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Vaccines and autoimmunity during the COVID-19 pandemic

Velikova T. COVID-19 vaccines and autoimmunity

Abstract

To control the pandemic, efficient vaccines must be applied to the population, including patients with autoimmune diseases. Therefore, one can expect that coronavirus disease 2019 (COVID-19) vaccines may influence the underlying autoimmune processes in these patients. Additionally, it is essential to understand whether COVID-19 vaccines would be effective and safe and provide long-lasting immunological protection and memory. However, the currently available and approved COVID-19 vaccines turned out to be safe, effective, and reliable in patients with autoimmune inflammatory and rheumatic diseases. Furthermore, most patients said they felt safer after getting vaccinations for COVID-19 and reported enhanced overall quality of life and psychological wellbeing. In general, the COVID-19 vaccines have been shown as highly tolerated by autoimmune patients. Such findings might comfort patients who are reluctant to use COVID-19 vaccines and assist doctors in guiding their patients in vaccination timely.

Core Tip: Coronavirus disease 2019 (COVID-19) vaccines have created concerns about their efficacy and safety, notably in autoimmune patients. Which vaccine adverse events are related to the underlying autoimmunity is unclear. Additional data is needed to evaluate the immunological impact of COVID-19 vaccines in terms of effectiveness and immune-driven adverse effects that might provoke a disease flare in individuals with a history of autoimmune-related symptoms. However, the risk of autoimmune disease flare after vaccination was considered low, while the immune responses after vaccination showed great immunogenicity for these patients. In addition, vaccination

will considerably decrease related morbidity and mortality from COVID-19 in autoimmune settings.

INTRODUCTION

We still do not know all the mechanisms involved in the immune system - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interaction during coronavirus disease 2019 (COVID-19) infection. However, it was demonstrated that the virus possesses a tremendous ability to inhibit the immune mechanisms, both innate and adaptive[1]. Nevertheless, making the immunity non-adequate or sufficient to prevent reinfection[2], there are still controversial data on which immunity is better - naturally acquired or vaccine[3].

There are concerns regarding people living with autoimmune diseases as well. Since, in the case of autoimmune diseases, the body's immune system is overactive and destroys its own cells with various mechanisms, including autoantibodies and immune cells[4,5], one can expect that COVID-19 vaccines may influence the autoimmune processes in these patients. Additionally, it is essential to understand whether COVID-19 vaccines would be effective and safe in autoimmune disease patients and whether vaccines will provide long-lasting immunological protection and memory[6]. However, medical society has a consensus on one thing - to take control of the pandemic, efficient vaccines must be applied to the population. This approach also includes vaccinating patients with autoimmune diseases as well.

CAN THE COVID-19 VACCINES CAUSE AUTOIMMUNITY?

Data showed that the immune hyperactivation and cytokine-excessive release in patients with COVID-19 resulted in multi-organ failure and death[7]. In line with this, patients with already activated immune system could be more prone to severe SARS-CoV-2. However, this was not proved for autoimmune diseases. The main concerns are severe patient outcomes on immunosuppressive therapy or developing severe clinical

complications[8]. Indeed, it was shown that SARS-CoV-2 could induce a robust immune response in immunocompromised patients[9,10].

On the other hand, COVID-19 vaccines have also created concerns about their efficacy and safety, notably in autoimmune patients. We recently published a paper addressing the known pros and cons of vaccinating patients with autoimmune disorders, stressing the absence of data on the advantage and disadvantages of newly discovered COVID-19 in patients with autoinflammatory and rheumatic diseases[11]. Various pathways that contribute to the increase in acute autoimmune response have been suggested[12]. For example, molecular mimicry, *i.e.,* antibodies against SARS-CoV-2 spike glycoproteins, has the theoretical potential to trigger autoimmunity, as Vojdani and Kharrazian[13] demonstrated lately. Talotta[14] further suggest that injecting a nucleic acid vaccination might put young women in danger of undesired, unexpected immunological side effects, especially those already susceptible to autoimmune or auto-inflammatory disease. However, even in the autoimmune population, serious adverse events are rare[15,16].

Akinosoglou *et al*[7] further hypothesize that, although immunization with COVID-19 is not the cause for *de novo* immune-mediated adverse events. Contrarywise this, the immunological reaction might lead to dysregulation of the pre-existing underlying pathways. This might result from the polyclonal expansion of the B cells, leading to the development of immunological features of autoimmunity. It should be noted that autoimmune disorders can be provoked in genetically sensitive individuals, with various autoimmune mechanisms involved, including epitope spreading and bystander activation[17]. Which vaccine adverse events are related to the underlying autoimmunity is unclear. An unsolved issue remains whether to provide a second dosage after such reactions in patients with rheumatic diseases. Additional data is needed to evaluate the immunological impact of COVID-19 vaccines in terms of effectiveness and immune-driven adverse effects that might provoke a disease flare in individuals with a history of autoimmune-related symptoms[7].

COVID-19 VACCINES AND PATIENTS WITH AUTOIMMUNE DISEASES

As demonstrated previously, elderly populations with chronic disorders such as diabetes, asthma, and cardiovascular disease are especially susceptible to severe SARS-CoV-2[18]. The same concerns were raised regarding patients with autoimmune inflammatory rheumatic diseases (AIIRDs)[19,20]. However, recent studies demonstrated that patients receiving immunosuppressive therapy for AIIRDs produced sufficient and protective immune response after SARS-CoV-2 mRNA vaccination without experiencing severe side effects or flares[21].

Since AIIRD patients are usually not included in phase III clinical trials of vaccines, immunological response to AIIRD-19 vaccination in AIIRD patients under the immunosuppression treatment remains unknown. Although the COVID-19 vaccine efficacy was demonstrated between 60%-95% for the different vaccines and acceptable safety, uncertainty in AIIRD patients for the COVID-19 vaccines, especially the novel RNA and viral vector vaccines, led to hesitancy in both physicians and patients[22,23]. However, the currently available and approved COVID-19 vaccines turned out to be safe, effective, and reliable in patients with AIIRD. Furthermore, unless contraindicated for medical conditions, such as previous allergy/anaphylaxis to the COVID-19 vaccine or its ingredients, any patient with AIIRD should receive one of the available COVID-19 vaccines.

Patients have to continue immunosuppressive therapy for their underlying AIIRD, which may include biological and selective synthetic disease-modifying anti-rheumatic medications. Korean College of Rheumatology issued guidelines recommending limiting corticosteroids to the lowest possible dosage without exacerbating AIIRD. Methotrexate may be deferred for 1-2 wk following each injection to increase vaccine response. The duration of rituximab and abatacept infusions may be adjusted[21]. The overall vaccine benefits exceed possible vaccine dangers, as the study showed. Additionally, the risk of disease flare of AIIRD after vaccination is low. However, the currently accepted surrogate markers for the immune response after vaccination (*i.e.*,

antibodies against SARS-CoV-2 and activated T cells) showed great immunogenicity of the vaccines in these patients[21].

Another concern that must be discussed is assessing vaccine effectiveness in the IV phase, a.k.a. the real-world studies. Clinical studies investigating high-risk for infection people, *i.e.*, healthcare workers, showed that the absolute risk of testing positive for SARS-CoV-2 after vaccination with mRNA vaccine in a cohort of healthcare workers was 0.97%-1.19%[24]. One must consider that the healthcare staff was younger and more susceptible to SARS-CoV-2 than the clinical trial participants. As stated above, hesitancy in autoimmune patients may have arisen because these individuals were mainly omitted from vaccination studies of COVID-19. Boekel *et al*[18] have already shown that more than one-third of autoimmune patients are reluctant to get vaccinations against COVID-19. The primary reasons for worrying are the anticipated side effects and the lack of long-term studies.

Additionally, there are currently very little data on the safety of COVID-19 vaccines in patients with autoimmune disorders, and no research available can compare the impact of different types of vaccinations and between patients and healthy controls. For example, worldwide vaccination recommendations for COVID-19 for autoimmune illness patients is based on experts' opinion[25]. In their previous study, Boekel *et al*[26] presented the results from a survey that evaluated the adverse events following COVID-19 vaccinations in systemic AIIRD patients and healthy control (Netherlands Trial Register, trial ID NL8513 and NCT04498286). Of all participants, 1780 patients and 660 controls accomplished the questionnaire, whereas 46% and 41% of patients received ChAdOx1 nCoV-19 (AstraZeneca) and BNT162b2 (Pfizer/BioNTech), respectively. Thirteen percent of patients were vaccinated with Moderna. Half of the patients and controls reported at least one mild adverse event, and about 20% of all participants - had moderate adverse events. Severe adverse events remained below 1%, with no serious adverse events. Complaints of joints and bones were stated more frequently by patients with AIIRD than controls (10% *vs* 1%, respectively). Fortunately, only 2% of

patients reported flare or deterioration of the disease up to 2 mo after COVID-19 vaccination[26].

The results from the survey show that, regardless of the kind of vaccine, adverse effects of immunization with COVID-19 in patients with autoimmune disorders are equivalent to controls. The adverse effects included also predicted local or systemic hyperreactivity responses, which were largely self-limiting. The incidence of individuals who reported adverse events in the clinical trials was lower than the number said[15], similar to the national study of COVID-19 adverse events in the United Kingdom general population[27]. In conclusion, the survey demonstrated that the vaccines against COVID-19 do not tend to induce autoimmunity flares, as shown in previous limited studies that evaluated mRNA vaccines' impact on patients with autoimmune diseases[20,28].

Known pathophysiological effects mRNA may be both immunostimulatory and immunosuppressive to the innate immune system as COVID-19 vaccines are the first to be widely applied, and prospective, monitored studies of the long-run effects of COVID-19 vaccines on their activities require robust conclusions[11]. Nevertheless, most participants said they felt safer after getting vaccinations for COVID-19, and 20% of individuals with autoimmune disorders reported enhanced overall quality of life and psychological wellbeing[26]. If we compare these adverse effects associated with the application of COVID-19 vaccines with autoimmune complications during SARS-CoV-2 infection[29], the benefits of vaccines significantly outweigh the side effects of vaccination. This comparison is presented in Figure 1.

CONCLUSION

In general, the COVID-19 vaccines have been shown as highly tolerated by autoimmune patients. Such findings might comfort patients who are reluctant to use COVID-19 vaccines and assist doctors in guiding their patients in vaccination timely. Therefore, the therapy and management of COVID-19 should be given priority to reduce the catastrophic effect of COVID-19 in autoimmune patients, and SARS-CoV-2

immunization is one of the most effective protection against infection. In return, the initial thing to assess COVID-19 vaccines' safety and efficiency is to analyze significant research with new data. In addition, medical practitioners should counsel their patients, as this might considerably decrease related morbidity and mortality from COVID-19 and support SARS-CoV-2 vaccinations in autoimmune settings.

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