Presence of specific T cell response after SARS-CoV-2 vaccination in rheumatoid arthritis patients receiving rituximab

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Dear Editor,

A series of observations have shown that vaccination against SARS-CoV-2 in patients with immune-mediated diseases treated with rituximab is followed by the absence of production of neutralizing antibodies to RBD [1]. A previous study in 126 patients focused on the role of rituximab in vaccination against SARS-CoV-2 [2]. Another recent study shows that only patients who had repopulated for B lymphocytes exhibited an immune response to the vaccine against SARS-CoV-2. In the study, 11 patients repopulated but only 7 responded [3].

The aim of our study was to evaluate the humoral and cellular immune response to two doses of COVID-19 vaccine BNT162b2 mRNA in a series of patients with rheumatoid arthritis treated with rituximab.

We evaluated a group of patients with rheumatoid arthritis who had received the last infusion of rituximab 6 months earlier (group A 4 patients), a group of patients who had received the last dose of rituximab 9 months earlier (group B 5 patients) and a group of patients who had received rituximab 12 months earlier (group C 5 patients). All patients received two doses of BNT162b2 mRNA COVID-19 vaccine 21 days apart. Patients underwent evaluation of the

lymphocyte subpopulations with determinations of the B lymphocyte population (CD27 – naive, CD27 + memory, CD38 +, CD20 +, CD19 +) evaluated by flow cytometry (FACS CANTO II, BD Biosciences), before the vaccination and 3 weeks after the second dose of vaccine. The value of anti-SARS-CoV-2 Spike-RBD IgG antibodies (IgG antibodies against S1-RBD protein) quantified by FEIA (ThermoFisher, Uppsala Sweden) was determined 3 weeks after the second dose of vaccine. In addition, SARS-CoV-2-specific T cell responses were determined by incubating isolated T cells with a SARS-CoV-2-specific peptide mix (a peptide mix of the SARS-CoV-2 spike protein) and measuring the release of interferon γ by activated T cells using an ELISA system (IFN- γ release assay, IGRA) according to the protocol of the manufacturer (SARS-CoV-2-IGRA, Euroimmun, Lubeck, Germany). All patients were in clinical remission at the time of vaccination and discontinued methotrexate in the week of the first and second vaccine administration according to the published recommendations [4, 5].

Table 1 shows the characteristics of the 14 patients. Four of the 14 patients had no or low values of anti S1-RBD antibodies. The evaluation of IFN- γ production by the IGRA test showed in the 4 patients a mediated CD8 + T cell response with a value of > 2500 mU/mL.

Literature data have shown a correlation between antibody response and circulating levels of CD19 + B lymphocytes after vaccination against SARS-CoV-2 in patients with immune-mediated diseases. However, we can observe a T cell mediated immune response even in patients with B cell depletion. This has recently been observed also by other authors [6]. It is not yet clear what level of immunogenicity is representative of vaccine efficacy. We do not know which extent of T cell response and for how long it is adequate to protect patients against virus infection after vaccination, but preliminary studies are promising. Our data also indicate that treatment with RTX may not preclude SARS-CoV-2

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Table 1 Summary of patients' characteristics

Pt	Age	Number RTX cycle	RTX week before	Predn dose	MTX dose	CD3 + cells/mL	CD3 + CD4 + cells/mL	CD3 + CD8 + cells/mL	CD3 – CD56 + CD16 + cells/mL	CD19 + cells/mL	CD20 + cells/mL	CD27 – naïve cells/mL	CD27 + memory cells/mL	CD38 + cells/mL	IgG SARS- CoV-2 RBD BAU/WHO mL	IGRA IFN- γ mU/mL
1	58	4	24	5	10	1123	545	346	234	6	2	46	11	12	232	
2	61	5	25	5	10	1342	634	532	342	9	5	34	12	15	569	
3	44	3	24	5	10	1546	657	432	223	9	6	21	6	11	356	
4	46	6	26	5	10	678	325	286	127	3	2	8	2	2	0.7	2500
5	68	8	37	2.5	12.5	583	395	188	350	147	131	139	6	6	1632	
6	76	9	36	5	12.5	1439	1158	293	420	31	25	23	3	3	164	2500
7	69	8	44	2.5	10	2245	1932	290	440	2.2	1	10	17	17	0.7	2500
8	56	3	38	2.5	10	2037	901	1098	291	177	200	197	16	16	480	
9	52	6	40	2.5	10	1484	1110	355	254	31	26	25	4	4	10.5	
10	33	3	54	2.5	12.5	1560	1003	514	165	52	20	17	6	20	980	
11	59	9	56	2.5	10	1548	903	606	213	183	131	109	15	113	1632	
12	58	6	54	5	10	2339	1123	1094	438	383	491	476	19	236	1632	
13	80	9	56	5	15	530	439	82	197	10	77	75	2	65	296	
14	43	6	55	5	10	823	612	206	313	67	62	93	11	6	0.7	2500

vaccination, as a cellular immune response will be activated even in the absence of circulating B lymphocytes.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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