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Attenuated humoral immune response following anti-SARS-CoV-2 vaccine in heavily pretreated patients with multiple myeloma and AL amyloidosis

To The Editor:

SARS-CoV-2 (COVID-19) is a life-threatening disease that has rapidly spread around the world, reaching a mortality rate of > 4.7 million. Cancer patients are at increased risk of COVID-19 complications, and those with hematological malignancies have a more severe infection course than patients with solid tumors. Among hospitalized COVID-19 patients, those with blood cancer have a 2-fold higher death risk, demonstrating 28-day mortality of ~40%.[1]

Multiple myeloma (MM) is associated with significantly impaired humoral and cellular immunity, and novel anti-MM therapies may further affect the immune system. These factors contribute to diminished immune response to various types of pathogens, including viral respiratory tract infections. Several large studies demonstrate inferior COVID-19 outcomes in patients with plasma cell neoplasms compared with general population.[2,3]

Devastating effects of SARS-CoV-2 pandemic resulted in unprecedented efforts to develop anti-COVID-19 vaccines. To date, two mRNA vaccines (BNT162b2 [Pfizer], mRNA-1273 [Moderna]) are approved by the FDA based on their high anti-COVID-19 protection, as evidenced by phase-3 trials, which included a very limited number of patients with blood cancers.

To induce optimal postvaccination immunity, an intact host immune status, in terms of antigen presentation, B- and T-cell activation, and plasma B-cell antibody generation, is required. Hence, hosts lacking functional immune cells may be incapable of producing a full-range response to SARS-CoV-2 vaccines. Yet, most experts recommend vaccination of immunocompromised patients as long as the vaccine is safe, even if the expected protection is decreased.

The current noninterventional single-center prospective study evaluated serological responses to two doses of BNT162b2 (administered 21 days apart) and the persistence of these responses in newly diagnosed and pretreated MM and light chain (AL) amyloid patients, recruited between 1/2021 and 4/2021 upon signing informed consent.

Based on the Guidance by the International Myeloma Society, in patients with active progressive MM, ongoing anti-MM therapy was not stopped because of vaccination. In patients with stable disease, treatment was interrupted 7 days before the first dose and reintroduced 7 days after the second dose. If a long pause was too risky, the first and second vaccine doses were administered 2–7 days post the last dose of anti-MM therapy and up to 10 days before the next MM-therapy dose. Lenalidomide monotherapy was not interrupted. Intravenous immunoglobulin (IVIg) was stopped 14–28 days before the first vaccine dose and reintroduced ≥ 14 days after the second dose.

According to the study protocol, serology tests are performed 1, 3, 6, and 12 months after second vaccination. To date, tests have been conducted 1 month (±1 week) and 3 months (±2 weeks) after the second BNT162b2 dose, using the SARS-CoV-2 IgG II Quant assay (Abbott©). The result is considered positive if the IgG level is ≥ 150 AU/mL, undetermined if the IgG level is between 50 and 150 AU/mL, and negative if it is < 50 AU/mL.

Patient demographics, comorbidities, hematological disease characteristics, anti-cancer treatment, disease activity, and laboratory data prevaccination were collected from medical records. Vaccination side effects were recorded. All patients were followed for symptomatic COVID-19 at least 1 week post-second vaccination. Patient serological responses were compared with those of the control group comprising Rambam employees without myeloma (1:3 ratio), matched by sex and age. Descriptive statistics were performed for all evaluated parameters. A logistic regression model was employed to predict a positive serological result based on several independent parameters.

The study included 186 patients: 10 with newly diagnosed MM, 168 with MM, and 8 with AL amyloid, either on active anti-MM therapy (n = 141 [80%]) or previously treated. Patients received a median of two lines of therapy (range 1–8). Based on the common practice, 23 patients (13%) were treated with IVIg due to hypogammaglobulinemia and recurrent severe bacterial infections.

One month after second vaccination (mean 33.93 ± 7.533 days), 176 patients (94%) underwent serological evaluation, with results categorized as negative, undetermined, and positive in 36 (20%), 11 (7%), and 129 (73%) patients, respectively. In univariate analysis, older age at vaccination was associated with negative serological response 1 month after second vaccination ($p = .043$). Gender, smoking, body mass index, and comorbidities (hypertension, diabetes mellitus, and ischemic heart disease) did not influence the response (Table S1). Patients on active anti-MM therapies and those who were heavily pretreated (average of 3.58 vs. 1.58 lines of therapy), particularly patients receiving anti-CD38 immunotherapy, displayed higher frequency of negative response (Table 1). Patients with negative results presented with lower lymphocyte, hemoglobin, albumin, and IgG levels than those who developed serological response (Table 1). Among patients with negative response, 41.7% were treated with IVIg, while among those with a positive result, 5.4% received IVIg ($p < .0001$). Previous autologous stem cell transplantation and disease activity at vaccination did not influence the response.

In multivariate analysis, older age at vaccination ($p = .019$), multiple lines of anti-MM treatment ($p = .004$), and anti-CD38 immunotherapy ($p = .01$) predicted a negative serological response. Three months after second vaccination, 129/186 patients (69%) underwent

TABLE 1 Correlation of anti-myeloma therapy and blood workup with serological response 1 month after second anti-COVID-19 vaccination

	Negative	Positive	Undetermined	*p*-value
MM treatment	n = 36	n = 129	n = 11	
Patients on active treatment	35 (97%)	91 (70.5%)	11 (100%)	**<.001**
Patients not on active treatment	1 (3%)	33 (28%)	0	
Lines of therapy, mean ± SD	3.58 ± 2.00	1.58 ± 0.94	2.36 ± 2.06	[a]**<.001**
				[b]**.034**
s/p ASCT; yes	19 (53%)	83 (64%)	7 (64%)	.45
Specific anti-MM therapy				
Immunomodulators (n=82)	20 (57%)	55 (60%)	7 (64%)	.91
Proteasome inhibitors (n=63)	10 (29%)	46 (50.5%)	7 (64%)	**.04**
Anti-CD38 immunotherapy (n=50)	19 (61%)	27 (30%)	4 (40%)	**.007**
Treatment with IVIg (n=23)	15 (41.7%)	7 (5.4%)	1 (9.1%)	**<.0001**
Blood workup (mean ± SD)	n = 33	n = 118	n = 10	
Neutrophil count (×1000/μL), mean ± SD	3.58 ± 2.5	3.37 ± 1.7	3.79 ± 3.32	.97
Lymphocyte count (×1000/μL), mean ± SD	1.06 ± 0.71	1.5 ± 0.81	1.07 ± 0.46	[a]**<.001**
Hemoglobin (g/dL), mean ± SD	11.078 ± 1.60	12.29 ± 1.64	11.73 ± 2.07	[a]**.001**
Platelet count (×1000/μL), mean ± SD	165.97 ± 84.3	177.84 ± 67.2	117.36 ± 78.82	[b]**.018**
				[c]**.001**
Creatinine level (mg/dL), mean ± SD	1.42 ± 1.1	1.34 ± 1.64	1.08 ± 0.35	.38
Albumin level (g/dL), mean ± SD	3.85 ± 0.4	4.08 ± 0.34	3.89 ± 0.25	[a]**.002**
Polyclonal IgG (mg/dL), mean ± SD	686.87 ± 1190	760.24 ± 448	561.46 ± 252	[a]**<.001**
IgA (mg/dL), mean ± SD	125.24 ± 295	177.46 ± 458	76 ± 78	[a]**<.001**
IgM (mg/dL), mean ± SD	14.21 ± 9	39.13 ± 39	38.76 ± 21	[ab]**<.001**

Abbreviations: IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; MM, multiple myeloma; s/p ASCT, status post autologous stem cell transplantation

Note: The values in bold type represent statistically significant findings.

[a]Negative versus positive.

[b]Negative versus undetermined.

[c]Positive versus undetermined.

serological evaluation. The response was negative in 34 (26%), undetermined—in 19 (15%) and positive in 76 (59%) individuals. Results of tests performed at both time points were available for 120 patients. Among the 90 patients seropositive 1 month after second vaccination and re-evaluated at 3 months, 68 (76%) remained seropositive. Notably, 2/25 patients, seronegative at 1 month, got infected with COVID-19 and became seropositive at 3 months. The rate of positive responses was significantly lower in the patient cohort compared with controls, both 1 and 3 months after second vaccination, equating to 90/120 (75%) versus 357/360 (99.2%; $p < .001$) and 68/120 (56%) versus 355/360 (98.6%; $p < .0001$). Vaccination-related side effects in patients included: local pain (10%), fever (1.7%), and muscle pain (2.8%). Twelve patients (6.4%) experienced myeloma progression during the first month after the second vaccine dose.

A subanalysis of 137 patients on active anti-MM therapy demonstrated that 1 month after second vaccination, 35 (25%) patients had negative, 11 (8%)—undetermined and 91 (66%)—positive serological results. Among 50 patients, receiving anti-CD38 therapy during vaccination, results were negative in 38% and positive in 54% of individuals ($p = .007$). Serological responses at both 1 and 3 months post-second vaccination were evaluated in 95 patients on active therapy, with positive results documented in 65 (68%) and 48 (50.5%) of them, respectively.

The influence of anti-CD38 immunotherapy was further emphasized in the quantitative assessment of neutralizing antibody titers post-vaccination. One month after second vaccination, the median (25%–75%) titers of neutralizing antibodies were: 4149 (887–10 432) in 39 patients not on active therapy, 895 (110–7488) in 87 patients on active therapy excluding anti-CD38 agents, and 193 (17.5–744.5) in 50 patients receiving anti-CD38 therapy. At 3 months post-second vaccination, the corresponding values were: 912.5 (232–2234) in 32, 190 (54–2226) in 59, and 96 (9–347) in 39 patients, respectively (Figure S1).

At the time of analyses, most patients were 6 months after second vaccination. Four of them developed COVID-19 at least 1 week after the last vaccine dose (1 died of this disease, 1 had a severe course, but recovered, 2 had mild disease). Two patients displayed a negative serological result 1 month after second vaccination, which converted to positive following their COVID-19 resolution. One patient was seropositive at 1 month after vaccination and his disease course was mild. The patient who died did not undergo serological evaluation.

High COVID-19-associated mortality among myeloma patients calls for most efficient measures aiming to prevent virus contamination. mRNA anti-COVID-19 vaccines have proved highly effective in general adult population; however, immunocompromised patients have been extremely underrepresented in those clinical trials.

Seroconversion is a useful tool in predicting vaccine efficacy.[4] While clinical trials of mRNA anti-COVID-19 vaccines demonstrate an association of seroconversion with disease prevention in general population, corresponding data regarding patients with hematological malignancies are limited.

Results of the current study show that a significant portion of MM patients develops serological response to anti-COVID-19 vaccines. Comparison of our findings with those of the UK study[5] demonstrates a significant increase in the number of positive serological results after the second vaccine dose (56% in the UK MM cohort after one vaccination versus 73% in our cohort after two vaccinations). These data point to the importance of a full vaccination course (2 doses) in immunocompromised patients.

Among our patients, those who received more lines of anti-MM treatment and those on active therapy at the time of vaccination, particularly patients receiving anti-CD38 therapy, demonstrated a lower rate of positive serological results. Notably, one patient treated with daratumumab had a negative serological response after 1 and 3 months from second vaccination. Six months after second vaccination, while she was 3 months off-therapy, her serological result became positive, with no evidence of COVID-19 infection. This may suggest that the humoral decay associated with daratumumab could be temporary and the immune response to the vaccination may improve after deferral of anti-CD38 therapy. Our finding could contribute to the emerging consideration for temporary discontinuation of anti-CD38 therapy at the time of COVID-19 pandemic spike in patients with good response to anti-MM therapy.

Anti-myeloma agents are known to affect the function of T- and B-cells and the immune microenvironment. Thus, it is not surprising that heavily pretreated myeloma patients exhibit reduced ability to produce an effective immune response.

Additionally, MM patients frequently present with immunoparesis, which is commonly managed with IVIg if accompanied with recurrent infections. In our cohort, hypogammaglobulinemia and IVIg treatment are found to be significantly associated with decreased rates of seropositive results that might be attributed to reduced humoral response related to both these factors.

In the present study, the durability of patient serological response is reduced compared with that in controls, as demonstrated by a significantly higher rate of conversion from a seropositive to seronegative result 3 months after second vaccination. Hence, immunocompromised individuals may need a booster vaccine dose to enhance their response.[6]

Our study has several limitations. Levels of IgG antibodies developing in response to vaccination do not reflect the full range of immune response. Cellular immunity analyses (e.g., T-cell subpopulations, NK cells, etc.) could add to our understanding of the protective effect of vaccination. Furthermore, infection rates significantly decreased during the study period owing to the accomplishment of anti-COVID-19 vaccination. This precluded the assessment of the protective effect of such vaccination in MM patients.

The current study demonstrates that the majority of MM and AL amyloid patients generate reliable humoral immune response after two vaccinations with BNT162b2. Multiple lines of anti-MM treatment and anti-CD38 immunotherapy are associated with a negative serological response. Despite their vaccination, patients who have not developed serological response may remain unprotected from COVID-19, although other immune mechanisms might mediate some protection in such cases. To achieve a more efficient and durable serological response in MM patients, the currently applied vaccination schedule, dosage, and the number of doses administered may need to be modified. Serological monitoring could be used to guide the timing of vaccination boost. A longer follow-up is required to assess the degree of protection provided by anti-COVID-19 vaccination. Further clinical trials are warranted to determine the optimal regimen of vaccine administration in this vulnerable patient population.

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CONFLICT OF INTEREST

The authors have no conflicts to declare.

AUTHOR CONTRIBUTION

Neta Schiller Salton performed research, interpreted the data, and approved the final version of the article. Moran Szwarcwort performed research and approved the final version of the article. Inna Tzoran collected data and approved the final version of the article. Netanel A. Horowitz collected data and approved the final version of the article. Tsila Zuckerman collected data and approved the final version of the article. Nurit Horesh collected data and approved the final version of the article. Yael Shachor-Meyouhas performed research and approved the final version of the article. Khetam Hussein performed research and approved the final version of the article. Noa Lavi designed and performed research, wrote the article, and approved the final version of the article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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