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Adequate Antibody Response to COVID-19 Vaccine in Patients with Monoclonal Gammopathies and Light Chain Amyloidosis

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Keywords: vaccine for SARS-CoV-2, COVID-19, multiple myeloma, immunosuppression, antibodies, monoclonal gammopathy of unknown significance

Abbreviations: MG, monoclonal gammopathy; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; SMM, smoldering multiple myeloma; AL, light chain amyloidosis; HCW, healthcare workers; SPE, serum protein electrophoresis; FLC, free light chain; RFU, relative fluorescence unit; dara, daratumumab; bort, bortezomib; lena, lenalidomide; carfil, carfilzomib.

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ABSTRACT

Objective: Determine the COVID-19 seroconversion rate for patients with multiple myeloma receiving a COVID-19 vaccine.

Materials and Methods: After 45 patients received their second COVID-19 vaccine dose, their serum IgG antibodies were measured: 22 with monoclonal gammopathy (MG) of unknown significance, 3 with smoldering myeloma, 2 with light chain amyloidosis, and 18 with MG (9 in remission, 6 out of remission, and 3 with free light-chain gammopathy alone). A second serum specimen was retained for 16 patients with MG. Their antibody levels were compared to those of 78 uninfected healthy vaccinated control patients.

Results: Three patients with MG had low antibody levels on blood collected 98, 100, and 113 days after the initial vaccine dose (2 with MG of unknown significance and 1 with hypogammaglobulemia). The other 40 patients with MG (seroconversion rate 93%) and both patients with amyloidosis produced antibodies. Relative to days after vaccination, patients with MG had lower antibody levels than control patients.

Conclusion: After receiving a COVID-19 vaccine, most patients with MG produce anti-SARS-CoV-2 antibodies comparable to levels in uninfected vaccinated healthy control patients.

In the past century, there have been several major pandemics caused by viral infections. The development and implementation of vaccines are among the key measures to arrest these outbreaks. Although smallpox has been eradicated and polio has largely been eliminated, influenza continues to be a major health concern, and there are no vaccines available for HIV. The release of vaccines has reduced the incidence and severity of SARS-CoV-2, the causative agent producing COVID-19. As of this report, 3 vaccines have been approved by the U.S. Food & Drug Administration under emergency use authorization. The Pfizer-BioNTech and Moderna vaccines are based on mRNA technology, and the Johnson & Johnson vaccine uses a modification of an adenovirus. Other COVID-19 vaccines are available in other parts of the world.

Multiple myeloma (MM) is a disease associated with impaired immunity, which is a manifestation of both the disease itself and the treatment given. Smoldering multiple myeloma (SMM) is a precancerous condition that is characterized by lower concentrations of myeloma proteins and the absence of symptoms. Monoclonal gammopathy of unknown significance (MGUS) is a benign condition. Both MGUS and SMM are not treated but can progress to MM over time. Amyloidosis is a disease characterized by the presence of misfolded proteins that deposit into various solid organs of the body. The most common form found in the United States is amyloid light chain (AL) amyloidosis. Many patients have excess free lambda light chains. Immunomodulatory treatment of amyloidosis[1] and medications to prevent organ transplant rejection result in immunosuppression.

The International Myeloma Working Group examined patients with myeloma who contracted COVID-19 and found significantly higher risks for death (33%) relative to individuals who had no preexisting chronic disease.[2] Therefore, vaccination against SARS-CoV-2 is recommended by many physicians.[3] There is no guarantee that a vaccination will necessarily produce adequate immune protection. In a study of a high-dose influenza vaccine, Branagan et al[4] showed that only 39% of patients with MM developed antibodies against 3 flu strains (H1N1, H3N2, and influenza B). Higher rates of antibody production were observed with administration

of a booster injection, a procedure that is not routinely performed for infection prophylaxis among healthy individuals. The vaccine used in their study was an inactivated influenza virus and different in principle from 2 mRNA vaccines released in later 2019. It is not known if the mRNA vaccines are indeed more immunogenic.

The purpose of this study was to examine COVID-19 antibody levels in patients with MM (active and in remission), SMM, MGUS, and AL after administration of a COVID-19 vaccine.

Materials and Methods

We recruited 46 patients seen at the Zuckerberg San Francisco General Hospital (ZSFG; San Francisco, CA) who exhibited a monoclonal gammopathy (MG) at one point during their medical history. Remnant serum specimens were retained from the ZSFG clinical laboratory as part of the patients' routine follow-up tests for serum protein electrophoresis (SPE) and serum free light chains (FLC). Medical records were reviewed for routine testing conducted at ZSFG for the presence of the SARS-CoV-2 virus using molecular assays in regular use at ZSFG. The manufacturer of the vaccine and the number of days from the date of the vaccine inoculations were recorded. One patient with MG tested positive for COVID-19 and was omitted from the study. Thirty-four patients tested negative for a COVID-19 infection during their hospitalization visits and had no medical history of an infection. For 16 patients with MG, a second blood specimen was retained from a follow-up visit a few weeks or months after their first specimen was retained and tested. For a control group, we recruited 78 ZSFG healthcare workers (HCW) who self-reported that they were healthy and free of a prior COVID-19 infection. Because of varying COVID-19 vaccine availability at the time, more Moderna vaccine was used for the MG group and more Pfizer-BioNTech vaccine was used for the HCW group. Protocols were reviewed and approved by the Institutional Review Board of the University of California, San Francisco with written consent from the HCW group and no consent for the MG group.

Blood from patients with MG was collected between February and July 2021. Specimens were centrifuged, and the serum was tested using SPE (Hydrasis 2 System, Sebia, Norcross, GA), total protein (Siemens Advia 1800, Tarrytown, NY) and for FLC (Diazyme, San Diego, CA). We confirmed MG using immunofixation electrophoresis (Sebia). The IgG antibodies to COVID-19 were measured with a quantitative assay using Pylon (ET Healthcare).[5] This assay produces relative fluorescence units (RFUs), which are indicative of the antibody titer, and is directed to both the nucleocapsid protein and the receptor binding domain (RBD) of the spike protein of SARS-CoV-2. As such, this assay cannot differentiate between antibodies produced as a result of a COVID-19 infection (antibodies to both proteins) and those produced by the vaccine alone (antibodies to the RBD of the spike only). A cutoff of 50 RFUs was considered as positive for this assay.

For 9 patients with MG, there were no COVID-19 molecular or antigen test results reported in the medical records. Serum from 5 of these individuals was tested for the presence of COVID-19 IgG antibodies using the Abbott Architect i2000 assay that is directed to the nucleocapsid protein. A positive result is indicative of a prior COVID-19 infection. The Student's *t*-test was used to compare the means of sex and vaccine type, and a plot of the log antibody level vs days after the first vaccine was performed for the MG and HCW groups using MedCalc version 19.6.4 (Ostend, Belgium).

Results

TABLE 1 lists the medical history of the patients with MG enrolled in the study. Overall, there were 35 men (78%; age range, 36–91 years) and 10 women (22%; age range, 49–77 years). Of the 9 patients with no record of a SARS-CoV-2 polymerase chain reaction test, 5 had negative antibodies toward the virus's nucleocapsid protein, indicating that the presence of the vaccine was responsible for the antibodies found in the sera of these individuals. There was an insufficient volume of specimen to test the remaining 4 patients. None of these patients had a medical history suggestive of a COVID-19 infection; therefore, we included them as not having been previously infected. Serum from the 1 excluded patient with MG who had a prior COVID-19 infection was positive for the presence of the nucleocapsid protein. For the purposes of this report, we presume that the other 4 nontested patients did not have a prior COVID-19 infection.

The distribution of manufacturers was as follows: 28 Moderna (62%), 16 Pfizer-BioNTech (36%), and 1 Johnson & Johnson (2%). There were 22 patients with MGUS, 3 with SMM, 18 patients with a diagnosis of MM (including 3 with FLC disease only and 6 in remission indicating hypogammaglobulinemia), and 2 with AL amyloidosis. For the latter 2 groups, patients were in various stages of medical management (the therapeutic regimens used to treat these patients are shown in **TABLE 1**). For the HCW group, there were 46 men (66%; age range, 28–75 years) and 24 women (34%; age range, 28–68 years). All of these participants were negative for the presence of antibodies directed toward the nucleocapsid protein (Abbott assay). The distribution of vaccine manufacturers was as follows: 37 Moderna (47%), 41 Pfizer-BioNTech (53%), and 0 Johnson & Johnson (0%). More patients with MG than the HCW received the Moderna vaccine ($P < .05$).

We found that 76 of 78 (99%) individuals tested had a positive IgG result within 16 days (range, 16–159 days) of their first vaccine dose (range, 199–6218 RFU). **FIGURE 1A** shows the distribution of results vs days from the first vaccination. The 1 individual who was negative (9 RFU) had blood taken at 9 days after the first vaccine. Antibody levels were generally lower per days after vaccination for the MG group vs the HCW group.

FIGURE 1B shows the SARS-CoV-2 IgG response from all patients in the MG group (including second draws). Results are plotted relative to days after the first dose of the vaccine. Similar results were obtained when plotted to days after the second dose (data not shown). Of the 45 patients with MG who received the vaccine, 42 had IgG levels above the assay's cutoff concentration. The 3 patients (numbers 41, 12, and 13 from **TABLE 1**) had a negative IgG level after blood was collected at 94, 100, and 113 days after they received the vaccine (5, 9, and 13 RFU, respectively). The first patient had MG with hypogammaglobulinemia (**FIGURE 2B**, given the Pfizer-BioNTech vaccine) and the other 2 had MGUS (**FIGURE 2C** and **2D**, given the Moderna and Pfizer-BioNTech vaccines, respectively), with 1 exhibiting immune suppression. The seroconversion rate for the MG group was 40 of 43 (93%). There was an insufficient number of patients within the MG group to determine whether IgG antibody results were different between the MGUS SMM, MG or AL groups, or the therapies used within the MG group. We were also unable to determine whether there were any differences between the types of vaccine used.

Repeat blood sampling was available for 16 patients with MG. Five of these patients initially had negative antibodies when blood was collected at 4, 16, 18, 21, and 28 days after the first dose. When these individuals

TABLE 1. Summary of Patients with MG

Patient (n)	Age (y)/ Sex	Dose Days	Vaccine Type	Free K (mg/dL)[a]	Free λ (mg/dL)	K/λ	Treatment	Myeloma Subtype	Total Protein (g/dL)[b]	Gammaglobulin (g/dL)	Prior Infection[c]
MGUS											
1	66/F	60	Moderna	2.28	1.29	1.77	None	IgG-λ	6.7	1.13	Neg
2	73/M	69	Moderna	5.12	1.93	2.65	None	IgG-K	7.2	1.11	Unknown
3	79/M	44	Moderna	6.69	4.6	1.45	None	IgG-K	6.2	0.73	Neg NP
4	60/F	71	Moderna	0.96	0.68	1.35	None	IgA-K	7.3	0.44	Neg
5	68/M	28	Moderna	0.82	0.76	1.08	None	IgM-K	7.6	0.27	Neg
6	65/M	39	Moderna	NP	NP	NP	None	IgM-K	7.2	1.11	Neg
7	66/M	70	Pfizer	4.8	1.39	3.45	None	IgG-K	8	2.2	Neg
8	69/M	27	Moderna	8.56	1.62	5.28	None	IgG-K	7.2	1.14	Neg
9	68/M	25	Moderna	NP	NP	NP	None	IgG-K	6.7	0.75	Neg
10	67/M	101	Moderna	2.43	1.08	2.25	None	IgG-K	7.1	2.5	Neg
11	69/F	96	Moderna	NP	NP	NP	None	IgG-λ	8	3.8	Neg
12	73/M	100	Moderna	6.49	2.34	2.94	None	IgG-K	8.4	2.6	Neg
13	91/M	113	Pfizer	6.66	8.33	0.8	None	IgM-K	5.9	1.4	Neg
14	54/F	64	Pfizer	9.87	2.08	4.75	None	IgG-K	8.1	2.71	Unknown
								IgM-K			
15	73/M	107	Pfizer	15.34	6.49	2.36	None	IgA-K	1.4	0.58	Neg
16	63/M	125	Moderna	NP	NP	NP	None	IgG-K	8.8	3.32	Neg
17	77/F	99	Moderna	2.6	1.75	1.49	None	IgG-λ	5.5	0.57	Unknown
18	65/M	154	Moderna	6.01	2.2	2.73	None	IgG-K	8.1	1.8	Neg
								IgM-K			
19	71/M	112	Pfizer	8.12	2.26	3.59	None	IgM-K	7.5	1.76	Neg
20	66/M	100	Moderna	4.55	3.28	1.39	None	IgG-λ	6.3	1	Neg
21	60/M	58	Pfizer	18.61	4.06	4.58	None	IgG-λ	10.4	4.79	Neg
22	70/M	154	Moderna	5.83	3.07	1.9	None	IgG-K	5.7	0.3	Neg
SMM											
23	78/M	73	Moderna	5.58	1.33	4.2	None	IgG-K	7.2	1.38	Neg
24	66/M	60	Moderna	7.23	3.83	1.89	None	IgG-K	6.4	1.38	Neg
25	82/M	84	Moderna	11.91	7.26	1.26	None	IgA-λ	6.6	2.7	Neg NP
MM											
26	76/M	47	Moderna	2.33	0.69	3.38	Dara	IgG-K	7.1	0.7	Neg NP
								Free K			
27	67/M	33	Moderna	4.08	2.37	1.72	Lena	IgA-K	6.9	0.88	Neg
								Free K			
28	59/M	18	Pfizer	0.88	8.37	0.09	Dara	IgA-λ	6.8	0.38	Neg
								IgG-λ			
29	72/M	56	Pfizer	3.06	1.51	2.03	Bort, lena	Free λ	6.8	0.46	Neg
30	68/M	21	Pfizer	57.9	2.96	19.56	Bort	IgG-K	7.6	0.27	Neg
31	55/M	28	Pfizer	2.14	0.81	2.64	Lena	IgA-K	6.6	0.4	Neg
32	52/M	70	Moderna	1.16	0.87	1.33	Bort, lena	IgG-K	7	0.5	Neg
33	62/M	40	Moderna	3.48	1.91	1.82	None	IgG-K	6.2	1.14	Neg
34	56/F	163	Moderna	53.6	0.94	57.09	Bort	IgG-K	7.6	2.31	Neg
Free light chain											
35	65/F	32	Pfizer	2.51	1.73	1.45	Lena	Free λ	6.1	0.59	Neg
36	73/F	98	Moderna	NP	NP	NP	None	Free λ	NP	NP	Neg
37	57/M	65	Pfizer	0.95	15.46	0.66	Poma, lena	Free λ	5.6	0.24	Neg
MM with hypogammaglobulinemia											
38	59/M	4	Pfizer	1.85	8.36	0.22	Bort	IgG-λ	6.4	0.33	Neg

TABLE 1. Continued

Patient (n)	Age (y)/ Sex	Dose Days	Vaccine Type	Free K (mg/dL)[a]	Free λ (mg/dL)	K/λ	Treatment	Myeloma Subtype	Total Protein (g/dL)[b]	Gammaglobulin (g/dL)	Prior Infection[c]
								Free λ			
39	36/M	14	Pfizer	0.54	8.18	0.07	Carfil	IgD-λ	6.7	4.2	Neg NP
40	49/F	66	Moderna	1.71	1.13	1.51	Lena	IgG-K	6.1	0.46	Neg
41	55/F	10	Pfizer	1.21	0.86	1.41	Dara	IgG-K	5.8	0.35	Neg
								Free K			
42	61/M	16	Moderna	0.98	0.72	1.36	Dara	IgG-K	6.3	0.32	Neg NP
43	58/M	52	Moderna	2.62	1.45	1.81	None	IgG-K	5.9	0.45	Neg
Amyloidosis											
44	59/M	2	Janssen	3.43	3.35	1.02	Dara, lena	Free λ	3.9	0.43	Unknown
45	66/M	73	Pfizer	4.05	3.68	1.1	Dara, lena	Free λ	1.1	0.56	Neg

bort, bortezomib; carfil, carfilzomib; dara, daratumumab; lena, lenalidomide; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; NP, not performed; poma, pomalidomide; SMM, smoldering multiple myeloma.
[a]Reference range: free K: 0.33–1.94 mg/dL; free λ: 0.57–2.63 mg/dL; K/λ: 0.26–1.65.
[b]Reference range: total protein: 6.4–8.3 g/dL; gammaglobulin: 0.6–1.6 mg/dL.
[c]Neg NP: negative for the nucleocapsid protein (ie, no natural infection).

FIGURE 1. **Log IgG antibody response vs days after the first vaccination for SARS-CoV-2. A, Healthcare workers (log[y] = –0.00225x + 3.26; *r* = 0.19, *P* = NS). B, Patients with monoclonal gammopathy (log[y) = 0.0024x + 2.40; *r* = 0.10; *P* = NS). The cutoff concentration is indicated by the dotted line. NS, not significant.**

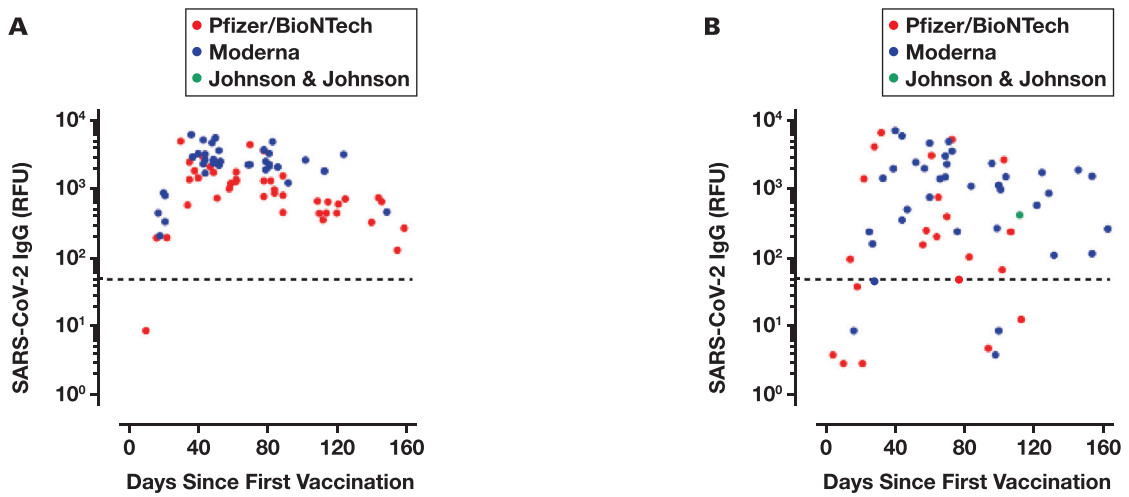
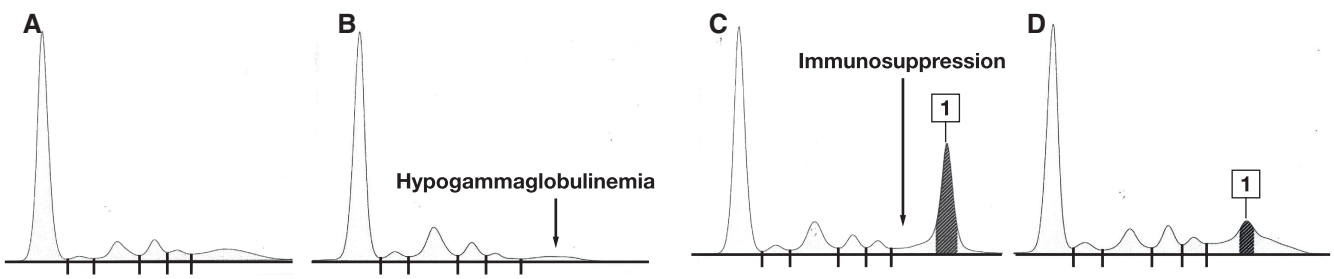


FIGURE 2. **Densitometric serum protein electrophoresis scans. A, Healthy patient. B–D, Patients with no antibody production (patients 41, 12, and 13, respectively, from TABLE 1) after a COVID-19 vaccine.**



returned for a repeat blood draw (between 14 and 84 days), all but 1 had seroconverted to produce positive IgG antibodies.

Discussion

Research has shown that MGUS, which is a benign condition, has an incidence of 1.5% among individuals older than age 50 years and 3% for those older than age 70 years.[6] Although these patients are not immune suppressed because of the presence of polyclonal antibodies, they nevertheless have a higher risk of developing infections. In a study by Kristinsson et al,[7] patients with MGUS had a 2.7-fold higher risk for developing an influenza infection at a 5- and 10-year follow-up. Patients with SMM are characterized by a more advance premalignant phase than patients with MGUS, with 3 g/dL of monoclonal proteins and >10% of plasma cells in the bone marrow but no end-organ damage.[8] Our studies showed that for MGUS and SMM, SARS-CoV-2 antibodies are routinely detected in the serum after vaccination.

A more interesting question is whether antibodies are produced in patients with myeloma who exhibit immune suppression. A hallmark of this disease is the inability of patients to produce a polyclonal antibody response against common antigens, in favor of the malignant proliferation of a single B-cell clone (**FIGURE 2C**). In contrast to patients with MGUS, patients with myeloma have a 10-fold higher risk for an influenza infection.[9] This has led the European Myeloma Network to make a recommendation for influenza vaccinations for patients with MGUS, SMM, and MM.[10] Existing data are currently insufficient to inform on the optimal timing of COVID-19 vaccination among people who are planning to receive or who are receiving immunosuppressive therapies. In our study, regardless of the subtype, antibodies were produced in nearly all the patients with MM studied. As shown in **TABLE 1**, patients 36 through 42 had low gammaglobulin levels (reference range, 0.6–1.60 g/dL). This finding is relevant because the COVID-19 vaccine produces IgG antibodies that migrate within this electrophoretic region.

There have been a few recent reports of COVID-19 antibody response in patients with MM. In the United Kingdom, Bird et al[11] tested blood 21 days after vaccine administration (Pfizer-BioNTech and AstraZeneca) and reported an antibody positivity rate of 56%. There was no difference in the efficacy of the 2 vaccines used. In Italy, Pimpinelli et al[12] tested blood 5 weeks after administration of the Pfizer-BioNTech vaccine and reported that 78.6% of 42 patients with MM had antibodies. In perhaps the largest study of patients with MM to date, Van Oekelen et al[13] tested 260 patients with MM who received either the Pfizer-BioNTech (69%) or Moderna (27.2%) vaccine in the United States and reported an antibody positivity rate of 84.2%. The positivity rate found in this study (93%) is not significantly different from Pimpinelli et al[12] and Van Oekelen et al[13] but statistically higher than what was found in Bird et al.[11] The number of enrollments between this and the previous studies was too small to make any general conclusions as to why the antibody incidence rate was different. Laboratory tests for neutralizing antibody response may provide more information regarding humoral immune status. Terpos et al[14] showed that 22 days after patients were given the Pfizer-BioNTech vaccine, patients with MG had lower neutralizing antibody titers than healthy control patients (25% vs 55%). This study was limited in that only 1 dose of the vaccine had been given at the time of blood collection. We did not perform testing of serum antibodies using a surrogate virus neutralization test for our specimens.

In addition to patients with immune suppression due to their MG disease, treatment of patients using immunomodulatory drugs such as daratumumab lowers monoclonal antibody concentrations, leading to disease remission. This drug binds to CD38, a type II transmembrane glycoprotein that is expressed on plasma cells from patients with MM, resulting in cell death through complement-dependent, antibody-dependent cytotoxicity, phagocytosis, and apoptosis.[15] Daratumumab is also being used to treat AL amyloidosis. Very low gammaglobulin bands from SPE testing can be observed after treatment using this biologic agent.[16]

After administration of a COVID-19 vaccine, antibodies are consistently produced within 120 days after the first injection[17] and gradually decline over the ensuing months.[18] Our study showed that 93% of patients with MG had an adequate antibody response to a COVID-19 vaccine and were likely protected against SARS-CoV-2 infection. For the 3 patients with MG who exhibited no IgG response at or after 98 days, it is not known if their initial response declined to baseline levels or if they never had an antibody response. Nevertheless, these individuals may be at increased risk.

These results are significantly different from those of patients who have received a solid organ transplant and have been treated with immunosuppressive drugs. In a study of 658 patients who had received transplant, Boyarsky et al[19] showed a response rate of 15% after the first dose and 54% after the second dose of either the Pfizer-BioNTech or Moderna 2-dose vaccine. A different antibody assay than in the current work was used for that study, but this is not likely the reason for the differences in the incidence of antibody production. In contrast, Al-Janabi et al[20] showed that 92% of patients treated with immunomodulators for immune-mediated inflammatory disease produced antibodies after receiving a Pfizer-BioNTech vaccine. Immunomodulators are more selective than immunosuppressants and enable more retention of the host's immune response.

Study Limitations

This was an observational study using remnant blood specimens from routine clinical evaluations. For those patients who had repeat visits, the appointment schedule was fixed by the attending physicians and therefore was not controlled. As such, there may have been a selection bias. Another limitation is the higher proportion of patients with MG than HCW participants receiving the Moderna vaccine. We have previously shown that relative to the date of the second vaccine dose, individuals receiving the Moderna vaccine have higher antibody levels, and these declined at a slower rate than levels in those receiving the Pfizer-BioNTech vaccine.[18] However, this situation should not affect the overall rate of seroconversion. This study was further limited by the small numbers of patients enrolled with MG, which prohibited an analysis of subgroups (eg, disease status or therapy). We also do not have data on breakthrough infections or the role that T-cells have on immunity. Research has shown that B-cell function as determined by antibody production is only part of a patient's immune response to a SARS-CoV-2 infection. Exposure to viral proteins also produces a T-cell response. Although we are not able to assess T-cell function after administration of a COVID-19 vaccine, we expect that patients with MG should be capable of producing a cellular response because this disease disrupts humoral immunity to a greater extent than cellular immunity.

Conclusion

We found that 93% of patients with MG were able to produce an antibody response to a COVID-19 vaccine. Of the 3 patients with negative antibodies, 1 had hypogammaglobulinemia, 1 had immunosuppression because of the monoclonal band, and 1 had an adequate gammaglobulin response. Because the incidence of MM is low, it may be cost-effective to measure serum antibody levels after administration of a COVID-19 vaccine to find those few individuals who have a COVID-19 vaccine failure. Our study was insufficiently powered to determine whether immunosuppression was associated with a poor antibody response, and we have no data on breakthrough infections. Recently, a fully vaccinated former US Secretary of State with a history of MM died of complications from a COVID-19 infection. It is unknown whether the Secretary exhibited a low COVID-19 serum antibody response or hypogammaglobulinemia at the time of death. If both were present, then his case could illustrate how SPE could be a screening tool to justify COVID-19 antibody testing to assess B-cell immunity against a breakthrough infection. Detection of low total serum IgG could be a more cost-effective alternative than SPE testing. A study of antibody levels of patients with MG who become infected with SARS-CoV-2 after being fully vaccinated will be necessary to document the utility of this strategy.

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