying pathological immune variables and degree of immune suppression.

There are a number of factors at play that may provide unique challenges to the response of patients with lupus to SARS-CoV-2 vaccines. Quantitative and qualitative lymphocyte defects are prevalent in SLE. Lymphopenia is one of the most common haematological manifestations in SLE,[26] resulting from a combination of lymphocytotoxic antibodies, complement-mediated cytolysis, impaired lymphopoiesis, and side effects of immunosuppressants and B-cell depleting agents.[27 28] In addition, CD8+ T-cell responses are dampened in patients with SLE, and the compromised cytotoxicity results in susceptibility to viral infections.[29–32] Furthermore, decreased immunogenicity and inadequate immune responses have been reported in patients with SLE receiving vaccines against pneumococcus and influenza.[33–35] Any condition that shortens durability of responses that build immunity or impairs immunological memory might weaken the long-term efficacy of vaccinations in patients with SLE. Some clinical evidence supports this theory. Serial antibody titers to capsular polysaccharides were followed up for 3 years in 19 patients with SLE after immunisation with polyvalent pneumococcal polysaccharide vaccine; at year 3, the antibody levels of vaccinated patients with SLE dropped below the threshold of protection in 8 of 19 (42%) patients, and 1 patient developed a pneumococcal pneumonia.[36] Taken together, these data illustrate that much remains to be learnt about vaccine responses in SLE. In the setting of dysregulated cellular and humoral immunity, patients with SLE might require modifications in vaccination strategies to achieve adequate and durable immune responses.

Previous studies have established that similar type I interferon and proinflammatory cytokine pathways are shared between SLE and COVID-19,[2 3 5 6] which could either potentiate or dysregulate immune responses to SARS-CoV-2 vaccines while triggering disease activity in previously stable lupus. Vaccine-associated enhanced respiratory disease was not observed in either the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) vaccines trials; the risk of vaccine-associated enhanced respiratory disease was observed in animal models of SARS-CoV and Middle East respiratory syndrome coronavirus infections, and it was associated with vaccine antigens that induce antibodies with poor neutralising activity and Th2-biased responses.[37 38] The imbalance of Th1/Th2 subsets is important in the pathogenesis of SLE,[39–41] which raises concern for a potential risk of developing vaccine-associated enhanced respiratory disease in patients with lupus. A second concern is that the SARS-CoV-2 vaccine delivers mRNA encoding S protein that is likely degraded by normal cellular process[42] and could interact with a number of cytoplasmic RNA-binding proteins involved in the post-transcriptional regulation of inflammation; these pathways play a role in the pathogenesis of autoimmune diseases, as a consequence worsening SLE.[43] Similarly, RNA vaccines could trigger Toll-like receptors, setting

off the production of type I interferons.[44] However, there are no data yet to suggest that the dose and timing of an intramuscular injection of RNA vaccine would have any significant impact on the immune cells that underlie the pathogenic mechanisms of SLE.

The safety of routine immunisations against common pathogens has been well established in patients with SLE. Patients with SLE have been vaccinated against pneumococcus,[45] hepatitis B virus (HBV),[46] *Haemophilus influenzae* type B,[47] human papilloma virus (HPV)[48 49] and varicella zoster virus with minimal concerning side effects.[50 51] However, inactivated influenza vaccines were reported to trigger transient increases in a variety of serum autoantibody titres in patients with SLE, including ANA, dsDNA, anticardiolipin, anti-Smith, anti-RNP, anti-Ro and anti-La. This transient increase in autoantibody response is not necessarily or consistently associated with significant increases in clinical disease activity in all studies following these vaccinations.[25 52 53] On the other hand, prospective monitoring for flares has been inconsistent. SLE flares occurred in only 4 out of 73 patients with SLE (5%) within 3 months of immunisation against poliomyelitis in a nationwide campaign following a 1988 Israeli outbreak.[54] A body of data is accumulating describing new-onset SLE or lupus-like syndromes following administration of HBV and HPV vaccines, but no causal relationships have been established.[55–58]

The current mRNA vaccines for COVID-19 possess the advantages of enhanced stability and translational efficacy that potentiate the persistence of immunogen expression[59]; additionally, the high immunogenic potency elicits strong immune responses.[60 61] These two advantages, when combined together, may cause more immune stimulation than conventional vaccines that could potentially induce exacerbations in patients with existing autoimmune disorders or unmask de novo autoimmune diseases in predisposed individuals. Insights into the complex immune responses to mRNA vaccines in patients with autoimmune disease might provide clues to better treat the disease itself. For example, delivery of mRNA vaccine encoding multiple sclerosis specific autoantigens in a murine model successfully delayed onset and reduced severity of established disease by inducing antigen-specific tolerisation without general immunosuppression.[62] Understanding the immunogenicity, efficacy, and safety of mRNA vaccines in people with autoimmune conditions could be of value in the therapeutic translation of this mRNA strategy.[63] As mRNA vaccines continue to be distributed over the next couple of months across the USA, observational research will be critical in determining the impact of COVID-19 vaccination in patients with autoimmune disease from both an efficacy and safety perspective.

Although the potential risks of COVID-19 vaccination remain unknown for patients with SLE and optimal dosing for efficacy could be different from the general population, the risks of not receiving the vaccine are far greater at the present time. When immunised, it seems reasonable to take steps so that patients with lupus will be as stable as possible without receiving more immune suppression than needed to control disease activity. After vaccination, it might be worthwhile to monitor both SARS-CoV-2 antibody response and a full array of autoantibody titers. Close follow-up to identify early flares is also prudent. Because efficacy of the vaccine is unclear both in overly immunosuppressed patients and in those with disordered immune activity, patients with lupus should continue high vigilance in social distancing, wearing masks and avoiding unnecessary contact with other individuals.[64]

The American College of Rheumatology COVID-19 Vaccine Clinical Guidance Task Force has just released a guidance document attempting to shed light on the complexities of vaccinating patients with autoimmune rheumatic diseases. The main guidance statements align with our suggestions. Patients with autoimmune rheumatic diseases should receive the COVID-19 vaccines and should be prioritised before the general population. Specific submissions regarding the timing and changes to commonly used medications are included with the caveat that these need to be individualised.[65]

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