

# Myeloma patients with COVID-19 have superior antibody responses compared to patients fully vaccinated with the BNT162b2 vaccine

Maria Gavriatopoulou,<sup>1</sup>  
 Evangelos Terpos,<sup>1</sup>   
 Panagiotis Malandrakis,<sup>1</sup>  
 Ioannis Ntanasis-Stathopoulos,<sup>1</sup>   
 Alexandros Briasoulis,<sup>1</sup>  
 Sentiljana Gumeni,<sup>2</sup> Despina Fotiou,<sup>1</sup>  
 Eleni-Dimitra Papanagnou,<sup>2</sup>  
 Magdalini Migkou,<sup>1</sup>   
 Foteini Theodorakakou,<sup>1</sup>  
 Evangelos Eleutherakis-Papaiaikovou,<sup>1</sup>  
 Nikolaos Kanellias,<sup>1</sup> Ioannis  
 P. Trougakos,<sup>2</sup>   
 Efstathios Kastritis<sup>1</sup>  and  
 Meletios-Athanasios Dimopoulos<sup>1</sup> 

<sup>1</sup>Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, and  
<sup>2</sup>Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece

Received 3 August 2021; accepted for publication 3 September 2021

Correspondence: Maria Gavriatopoulou, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528 Athens, Greece.  
 E-mail: mariagabria@gmail.com

## Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a worldwide pandemic and has become a major global health concern and, therefore, the development of effective and safe vaccines and novel therapeutic agents is a global priority.<sup>1</sup> Patients with multiple myeloma (MM) are at increased risk of infections due to their immunocompromised state, older age and comorbidities.<sup>2,3</sup> Coronavirus disease 2019 (COVID-19) causes moderate to severe acute respiratory dysfunction in 77% of MM patients and leads to a critical

## Summary

Patients with multiple myeloma (MM) have a suboptimal antibody response following vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and lower seroconversion rates following coronavirus disease 2019 (COVID-19) compared with healthy individuals. In this context, we evaluated the development of neutralising antibodies (NAbs) against SARS-CoV-2 in non-vaccinated patients with MM and COVID-19 compared with patients after vaccination with two doses of the BNT162b2 vaccine. Serum was collected either four weeks post confirmed diagnosis or four weeks post a second dose of BNT162b2. NAbs were measured with a Food and Drug Administration-approved enzyme-linked immunosorbent assay methodology. Thirty-five patients with COVID-19 and MM along with 35 matched patients were included. The two groups did not differ in age, sex, body mass index, prior lines of therapy, disease status, lymphocyte count, immunoglobulin levels and comorbidities. Patients with MM and COVID-19 showed a superior humoral response compared with vaccinated patients with MM. The median (interquartile range) NAb titre was 87.6% (71.6–94%) and 58.7% (21.4–91.8%) for COVID-19-positive and vaccinated patients, respectively ( $P = 0.01$ ). Importantly, there was no difference in NAb production between COVID-19-positive and vaccinated patients who did not receive any treatment (median NAb 85.1% vs 91.7%,  $P = 0.14$ ). In conclusion, our data indicate that vaccinated patients with MM on treatment without prior COVID-19 should be considered for booster vaccine doses.

**Keywords:** severe acute respiratory syndrome coronavirus-2, coronavirus disease 2019, multiple myeloma, antibodies, humoral immunity.

condition in approximately 8% of them.<sup>3–5</sup> Among hospitalised patients with COVID-19 and haematological cancers, the risk of death has been estimated to be approximately 39%.<sup>6</sup> Furthermore, lower seroconversion rates following COVID-19 have been reported among patients with solid and haematological malignancies compared with convalescent individuals without cancer.<sup>7–10</sup> Herein, we evaluated the development of neutralising antibodies (NAbs) against SARS-CoV-2 in non-vaccinated MM patients who were diagnosed with COVID-19 compared with patients after vaccination with two doses of the mRNA BNT162b2.

## Methods

The analysis was performed in the context of an ongoing large prospective study (NCT04743388) evaluating the kinetics of anti-SARS-CoV-2 antibodies after COVID-19 vaccination. We evaluated MM patients diagnosed with COVID-19 confirmed by polymerase chain reaction (PCR) matched for age, gender, line of treatment, type of myeloma, type of treatment and response with vaccinated myeloma patients during the same time period (January–May 2021). Major exclusion criteria for both COVID-19 group and vaccine control group included: (i) autoimmune disorder under immunosuppressive therapy or other active malignant disease; (ii) HIV or active hepatitis B and C infection; (iii) end-stage renal disease; and (iv) prior diagnosis of COVID-19 for the vaccine group. Serum was collected in the COVID-19 group four weeks post confirmed diagnosis and in the vaccine group on day 50 (four weeks) post second dose of BNT162b2. NAbs against SARS-CoV-2 were measured using a FDA-approved enzyme-linked immunosorbent assay methodology (cPass™ SARS-CoV-2 NAb Detection Kit; GenScript, Piscataway, NJ, USA). This method enables the indirect detection of potential SARS-CoV-2 NAb in blood. The percentage (%) of antibody-mediated inhibition of SARS-CoV-2 receptor-binding domain (RBD) binding to the human host receptor angiotensin-converting enzyme type 2 is estimated and reported.

## Results and discussion

We evaluated 35 patients with COVID-19 and MM (six smouldering MM and 29 symptomatic MM), along with 35 matched fully vaccinated patients.

Among the COVID-19 patients 13 were diagnosed with mild, 12 with moderate and 10 with severe disease. 22/35 patients were hospitalised and 10/35 were intubated. Seven (20%) patients died due to COVID-19. During the disease course 21 patients (60%) were treated with dexamethasone. Type of treatment was not different between COVID-19-positive and vaccinated MM patients. Between the two patient groups, there was no difference in terms of age [median (interquartile range (IQR)) 65 (59) for COVID-19-positive *versus* 66 (74) for COVID-19 vaccinated, respectively,  $P = 0.76$ ], gender [males: 19/35 (54.3%) vs 16/35 (45.7%), respectively,  $P = 0.47$ ], body mass index (median 27 vs 26 kg/m<sup>2</sup>, respectively,  $P = 0.56$ ) asymptomatic disease [6/35 (18.2%) in both groups,  $P = 1$ ], prior lines of treatment [range: 1–7 vs 1–6, respectively,  $P = 0.99$ ], and type of treatment ( $P = 0.87$ ). Among the COVID-19-positive patients, six (20.7%) patients were in stringent complete response/complete response (SCR/CR), six (20.7%) patients in very good partial response (VGPR), 12 (41.4%) patients in partial response (PR), two (6.9%) in minor response/stable disease (MR/SD) and one (3.5%) in progressive disease (PD). Among the vaccinated patients, 10 (34.5%) patients were in SCR/CR, 4 (13.8%)

patients in VGPR, 11 (37.9%) patient in PR, 1 (3.5%) patient in MR/SD and 1 (3.5%) patient in PD ( $P$  value = 0.93 for the comparison between COVID-19-positive and vaccinated patients). Also, no differences between COVID-19-positive and vaccinated patients were noted in the median lymphocyte count (1 200 vs 1 400/ $\mu$ l, respectively,  $P = 0.08$ ) and in the median immunoglobulin values (immunoglobulin G 732 vs 747 mg/dl, respectively,  $P = 0.29$ ; immunoglobulin A 90 vs 61 mg/dl, respectively,  $P = 0.7$ ; immunoglobulin M 26 vs 25 mg/dl, respectively,  $P = 0.97$ ). The incidence of comorbidities was also similar between the two groups (cardiovascular diseases 55.2% vs 44.8%, respectively,  $P = 0.47$ ; diabetes mellitus 66.7% vs 33.3%,  $P = 0.28$ ; chronic pulmonary disease 50% each,  $P = 1.0$ ).

Most importantly, patients with MM and COVID-19 showed a superior humoral response compared with vaccinated patients with MM. The median (IQR) NAb titre was 87.6% (71.6–94%) and 58.7% (21.4–91.8%) for COVID-19-positive and vaccinated patients respectively ( $P = 0.001$ ; Fig 1). Furthermore, we matched the patients 1:1 and compared the two groups. The mean difference in NAb titre was 21.7%  $\pm$  41.8% higher in the COVID-19 group ( $P = 0.007$ ). The pre-vaccination median NAb level in the cohort of vaccinated patients was 13% (IQR 7.4–24.5%). In both groups, 27 out of 35 patients were receiving active treatment for MM at the time of NAb evaluation. Among those on active anti-myeloma treatment, the median (IQR) NAb titre was 88% (71.6–96.3%) for COVID-19-positive patients and 35.4% (17.5–85.5%) for vaccinated MM patients ( $P = 0.001$ ). However, there was no difference in NAb production between COVID-19-positive and vaccinated patients who did not receive any treatment (median NAb 85.1% vs 91.7%,  $P = 0.14$ ). A significant difference in median NAb titre between patients on active treatment compared with those off treatment was noted only among vaccinated patients [35.4% (IQR 17.5–85.5%) vs 91.7% (IQR 75.9–95%), respectively,  $P = 0.005$ ]. No difference was noted among patients with previous COVID-19 [median (IQR) 88% (71.6–96.3%) vs 85.1% (65.1–89.3%), respectively,  $P = 0.7$ ]. These findings should be interpreted with caution due to the small patient number in each subgroup.

Interestingly, no significant differences in NAb production were noted among COVID-19-positive patients according to disease severity ( $P = 0.35$ ) or administration of dexamethasone during the COVID-19 disease course ( $P = 0.052$ ). Furthermore, no specific anti-myeloma treatment was associated with an inferior humoral response both among COVID-19-positive ( $P = 0.44$ ) and vaccinated patients ( $P = 0.16$ ). However, these results should be interpreted with caution due to small patient numbers in the subgroups.

To our knowledge this is the first report to compare the NAb-mediated humoral response in patients with MM after two doses of vaccination with the BNT162b2 vaccine and non-vaccinated patients who were diagnosed with COVID-19. The humoral response to natural infection generates higher levels of NAb than vaccination against SARS-CoV-2. The more robust NAb production might be associated with

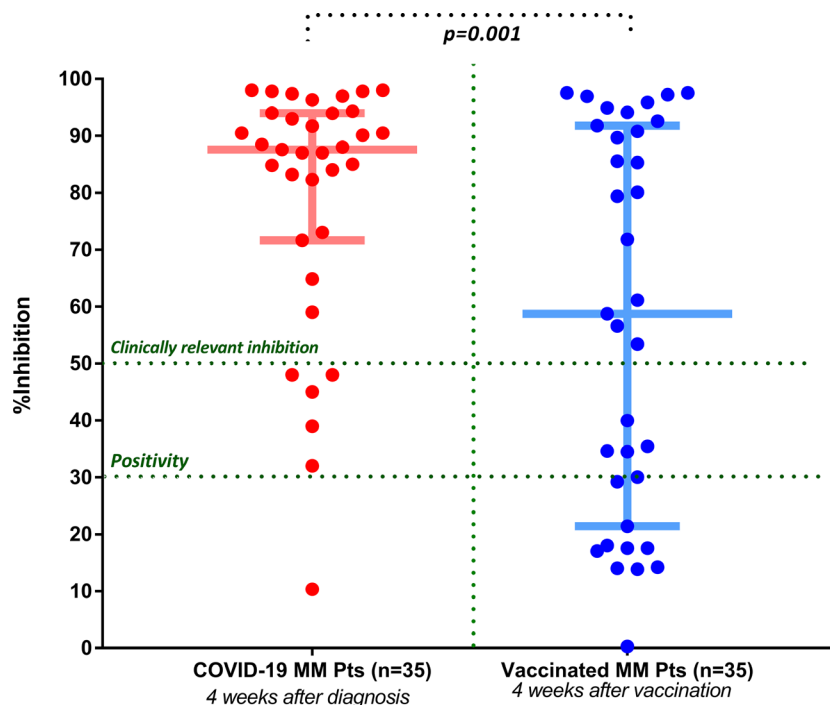


Fig 1. Patients with MM and COVID-19 showed a superior humoral response compared with vaccinated patients with MM. The median (IQR) NAb titre was 87.6% and 58.7% for COVID-19-positive and vaccinated patients ( $P = 0.01$ ). IQR, interquartile range; MM, multiple myeloma; NAb, neutralizing antibody. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

the exposure of the immune system to several antigenic determinants during infection instead of the selected epitopes of each vaccine. Furthermore, differences in the inflammatory context and the anatomic sites of immune response induction may have an impact on NAb production.<sup>11</sup> Another point to consider is that immunocompromised patients, including those with MM, may present high viral loads and delayed viral clearance. Therefore, antibody expansion and epitope spreading is prolonged, which may result in enhanced humoral response.<sup>11,12</sup>

The underlying causes for suboptimal humoral response to vaccination in patients with plasma cell dyscrasias post vaccination are multifactorial and it seems that both disease-related immune dysregulation and therapy-related immunosuppression are involved.<sup>13</sup> Active treatment may impair immune response to vaccines, whereas both myeloma microenvironment and anti-myeloma treatment may impair T-cell function, as well.<sup>14–16</sup> Patients with MM often show suboptimal seroconversion rates after a single-dose vaccine against bacteria and viruses and, therefore, booster doses are needed to assure adequate protection, such as the case with the seasonal flu vaccine.<sup>16,17</sup> We should also take into consideration that the production of NAb titres at a level of  $\geq 50\%$  on D22 after the first BNT162b2 dose has been low even among healthy individuals aged 65–85 years.<sup>18</sup> To the contrary, higher antibody titres after a single dose of mRNA-based vaccine against SARS-CoV-2 have been detected in individuals who have recovered from COVID-19.<sup>19</sup>

Importantly, our data show that the actual infection can stimulate the immune response and patients with MM and COVID-19 present a superior NAb response against SARS-

CoV-2 compared with fully vaccinated patients with two doses of BNT162b2. This finding is more pronounced among patients receiving active treatment for MM. In this context, a multicentre study in Israel showed that the majority of the individuals with breakthrough infections despite vaccination with BNT162b2 had comorbidities including cancer, that may result in inferior humoral response.<sup>14</sup> The main limitations of our study include the relevant limited number of patients enrolled, the short follow-up period and the absence of data on T-cell-induced response, which is currently under investigation. Furthermore, NAb evaluation at later time-points could investigate the kinetics of NAb production among patients with previous COVID-19 compared with vaccinated patients with MM. The observed differences in NAb production might be attributed to different NAb kinetics between the two patient groups and a putative delayed humoral response in immunocompromised patients.

In conclusion, our data suggest that patients with MM under treatment may present a superior humoral response against SARS-CoV-2 following recovery from COVID-19 compared with vaccination against SARS-CoV-2. A further analysis including a larger number of patients could enable the characterisation of specific patient and disease characteristics that may have an impact on antibody production following exposure to SARS-CoV-2 or its cellular components.

## Acknowledgements

We thank Mrs Ioanna Charitaki, Mrs Tina Bagratuni, PhD and Mrs Nikoletta-Aikaterini Kokkali, Christine Ivy Liacos, PhD for administrative, technical, or material support. We

also thank SYN-ENOSIS (Greece), AEGEAS (Greece), IEM-BITHEK (Greece), Nikolao and Theano Vafeia for partially funding this study, as well as all of the study participants for donating their time and samples.

### Author contributions

MG designed and performed research, analyzed data and wrote the manuscript, ET designed and performed research and analyzed data, IPT and M-AD contributed vital new reagents or analytical tools, performed research, analyzed data, and reviewed all drafts of the manuscript and approved the final version; and PM, AB, SG, DF, E-DP, MM, FT, EE-P, NK, EK and IN-S performed research, analyzed data, reviewed all drafts of the manuscript and approved the final version.

### Conflicts of interest

The authors declare no relevant conflicts of interest.

### References

- Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, Fotiou D, Migkou M, Tzanninis IG, et al. Emerging treatment strategies for COVID-19 infection. *Clin Exp Med*. 2021;21:167–79.
- Dumontet C, Hulin C, Dimopoulos MA, Belch A, Dispenzieri A, Ludwig H, et al. A predictive model for risk of early grade  $\geq 3$  infection in patients with multiple myeloma not eligible for transplant: analysis of the FIRST trial. *Leukemia*. 2018;32:1404–13.
- Terpos E, Engelhardt M, Cook G, Gay F, Mateos MV, Ntanasis-Stathopoulos I, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN). *Leukemia*. 2020;34:2000–11.
- Chari A, Samur MK, Martinez-Lopez J, Cook G, Biran N, Yong K, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood*. 2020;136:3033–40.
- Martinez-López J, Mateos MV, Encinas C, Sureda A, Hernandez-Rivas JA, Lopez de la Guia A, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. *Blood Cancer J*. 2020;10:103.
- Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;136:2881–92.
- Liu T, Zeng G, Tao H, Shi Y, COVID-19 in Cancer Patients Research Group, Wang T, et al. Low prevalence of IgG antibodies to SARS-CoV-2 in cancer patients with COVID-19. *Int J Cancer*. 2020;147:3267–9.
- Marra A, Generali D, Zagami P, Cervoni V, Gandini S, Venturini S, et al. Seroconversion in patients with cancer and oncology health care workers infected by SARS-CoV-2. *Ann Oncol*. 2021;32:113–9.
- Roeker LE, Knorr DA, Pessin MS, Ramanathan LV, Thompson MC, Leslie LA, et al. Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia. *Leukemia*. 2020;34:3047–9.
- Soldsky ML, Galvez C, Russias B, Detourbet P, N'Guyen-Bonin V, Herr AL, et al. Lower detection rates of SARS-COV2 antibodies in cancer patients versus health care workers after symptomatic COVID-19. *Ann Oncol*. 2020;31:1087–8.
- Röltgen K, Boyd SD. Antibody and B cell responses to SARS-CoV-2 infection and vaccination. *Cell Host Microbe*. 2021;29:1063–75.
- Röltgen K, Powell AE, Wirz OF, Stevens BA, Hogan CA, Najeeb J, et al. Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome. *Sci Immunol*. 2020;5:eabe0240.
- Van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, 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.
- Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Neshet L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*. 2021. <https://doi.org/10.1016/j.cmi.2021.06.036> [Online ahead of print].
- Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, Terpos E, Dimopoulos MA. SARS-CoV-2 vaccines in patients with multiple myeloma. *Hemasphere*. 2021;5:e547.
- Ludwig H, Boccadoro M, Moreau P, San-Miguel J, Cavo M, Pawlyn C, et al. Recommendations for vaccination in multiple myeloma: a consensus of the European Myeloma Network. *Leukemia*. 2021;35:31–44.
- Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiropoulos I, Sklirou AD, Ntanasis-Stathopoulos I, et al. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. *Blood*. 2021;137:3674–6.
- Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. *N Engl J Med*. 2020;383:2439–50.
- Saadat S, Rikhtegaran Tehrani Z, Logue J, Newman M, Frieman MB, Harris AD, et al. Binding and neutralization antibody titers after a single vaccine dose in health care workers previously infected with SARS-CoV-2. *JAMA*. 2021;325:1467–9.