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REVIEW ARTICLE

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COVID vaccination in patients under treatment with rituximab: A presentation of two cases from Iran and a review of the current knowledge with a specific focus on pemphigus

Parvaneh Hatami[1] | Kamran Balighi[1,2] | Hamed Nicknam Asl[3] | Zeinab Aryanian[1,4]

[1]Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Dentistry, Rafsanjan University of Medical Sciences (RUMS), Rafsanjan, Iran

[4]Department of Dermatology, Babol University of Medical Sciences, Babol, Iran

Correspondence
Zeinab Aryanian, Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran
Email: z_aryanian@yahoo.com

Abstract

SARS-COV2 vaccines were approved without long-term monitoring due to emergent situations. This has raised some issues about the timing and protocol of receiving vaccines in specific situations such as patients receiving immunomodulatory agents including rituximab, which is widely used for various disorders such as multiple sclerosis, pemphigus, and many rheumatologic disorders. We described two cases of pemphigus vulgaris (a new case and one with flare-up) following vaccination with Astrazeneca in Iran and reviewed the existing data in this regard through searching on PubMed, Google Scholar, and Scopus. All of the relevant papers published until June 28, 2021, which we could access their full-texts were included. We found some recommendations made by rheumatologists, neurologists, and dermatologists in regard to vaccination timing in this group of patients and tried to summarize them to provide a practical guide for clinicians. Clinicians should perform a careful, individualized risk–benefit assessment for their patients and consider a delay in rituximab administration after completion of COVID vaccination if there is not any considerable risk of disease relapse or organ failure. Moreover, choosing vaccines with potential of providing protection after single dose, especially in countries with limited access to vaccines may be a reasonable approach.

KEYWORDS
Astrazeneca, Bharat, COVID-19 vaccine, Moderna, Pfizer, Sputnik

1 | INTRODUCTION

Coronavirus disease 2019 or COVID-19 caused by SARS-Cov-2, first reported in Wuhan, China in December 2019 and soon become a serious public health issue and later become a pandemic on March 2020.[1] Since the COVID-19 outbreak posed a significant burden on the health care system across the world and made the year 2020 the most challenging year in this regard, SARS-COV2 vaccines were approved without long-term monitoring and definite protocols preparedness due to emergent situations. This has raised some issues about timing and protocol of receiving vaccines in specific situations such as patients receiving immunomodulatory agents.

Here, we have reported a new case of pemphigus vulgaris (PV) and another case of PV flare-up from Iran, both following vaccination with Astrazeneca and reviewed the existing data about the vaccination response in patients receiving rituximab (RTX) treatment with a focus on patients suffering from PV.

2 | CASE PRESENTATION

2.1 | Case 1

Our first case was a 34-year-old man, otherwise healthy with a history of vaccination with Astrazeneca in late July and initiation of sore

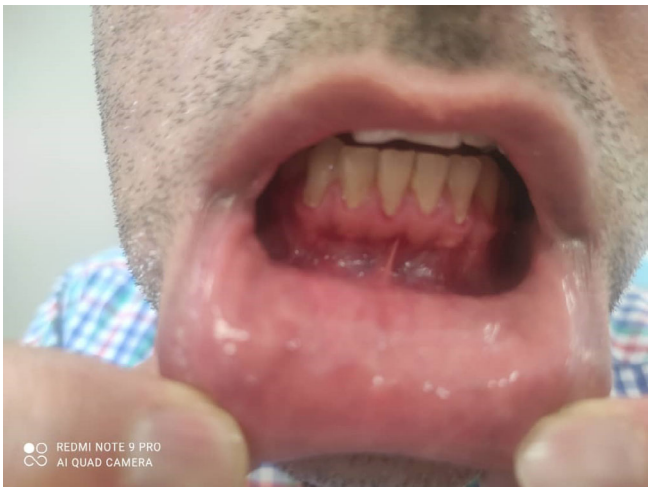

FIGURE 1 A new case of mucosal pemphigus vulgaris (PV) following getting Astrazeneca. Mucosal lesions were dramatically improved by prednisolone 80 mg/kg and Azaram 150 mg/kg

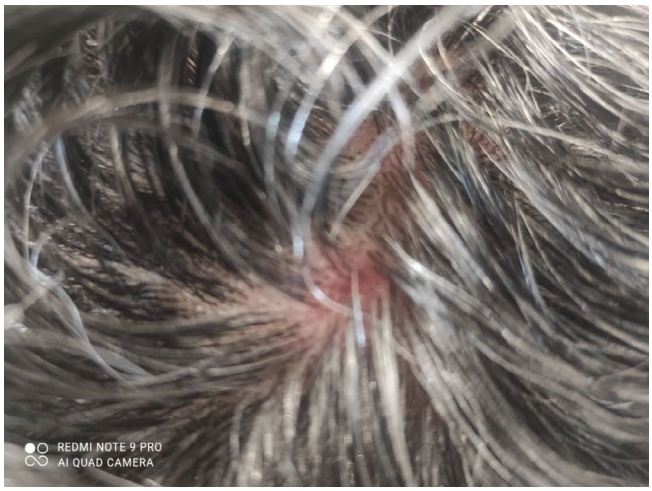

FIGURE 2 Flare up of pemphigus vulgaris (PV) following getting Astrazeneca in a patients who was experiencing a partial remission

throat and gingivitis a few days after that. When he came to our outpatient clinic, some mucosal erosions on his tongue and buccal parts were noted (Figure 1). Histopathological evaluation and direct immunofluorescence study confirmed the diagnosis of PV for him and treatment was initiated with prednisolone 1 mg/kg and Azathioprine 150 mg/day.

2.2 | Case 2

Our second case was a 61-year-old man with confirmed diagnosis of PV came to us with complain of developing new lesions on the scalp about 1 week after vaccination with Astrazeneca. He was initially treated with a cycle of rituximab (four weekly infusions at the dose of 500 mg) and went into partial remission about 4 months ago. On physical examination, some erosions and crusts were noted on the scalp and trunk (Figure 2). The dose of prednisolone was risen to 20 mg/kg.

3 | DISCUSSION

With the progression of COVID vaccination programs across the world, the question arises about the effect of vaccination in patients receiving immune-modulators and any preparedness needed for them such as withholding or interrupting medication cycles or delaying vaccination.

Immunotherapy has become one of the best treatment modalities for different disorders during the last decades[2–6] and RTX, a monoclonal antibody targeting CD20 on B lymphocytes, has recently shown a great promising effect in treating various disorders including PV. Since a B cell depletion occurs during RTX therapy, it is not surprising that a higher risk of SARS-Cov-2 infection in patients treated with RTX has been reported in some studies.[7,8] However, the safety of RTX in the COVID era is still a controversial issue. In a review of two phase III trials of RTX, no increased susceptibility to respiratory infections including COVID-19 was reported in patients with pemphigus who received rituximab as their first-line treatment,[9] which was in line with Aryanian et al. study which was earlier conducted.[2]

Previous studies about the effect of RTX on immunological response following inactivated vaccines showed attenuated, yet meaningful response,[10] but there is not any similar study on live attenuated vaccines in the literature due to safety concerns of these vaccines in those receiving RTX.[11]

In fact, impaired humoral and even cellular immunological response to some vaccines including influenza, pneumococcal polysaccharide, and tetanus toxoid vaccines was reported in patients receiving RTX.[12,13] However, it seems that T cell responsiveness improves faster than humoral immunity[14] and also T-cell dependent recall response, unlike primary antigen exposure response, might preserve after rituximab treatment,[15] which does not happen regarding humoral response.[14]

Since interferon-gamma (IFN-γ) is a key component of the T-helper-1 response, IFN γ release assays (IGRA) have shown to be a good marker of cellular immunity following COVID-19 infection up to 7 months post-infection.[16] Ferguson et al. showed that the SARS-Cov-2 IGRA could be a substituting method of assessing immunological response in those with impaired antibody response following COVID vaccination.[17] However, it is not clear if a robust cellular immunological response in the absence of humoral immunity provides enough protection against COVID-19.

Bonelli et al. evaluated humoral and cellular immunity after receiving the Pfizer vaccine in five patients who were treated by RTX. They found that humoral immunity was associated with the amount of B cell depletion in patients. However, T cell-mediated immunity was noted even in B cell depleted patients, which revealed the effectiveness of vaccine, at least regarding cellular immunity.[18] This robust cellular immunological response despite the absence of humoral

response was also reported in a patient with multiple sclerosis (MS) under treatment with RTX.[17]

Spiera et al. investigated the humoral immunity following COVID vaccination in 89 patients with rheumatologic disorders under treatment with RTX and other anti-rheumatologic drugs and found diminished humoral response only in patients receiving RTX, except for one patient on belimumab, another B cell targeting agent, who also showed a negative serological response. Based on their results, the longer time duration between last RTX cycle and vaccination, the more likelihood of having humoral response.[19]

The possibility of diminished efficacy of COVID vaccines in patients treating with RTX is not the only concern among patients and clinicians. In fact, the safety of adenovirus-based vaccines has not been proved yet, especially in patients with autoimmune disorders such as MS or PV and there is some reports of disease flare-up following vaccination with Sputnik V.[20]

In our short-time experience about probable COVID-19 vaccine-associated pemphigus flare-up in Iran, we noticed that non-adenovirus based vaccines such as Sinopharm, which was used for most of our patients, were relatively safe in this regard.

It is worthy to note that some new cases of PV following COVID infection or its vaccines including those without adenovirus such as Pfizer were reported in literature 21–23 that makes it even more challenging to choose an appropriate approach to remedy this complex issue.

On the other hand, immune suppression is among the COVID-19-related mortality risk factors.[24] Hence, the risk of severe COVID infection in this group of patients along with the attenuated efficacy of the COVID vaccine should be borne in mind when making decision about vaccination or using immunomodulatory agents during this pandemic.

In fact, these uncertainties raised among various specialists including rheumatologists, neurologists, hematologists, and dermatologists, necessitates the preparedness of a comprehensive guideline in this regard.

The ideal timing of vaccination is unknown. Some authors suggest that the influenza vaccine recommendations needed to be performed regarding COVID vaccines. Therefore, they recommend COVID vaccination at least 4 weeks before RTX infusion and 12–20 weeks after that (assuming a 6-month gap between RTX treatment courses).[11,25] The American college of Rheumatology guideline for COVID vaccination also suggests a 4-week gap between RTX therapy and vaccination.[26]

Regarding assessment of vaccine efficacy in patients receiving RTX, despite the CDC recommendation against routine serologic assessment following vaccination, it seems that regular assessment of neutralizing antibody level and also IFN γ IGRA, if possible, following vaccination of these patients could be a helpful guide to choose appropriate timing of revaccination after humoral immune reconstitution in case of attenuated immunological response or emergence of new virus variants which necessitates receiving new vaccines.

4 | CONCLUSION

In conclusion, clinicians should perform a careful, individualized risk–benefit assessment for their patients and consider a delay in RTX administration after completion of COVID vaccination if there is not any considerable risk of disease relapse or organ failure. Moreover, choosing vaccines with potential of providing protection after single dose, especially in countries with limited access to vaccines may be a reasonable approach.

Moreover, we suggest to use of non-adenovirus-based vaccines in patients with autoimmune disorders such as PV to avoid possible relapsing of underlying disorder.

Overall, we think that in areas with a serious situation due to Coronavirus outbreak, it is rational to choose our vaccination strategy based on vaccine and also laboratory tests accessibility; If vaccines are easily accessible, the patients could be vaccinated after 4 weeks of RTX infusion and then, the need to or timing for next booster doses could be determined after assessing neutralizing antibody level and/or IGRA. On the other hand, in areas with limited access to these tests and vaccines, using strict preventive measures including patient isolation and postponing the vaccination at least for 12 weeks after rituximab administration might be a reasonable protocol.

Further studies are needed to find an optimal time frame of vaccination and find out if there is a need for booster doses in patients under treatment with RTX.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

ETHICAL APPROVAL

Any aspect of the work that has involved human patients has been conducted obtaining the ethical approval of all relevant bodies.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Parvaneh Hatami https://orcid.org/0000-0002-3531-2907
Kamran Balighi https://orcid.org/0000-0002-8059-670X
Zeinab Aryanian https://orcid.org/0000-0001-7077-1458

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