COVID-19 in 2022

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COVID-19 vaccination in individuals with inflammatory rheumatic diseases

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Since the start of the SARS-CoV-2 vaccination campaign, our knowledge of the effects of vaccines in people with inflammatory rheumatic diseases has remained incomplete. In particular, the effects of immunomodulatory therapies on vaccine success are poorly understood. Three notable papers from the past year have helped to fill these knowledge gaps.

The SARS-CoV-2 pandemic has paralysed the world. Faced with the constant fear of severe or even fatal infections with rapid spread throughout the population, unprecedented precautionary measures such as large-scale, strict and prolonged lockdowns and bans on social contact have imposed restrictions on private, social and professional lives. The way out of this stressful and dangerous situation has been achieved by worldwide vaccination campaigns, which have increasingly built up immunity in populations since the beginning of 2021. Studies on the efficacy and safety of the vaccines, some of which are based on new mRNA technology, have shown rapid and strong development of immunity in healthy populations. Unfortunately, individuals with immune systems compromised by disease (such as an inflammatory rheumatic disease (IRD)) or by therapy were explicitly excluded from participation in the large registration trials for the vaccines. The effectiveness and safety of vaccination in these vulnerable individuals was therefore not known. In the spring of 2021, initial observations were published showing that people with IRDs and other immune-mediated inflammatory diseases (IMIDs) have high seroconversion rates, suggesting that vaccines are effective and safe in this population[1–3]. However, many questions remained that are of great importance in the care of patients with IRDs. For example, it was not clear whether all drugs used for the treatment of IRDs are comparable in terms of vaccine responses. Several observations suggested that rituximab, mycophenolate, cyclophosphamide, methotrexate, abatacept and glucocorticoids, especially at higher doses, would have negative effects on the humoral vaccination response[3,4]. Other questions related to the persistence of immunity achieved under ongoing immunosuppression, and whether affected individuals should be vaccinated more frequently than those with no immunosuppression. A related issue was whether certain medications should be paused before, during or after vaccination, and notably, whether an immune response could be achieved at all in patients receiving highly potent immunosuppression with rituximab. This question was particularly important, as early evidence indicated that patients on rituximab therapy were at an increased risk of severe and potentially fatal outcomes of SARS-CoV-2 infection[5], and that persistent depletion of B cells is associated with an insufficient vaccine response[6].

Results published in 2022 have provided answers to some of these questions[7–9]. Wieske et al. analysed humoral immune responses after second and third vaccinations against SARS-CoV-2 in a large cohort of individuals with various IMIDs, including IRDs such as rheumatoid arthritis (RA), spondyloarthritides, soft connective tissue diseases and vasculitides, who were treated with systemically acting immunomodulatory and/or immunosuppressive drugs alone or in combination[7]. The analysis covered both the concentrations of anti-SARS-CoV-2 immunoglobulins in the sera of the vaccinated individuals and the induction of neutralizing antibodies to the virus. The study had several notable results. The humoral immune responses in these individuals did not vary according to the different diseases. Although concentrations of anti-SARS-CoV-2 serum antibodies were moderately lower in individuals with IRDs than in those without, and they did not increase after a third vaccination, there was no difference in seroconversion rates between individuals with or without IRDs. Importantly, and of particular relevance to people with IRDs, regardless of the concentration of anti-SARS-CoV-2 serum antibodies, the neutralizing capacity (against the original SARS-CoV-2 virus strain WA1/2020) and the ability to generate a rapid and sufficient immune response after re-exposure to antigen did not differ between individuals with or without IRDs. Thus, it reassuringly indicates that the risk of infection and the development of severe disease is not increased for people with IRDs. However, the results also showed that seroconversion is achieved less frequently under ongoing therapy with mycophenolate, spingosine-1-phosphate inhibitors or rituximab than with other treatments, and that for rituximab in particular, even repeated vaccination does little to change this situation.

Key advances

- Although SARS-CoV-2 vaccination seroconversion rates are lower in individuals with inflammatory rheumatic diseases under immunomodulatory therapy, the neutralizing capacity of anti-SARS-CoV-2 antibodies does not differ between affected and non-affected individuals[7].
- In contrast to the humoral immune response, the cellular immune response to SARS-CoV-2 vaccination in patients receiving rituximab is maintained[8].
- After rituximab therapy, determination of peripheral blood B cells may be a means to facilitate successful immunization, as the threshold for a successful immune response is 10 B cells per microlitre of peripheral blood[9].

Rituximab poses a particular challenge for vaccination success in people with IRDs. Although, for some patients, it seems possible to change long-term therapy with rituximab to a different therapeutic regimen, thereby enabling successful immunization, this approach is not necessarily possible in other situations such as in remission induction and maintenance of ANCA-associated vasculitis (AAV). However, the recommendation that necessary rituximab therapy should be modified in favour of attaining a vaccination response should also take into consideration the extent of the limitation of vaccination-induced protection under rituximab therapy. After all, for sufficient immunity against viral infection, targeted cellular immunity is important as well as humoral immunity. Although the humoral aspect of the vaccine response is impaired in patients receiving rituximab, evidence suggests that the cellular aspect is not[10]. In 2022, Jyssum et al. published the results of a study that examined humoral and cellular immunity in patients who were repeatedly vaccinated against SARS-CoV-2 while receiving rituximab therapy for RA[8]. The results confirmed that patients receiving rituximab therapy were less likely to seroconvert than those on other therapies. The likelihood of seroconversion was a function of the time interval since the last rituximab administration. Interestingly, however, after a second vaccination, 21.8% of individuals had antibodies against SARS-CoV-2, but 53% of individuals had a $CD4^+$ T cell response, and as many as 74% of individuals had a $CD8^+$ T cell response. Although a third vaccination resulted in seroconversion in an additional 16% of people, all individuals studied had detectable T cell responses after the third vaccination, which was given 6–9 months after the last rituximab administration. These data demonstrate the divergent dynamics of humoral and cellular anti-SARS-CoV-2 immune responses in patients receiving rituximab therapy, and they also show that even in the absence of a measurable humoral immune response, a protective T cell response develops in most people. Discontinuation of a medically advisable rituximab therapy, therefore, does not seem to be necessary to address concerns about a lack of immunological protection against SARS-CoV-2.

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The number of peripheral B cells starts to recover at the earliest 4 months after rituximab treatment. For this reason, the current EULAR recommendations state that vaccination should occur at the earliest 4 months after rituximab administration. However, the interval between treatment and the appearance of the first peripheral B cells is variable. Therefore, the recommendation to vaccinate after only 4 months is not necessarily a safe one, because without B cells there will be no humoral response, and in many patients 4 months may not be long enough for peripheral B cells to reappear. Jyssum et al. identified a correlation between the humoral immune response and the interval from the last rituximab administration[8], but they did not identify a robust parameter that would indicate the likelihood of successful vaccination. Results published by Stefanski et al. identified just such a parameter[9]. They studied antibody and T cell responses to SARS-CoV-2 after vaccination in individuals with RA or AAV on ongoing rituximab therapy, and correlated the responses with peripheral B cell counts. Their findings indicated that a minimum of 10 B cells per microlitre of blood is the threshold above which a sufficient humoral and cellular immune response to SARS-CoV-2 vaccine is established. The peripheral B cell count thus represents an initial biomarker of vaccine success in patients with IRDs on ongoing B cell-depleting therapy. Determination of the B cell count can therefore enable the care of these patients to be objectively controlled while facilitating successful vaccination against SARS-CoV-2.

In summary, three studies published in the past year filled notable knowledge gaps relating to the efficacy of SARS-CoV-2 vaccination in individuals with IRDs. Although these individuals were explicitly excluded from the initial approval studies of the vaccines, the results indicate that they can be safely and successfully vaccinated against SARS-CoV-2, thereby enabling them to gain a measure of reassurance that they can achieve immunological protection and a return to regular life, despite the ongoing SARS-CoV-2 endemic.

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Competing interests

The authors declare no competing interests.