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Negative SARS-CoV2-antibodies after positive COVID-19-PCR nasopharyngeal swab in patients treated with anti-CD20 therapies

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We report eight patients from our tertiary care neurologic outpatient department treated with anti-CD20 therapies, of which six showed negative SARS-CoV2-antibodies [cut-off value for negative tests/assay: anti-nucleocapsid IgG 1.4 Index Alinity (Abbott, Abbott Park, IL, USA); anti-spike protein IgG 12.0 AU/ml; Liaison SARS-CoV-2 S1/S2 IgG (DiaSorin, Saluggia, Italy)] after a symptomatic infection with positive COVID-19 PCR nasopharyngeal swab. The remaining two patients had a strong positive response for anti-spike protein IgG (64.6 AU/ml) with negative anti-nucleocapsid IgG or a weak positive response for anti-spike protein IgG (29.3 AU/ml) and positive anti-nucleocapsid IgG (2.9 Index), respectively.

Six of these patients were treated with ocrelizumab [$n = 5$ with relapsing remitting (RR) multiple sclerosis (MS), $n = 1$ with primary progressive (PP) MS]. Two patients were treated with rituximab, one each for neuromyelitis optica spectrum disorder (NMOSD) and active secondary progressive (aSP) MS, respectively. Mean interval between last anti-CD20-infusion to positive COVID-19-PCR nasopharyngeal swab was 4.9 months (range 3–10 months); mean interval from positive COVID-19-PCR nasopharyngeal swab to SARS-CoV2-antibody testing was 3.8 months [range 1–9 month(s)]. Six patients were female, mean age was 51.1 years (range 37–69 years), mean disease duration was 7.8 years [range 1–16 year(s)] and mean expanded disability status scale (EDSS) was 3.1 (range 1.5–4.5). Four patients with COVID-19 were managed in an ambulatory setting, whereas four of our patients had a COVID-19-infection warranting hospitalisation, but none needed respiratory support. For further patients characteristics, see Table 1. All of the patients included in our case series signed an informed consent, which includes the publication of the medical data in an anonymised form and this work is in accordance with the regulations of our local ethical committee.

In accordance with other case reports,[1,2] these data highlight that patients treated with anti-CD20-therapies may lack an antibody response after symptomatic COVID-19. Our findings are in line with other case reports, but in our study we tested for several epitopes (anti-nucleocapsid IgG and anti-spike protein), whereas in previous case reports, only single epitopes were measured. Usually, a detectable anti-spike and anti-nucleocapsid IgG antibody response to SARS-CoV2 is present within few days after symptom onset.[3] The initial antiviral responses are driven mainly by T-cells, in particular CD8+ cytotoxic T-lymphocytes, and natural killer cells and less by B-cells, which may explain why patients on anti-CD20 therapies cope relatively well with viral infections. So far, it is uncertain to what extent COVID-19 results in a long-lasting immunity, but it is generally accepted that neutralising antibodies play a crucial role in protection against coronaviruses.[4] Therefore, the finding of a lacking antibody response after a symptomatic COVID-19 in patients treated with anti-CD20-therapies may imply an increased risk for re-infection. In addition, anti-CD20-therapies may lead to an absent antibody response to SARS-CoV2-vaccines, as has been predicted by Baker *et al.*[5] In our opinion, this should prompt closer surveillance including monitoring of the immune response in patients treated with anti-CD20-therapies after both infection and vaccination, in order to clarify whether these individuals remain at risk for SARS-CoV-2 infection. If vaccination or infection fails to protect a high proportion of patients on anti-CD20 therapy, the safekeeping of these vulnerable individuals

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Table 1. Patient characteristics.

Patient no.	Sex	Age (years)	First diagnosis	Diagnosis	EDSS	Last OCR/ RTX infusion	Start of OCR/RTX treatment	PCR test	Antibody test	SARS-CoV-2 IgG anti-Nucleocapsid	SARS-CoV-2 IgG anti-Spike protein	Symptoms	Management	Previous DMT (sequence)
1	F	37	2018	RRMS	1.5	10 July 2020	January 2019	20 October 2020	26 November 2020	Negative	Negative	Bilateral pneumonia	In-patient treatment	None
2	F	39	2009	RRMS	4	8 July 2020	May 2018	17 October 2020	09 December 2020	Negative	Negative	Pneumonia	Out-patient treatment	Interferon beta 1a, Natalizumab, Interferon beta 1b, Natalizumab, Glatirameracetate, Rituximab
3	F	55	2003	RRMS	3	12 June 2020	April 2018	27 September 2020	10 February 2021	Negative	Negative	Pneumonia	Out-patient treatment	Interferon beta 1a, Interferon beta 1b, Glatirameracetate, Natalizumab
4	F	53	2004	RRMS	4	4 June 2020	September 2018	23 October 2020	8 February 2021	Negative	Negative	Sepsis	In-patient treatment	Interferon beta 1a, Glatirameracetate, Natalizumab
5[a]	F	44	2017	NMOSD	3	3 July 2020	June 2017	3 December 2020	27 January 2021	Negative	Negative	Bilateral pneumonia	In-patient treatment	Interferon beta 1a, Fingolimod, Daclizumab
6	M	47	2020	RRMS	1	14 August 2020	July 2020	30 December 2020	17 February 2021	Negative	Negative	Pneumonia	Out-patient treatment	None
7	M	53	2014	PPMS	2.5	3 September 19	March 2019	31 March 2020	23 December 2020	Negative	Positive	Sepsis	In-patient treatment	None
8	F	69	2004	SPMS	4.5	7 February 2020	August 2017	7 December 2020	10 February 2021	Positive	Positive	Pneumonia	Out-patient treatment	Interferon beta 1b

[a]Patient 5 has first been diagnosed and treated with an RRMS diagnosis and was classified as NMOSD in 2017.
DMT, disease modifying treatment; EDSS, expanded disability status scale; NMOSD, neuromyelitis optica spectrum disorder; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

will depend on herd immunity and individual protective measures such as physical distancing and following hygiene rules.

Conflict of interest statement

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