

Use of rituximab in pemphigus vulgaris/foliaceus patients during COVID-19 pandemic

Utilização de rituximab em doentes com pênfigo vulgar/foliáceo durante a pandemia COVID-19

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Dear Editor,

The SARS-CoV-2 pandemic has raised safety concerns in pemphigus vulgaris/foliaceus (PV/PF) patients on systemic immunosuppressants. Rituximab (RTX) induces a prolonged B-cell depletion, which was initially associated with severe COVID-19 disease¹. Moreover, the approval of SARS-CoV-2 vaccines brought into question issues about efficacy, safety, and timing of vaccination in individuals receiving anti-CD20 monoclonal antibodies.

We aim to share the experience of our center regarding COVID-19 disease and vaccination in patients with PV/PF on RTX.

A retrospective analysis of the patients who received at least one infusion of RTX from January 2020 to March 2022 was performed. Data on SARS-CoV-2 vaccination and disease was obtained after consulting the hospital's clinical platforms. Secondly, a brief review of the literature on the incidence and severity of COVID-19 in patients with PV/PF under RTX and their vaccination was carried out.

In our Dermatology department, from January 2020 to March 2022, seven patients did at least one RTX infusion for the treatment of PV/PF. All patients were female, with a mean age of 46.6 years. During this period, three patients developed COVID-19, all with mild disease. Six patients were vaccinated, and one patient declined vaccination. Two of the vaccinated patients received the

vaccine at least 1 month before the beginning of the treatment and four of them were vaccinated more than 3 months after. Regarding the three patients that developed COVID-19, one had received two doses of the SARS-CoV-2 vaccine 5 months prior to the treatment, one had completed the two-dose schedule 3 months after the last RTX infusion, and the last one was unvaccinated. During the analyzed period, none of the patients experienced PV/PF flare due to SARS-CoV-2 vaccination or infection.

RTX induces prolonged B-cell depletion and decreased antibody production, leading to a higher infection susceptibility. In SARS-CoV-2 infection, the host's immune response is crucial for the evolution of the disease, with immunosuppression being considered an independent risk factor for severe disease. However, recovery from COVID-19 may not be determined exclusively by the development of neutralizing antibodies. In fact, a recent study showed that 11 out of 14 patients on RTX who recovered from COVID-19 had no measurable anti-SARS-CoV-2 antibodies titers².

The incidence and severity of COVID-19 in patients with PV/PF under RTX have also been investigated. However, there are few studies and conflicting results. For example, a recent analysis including 18 patients diagnosed with PV/PF concluded that the use of RTX was associated with five times higher incidence of the disease³. Another study that included 620 patients with

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Received: 12-08-2022

Accepted: 06-09-2022

DOI: 10.24875/PJDV.22000012

Available online: 09-12-2022

Port J Dermatol and Venereol. 2022;80(4):330-331

www.portuguesejournalofdermatology.com

PV/PF found that the risk of hospitalization decreases each month after the administration of RTX⁴. On the other hand, a larger analysis with a sample of 1236 patients with PV/PF concluded that the use of immunosuppressants, including RTX, was not associated with disease severity⁵. A smaller study of 211 patients showed similar results⁶.

In our sample, the use of RTX does not appear to be associated with severe illness since the three cases of COVID-19 were mild. In fact, while it is well established that RTX leads to a decrease in the humoral response lasting beyond 6 months, a possible protective role has been hypothesized. RTX can reduce the so-called “cytokine storm” responsible for severe disease, by decreasing the systemic pro-inflammatory state.

At the time of SARS-CoV2 vaccine approval, the only available recommendations for vaccination of patients on RTX were those of inactivated vaccines such as Influenza or tetanus⁷. However, the emerged SARS-CoV-2 vaccines are not inactivated, but mRNA or viral vector based. In these patients, vaccination timing is important and, according to the literature, vaccine humoral response recovery seems to occur six months after the last administration of RTX^{8,9}. Additionally, it has also been demonstrated that cell-mediated immunity is robust, which can counterbalance an eventual decrease in the humoral response to vaccination^{8,9}.

In fact, the ideal timing for vaccination after treatment with RTX is not yet fully established and the only precise recommendations are from the American College of Rheumatology, suggesting vaccine administration 2 to 4 weeks before the beginning of a treatment cycle¹⁰. Furthermore, the measure of CD19 B-cells may be a useful tool to define vaccination boosters and RTX dosing¹⁰.

In conclusion, the incidence and severity of COVID-19 among patients on RTX, especially those with autoimmune blistering disorders, have not been fully characterized. Although the vaccination of these patients is safe and effective, regarding the predictable robust cell-mediated response, the optimal timing for COVID-19 vaccination is not yet established. The increasing emergence of new pandemics, along with the wide use of biotechnological drugs, will certainly be a challenge in future clinical practice. Thus, it is important to better understand the real impact of these drugs on a patient's immune response, regarding not only the modification of the natural history of the disease but also, and most importantly, the need for vaccination schedule adjustment.

Funding

The authors received no financial support for the authorship or publication of this article.

Conflict of interests

The authors have no conflicts of interest to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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