

## Letter to the Editor (Case report)

Rheumatology Advances in Practice 2021;0:1–2

doi: 10.1093/rap/rkab038

Advance Access Publication 1 June 2021

### COVID-19 vaccine failure in a patient on rituximab therapy

#### Key message

- Concurrent rituximab use can result in an ineffective vaccination response to the coronavirus disease 2019 vaccine.

DEAR EDITOR, Severe coronavirus disease 2019 (COVID-19) is a well-recognized cause of morbidity and mortality across rheumatic diseases [1], and vaccines will play an important role in preventing illness. Immunosuppressive agents are commonly used in the treatment of rheumatological diseases, and among them, anti-CD-20 depleting therapies can result in an impaired humoral response to vaccines [2]. We had previously reported a case of COVID-19 vaccine failure in a patient on ocrelizumab therapy, an anti-CD19 mAb [3]. Here, we report another case of vaccine failure, this time in a patient on rituximab, an anti-CD20 mAb. A 73-year-old Caucasian male presented with nasal congestion, productive cough, myalgias and malaise of 4 days duration. Five weeks before, he had completed a two-dose series of the Pfizer-BioNTech COVID-19 vaccine given 21 days apart. He had a history of cryptogenic organizing pneumonia, intermittent asthma, type II diabetes mellitus, hyperlipidaemia and coronary artery disease. He was diagnosed with cryptogenic organizing pneumonia 2 years earlier, which was initially treated with prednisone and switched to rituximab owing to an inadequate treatment response. He was scheduled for i.v. rituximab infusion therapy at a dose of 375 mg/m<sup>2</sup> every 6 months, and his last dose was administered 10 days after he had received the second dose of the vaccine. His medications included metoprolol succinate, atorvastatin, ezetimibe, metformin, sitagliptin, and a budesonide and formoterol inhaler. There were no known allergies. The patient is retired and lives in New York City. Since the start of the COVID-19 pandemic, he had restricted his participation in social activities and wore a face mask in public. He denied any history of alcohol, tobacco or illicit drug use. On examination, the patient appeared comfortable. Vitals signs were within normal limits. His respiratory effort and breath sounds were normal, as was the remainder of the physical examination.

He tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via an RT-PCR nasopharyngeal swab. Given the high risk of progression to severe COVID-19 disease owing to his age and co-

morbidities, bamlanivimab and etesivimab, an mAb cocktail against SARS-CoV-2 was administered uneventfully.

Serological testing was performed before the mAb cocktail infusion with two separate assays, assessing the immunological response to the spike and nucleocapsid protein of SARS-CoV-2, respectively. He tested negative for antibodies to both the spike (S) and nucleocapsid (N) antigens. He reported resolution of his symptoms 3 days after the infusion.

Rituximab is an anti-CD20 mAb that binds to the CD20 antigen on the B cell surface, activating complement-dependent B cell cytotoxicity. B cells are believed to play a role in the development and progression of some autoimmune diseases. Signs and symptoms of those diseases are reduced by targeting B cells, and the progression of structural damage is delayed. Rituximab is widely used in patients with autoimmune disorders, haematological malignancies and vasculitides.

The B-cell-depleting nature of rituximab therapy can lead to an impaired humoral immune response to vaccination. Studies have shown a blunted influenza vaccine response in patients on rituximab. The effect was most pronounced if vaccinated <2 months, with an improved response if vaccinated >6 months after rituximab therapy [4].

In the vaccine clinical guidance by the ACR [5], patients with a low or mitigatable risk of COVID-19 should have their vaccination scheduled ~4 weeks before their next scheduled rituximab cycle; and after the completion of vaccination, should delay rituximab for 2–4 weeks after the second vaccine dose, if disease activity allows.

A recent review article in *Rheumatology* recommended avoiding vaccination after rituximab, ideally for 6 months; and if vaccination is imminent, consider delaying rituximab if there are no risks of organ failure or disease flare [6].

In our patient, rituximab was administered 10 days after the last dose of the vaccine, and the patient developed clinical disease 5 weeks after completing vaccination. The absence of spike protein antibodies indicates an inadequate humoral response after 5 weeks. Peak antibody response is expected 2 weeks after the second dose of the COVID-19 vaccine [7]. The two-dose regimen of the vaccine confers a 95% protection against infection [8], and this could explain vaccine failure rather than use of rituximab.

The half-life and prolonged B-cell-depleting effects of rituximab make it challenging to obtain an optimal window for vaccination. T-cell-mediated immunity after vaccination could have played a role in the mild nature of his illness, which was not accounted for by measuring only the humoral antibody response.

Our case highlights the challenges in vaccinating patients on immunosuppressive drugs. Finding an optimal window and obtaining post-vaccination antibody titres might be beneficial. Patients should continue to maintain a high adherence to preventive measures

against COVID-19. Further studies are needed to assess the efficacy of COVID-19 vaccine in patients on immunosuppressive therapies.

### Acknowledgements

All authors had access to the data and a role in writing the manuscript. The patient's consent was obtained for publication.

*Funding:* This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

*Disclosure statement:* The authors have declared no conflicts of interest.

### Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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Accepted 18 May 2021

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