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Cellular and humoral responses to fourth SARS-CoV-2 vaccination in a real-life cohort of patients with cancer

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Summary This study assessed cellular and humoral responses to the fourth dose of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) vaccines in patients with malignant diseases. Even though, clear indications of humoral, cellular, or combined response was evident in most patients undergoing active treatment, high intra- and interpatient heterogeneity in response patterns was observed.

Keywords SARS-CoV-2 · COVID-19 · Humoral immunity · Cellular immunity · Vaccine response

To the Editor,

Patients with cancer are at increased risk of adverse outcomes when infected with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and show an impeded humoral and cellular immune response to vaccination [1]. A fourth vaccination increased the humoral immunity against SARS-CoV-2 including Omicron sublineages [2]. However, data on effects of a fourth SARS-CoV-2 vaccination on cellular immunity, particularly in relation to antibody responses, are scarce [3].

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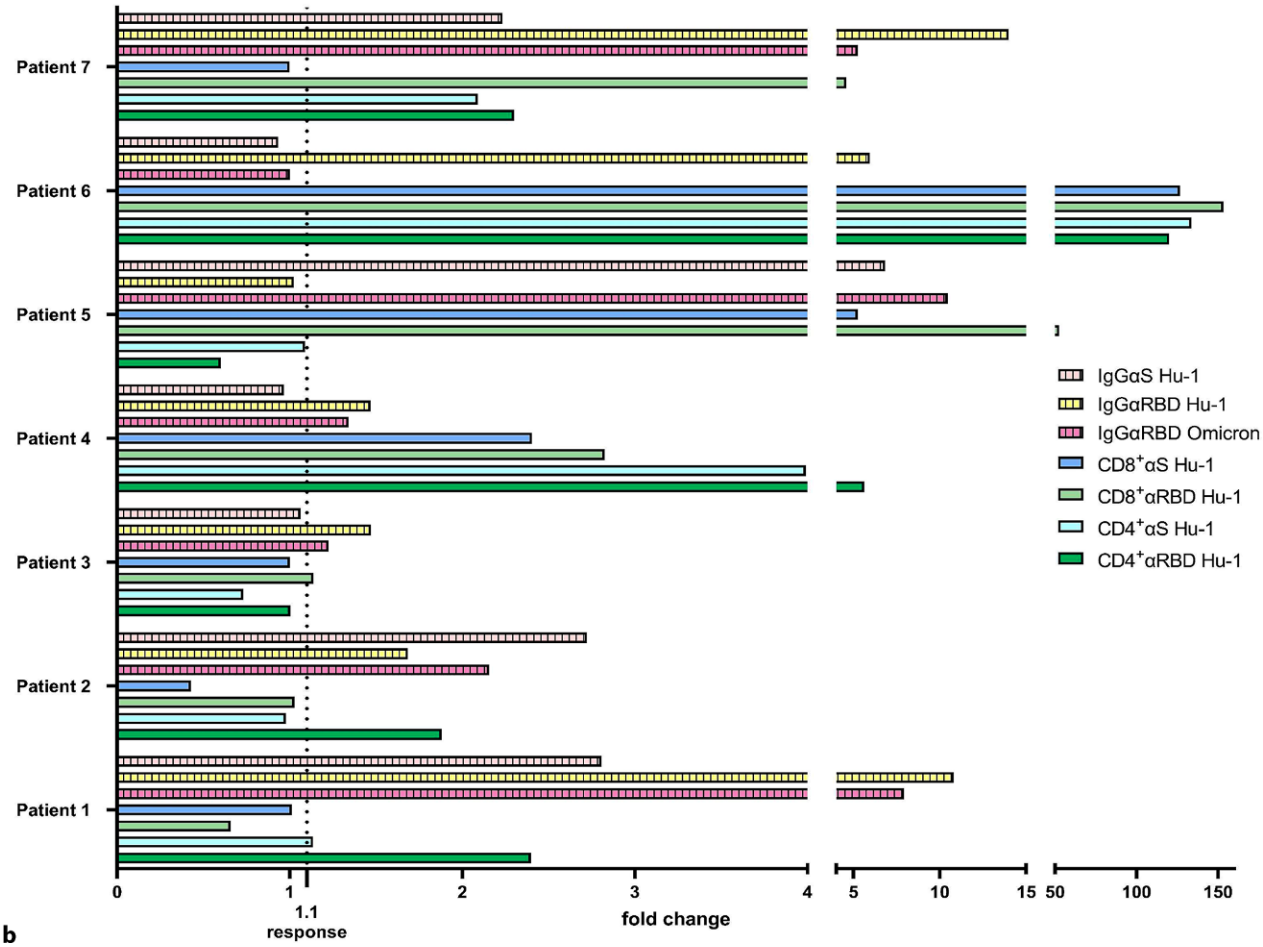
Methods To analyze specific cellular immunity after fourth immunization, SARS-CoV-2-specific $CD4^+$/$CD8^+$ T-cell responses were prospectively measured in seven patients with histologically confirmed neoplastic disease before and after the fourth vaccination against the SARS-CoV-2 spike protein (S) and the receptor binding domain (RBD). Moreover, IgG against S and RBD of Omicron (BA.4) and the SARS-CoV-2 wild-type (Wuhan-Hu-1), respectively, were assessed. An increase of antigen-specific proliferated cells and antibody levels of > 1.1-fold compared to baseline was defined as a vaccination response. This threshold was determined using the median fold change of antibody levels after 22 days in a patient cohort that did not receive the fourth vaccine dose. Assays were performed as described previously [4]. This study was approved by the ethics committee of the Medical University of Vienna (vote 1427/2022) and performed according to the Declaration of Helsinki and its amendments. Informed consent was obtained for all individuals included in the study. Descriptive statistical analysis was performed using GraphPad Prism, Version 9.4.1 (San Diego, CA, USA).

Results Six patients with solid tumors and one immunocompetent (no active immunosuppressive medication) patient with central neverous system (CNS) lymphoma (median age [range]: 64 years [45–78], seven men) were prospectively included and received a fourth vaccination (one mRNA-1273 and six BNT162b2). As patients were prospectively included in this study, no data on vaccine responses to previous vaccinations were available. Of these patients, six were undergoing active anti-neoplastic therapy. The baseline blood sampling was performed at a median of 7 months (range: 5–9 months) after the third vaccine dose and in median 10 days (range 7–36 days) before fourth dose, while the follow-up blood sampling

ID	Sex [1]	Age [years]	COVID-19 vaccines[2]				Blood sampling [days]			Entity	Treatment	Treatment to fourth vaccination[6] [days]
			1st	2nd	3rd	4th	Pre[3]	Between[4]	Post[5]			
1	m	64	BnT	BnT	BnT	BnT	251	7	21	Glioma	Bevacizumab	7
2	m	76	BnT	BnT	BnT	BnT	211	36	21	Gastric cancer	FOLFOX*/ Trastuzumab	7
3	m	45	BnT	BnT	BnT	BnT	157	14	20	CNS lymphoma	FERRERI+	443
4	m	64	AZD	AZD	BnT	BnT	233	26	21	Non-small cell lung cancer	Pemetrexed/ Pembrolizumab	12
5	m	78	Mod	Mod	Mod	Mod	240	9	19	Esophageal cancer	FOLFIRI#	9
6	m	67	Mod	Mod	BnT	BnT	259	10	21	Sarcoma	Doxorubicin	10
7	m	59	BnT	BnT	BnT	BnT	279	7	30	Pancreatic cancer	Nal-Irinotecan/ 5-FU	5
Median (Range)		**64** (45-78)						**10** (7-36)	**21** (19-30)			

a



b

Fig. 1 **a** Patients' characteristics. [1]*m* Male. [2]COVID-19 vaccines used for homologous or heterologous vaccination regimen: *AZD* ChAdOx1, *BnT* BNT162b2, *Mod* mRNA-1273. [3]Time between third COVID-19 vaccination and blood sampling before fourth vaccination. [4]Time between blood sampling before fourth vaccination and fourth vaccination. [5]Time between fourth COVID-19 vaccination and blood sampling after fourth vaccination. [6]Time between last cancer therapy and fourth COVID-19 vaccination. **FOLFOX* folic acid, 5-fluorouracil plus oxaliplatin; +*FERRERI* methotrexate, cytarabine, thiotepa plus rituximab; #*FOLFIRI* folic acid, 5-fluorouracil plus irinotecan. **b** Cellular and humoral response to fourth SARS-CoV-2 vaccine dose in individual patients including patient characteristics (entity, treatment, time from treatment to vaccination in days). Fold change of specific T-cell proliferation ($CD4^+$, $CD8^+$) after stimulation with spike protein (S) and RBD Hu-1 and total IgG against spike, RBD Hu-1, and RBD Omicron. Fold change > 1.1 is considered response to vaccination

Table 1 Specific $D3^+CD4^+$ and $CD3^+CD8^+$ cell proliferations before and after vaccination

		% $CD4^+$		% $CD8^+$	
ID	Antigen stimulated	Before	After	Before	After
1	S	44.93	51.03	7.96	8.07
	RBD-hu1	15.20	36.43	11.46	7.55
2	S	6.76	6.60	8.26	3.53
	RBD-hu1	4.01	7.53	3.89	4.00
3	S	49.55	37.34	26.29	26.35
	RBD-hu1	46.60	48.47	35.55	40.47
4	S	2.93	9.72	2.57	6.16
	RBD-hu1	0.97	2.62	0.87	2.45
5	S	8.92	9.72	1.18	6.16
	RBD-hu1	4.37	2.62	0.05	2.45
6	S	0.00	1.34	0.00	1.27
	RBD-hu1	0.00	1.13	0.00	1.53
7	S	13.23	27.65	7.43	7.80
	RBD-hu1	9.95	22.90	4.32	19.75

S spike protein, *RBD-hu1* receptor binding domain of the SARS-CoV-2 wild-type

Table 2 Specific antibody response before and after vaccination

	IgG to S		IgG to RBD-hu1		IgG to RBD-omicron	
ID	Before	After	Before	After	Before	Aftert
1	0.763	2.143	0.144	1.555	0.106	0.843
2	0.272	0.741	0.077	0.130	0.084	0.181
3	1.867	1.986	1.010	1.486	0.592	0.726
4	2.093	2.023	1.093	1.603	0.721	0.968
5	2.072	1.937	1.509	1.545	0.831	0.832
6	0.968	2.162	0.184	1.093	0.138	0.726
7	0.333	2.275	0.067	0.934	0.064	0.673

S spike protein, *RBD-hu1* receptor binding domain of the SARS-CoV-2 wild-type, *RBD-omicron* receptor binding domain of the Omicron variant

was done at a median of 21 days (range: 19–30 days) after the fourth vaccination (Fig. 1a).

Overall, clear signs of response on humoral, cellular, or combined humoral and cellular levels were observed in six of seven patients. However, a striking intra- and interpatient heterogeneity of immune response patterns was evident (Fig. 1b, Tables 1 and 2). Only two of seven patients (patients 4 and 6) responded with combined increases in S- and RBD-specific $CD4^+$ and $CD8^+$ T-cell proliferation. All other patients showed inconsistent increases in T-cell activity with low vaccination responses in at least one T-cell subpopulation. Additionally, humoral response did not consistently coincide with cellular vaccine responses: Patients 4 and 6, who had no increase or only a mild increase in antibody levels showed a pronounced cellular vaccine response. Interestingly, in patient 5 increased antibody levels against S without corresponding $CD4^+$ responses were found. Moreover, patients with distinct antibody increases only showed mediocre vaccine responses on a cellular level (patients 1, 2, and 7). One patient (patient 3) showed severely impeded humoral and cellular vaccine responses to the fourth vaccination applied 433 days after administration of the last B-cell targeting treatment (rituximab).

Conclusion

The most important limitation of this prospective study is its small sample size and the lack of a control group. However, we observed high intra- and interpatient heterogeneity with clear indications of humoral, cellular, or combined response to the fourth vaccine in most patients under active treatment. Of note, our observation indicates long-lasting impairment of specific immune responses for as long as 36 months after the last rituximab administration. These findings highlight the need for reliable identification of SARS-CoV-2 vaccine non-responders.

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Declarations

Conflict of Interest J.M. Berger, P. Gattinger and A.S. Berghoff, and declare that they have no competing interests. M.J. Mair reported receiving nonfinancial support from Pierre Fabre outside the submitted work. R. Valenta reported receiving personal fees from Viravaxx AG and Worg Pharmaceuticals; receiving grants from HVD Biotech, Viravaxx AG, and Worg Pharmaceuticals outside the submitted work; and holding a patent for Molecular Interaction Assay (pending) and a patent for SARS-CoV-2 vaccine (pending). M. Preusser reported receiving personal fees from Bayer, Bristol Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dohme, Tocagen, Adastra, and Gan & Lee Pharmaceuticals outside the submitted work. No other disclosures were reported.

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