DOI: 10.1002/hon.3051

WILEY

LETTER TO THE EDITOR

Response to SARS-CoV-2 vaccination and antibodies persistence in multiple myeloma patients

To the Editor:

Multiple Myeloma (MM) is a chronic hematologic disorder often associated with multiorgancomplications and increased susceptibility to infections.[1] COVID-19 have a more severe course and higher mortality rate in MM compared with general population.[2] Although SARS-CoV-2 vaccination is pivotal for infection prevention, its efficacy in hematologic patients is still object of debate.[3–5] In this study we evaluated the humoral response in 103 MM patients followed at a single center in Milan, Italy, undergoing SARS-CoV-2 mRNA vaccination from March until June 2021. Patients were selected according to the following criteria: ongoing antimyeloma treatment, recent chemo-immunotherapy (<6 months), stem cell transplant (SCT) within the last 12 months, and indication to receive immunosuppressive therapy in the next month.[6] Anti-Nucleocapside (anti-N) and anti-Spike (anti-S) IgG titer were tested (Elecsys Anti-SARS-CoV-2, Roche Diagnostics, Monza, Italy) for all patients 5 + 1 week after the second vaccine dose. Furthermore, in 25 responders to vaccine, Anti-N and anti-S titers were retested after 3 months Table 1 shows clinical and hematological features of enrolled patients according to their serological results. Patients were mainly females (53%), elderly (median age 70 years, 47–89), and with a diagnosis of IgG MM, while only 19 (18%) had a light-chain MM. Regarding the inclusion criteria, 94 subjects were on active therapy, 5 were off treatment from less than 6 months, 3 had received autologous stem cell transplant (ASCT) within the last 12 months, and 1 was vaccinated at diagnosis. Among the 94 patients on active treatment, 28 were receiving monoclonal antibodies (MoAbs, Daratumumab, Elotuzumab, Belantamab Mafodotin) and the others were on treatment with immunomodulatory drugs (IMiDs, Thalidomide, Lenalidomide or Pomalidomide), proteasome inhibitors (PI, Bortezomib or Carfilzomib) or both. Treatment schedules were not modified except for avoiding vaccination the day of MoAb infusion. Additionally immunomodulatory drugs discontinuation was discouraged. As for disease status, 89 patients displayed at least a partial response to therapy, 7 had a stable disease, and 7 were in progression. Median number of previous therapy lines was 1 (0–5). Patients received either mRNA-1273 (Moderna, 90%) or BNT162b2 (Pfizer-BioNTech, 10%) vaccine. One month after the second dose, 89 (86%) patients seroconverted (IgG anti-S titer >0.4 U/mL). Anti-N antibodies were detected in 14 subjects, 12 of them with a previous documented COVID-19 infection. As expected, these patients displayed significantly higherlevels of anti-S IgG after vaccination compared to infection-naïve subjects (7455 U/mL, 113–12,500 vs. 474 U/mL, 0.8–12500, $p = 0.0002$, Mann–Whitney U test). Responders were significantly younger (70 years, 47–86 vs. 76 years, 74–89, $p = 0.01$) and with disease response. In fact, patients with at least a partial response to therapy developed an antibodies titer in 90% of cases versus 65% of patients with stable disease or with active disease ($p = 0.02$). Furthermore, subjects with less than 2 previous therapy lines showed a better response to vaccination (93% vs. 61% in those with >2 lines, $p = 0.001$). Regarding the effect of ongoing therapies, we observed seroconversion in 80/94 (85%) patients on active treatment. In particular, MoAbs did not affect the rate of response in ourseries, and 22/28 (78%) patients seroconverted. However, MoAbs were associated with lower median anti-S titers compared to other anti-myeloma treatments (185 U/mL, 0.8–7500 vs. 702 U/mL, 10–12500, $p = 0.026$) and responding patients had been exposed to a lower number of treatment cycles compared to non-responders (15.8 cycles, 1–35 vs. 25.8 cycles, 21–30, $p = 0.03$).

Interestingly, prevaccination IgG levels of responders, were significantly higher thanseronegative ones (733 mg/dl, 111–1546 vs. 341 mg/dl, 45–795, $p = 0.0002$). Notably, prevaccination IgG levels from patients with IgG MM were included only for those with at least a partial response, thus ruling out patients with IgG levels higher than the upper limit of normality. Although we could not discriminate polyclonal from monoclonal IgG, this result was confirmed even by confining the analysis to the patients who were at least very good partial response.

Finally, gender, disease isotype, previous ASCT, vaccine type and lymphopenia did not impact on response to vaccination. In particular, 51/55 (93%) patients with a previous transplant seroconverted. In 25 responders to vaccine, SARS-CoV-2 antibodies titer was retested after 3 months (21 were in remission on therapy, 1 was in remission off therapy, and 3 underwent ASCT between the first and the second test).

Globally, anti-S IgG levels showed a non-statistically significant decrease (875 U/mL, 40.2–7500, at 1 month to vaccine vs. 453 U/mL, 8.79–7500, at 3 months). Interestingly, 4 patients had higher anti-S IgG titer at 3 months without seroconversion of anti-N IgG. Finally, no cases of COVID-19 infection were registered within this population after vaccination.

Seroconversion rate observed in our analysis was comparable with that defined by otherstudies[7,8]: MM patients respond worse to SARS-CoV-2 vaccine than the general population but still better

TABLE 1 Details of patients analyzed

	Negative	Positive	*p*
Median age in years (min-max)	76 (64–89)	70 (47–86)	0.01
Sex			
Male (n 48)	7 (15%)	41 (85%)	0.78
Female (n 55)	7 (13%)	48 (87%)	
Disease isotype			
IgG	8 (13%)	55 (87%)	
IgA	1 (5%)	16 (95%)	0.46
light-chain myeloma MM	5 (26%)	14 (74%)	
Other	0 (0%)	4 (100%)	
Inclusion criteria			
On therapy	14 (15%)	80 (85%)	
Off therapy <6 months	0 (0%)	5 (100%)	0.35
ASCT <12 months	0 (0%)	3 (100%)	
Disease onset	0 (0%)	1 (100%)	
Disease status			
At least partial response	9 (10%)	80 (90%)	0.02
Stable or progressive disease	5 (35%)	9 (65%)	
N° of previous lines of therapy			
<2	6 (7%)	76 (93%)	0.001
≥2	8 (38%)	13 (62%)	
Previous ASCT			
yes	4 (7%)	51 (93%)	0.25
no	10 (21%)	38 (79%)	
Therapy type			
Belantamab	1 (100%)	0 (0%)	
Daratumumab	0 (0%)	1 (100%)	
DRD	4 (18%)	18 (82%)	
DVD	0 (0%)	2 (100%)	
DPD	1 (100%)	0 (0%)	
EloRd	0 (0%)	1 (100%)	
KRD	1 (8%)	11 (92%)	
Kd	0 (0%)	2 (100%)	
R	0 (0%)	19 (100%)	
PVD	0 (0%)	1 (100%)	
PD	3 (100%)	0 (0%)	
Rd	4 (17%)	20 (83%)	
VTD	0 (0%)	5 (100%)	
MoAb based regimens	6 (21%)	22 (79%)	0.16
Other	8 (11%)	67 (89%)	
Vaccine type			
mRNA-1273 (Moderna)	12 (13%)	81 (87%)	0.53
BNT162b2 (Pfizer-BioNTech)	2 (20%)	8 (80%)	
Previous COVID19			
yes	0 (0%)	12 (100%)	0.14
no	14 (15%)	77 (85%)	

Abbreviations: ASCT, autologous stem cell transplant; DPD, DaratumumabPomalidomideDexamethasone; DRD, DaratumumabLenalidomideDexamethasone; DVD, DaratumumabBortezomibDexamethasone; EloRd, ElotuzumabLenalidomideDexamethasone; Kd, CarfilzomibLenalidomide; KRD, CarfilzomibLenalidomideDexamethasone; MoAbs, monoclonal antibodies; PD, PomalidomideDexamethasone; Pd, LenalidomideDexamethasone; PVD, PomalidomideBortezomibDexamethasone; R, Lenalidomide; VTD, BortezomibThalidomideDexamethasone.

than what observed in other hematological disease.[9] The peculiar-status of immunosuppression of our patients, related to the stringent inclusion criteria, reinforces this data and indicates, as predictors of worse response, age, active disease, low immunoglobulins of the non-paraprotein isotype levels, treatment with MoAbs, and a higher number of previous therapy lines. Among these risk factors, treatment is the only modifiable one, but seems to have a minor impact on seroconversion. Conversely, multiple therapy lines may have hampered immune system reactivity being responsible for lower responses, as also observed in patients with refractory disease. Of note, transplanted patients appeared to respond better to vaccination than those on active treatment, probably because of the deeper immunodeficiency of the latter. However, the heterogeneity in the time from transplant and in lenalidomide maintenance therapy do not allow definite conclusions about the effect of ASCT on vaccine response. On the whole, our data show that in MM patients SARS-CoV-2 vaccination should not be delayed or be a cause of a treatment schedule modification. Finally, although partial and preliminary, the data on antibodies persistence and the absence of cases of COVID-19 vaccine breakthr ough infection, encourage vaccination in this patient population. Future investigations would be needed to clarify the protective antibody levels in frail subjects, in the light of emerging SARS-CoV-2 variants and future vaccine boosters.

AUTHOR CONTRIBUTIONS

Loredana Pettine and Marta Bortolotti collected data and wrote the manuscript. Bruno Fattizzo, Marta Bortolotti, Dario Consonni and Matteo C. Da Vià did statistical analyses. Luca Baldini, Niccolò Bolli, Bruno Fattizzo, Alessandra Pompa and Matteo C. Da Vià revised the manuscript.

KEYWORDS
multiple myeloma, response to vaccination, SARS-CoV-2

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Loredana Pettine[1]
Marta Bortolotti[2]
Bruno Fattizzo[1,2]
Matteo C. Da Vià[1,2]
Dario Consonni[3]
Alessandra Pompa[1]
Niccolò Bolli[1,2]
Luca Baldini[1,2]

[1]*Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[2]*Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy*
[3]*Epidemiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

Correspondence
Loredana Pettine, Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Padiglione Marcora, Milan 20122, Italy.
Email: loredana.pettine@policlinico.mi.it

DATA AVAILABILITY STATEMENT

All requests for raw and analyzed data and materials will be promptly reviewed by IRCCS "Fondazione Ca' Granda Policlinico di Milano" to verify if the request is subject to any confidentiality and data protection obligations. Any data and materials that can be shared will be released via a material transfer agreement. Any request need to be sent to the corresponding author.

ORCID

Loredana Pettine https://orcid.org/0000-0001-9553-2082

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/hon.3051.

REFERENCES

1. Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica*. 2015;100(1):107-113. https://doi.org/10.3324/haematol.2014.107714
2. Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood*. 2020;136(26):3033-3040. https://doi.org/10.1182/blood.2020008150
3. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell*. 2021;39(8):1031-1033. https://doi.org/10.1016/j.ccell.2021.07.012
4. Malard F, Gaugler B, Gozlan J, et al. Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies. *Blood Cancer J*. 2021;11(8):142. https://doi.org/10.1038/s41408-021-00534-z
5. Ehmsen S, Asmussen A, Jeppesen SS, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. *Cancer Cell*. 2021;39(8):1034-1036. https://doi.org/10.1016/j.ccell.2021.07.016
6. https://www.gazzettaufficiale.it/eli/gu/2021/03/24/72/sg/pdf
7. Van Oekelen O, Gleason CR, Agte S, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. *Cancer Cell*. 2021;39(8):1028-1030. https://doi.org/10.1016/j.ccell.2021.06.014
8. Avivi I, Balaban R, Shragai T, et al. Humoral response rate and predictors of response to BNT162b2 mRNA COVID19 vaccine in patients with multiple myeloma. *Br J Haematol*. 2021;195(2):186-193. https://doi.org/10.1111/bjh.17608
9. Griffiths EA, Segal BH. Immune responses to COVID-19 vaccines in patients with cancer: promising results and a note of caution. *Cancer Cell*. 2021;39(8):1045-1047. https://doi.org/10.1016/j.ccell.2021.07.001