



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,<sup>1,2</sup> as well as immune dysregulation, have been reported.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup> 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,<sup>10</sup> 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	14 (70)		
IgA	4 (20)		
IgM	2 (10)		
MGUS risk °, n. (%)			
0 Low	15 (75)		
1 Low-intermediate	4 (20)		
2 High-intermediate	1 (5)		
Vaccine sequence, n. (%)			
<i>BNT162b2 mRNA x 3</i>	5 (25)		
<i>BNT162b2 mRNA x 2/mRNA-1273</i>	7 (35)		
<i>ChAdOx1 nCoV-19 x 2/mRNA-1273</i>	4 (20)		
<i>ChAdOx1 nCoV-19 x 2/BNT162b2 mRNA</i>	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. (%)			
<i>BNT162b2 mRNA x 3</i>	2 (18.2)		
<i>BNT162b2 mRNA x 2/mRNA-1273</i>	6 (54.5)		
<i>ChAdOx1 nCoV-19 x 2/mRNA-1273</i>	2 (18.2)		
<i>ChAdOx1 nCoV-19 x 2/BNT162b2 mRNA</i>	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  $\geq$  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 significantly 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%).<sup>4</sup> 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.<sup>11,12</sup> Indeed, in our previous experience, vaccination improved COVID-19 outcome, but not SARS-CoV-2 incidence.<sup>13</sup> 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.

**Authorship contributions:** PM and NS conceived and led the project. NS conducted database building, extraction and coding. PM and NS queried and analyzed the data. PM and NS wrote the main manuscript text and created all tables. All authors made a substantial intellectual contribution to the study, interpreted the data, discussed the results and reviewed, edited and approved the final version of the manuscript.

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