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COVID-19 Vaccine Responses in Patients With Plasma Cell Dyscrasias After Complete Vaccination

Mansi R. Shah,[1] Alissa Gabel,[1] Stephanie Beers,[1] Gratian Salaru,[2] Yong Lin,[3] Dennis L. Cooper[1]

Abstract

Patients with multiple myeloma are at increased risk for infection due to functional hypogammaglobulinemia and therapy related immunosuppression and are vulnerable to severe COVID-19 infections. We evaluated antibody response to currently available vaccines against SARS-CoV-2 in patients with plasma cell dyscrasias, most of whom had multiple myeloma. 95% of patients responded with detectable anti-spike antibody levels. Older age, ongoing treatment with anti-CD38 mAb and the J&J adenoviral vector vaccine were negatively associated with antibody response.

Introduction: Due to functional hypogammaglobulinemia, patients with multiple myeloma are at increased risk for infection and generally have poorer responses to vaccines. In this study, we examined antibody responses after complete COVID-19 vaccination in patients with plasma cell dyscrasias, most of whom were receiving treatment. **Patients and Methods:** Real world study of consecutive patients with multiple myeloma and other plasma cell dyscrasias (PCD) were evaluated after complete vaccination with either the 2-shot mRNA vaccines from BioNTech and Moderna or the 1-shot adenoviral vector vaccine from Johnson & Johnson (J&J). Patients received vaccines 1-4 months before antibody testing without controlling for the type of vaccine or the timing of drug therapy. Patients with a clinical history or antibody evidence of prior infection were excluded. Antinucleocapsid and quantitative anti-spike antibody levels were measured with the Roche Elecys assay. **Results:** Ninety-five percent of patients had detectable antibody responses. Multivariate analysis showed that higher age, ongoing anti-CD38 monoclonal antibody therapy and the J&J vaccine negatively affected quantitative response. A small number of ineffectively vaccinated patients receiving IVIG subsequently had detectable nucleocapsid and spike antibodies confirming the presence of the latter in currently administered IVIG. **Conclusions:** Nearly all PCD had detectable anti-spike antibodies after vaccination but age, anti-CD38 monoclonal antibody therapy, and the single-shot J&J vaccine negatively affected responses. In patients who received the J&J vaccine, second doses or heterologous mRNA vaccines should be tested. Quantitative antibody testing might make future management more rational, particularly in patients with poor responses.

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Introduction

Multiple myeloma (MM) is associated with abnormalities in innate and adaptive immunity[1] leading to an increased risk of mortality due to infection. Humoral immunity is compromised secondary to ineffective monoclonal gammopathy compounded by depression of uninvolved immunoglobulins and worsened by therapy-related immunosuppression.[2] Diminished T-cell responses, impaired renal function, and disease status are additional factors that may contribute to higher susceptibility to infections in patients with MM.[3,4]

The importance of the antibody response to SARS-CoV-2 infection recovery and vaccination has been recently demonstrated. A study of monoclonal antibody (mAb) therapy after SARS-CoV-2 infection showed benefit that was mainly limited to patients without detectable antibody at the time of administration whereas those with measurable antibody had few subsequent medical-attending events.[5] Similarly, after SARS-CoV-2 vaccination, normal volun-

[1]Division of Blood Disorders, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
[2]Division of Clinical Pathology, Robert Wood Johnson University Hospital, New Brunswick, NJ
[3]Department of Biostatistics and Epidemiology, Rutgers School of Public Health, New Brunswick, NJ

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Address for correspondence: Dennis L. Cooper, MD, Blood and Marrow Transplantation, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, 08901.
E-mail contact: dc1073@cinj.rutgers.edu

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teers were highly resistant to infection.[6,7] However, the efficacy of first dose vaccines is lower in immunocompromised patients including patients with MM.[8,9] Thus, there is considerable interest in assessing the antibody response after complete vaccination in patients with MM. In this study, we examined antibody responses in previously uninfected patients with plasma cell dyscrasias (PCD), most of whom were receiving treatment. We were particularly interested in patients receiving anti-CD38 mAbs because of their increasing importance in front-line therapy[10-13] and highly specific anti-plasma cell activity.

Materials and Methods

The Institutional Review Board (IRB) approved this retrospective analysis. The antibodies against SARS-CoV-2 nucleocapsid and spike protein were evaluated in patients with PCDs who received 2 doses of the mRNA vaccines BTN162b2[6] or mRNA-1273[7], or 1 dose of the Ad26.COV.S[14] vaccines. We included patients with MM, smoldering multiple myeloma (SMM), solitary plasmacytoma, and AL amyloidosis–with most patients on therapy. As this was a retrospective study, there was no attempt to control the type of vaccine that patients received nor was there a strategy of spacing treatment and vaccination.

After at least 14 days from the completion of vaccination, serum samples for nucleocapsid (indicating infection) and anti-spike SARS-CoV-2 antibodies were analyzed by using Elecsys Anti-SARS-CoV-2S assay on the Cobas e 601 with a positive detection threshold for the receptor-binding domain of S of at least 0.4U/mL, which correlates with neutralizing immunity mediated by vaccination.[15] The sensitivity and specificity of the immunoassay for the detection of spike antibodies in response to COVID-19 infections are 98.8% and 100%, respectively.[16] Because previous SARS-CoV-2 infection is known to strengthen the vaccine response[17,18], we excluded patients with a history of prior infection or a positive nucleocapsid antibody. Antibody measurement was performed between the dates of 4.15.21 and 7.1.21 with nearly all patients vaccinated 1-4 months before testing.

Kruskal-Wallis non-parametric tests were used for comparisons of the responses among vaccine type, therapy, severe immunoparesis, and exposure to anti-CD38 mAb (Figure 1). Multivariable rank regression model was used for the analysis of effect of age, anti-CD38 mAb therapy, and vaccine type on antibody response with Tukey's multiple adjustment method (Table 2).

Results

As the mRNA vaccines were given emergency authorization and available first, most patients received the 2-dose BTN162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines 21 and 28 days apart, respectively.[6,7] Only 11 patients received the 1-dose Ad26.COV2.S (Johnson &Johnson; J&J) vaccine.[14] 122 patients were tested. Thirty-three patients were excluded including 19 who had a prior history of COVID-19 infection and an additional 12 based on a positive nucleocapsid antibody detection. The demographics and responses of the study patients are shown in Table 1. Figure 1 demonstrates a comparison of the responses in patients with severe immunoparesis and according to therapy type. Nearly all patients responded to the currently used SARS-CoV-2 vaccines but patients receiving anti-CD38 mAb had significantly lower titers. There was a higher response after the mRNA vaccines compared to the J&J vaccine, but the difference was not statistically significant in patients receiving anti-CD38 mAb therapy, possibly because of lowpatient numbers and variability in the J&J group. After the J&J vaccine, 3 of 11 patients had anti-spike antibodies greater than 100 U/mL compared to 25 of 41 Pfizer-BioNTech and 28 of 37 Moderna patients. The 100 IU/mL target threshold is based on a preclinical study in baboons[19] and supported by a large clinical study.[20] Multivariate analysis in Table 2 showed that age, anti-CD38 antibody therapy and J&J vaccine negatively affected antibody response.

Two non-responding patients had HIV associated with low T cell counts, and there were 2 other nonresponders. Interestingly, one of the latter patients subsequently received intravenous immunoglobulin (IVIG) and a second test was positive for both antinucleocapsid and antispike antibodies, suggesting possible transfer from the IVIG. Accordingly, we tested 3 other patients with myeloma and 2 patients with lymphoma who had not been effectively vaccinated, and all became positive for antibodies against the nucleocapsid and anti-spike proteins after IVIG administration. One patient in this study had COVID-19 infection after complete vaccination. Because the antibody titer was low at 15 U/mL, the patient was referred for monoclonal antibody therapy and recovered uneventfully.

Discussion

The mRNA 2-shot vaccines developed by Pfizer-BioNTech and Moderna given 3 and 4 weeks apart, respectively, were highly effective in generating anti-SARS-Cov-2 spike antibody responses in patients with PCD, including ongoing treatment with anti-CD38 mAb or in the presence of severe immunoparesis. Nevertheless, anti-CD38 mAb-treated patients mounted a lower response than after other treatments, probably because of the specific toxic effect on plasma cells. Van Oekelen et al recently described similar findings of the inhibitory effect of anti-CD38 mAb on antibody response in patients with MM.[21] The attenuated but persistent vaccine responsiveness stands in contrast to the marked inhibitory effect of anti-B cell therapy in patients with CLL,[22] possibly due to separate immunopotentiating properties of anti-CD38 mAb such as the depletion of CD38+ regulatory T cells.[23]

Fewer patients received the J&J vaccine due to delayed availability, but it is concerning that the responses were less robust compared to the mRNA vaccines. This could be due to an inherently lower activity of the J&J vaccine or because the single-dose schedule may be inadequate for patients with MM. In a study of the first vaccination in elderly patients (reflecting the prioritization of older patients to receive vaccines first) with the BTN162b (Pfizer) vaccine in Greece, only 25% of patients compared to 54.8% of controls developed neutralizing antibodies (Nab) > 30% on day 22 and only 8.3% vs. 20.8% received Nab levels felt to be clinically protective.[9] In a similar study from the UK (with vaccines given 12 weeks apart), only 54% to 58% of myeloma patients had a positive antibody response at a median of 33 days after the first vaccine with no difference between the Pfizer and ChAd0 × 1 (Astra-Zeneca) products.[8] Our results in patients who predominantly received 2-shot vaccines showed that that nearly all achieved a measurable antibody response,

Figure 1 A comparison of the responses in PCD patients according to type of vaccine, therapy, severe immunoparesis, and exposure to anti-CD38 mAb. The mRNA vaccines resulted in statistically higher responses compared to the J&J vaccine. However, the differences between the 2 mRNA vaccines were not statistically different from each other. There was a significantly lower response in MM patients treated with anti-CD38 mAb regardless of vaccine type. Abbreviations: JJ = Johnson & Johnson; mAb = monoclonal antibody; MM = multiple myeloma.

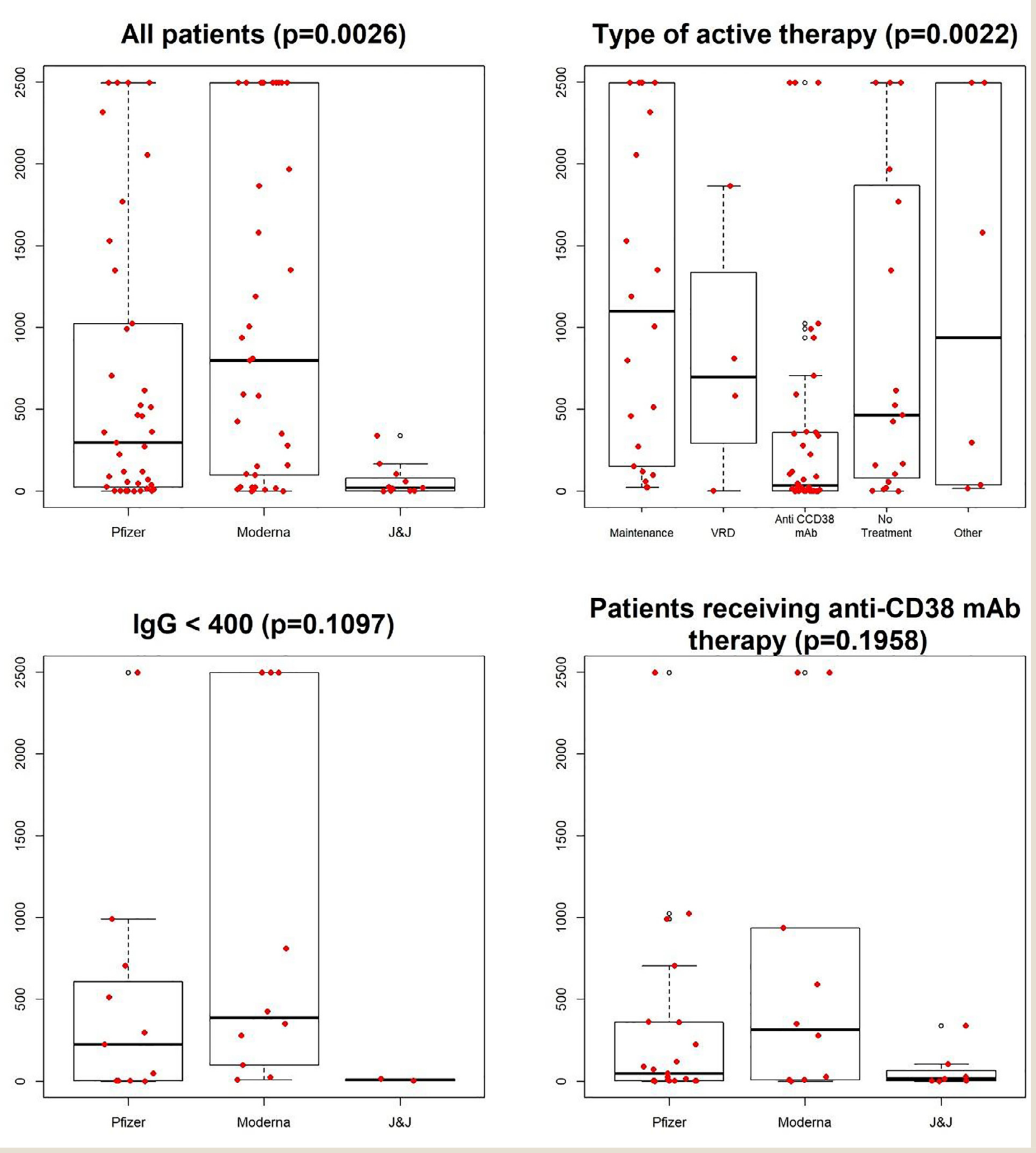

Table 1 Demographics and Vaccine Response in Patients Not Previously Infected (Negative Antinucleocapsid)

Vaccination Type	Pfizer-BioNT N = 41	Moderna N = 37	J&J N = 11	Positive Titer (%)	Median Titer
Median age (range)	65 (44-90)	63 (48-82)	67 (54-87)	95.5	295
Sex					
Female	21 (51.2)	23 (62.2)	7 (63.6)	48 (96)	337
Male	20 (48.8)	14 (37.8)	4 (36.4)	36 (94.7)	231
Ethnicity					
White	23 (56.1)	15 (40.5)	8 (72.7)	45 (97.8)	198
Black	6 (14.8)	11 (29.7)	2 (18.2)	16 (84.2)	224
Hispanic	4 (9.8)	5 (13.5)	1 (9.1)	9 (100)	759
Asian	8 (19.5)	6 (16.2)	0 (0)	14 (100)	361
Disease isotype					
IgG	28 (68.3)	19 (51.4)	7 (63.6)	50 (94.3)	139
IgA	4 (9.8)	5 (13.5)	1 (9.1)	10 (100)	284
Light chain	9 (22.0)	11 (29.7)	2 (18.2)	21 (95.5)	587
Nonsecretory	0 (0)	2 (5.4)	1 (9.1)	3 (100)	351
Disease status					
VGPR or CR	27 (65.9)	27 ((73.0)	6 (54.5)	59 (100)	486
PR	8 (19.5)	4 (10.8)	2 (18.2)	11 (78.6)	57
Progressive	2 (4.9)	2 (5.4)	3 (27.3)	7 (100)	167
Not determined	4 (9.8)	4 (10.8)	0 (0)	7 (87.5)	312
Severe immunoparesis *(IgG < 400)*	11 (26.8)	10 (27)	2 (18.2)	22 (95.7)	278
Previous ASCT	20 (48.8)	25 (67.6)	2 (18.2)	45 (97.8)	990
Therapy type					
Ongoing anti-CD38 mAb	21 (51.2)	10 (27)	7 (63.6)	35 (92.1)	36
Lenalidomide maintenance	9 (22)	12 (32.4)	1 (9.1)	22 (100)	1098
VRD	0 (0)	3 (8.1)	1 (9.1)	4 (100)	696
Other	3 (7.3)	3 (18.1)	0 (0)	6 (100)	937
No treatment	8 (19.5)	9 (24.3)	2 (18.2)	17 (94.4)	466

A response > 0.4 U/mL is positive. Abbreviations: VGPR* = very good partial response; CR* = complete response; PR* = partial response; ASCT = autologous stem cell transplant; VRD = Combination therapy of bortezomib, lenalidomide, dexamethasone. *According to IMWG 2016 criteria[34]

Table 2 Multivariate Analysis Demonstrating the Effect of Age, Anti-CD38 Monoclonal Antibody Therapy, and Vaccine Type on Antibody Response

	Comparisons	*P* Value	Adjusted *P* Value
Age	1-year difference	**.0044**	**.0044**
Vaccine type	J&J vs. Moderna	**.0072**	**.0194**
	J&J vs. Pfizer	**.0179**	**.0465**
	Moderna vs. Pfizer	.5145	.7903
Immunoparesis	No vs. Yes	.3807	.3807
Anti-CD38 mAb use	No vs. Yes	**.0005**	**.0005**

thereby implying the importance of the second vaccine in myeloma patients and suggesting that a 2-shot strategy should be considered for other pathogens in immunocompromised patients. In a recent study of myeloma patients, Branagan et al found that tandem doses of high dose influenza vaccines resulted in higher and more durable serologic responses compared to the standard-of-care single dose vaccine and this strategy will likely be incorporated in the International Myeloma Working Group guidelines[24] and have already been included in the European Myeloma Network guidelines.[25]

In patients who have received the J&J vaccine, it remains unclear whether they should be given a second shot with the same vaccine or an mRNA vaccine. Heterologous boosts are being tested and emerging results showed higher responses after the Pfizer mRNA vaccine than a second dose of the Astra-Zeneca ChAd0 × 1.[26]

Interestingly, we found that in 4 patients with MM and 2 patients with lymphoma receiving IVIG, there was evidence of nucleocapsid and low-level anti-spike antibodies, most likely a consequence of transfer from the IVIG preparation. Romero et al found that IVIG preparations began to routinely show anti-SARS-CoV-2 antibodies in the fall of 2020.[27] This would suggest that as a higher percentage of the population is vaccinated and/or infected, monthly IVIG might offer protection to immunocompromised patients. One small study of IVIG has shown a decrease in mortality with severe COVID-19 infection.[28]

Though not currently recommended outside of clinical trials, during the course of the study it became apparent that quantitative measurement of antibody responses were informative and potentially important for rational future management. As an example, there was a significant number of patients with evidence of asymptomatic infection based on a positive anti-nucleocapsid result. The incidence of asymptomatic infection in MM or other immunocompromised populations is not well established, which suggests that estimates of mortality after SARS-CoV-2 infection are likely overestimated.[29,30] In addition, while previously infected and vaccinated (I & V) patients cannot be considered completely protected against future disease, it is questionable whether these patients need a booster. We did not include previously infected patients in this study but the median antibody titer in the I & V population after vaccination was higher than the limit of the assay (>2499 U/mL) (data not shown).

At the other end of the spectrum, patients with a zero or low antibody response to the vaccine need counseling regarding their continued vulnerability to infection including the need for monoclonal antibody therapy if they test positive or have close exposure to a SARS-CoV-2 infected individual. Similarly, 2 recent studies of third mRNA booster doses showed that as many as half of non-responding patients did not have a response to the third dose.[30,31] Patients identified to have a low antibody response after full vaccination can be considered for clinical trials including prophylactic subcutaneously administered monoclonal antibodies or other strategies.

Major weaknesses of the current study include the small number of total patients and the low percentage of patients in important subcategories such as those who recently received transplant or who had progressive disease at the time of vaccination. More importantly, while nearly all patients generated an antibody response, the threshold antibody concentration for disease protection is unknown. There is variable data on T cell response, with reports of robust T cell responses not necessarily linked to the development of a high titer of neutralizing antibodies.[32] More recently, however, Aleman et al observed that only 35% of seronegative MM patients had a $CD4^+$ T cell response.[33] Our data are supportive that the mRNA 2-dose vaccines result in the development of anti-spike antibodies in nearly all patients with PCD. There was also a trend towards a poorer response to the J&J vaccine but these results should be considered preliminary due to the low number of patients and variability in this group. In addition, further studies are required to determine whether the high prevalence of vaccinated and/or previously infected individuals in the population can be leveraged into effective prophylactic therapy with IVIG.

Conclusions

Almost all PCD patients had detectable anti-spike antibodies against SARS-CoV-2 after vaccination. However, responses were lower in older patients, those receiving ongoing treatment with anti-CD38 mAb and after the 1-shot J&J vaccine. It remains unclear whether the latter group should receive a second dose of the same vaccine or a heterologous booster. Finally, this study highlights the potential importance of quantitative antibody testing for the rational approach to COVID-19 booster shots and possible monoclonal antibody therapy in patients with low anti-spike antibody after full vaccination.

Clinical Practice Points

- Multiple myeloma patients are at increased risk of infection because of functional hypogammaglobulinemia and treatment which often includes steroids and plasma cell toxic therapy
- Because of the nature of the underlying disease and the types of therapy used, the response to COVID-19 vaccines in patients with plasma cell dyscrasia (PCD) is uncertain.
- In this real-world study of consecutive patients with PCD, we examined antibody responses after the 3 available vaccines in the United States. We were particularly interested in the impact of different types of therapy, especially anti-CD38 mAb. We excluded patients with a clinical history or laboratory detection of prior infection.
- We found that nearly all patients (95%) had a detectable response but that lower responses were associated with older age, ongoing anti-CD38 mAb therapy and the J&J vaccine.
- Quantitative antibody measurement has the potential to make management of COVID-19 protection more rational. Clinical trials evaluating prophylactic monoclonal antibodies and other strategies for ineffectively vaccinated patients require further investigation. Some degree of passive immunity may also be possible after IVIG, which contains anti-spike antibodies reflecting the high prevalence of COVID-19 antibodies in the population secondary to infection and vaccination.
- In patients with prior J&J vaccine, second shots vs. heterologous mRNA vaccine needs further exploration.

Authors' Contribution

M.R.S. designed the research, performed research, analyzed the data, and wrote the paper; A.G. and S.B. performed research and reviewed the paper; G.S. analyzed the data and reviewed the paper; Y.L. analyzed the data and reviewed the paper; and D.L.C designed the research, performed research, analyzed the data, and wrote the paper.

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Disclosure

M.R.S., A.G., S.B., G.S., and Y.L.,have no conflicts of interest to declare. D.L.C. acknowledges clinical trial research funding from Janssen.

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