

VIEWPOINT

Vaccination of patients with inflammatory rheumatic diseases against SARS-CoV-2: considerations before widespread availability of the vaccines

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ABSTRACT

Vaccination against SARS-CoV-2 has become available and will hopefully end the current pandemic. Understandably, patients with inflammatory rheumatic diseases (iRMDs) and their physicians are feverishly preoccupied with questions about vaccination and the vaccines against SARS-CoV-2. However, as it will take months before all patients with iRMDs will have access to the vaccines, measures that are taken now in order to increase potential safety and efficacy of the vaccines may impose a risk for the patients with regard to reactivation of their underlying iRMD. The ad hoc commission 'Covid-19' and the board of directors of the German Society for Rheumatology have addressed this topic and have developed considerations, which are intended to answer urgent questions, to take away concerns and fears and to make initial recommendations for patients with iRMDs.

about vaccination and the vaccines against SARS-CoV-2. For patients with inflammatory rheumatic diseases (iRMDs), the burning questions are whether vaccination is safe, whether it will be effective and whether there were measures in place that may increase the safety and efficacy of the vaccination. As important as it is to deal with these topics early, the answers are difficult. There are two important reasons for this: First, there are no available data on the effectiveness and safety of a vaccination against SARS-CoV-2, neither for patients with a compromised immune system nor for patients treated with immunomodulatory or immunosuppressive drugs. Second, with very few exceptions, most SARS-CoV-2 vaccines are still awaiting approval in most countries. Moreover, even after the expected timely approval, current recommendations for prioritising populations in the national vaccination strategies see few, if any, patients with an iRMD as a population that should be vaccinated with high urgency. Thus, it will take months before vaccines become widely available for patients with iRMDs.

With this in mind, patients with iRMDs must be advised not to take actions in anticipation of vaccination and issues related to safety and efficacy that may lead to activation of the underlying iRMD until the vaccine is safely available. Such measures could bear an increased risk of infection with SARS-CoV-2, as activity of iRMDs contributes to the risk for COVID-19.⁶ At the same time, patients need to be informed about the possibilities of vaccination now, so that fears or even falsehoods about the new vaccines do not build up to an extent that vaccination is ultimately rejected. Finally, there may indeed be some situations that can be safely implemented in the

The SARS-CoV-2 pandemic is paralysing the world. In the absence of an effective treatment for SARS-CoV-2 infection and given that the disease caused by SARS-CoV-2 can be severe to fatal, preventing infection is the only measure to avoid the collapse of health-care systems worldwide. Immediately after the WHO declared the pandemic on 11 March 2020,¹ many countries have introduced restrictions on access and contact, which have far-reaching effects on the daily lives of all of us. With the first reports of the new virus, enormous efforts have been started worldwide to develop vaccines. In recent weeks, initial clinical data on the first vaccines have been published²⁻⁵ and there is justified optimism that several of the vaccines will provide sufficient protection. As they will be available shortly, they may thus put an end to restrictions on public and private life.

Understandably, patients and physicians alike are feverishly preoccupied with questions



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treatment of patients with iRMDs early so that within the next 6 months these patients have the highest possible probability of responding to vaccination with clinically significant immune protection.

The ad hoc commission 'COVID-19' and the board of directors of the German Society for Rheumatology (Deutsche Gesellschaft für Rheumatologie e.V.) have addressed this topic and developed the following considerations, which are intended to answer urgent questions, to take away concerns and fears and to make initial recommendations for patients with iRMDs.

1. As of 15 January 2021, there are still no data on the safety and efficacy of the various SARS-CoV-2 vaccines in patients with iRMDs or in patients taking immunosuppressive/immunomodulating therapy. Patients with known or suspected immunodeficiencies were excluded from the phase III studies of the BioNTech, Moderna and AstraZeneca/Oxford vaccines. Therefore, only a limited number of patients with autoimmune diseases were vaccinated in these trials and no detailed reports on these patients are currently available.
2. All vaccines currently in late-stage development are non-live vaccines. As known, inactivated vaccines can be used without restriction in patients with iRMDs and in patients under immunosuppressive/immunomodulating therapy. Classic inactivated vaccines under development for vaccination against SARS-CoV-2 are vaccines based on adjuvant proteins. Vaccines based on non-replicable vectors and vaccines based on messenger RNA (mRNA) ('mRNA vaccines') can also be considered as non-live, inactivated vaccines and should therefore not pose a risk to patients with iRMDs and patients under immunosuppressive/immunomodulating therapy.
3. Live vaccines (vaccines based on attenuated viruses) should not be used in patients with iRMDs under immunosuppressive/immunomodulating therapy. Importantly, all vaccines against SARS-CoV-2 that are currently in late-stage development are non-live vaccines.
4. For 'mRNA vaccines' the following applies: These are not live vaccines. The mRNA does not integrate into the human genome, it does not affect or reprogramme human DNA and no substances are administered with the vaccine from which the vaccinated organism could assemble complete or infectious virus particles. An 'mRNA vaccine' leads to the temporary production of viral proteins against which the immune system can produce potentially protective antibodies. It can therefore be assumed that the use of an 'mRNA vaccine' can be recommended for patients with iRMDs and under immunosuppressive/immunomodulating therapy.
5. The toll like receptors (TLR) 7 and 8 bind single-stranded viral RNA. TLR7 is also of crucial importance in triggering the immune response against SARS-CoV-2.⁷ On the other hand, TLR7 plays a significant role in the pathogenesis of autoimmune disorders such as systemic lupus erythematosus (SLE). It is reassuring that no excessive activation of the innate immune system was observed in the phase III clinical trials of the mRNA vaccines. Thus, the available data suggest that the mRNA-based vaccines are safe also in patients where activation of TLRs 7 and 8 is implicated into the pathophysiology of the underlying iRMD, for example, in patients with SLE. On a related thought, it cannot be completely excluded that mass expression of an antigen, such as the spike protein in mRNA vaccines, will result in antigen/antibody complexes that might cause autoimmune phenomena. Definite answers to these concerns may be deduced from the safety data of ongoing phase III clinical trials as soon as they will be openly available.
6. Whether patients with iRMDs and patients under immunosuppressive/immunomodulating therapy can build up a serum titre of anti-SARS-CoV-2 antibodies similar to the level observed in individuals not suffering from iRMDs and/or not taking immunosuppressive/immunomodulating therapy remains to be determined. Irrespective of these thoughts, vaccination even with the result of a lower titre of neutralising antibodies is better than no vaccination. This may be of particular relevance to patients requiring therapy with rituximab (see statement 8 and reference 8).⁸ Data from ongoing vaccination studies and observations are continuously evaluated.
7. Irrespective of the considerations regarding SARS-CoV-2, vaccination against pneumococcus and especially influenza should be carried out in accordance with the recommendations of the national and international standing committees on vaccination. Data on interactions between these and other known vaccines on one hand and the SARS-CoV-2 vaccines on the other are not available. A minimum interval of 14 days before the start and after the end of the vaccination series against SARS-CoV-2 should be observed with other vaccinations (with the exception of emergency vaccinations).⁸
8. For basic considerations of vaccine effectiveness, immunosuppression at the time of vaccination should be as low as possible. The following applies to SARS-CoV-2: The risk of reactivation of the underlying rheumatic disease after discontinuation of an immunomodulatory/immunosuppressive therapy to potentially improve the vaccination response is considered to be significant. Therefore, it is not recommended at this time (January 2021) to change the existing immunomodulatory/immunosuppressive therapy because of a vaccination which is currently not available. Vaccinations in patients with an activated immune system are not recommended at present and an activation of the underlying iRMD may require glucocorticoid therapy, which imposes an additional risk for contracting SARS-CoV-2 and also may weaken the immune response against the vaccine. An exception is the administration of a long-acting B cell-depleting substance (eg, rituximab). According to the current EULAR recommendations for vaccination,⁸ vaccination should be performed at least 6 months after the administration of rituximab and

4 weeks before the next course of B cell-depleting therapy. Thus, in view of vaccination against SARS-CoV-2, a pause or change to alternative therapies should be considered now, taking into account the risk of reactivating the underlying disease on the one hand and to preserve an optimal vaccination response on the other. In cases when this is not feasible, vaccination under B cell-depleting therapy should be planned, taking into consideration a potential suboptimal response to the vaccine.

Time will fly and these thoughts may hopefully become outdated and irrelevant very soon. While vaccination is not yet widely available, our thoughts may help to guide our patients in the best possible way in these unprecedented times.

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