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LETTER

Mild COVID-19 despite inadequate antibody response after repeated vaccinations in rheumatic disease patients with rituximab-induced B cell depletion: a case series

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B cell depletion by medications such as rituximab (RTX) is an indispensable therapeutic approach in many autoimmune and oncological indications. Unfortunately, RTX treatment has put patients at higher risk of COVID-19-related hospital admission and death.[1] Moreover, RTX treatment and low B cell counts are associated with inadequate antibody responses, even after a third vaccination.[2] T cell responses seem largely intact,[3] but the impact on clinical protection remains unclear. Given the current predominance of SARS-CoV-2 Omicron sublineages, a reduced neutralisation capacity of antibodies must also be considered. However, this may be mitigated by booster vaccinations, and T cell immunity is largely preserved across variants.[4] Overall, Omicron is associated with milder courses of disease.[5] Open questions remain regarding immunogenicity and clinical outcomes of COVID-19 in RTX patients, especially after repeated vaccinations and in times of the Omicron variant.

In this letter, we present a case series of all 7 patients out of an initial 49 RTX-treated patients with at least two visits in our VACCIMMUN Study who were diagnosed with SARS-CoV-2 infection until June 2022. The patients had received their last RTX infusion 6–13 months before infection but all still had very low or no measurable B cells shortly before infection. All patients had three vaccinations with 30 µg BNT162b2 and six patients had additional fourth or even fifth vaccinations with 100 µg mRNA-1273 before infection (table 1). Immunogenicity was measured by assessment of anti-S and anti-RBD antibodies (SeraSpot by Seramun) as well as a pseudoneutralisation test against wild type SARS-CoV-2 (cPass by GenScript) and showed very low or no antibodies and negative neutralisation results in all patients shortly before infection. T cell responses were measured by interferon-gamma release assay (Quan-T-Cell by Euroimmun) in four patients before infection. Two had positive results and two were not interpretable because they lacked adequate reaction to mitogen controls. The coronavirus variant was sequenced as Omicron in patient 2 and Omicron was predominant for patients 3–7 at the time of infection. None of the patients received therapeutic anti-SARS-CoV-2 antibodies due to patient preference or unavailability. In addition to RTX treatment, most patients had concomitant risk factors, such as adipositas or advanced age. Nonetheless, all patients developed mild ambulatory COVID-19 with scores from 1 to 2 out of 10 according to the WHO clinical progression scale.[6] Headache and common cold symptoms including fever were the most frequent symptoms. None of the patients required additional oxygen or hospital admission. Outcome was good in all cases, yet two patients reported ongoing sequelae (decrease in taste and smell, occasional headache and limb pain) after 3 months. After infection, five out of six measured patients showed T cell responses. The patient without a T cell response had a low mitogen positive control but showed a very good antibody response.

This case series demonstrates that mild COVID-19 may not be uncommon after repeated vaccinations against SARS-CoV-2 even in patients with very low peripheral B cells without an adequate antibody response.

Table 1 Patient characteristics and immunogenicity before and after COVID-19

Patient number	1	2	3	4	5	6	7
Patient characteristics							
Age (years)	67	55	44	45	57	58	60
Gender	Female	Male	Male	Female	Male	Female	Male
Diagnosis	RA	RA	RA	IgG4	MPA	GPA	EGPA
Immunosuppressive therapy	RTX	RTX, MTX	RTX, MTX	RTX	RTX, Pred, HCQ	RTX, Pred, AZT	RTX, MTX
Months from last RTX to infection	8	6	12	10	7	7	11
Further risk factors	Age	BMI=32	COPD, BMI=34	DM2, HT, BMI=50, OSA, 40 py	HT, BMI=33, 40 py	HT, BMI=30	CNI, stroke, hemiparesis
Vaccinations							
Vaccinations before infection	4	4	4	5	3	4	4
Last vaccination to infection (days)	29	35	19	6	36	25	30
B cells status							
Assessment to infection (days)	0	35	19	6	36	25	30
CD19 positive cells (cells/nl)	0.02	0.00	0.00	0.02	0.00	0.00	0.00
Immunogenicity before/after infection							
Assessment before/after infection (days)	0/70	4/28	19/27	6/22	8/20	25/30	2/57
Neutralisation capacity (%)	13.4/0	0/0	12.4/0	14.2/**99.5**	22.9/18.7	0/0	0/24.2
IgG against RBD (BAU/ml)†	0/12.4	0/0	2.3/0	**139**/**2845**	1.7/2.0	0/5.2	5.2/31.6
IgG against spike protein (BAU/ml)†	0/1.6	0/0	2.1/44.7	39.7/**1928**	0/3.6	0/10.8	**59.5**/**310**
T cell response (mIU/ml)	n.a./**182***	n.a./**858**	**357**/**982**	40*/85*	0*/**328**	n.a./n.a.	**474**/**930**
Infection							
Date of positive PCR	07 December 2021	14 January 2022	22 January 2022	27January 2022	08 February 2022	08 February 2022	13 February 2022
Omicron prevalence at infection (%)	<1	84; Omicron proven	94	94	99	99	99
Symptoms of COVID-19	Cough, joint pain	Cough, fever, headache, limb and joint pain	Sore throat, headache, shivering	Cough, sore throat, headache, limb pain, fatigue	Cough, headache, shivering, decreased taste/smell	None	Cough, rhinitis, headache, fever
Medication for COVID-19	None	Ibuprofene, clarithromycine	None	None	Acetylsalicylic acid	None	Acetaminophene
WHO rating scale (0 to 10)‡	2	2	2	2	2	1	2

Lower limit of normal for B cells: 0.1 /nl; positive immunogenicity test results in bold letters: >30% for neutralisation capacity, >1 S/CO for IgG which corresponds to >64.2 BAU/ml against RBD and >58.6 BAU/ml against spike protein, >200 mIU/ml=positive and >100 mIU/ml=borderline positive or >135 mIU/ml=positive in case of negative controls <100 mIU/ml for T cell response.
*Low response to mitogen positive control.
†Converted from semiquantitative S/CO values by conversion formula supplied by manufacturer.
‡According to Marshall *et al*.[6]
AZT, azathioprine; BMI, body mass index in (kg/m²); CD, cluster of differentiation; CNI, chronic renal insufficiency; COPD, chronic obstructive pulmonary disease; DM2, diabetes mellitus type II; (E)GPA, (eosinophilic) granulomatosis with polyangiitis; HCQ, hydroxychloroquine; HT, hypertension; IgG, immunoglobulin G; IgG4, immunoglobulin-4-associated disease; MPA, microscopic polyangiitis; MTX, methotrexate; n.a., test result not available; OSA, obstructive sleep apnoea; Pred, prednisolone; py, pack years of smoking; RA, rheumatoid arthritis; RBD, receptor binding domain; RTX, rituximab;

Calabrese *et al* previously reported a 39% hospitalisation rate and a positive effect of therapeutic antibodies in B cell depleted patients after basic immunisation and in times of the original virus variant.[1] Omicron prevalence, longer time since the last RTX infusion and T cell activation after repeated vaccinations may have contributed to the fact that none of the patients in our cohort required hospitalisation. The infection triggered increased T cell or B cell responses in all symptomatic patients, which underlines that immunogenicity is possible despite very low B cells. In patients for whom RTX treatment remains indispensable, we advocate repeated vaccinations despite low B cells, testing of immunogenicity and consideration of early antiviral treatments or prophylaxis, especially in persistent non-responders.

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