LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.1998485

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Cellular response to COVID-19 vaccines in hematologic malignancies patients: a new hope for non-responders?

Imane Saad Albichr[a]*, Julien De Greef[b]*, Eric Van Den Neste[c], Xavier Poiré[c], Violaine Havelange[c], Marie-Christiane Vekemans[c], Sarah Bailly[c], Jean-Cyr Yombi[b], Samy Mzougui[a], Anaïs Scohy[a] and Benoît Kabamba-Mukadi[a]

[a]Department of Microbiology, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium; [b]Department of Internal Medicine and Infectious Disease, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium; [c]Department of Hematology, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium

ARTICLE HISTORY Received 29 August 2021; revised 1 October 2021; accepted 12 October 2021

KEYWORDS COVID-19; SARS-CoV-2; vaccine; cellular immunity; hematologic malignancies

SARS-CoV-2 vaccines offered great hope in controlling the worldwide COVID-19 pandemic. At present, SARS-CoV-2 vaccines have shown excellent efficacy to prevent COVID-19 but immunocompromised patients were left-off most vaccine clinical trials albeit their extreme vulnerability [1]. Indeed, immunosuppression is associated with a higher risk of developing severe COVID-19 with mortality rates over 30% reported in patients with hematologic malignancies (HM) [2]. The limited available data on serological response following SARS-CoV-2 vaccination in this specific population showed disappointing results [3–5]. However, these studies only investigated humoral immunity. Yet, cellular immunity is of paramount importance in controlling viral infection and has shown to be effective and correlated with better outcome. It can be assessed through assays measuring interferon-gamma release by peripheral blood mononuclear cells exposed to viral antigens [6]. We aimed to evaluate cellular immunity in fully vaccinated HM patients with no history of COVID-19 and no detectable serological response. Among 16 seronegative patients, 9 patients mounted a cellular response to SARS-CoV-2 vaccines.

Patients with HM followed at Cliniques universitaires Saint-Luc, a tertiary hospital in Brussels, Belgium, were proposed study inclusion consecutively during their routine hematology appointments if they had been vaccinated against SARS-CoV-2 and had no previous history of COVID-19. Patients were included between June 9 and 22, 2021. In this study, we analyzed patients who had been previously identified during routine follow-up as vaccine non-responders (i.e. with a negative SARS-CoV-2 serology drawn after a completed 2 injections vaccine schedule). Seronegativity was confirmed at inclusion using a standardized immunoassay detecting antibodies (Ab) directed against the Receptor Binding Domain (RBD) and the nucleocapsid (N) [Elecsys anti-SARS-CoV-2, Roche Diagnostics GmbH, Mannheim, Germany - positive threshold $>$0.8 U/mL (Anti-RBD) and $>$1.0 index (Anti-N), upper limit of detection 250 U/mL (anti-RBD)]). T-cell response was measured with a whole blood interferon-gamma (IFN-ϒ) release assay (IGRA) using SARS-CoV-2 spike protein antigens to activate T cells, following manufacturer's instructions (SARS-CoV-2 IGRA, Euroimmun, Lübeck, Germany- positive threshold $>$100 mIU/mL. Further analytical details and study flowchart is available as Supplementary appendix. All patients signed informed consent and the study received IRB approval (B4032021000056).

Among 16 seronegative patients, 14 were included in the final analysis after exclusion of 2 patients with uninterpretable IGRA results (fail of unspecific stimulation of T lymphocytes). Median age was 66 (range: 37–77) years and 3/14 were females. Patients presented the following lymphoid malignancies: chronic lymphocytic leukemia (CLL, 5/14), non-Hodgkin B-cell lymphomas (NHL, 6/14), Waldenström's macroglobulinemia (WM, 2/14), and acute lymphoblastic leukemia (ALL, 1/14). At initiation of vaccination against COVID-19, 10 patients were receiving ibrutinib, 5 patients were receiving anti-CD20 treatments (4 rituximab and 1 obinutuzumab), including 3 patients receiving a combination of ibrutinib and rituximab. One ibrutinib-treated patient had discontinued rituximab for

CONTACT Imane Saad Albichr imane.saadalbichr@uclouvain.be Department of Microbiology, Cliniques universitaires Saint-Luc, Brussels, Belgium. Avenue Hippocrate, 10, Brussels 1200, Belgium

Supplemental data for this article can be accessed here.

*These authors contributed equally to the work.

Table 1. Comparison of hematologic malignancy patients with positive versus negative SARS-CoV-2 IGRA test after COVID-19 vaccination.

	IGRA positive patients ($n = 9$)	IGRA negative patients ($n = 5$)	p-value
Age (range)	66 (37–76) years	67 (51–77) years	
Sex (N)			
Male	6	5	
Female	3	0	
Vaccine type (N)			
BNT162b2	7	5	
mRNA-1273	2	0	
IGRA values mUI/mL (mean ± SEM)	1509.6 (±343.7)	7.8(±3.7)	<.001
IgG levels (g/L) (mean ± SEM)	5.4 (±0.76)	7.9 (±1.2)	.169
Lymphocyte count/mm^3 (mean ± SEM)	2664 (±595)	1262 (±510)	.112
Hematologic malignancy type (N)			
CLL	4	1	
Non-Hodgkin B-cell lymphoma	4	2	
ALL	0	1	
Other	1	1	
Ongoing treatment (N)			
Ibrutinib + rituximab	1	2	
Ibrutinib alone	5	2	
Rituximab alone	1	0	
Obinutuzumab and lenalidomide	1	0	
Pemetrexed and mercaptopurin	0	1	
No treatment	1	0	
Received anti-CD20 during the last year (*N*)	4	2	

7 months. Further details are provided in Table 1. Two patients (2/14) had autologous stem cell transplant (ASCT) in 2016 and 2018, respectively. All fourteen patients had completed a full COVID-19 vaccination scheme (i.e. 2 injections) with BNT162b2 (12/14) and mRNA-1273 (2/14) vaccines. Median time between vaccination completion and IGRA testing (median ± IQR) was 2.5 months (±1).

Nine patients (9/14) mounted a cellular response (positive IGRA test) [IFN-ϒ value (mean ± SEM): 1509.6 (±343.7) mUI/mL] (Figure 1). Six out of ten patients (6/10) receiving ibrutinib, and 4/6 patients that had received rituximab within the last year had a positive IGRA test. Both patients that had ASCT showed a positive lymphocyte T response. Among the five patients that did not develop cellular immunity, two (2/5) had NHL, one (1/5) had CLL, one (1/5) had ALL and one (1/5) patient had WM. Two patients (2/5) were receiving ibrutinib with rituximab and two (2/5) others were treated only with ibrutinib. One patient was under maintenance therapy for ALL. All negative patients received the BNT162b2 vaccine.

Mean lymphocyte count was 2664 (±595)/mm^3 in the IGRA-positive group and 1262 (±510)/mm^3 in the IGRA-negative group (p-value: 0.112, Mann-Whitney test). Mean IgG level was 5.4 (±0.76) g/L and 7.9 (±1.2) g/L in the IGRA positive and negative group, respectively (p-value: 0.169, Mann-Whitney test). None had received intravenous immunoglobulin.

Features of HM patients according to their IGRA results are displayed in Table 1.

Several studies showed that patients with HM, particularly lymphoid malignancies, had a lower antibody response to COVID-19 vaccines than general population and might be left unprotected from SARS-CoV-2 infection

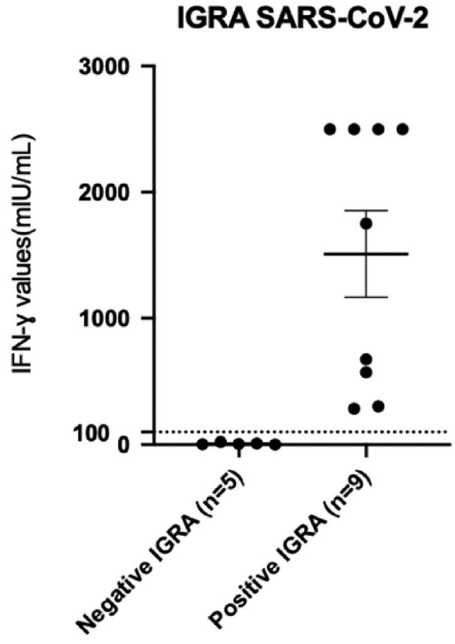

Figure 1. IFN-ϒ values (mIU/mL) in hematology malignancies patients using EUROIMMUN IGRA SARS-CoV-2.
IFN-ϒ values (mIU/mL) in IGRA positive ($n = 9$) and negative ($n = 5$) HM patients. Positive threshold >100 mIU/mL (dot line). Mean ± SEM in IGRA positive patients: 1509.6 (±343.7) mIU/mL.

[3–5]. Patients with CLL showed the poorest response [7]. In a study including 67 HM patients, only 23% of patients with CLL developed SARS-CoV-2 antibodies after full vaccination compared to 61.1% of patients with other HM even though 69.2% of CLL patients were not actively undergoing cancer therapy [4]. Ibrutinib and anti-CD-20 antibody therapy also seems to highly affect antibody response to vaccine [5,7].

Similar results were shown in vaccinated rheumatologic patients treated with anti-CD-20. Mrak *et al.* observed a high rate of patients developing T-cell response even if they failed to seroconvert. Cellular immunity was not correlated to humoral immune response [8].

There is still little information available on cellular vaccine immunity in HM patients. The only study published so far showed a higher rate of cellular immunity responders after two doses of BNT162b2 compared to humoral responders with, in some cases, the presence of T-cell immunity in the absence of SARS-CoV-2 antibodies. Yet, reduced T-cell response compared to normal healthy individuals has been detected in HM patients [9]. Beyond COVID-19, few studies have specifically assessed T-cell response after vaccination in this population. Response to the H1N1 inactivated vaccine in HM patients has been reported in two different comparative studies. While antibody response appeared lower, specific T-cell response were not significantly different between patients with HM and controls [10,11]. More recently, a robust specific cellular immune response has been shown in HM patients receiving adjuvanted recombinant zoster vaccine [12].

Evidence is emerging about the role of cellular immunity in protecting against COVID-19. In acute and convalescent COVID-19 patients, SARS-CoV-2-specific T-cell responses were associated with milder disease pointing out the importance of cellular immunity in containing SARS-CoV-2 infection [13]. Moreover, SARS-CoV-2 cellular immunity response with no detectable antibodies was observed in infected individuals indicating that cellular immunity might be induced and maintained in the absence of humoral response [6]. These observations support an important role of cellular immunity for resolving SARS-CoV-2 infection. However, the importance of humoral response should not be overlooked, as illustrated by the poor prognosis of patients treated with anti-CD20 therapy and their risk of protracted COVID-19 course [14].

Cross-reactive SARS-CoV-2 T-Cell response due to previous common cold human coronaviruses infections has been reported with ELISpot assay or flow cytometry [13]. However, there is currently no evidence of cross-reactivity with IGRA assays [15].

Our findings are encouraging for HM patients especially for those who did not produce antibodies after full vaccination. However, our study included only fourteen patients and our results need to be confirmed on larger HM cohorts.

Whether vaccine-induced cellular immunity against SARS-CoV-2 alone can prevent COVID-19 is not clear and needs further investigation. Nevertheless, our data supports the utility of vaccination in HM patients, including patients with ibrutinib and anti-CD20 therapies, since they still mounted a cellular immunity, and could suggest a possible benefit from additional vaccine doses. Meanwhile, however, we believe strong adherence to barrier measures should be maintained in vulnerable populations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

[1] Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. JAMA. 2021;325(13):1318–1320.
[2] Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and Meta-analysis of 3377 patients. Blood. 2020; 136(25):2881–2892.
[3] Maneikis K, Šablauskas K, Ringelevičiūtė U, et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. Lancet Haematol. 2021;8(8):e583–e592.
[4] Agha M, Blake M, Chilleo C, et al. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. medRxiv. 2021. 2021.04.06.21254949.
[5] Addeo A, Shah PK, Bordry N, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. Cancer Cell. 2021;39(8):1091–1098.e2.
[6] Ong DSY, Fragkou PC, Schweitzer VA, et al. How to interpret and use COVID-19 serology and immunology tests. Clin Microbiol Infect. 2021;27(7):981–986.
[7] Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137(23):3165–3173.
[8] Mrak D, Tobudic S, Koblischke M, et al. SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. Ann Rheum Dis. 2021;80(10):1345–1350.
[9] Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021;22(6): 765–778.
[10] Mariotti J, Spina F, Carniti C, et al. Long-term patterns of humoral and cellular response after vaccination against influenza A (H1N1) in patients with hematologic malignancies. Eur J Haematol. 2012;89(2):111–119.
[11] de Lavallade H, Garland P, Sekine T, et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica. 2011;96(2): 307–314.
[12] Dagnew AF, Ilhan O, Lee W-S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019;19(9):988–1000.
[13] Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021;184(4):861–880.

[14] Duléry R, Lamure S, Delord M, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy. Am J Hematol. 2021;96(8):934–944.

[15] Huzly D, Panning M, Smely F, et al. Validation and performance evaluation of a novel interferon-γ release assay for the detection of SARS-CoV-2 specific T-cell response [Internet] 2021; [cited 2021 Aug 25]. p. 2021.07.17.21260316. Available from: https://www.medrxiv.org/content/10.1101/2021.07.17.21260316v1.