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Scientific Letter

Humoral Immune Response after anti-SARS-CoV-2 Vaccine "Booster" Dose in Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS)

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To the editor.

Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant plasma cell disorder reported in approximately 3-4% of individuals aged > 50 years, characterized by a low risk (about 1% per year) of progression into "overt" myeloma or other lymphoproliferative diseases. It is usually asymptomatic, but a higher risk of deep venous thrombosis and infections,[1,2] as well as immune dysregulation, have been reported.[3] About this last point, considering that vaccination against SARS-CoV-2 is the main strategy to prevent adverse outcome of COVID-19 (declared a pandemic by the World Health Organization in March 2020), the evaluation of humoral response to COVID-19 vaccines has gained increasing interest as valuable surrogate of vaccine effectiveness. In this field, several papers investigated antibody response to anti-SARS-CoV-2 vaccination in patients with hematological diseases; by contrast, few data are available about patients with MGUS. Terpos et al.[4] reported no significant differences in terms of "neutralizing antibody response" between MGUS patients and healthy controls (HCs); in particular, in this analysis, 21 of 25 patients (84%) achieved clinically relevant antibody response after two vaccine doses. Abella et al.[5] confirmed these data, reporting no differences in the vaccine-induced humoral responses between uninfected MGUS subjects (n=15) and HCs after two doses. Storti et al.[6] evaluated humoral and cellular response after two doses of anti-SARS-CoV-2 vaccine in 40 patients with monoclonal gammopathies at different stages of disease, including 6 patients with MGUS, reported as "responders". Konishi et al.[7] evaluated antibody titer in 13 MGUS patients after three doses of anti-SARS-CoV-2 vaccine, comparing it with that of HCs after two doses and no differences were described. Further studies concerning plasma cell dyscrasia and including patients with MGUS have been published, but they report generalized data without clearly distinguishing between MGUS and other conditions.[8,9] While most of the studies investigated humoral response after two vaccine doses, our present, real-life observational study, aimed to evaluate the rate of response and the titers of anti-spike IgG antibodies after a "booster" (third) dose. Secondary outcomes included comparisons of anti-spike IgG titers between MGUS patients and age and sex-matched healthcare workers, who were enrolled in the study as HCs.

Data of MGUS patients were extracted from medical records; further information was taken from "Infections Regional Information System (IRIS)", a regional (Puglia, Italy) platform by which authorized medical health workers can view the results of the nasopharyngeal swabs for SARS-CoV-2 performed, along with other information. Quantitative determination of anti-spike IgG antibodies was performed using a commercially available Abbott immunoassay, at least two weeks after the "booster" dose. Results were reported as arbitrary units AU/ml. Informed consent was obtained prior to the collection of data and specimens. Statistical analyses were carried out using GraphPad Prism version 8.3.0 (GraphPad Software Inc., San Diego, CA, USA).

Twenty COVID-19-naïve and fully vaccinated MGUS patients followed at Hematology Unit - AOU Policlinico di Bari (Italy) were enrolled in this study. Mean age was 63.15 years (range 39-86). Characteristics of MGUS patients are reported in Table 1A. The most frequent MGUS-isotype was IgG (70%), followed by IgA (20%) and IgM (10%). Most of patients (95%) were at low or low-intermediate risk, according to Mayo Clinic prognostic model.

After a mean number of 96 days (range 14-180) from third vaccine dose, all MGUS patients (100%) achieved a titer greater than 50 AU/mL; thus, they were all considered as "responders". Notably, in contrast with previously reported data,[10] administration of the first two doses of ChAdOx1 was not associated to lower

Table 1. A) Characteristics of fully vaccinated MGUS patients enrolled in the study. **B**) Comparison between MGUS patients and healthy controls after three vaccine doses. **Abbreviations:** NA: not applicable; NS: not statistically significant; SD: standard deviation; °Rajkumar et al. Blood 2005;106(3):812-7. MGUS: monoclonal gammopathies of undetermined significance.

A	
Total n. of MGUS patients	20
Mean age, years +/- SD (range)	63.15 +/- 12.59 (39-86)
Gender (male/female)	12/8
MGUS subtype, n. (%) IgG IgA IgM	 14 (70) 4 (20) 2 (10)
MGUS risk °, n. (%) 0 Low 1 Low-intermediate 2 High-intermediate	 15 (75) 4 (20) 1 (5)
Vaccine sequence, n. (%) *BNT162b2 mRNA x 3* *BNT162b2 mRNA x 2/mRNA-1273* *ChAdOx1 nCoV-19 x 2/mRNA-1273* *ChAdOx1 nCoV-19 x 2/BNT162b2 mRNA*	 5 (25) 7 (35) 4 (20) 4 (20)
Mean number of days between "booster" dose and blood collection +/- SD (range)	95.95 +/- 36.53 (14-180)
Mean anti-spike IgG antibodies titer (AU/mL) + / - SD (range)	17,490 +/- 17,190 (1483 – 54390)
Total SARS-CoV-2 positive MGUS after "booster" dose, n. (%)	4 (20)
Mean number of days from last vaccine dose to SARS-CoV-2 infection, +/- SD (range)	176.8 +/- 49.80 (139-244)
Mean value (g/dL) of monoclonal protein +/- SD (range) before and after vaccination	0.84 +/-0.45 (0.12-1.72) vs 0.82 +/- 0.44 (0.10-1.71); P-value: NS

B	**MGUS**	**Healthy Controls**	**P-value**
Number of subjects	11	11	-
Gender (male/female)	5/6	5/6	NS
Median age, years (range)	52 (39-64)	52 (39-64)	NS
Vaccine sequence in SARS-CoV-2 positive MGUS pts, n. (%) *BNT162b2 mRNA x 3* *BNT162b2 mRNA x 2/mRNA-1273* *ChAdOx1 nCoV-19 x 2/mRNA-1273* *ChAdOx1 nCoV-19 x 2/BNT162b2 mRNA*	 2 (18.2) 6 (54.5) 2 (18.2) 1 (9.1))	 11 (100)	 -
Median number of days between "booster" dose and blood collection, (range)	91 (7-126)	43 (31-48)	0.0165
Median anti-spike IgG antibodies titer (AU/mL) (range)	20,210 (6,263 -54,390)	4,006 (824.6-18,180)	0.0025
SARS-CoV-2 infection n. (%)	2 (18.2)	6 (54.5)	0.1827
Median number of days from last vaccine dose to SARS-CoV-2 infection, (range)	214.5 (185-244)	201 (62-304)	NA

antibody titer compared to that after two BNT162b2 doses. We did not find any correlation between gender (p-value=0.1768), MGUS-subtype (p-value=0.1956), MGUS risk-stratification (p-value=0.1647), sequence of vaccine doses (p-value=0.4144), days from third vaccine dose to blood collection (p-value=0.3347) and titer of anti-spike IgG antibodies. Age ≥ 63 years (vs < 63) was instead associated with a significant lower antibody titer (p-value=0.0122). Despite immune stimulation, monoclonal protein remained stable after vaccination in all MGUS patients analyzed (**Table 1A**). Four MGUS patients (20%) experienced a breakthrough infection, asymptomatic or with mild symptoms, after a mean number of 177 days (range 139-244) from the "booster" dose. In these patients the median titer of anti-spike IgG antibodies of 4,741 AU/mL (range: 3,218 – 20,210) before infection was not significantly different (p-value= 0.2376) from that of uninfected MGUS patients (12,870 AU/ml; range: 1,483-54,390). These cases of infection were reported between May and August 2022 and attributable realistically to Omicron BA.2, BA.4 and BA.5 variant of SARS-CoV-2.

Then we compared serological response of MGUS patients with those of age and sex matched healthcare

workers, enrolled in the study as HCs. It was possible only for 11 patients; the remaining nine ones were older than HCs and therefore not comparable with healthcare workers.

All HCs had received three doses of BNT162b2 mRNA vaccine. Quite unexpectedly, the median titer of anti-spike IgG antibodies was significant higher in MGUS patients than in HCs (p-value=0.0025) (**Table 1B**). This might be due to longer time frame between "booster" dose and blood collection in MGUS patients than HCs (91 vs 43 days; p-value: 0.0165). Indeed, it is known that antibody titer progressively increases after vaccine-dose and gradually declines over the ensuing months. Regarding the number of cases of breakthrough infection, it was higher (but not significantly; p-value= 0.1827) in HCs than MGUS patients, probably due to the major infectious risk of healthcare workers.

Though still preliminary, to the best of our knowledge, this is the first report of serological response after three doses of anti-SARS-CoV-2 vaccines in MGUS patients. Obviously, the study has several limitations, such as the limited number of patients enrolled, the lack of information about serological response after second dose (before third dose), the lack of information regarding neutralizing IgG antibodies against nucleocapsid and receptor-binding domain cellular (this study evaluated only anti-spike IgG antibodies), the different timing of blood collection (among MGUS patients and between MGUS patients and HCs), the lack of data on antigen-specific B- and T-cell responses information. Notwithstanding, our study highlights some relevant points. First, humoral immune response is not attenuated in MGUS patients after three doses of anti-SARS-CoV-2 vaccine, confirming data after two doses; notably, all patients (100%) achieved clinically relevant antibody response, improving reported data after two vaccine doses (84%).[4] This aligns with reported data that MGUS patients did not show an increased incidence of SARS-CoV-2 infection compared to the general population and that MGUS did not appear to represent a risk for a poorer COVID-19 outcome.[11,12] Indeed, in our previous experience, vaccination improved COVID-19 outcome, but not SARS-CoV-2 incidence.[13] Second, to date it is the only study to report a long persistence (until 180 days) of anti-spike IgG antibodies after "booster" dose in MGUS patients, although a clear-cut relationship between these antibodies and protection against the virus have not been unequivocally established. Third, this is the first study including a case-control analysis of serological response after "booster" dose of anti-SARS-CoV-2 vaccine in MGUS patients. However, further studies on a larger number of patients are needed to achieve greater generalizability of our findings.

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Competing interests: The authors declare no conflict of Interest.

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References:

1. Kristinsson SY, Björkholm M, Andersson TM, Eloranta S, Dickman PW, Goldin LR, Blimark C, Mellqvist UH, Wahlin A, Turesson I, Landgren O. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. Haematologica. 2009 Dec;94(12):1714-20. https://doi.org/10.3324/haematol.2009.010066 PMid:19608666 PMCid:PMC2791946
2. Kristinsson SY, Tang M, Pfeiffer RM, Björkholm M, Goldin LR, Blimark C, Mellqvist UH, Wahlin A, Turesson I, Landgren O. Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study. Haematologica. 2012 Jun;97(6):854-8. https://doi.org/10.3324/haematol.2011.054015 PMid:22180421 PMCid:PMC3366650
3. Zavidij O, Haradhvala NJ, Mouhieddine TH, Sklavenitis-Pistofidis R, Cai S, Reidy M, Rahmat M, Flaifel A, Ferland B, Su NK, Agius MP, Park J, Manier S, Bustoros M, Huynh D, Capelletti M, Berrios B, Liu CJ, He MX, Braggio E, Fonseca R, Maruvka YE, Guerriero JL, Goldman M, Van Allen EM, McCarroll SA, Azzi J, Getz G, Ghobrial IM. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. Nat Cancer. 2020 May;1(5):493-506. https://doi.org/10.1038/s43018-020-0053-3 PMid:33409501 PMCid:PMC7785110
4. Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, Briasoulis A, Gumeni S, Malandrakis P, Fotiou D, Papanagnou ED, Migkou M, Theodorakakou F, Roussou M, Eleutherakis-Papaiakovou E, Kanellias N, Trougakos IP, Kastritis E, Dimopoulos MA. The neutralizing antibody

response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment. Blood Cancer J. 2021 Aug 2;11(8):138.
https://doi.org/10.1038/s41408-021-00530-3
PMid:34341335 PMCid:PMC8327056

5. Abella E, Trigueros M, Pradenas E, Muñoz-Lopez F, Garcia-Pallarols F, Ben Azaiz Ben Lahsen R, Trinité B, Urrea V, Marfil S, Rovirosa C, Puig T, Grau E, Chamorro A, Toledo R, Font M, Palacín D, Lopez-Segui F, Carrillo J, Prat N, Mateu L, Clotet B, Blanco J, Massanella M; VAC-COV-GM-HMAR, KING Cohort Extension and CoronAVI@S studies. Efficacy of SARS-CoV-2 vaccination in patients with monoclonal gammopathies: A cross sectional study. Life Sci Alliance. 2022 Aug 12;5(12):e202201479.
https://doi.org/10.26508/lsa.202201479
PMid:35961779 PMCid:PMC9375155
6. Storti P, Marchica V, Vescovini R, Franceschi V, Russo L, Notarfranchi L, Raimondi V, Toscani D, Burroughs Garcia J, Costa F, Dalla Palma B, Iannozzi NT, Sammarelli G, Donofrio G, Giuliani N. Immune response to SARS-CoV-2 mRNA vaccination and booster dose in patients with multiple myeloma and monoclonal gammopathies: impact of Omicron variant on the humoral response. Oncoimmunology. 2022 Sep 6;11(1):2120275.
https://doi.org/10.1080/2162402X.2022.2120275
PMid:36105747 PMCid:PMC9467550
7. Konishi Y, Sklavenitis-Pistofidis R, Yue H, Ferrari F, Redd RA, Lightbody ED, Russo M, Perry J, Horowitz E, Justis AV, Shayegh NA, Savell A, Prescott J, Varmeh S, Nowak RP, Hamilton M, Auclair D, Marinac CR, Trippa L, Fischer ES, Ghobrial IM. Attenuated response to SARS-CoV-2 vaccine in patients with asymptomatic precursor stages of multiple myeloma and Waldenstrom macroglobulinemia. Cancer Cell. 2022 Jan 10;40(1):6-8.
https://doi.org/10.1016/j.ccell.2021.12.003
PMid:34895486 PMCid:PMC8654583
8. Gung C, McGuire R, George M, Abdulkareem A, Belden KA, Porcu P, Martinez-Outschoorn U, Binder AF, Chervenova I, Alpdogan O. Antibody Response to SARS-CoV-2 Vaccination in Patients With Lymphoproliferative Disorders and Plasma Cell Dyscrasias: Anti-Lymphoma Therapy as a Predictive Biomarker of Response to Vaccination. Front Oncol. 2022 Jul 7;12:840451.
https://doi.org/10.3389/fonc.2022.840451
PMid:35875166 PMCid:PMC9300919
9. Wu AHB, Wang CC, Ong CM, Lynch KL. Adequate Antibody Response to COVID-19 Vaccine in Patients with Monoclonal Gammopathies and Light Chain Amyloidosis. Lab Med. 2022 May 5;53(3):314-319.
https://doi.org/10.1093/labmed/lmab113
PMid:35026018 PMCid:PMC8807219
10. Jolliffe DA, Faustini SE, Holt H, Perdek N, Maltby S, Talaei M, Greenig M, Vivaldi G, Tydeman F, Symons J, Davies GA, Lyons RA, Griffiths CJ, Kee F, Sheikh A, Shaheen SO, Richter AG, Martineau AR. Determinants of Antibody Responses to SARS-CoV-2 Vaccines: Population-Based Longitudinal Study (COVIDENCE UK). Vaccines (Basel). 2022 Sep 23;10(10):1601.
https://doi.org/10.3390/vaccines10101601
PMid:36298466 PMCid:PMC9610049
11. Rognvaldsson S, Eythorsson E, Thorsteinsdottir S, Vidarsson B, Onundarson PT, Agnarsson BA, Sigurdardottir M, Thorsteinsd√≥ttir I, Olafsson I, Runolfsdottir HL, Helgason D, Emilsdottir AR, Agustsson AS, Bjornsson AH, Kristjansdottir G, Thordardottir AR, Indridason OS, Jonsson A, Gislason GK, Olafsson A, Steingrimsdottir H, Kampanis P, Hultcrantz M, Durie BGM, Harding S, Landgren O, Palsson R, Love TJ, Kristinsson SY. Monoclonal gammopathy of undetermined significance and COVID-19: a population-based cohort study. Blood Cancer J. 2021 Dec 1;11(12):191.
https://doi.org/10.1038/s41408-021-00580-7
PMid:34853309 PMCid:PMC8635472
12. Sgherza N, Curci P, Rizzi R, Strafella V, Di Gennaro D, Vitucci A, Palma A, Rossi AVR, Albano F, Stefanizzi P, Tafuri S, Musto P. Incidence and outcome of SARS-CoV-2 infection in patients with monoclonal gammopathy of undetermined significance: a case-control study. Haematologica. 2022 Feb 1;107(2):555-557.
https://doi.org/10.3324/haematol.2021.279895
PMid:34732044 PMCid:PMC8804555
13. Sgherza N, Di Gennaro D, Curci P, Rizzi R, Roccotelli D, Croce M, Avantaggiato M, Ruga L, Strafella V, Vitucci A, Palma A, Russo Rossi AV, Troiano T, Larocca AMV, Chironna M, Tafuri S, Albano F, Musto P. SARS-CoV-2 infection incidence and outcome before and after fully vaccination in patients with monoclonal gammopathy of undetermined significance. Hemasphere. 2022 Nov 9;6(12):e800.
https://doi.org/10.1097/01.HS9.0000846660.15920.42
PMCid:PMC9429539