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QUALITY IMPROVEMENT

Anti-Spike Antibody Responses in Allogeneic Stem Cell Transplant Recipients to Two Doses of COVID-19 mRNA Vaccination: A Retrospective, Single-Center Analysis

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients were excluded from the initial SARS-CoV-2 mRNA vaccination efficacy trials. Suboptimal vaccine responses have been reported in immunocompromised cohorts such as patients with solid tumors or hematologic malignancies, suggesting the need for additional research. Widespread data on the antibody responses and vaccine efficacy in allo-HSCT recipients is limited. In our single-center, retrospective study, we analyzed the anti-spike IgG antibody responses in 75 allo-HSCT recipients who received a series of two doses of mRNA vaccination. We collected data on previous COVID-19 infection, B and T lymphocyte recovery, donor types, graft-vs.-host disease (GVHD), and immunosuppressive medications at the time of vaccination. With the original variant, a cutoff of 4,160 arbitrary units (AU)/mL has been correlated with a 0.95 probability of a viral neutralization. We also examined the number of allo-HSCT recipients who achieved this conservative threshold. To our knowledge, no correlate exists for the currently prevalent Omicron variant and viral neutralization. Despite 29.3% (22/75) of patients being on systemic immunosuppressive medications due to chronic GVHD, positive antibody responses > 50 AU/mL were seen in 96% of patients. However, only 48% (36/75) of patients were above the neutralizing antibody threshold. Those with previous COVID-19 infection had significantly higher antibody responses. Although encouraging, the variability of the responses underscores the concept of ongoing antibody monitoring as well as consideration of additional doses of the COVID-19 vaccine in this cohort.

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COVID-19 mRNA vaccinations have been shown to be effective by reducing severe disease-related symptoms and hospitalization in phase III trials (Polack et al., 2020). Patients with malignancies have been shown to be at higher risk for morbidity and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Madan et al., 2020). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients are among the most immunocompromised patients due to multiple factors, including conditioning regimens, immunosuppressive medications, and potential for graft-vs.-host disease (GVHD). The emergence of antibody testing to validate vaccine efficacy can guide individualized recommendations regarding the risk of COVID-19 complications. Published reports suggest that solid organ transplant patients have largely inadequate responses to two doses of mRNA vaccination (Boyarsky et al., 2021). Additionally, variable responses have been seen in patients with hematologic malignancies, such as those with multiple myeloma (Van Oekelen et al., 2021). Because allo-HSCT recipients were not part of initial vaccine efficacy trials, widespread data on vaccine responses in these patients are somewhat limited.

SUBJECTS AND METHODS

In our single-center, retrospective study, we included patients post allo-HSCT who completed a series of two doses of mRNA vaccination (either Pfizer-BioNTech or Moderna) and had quantitative measurements of anti-spike IgG (immunoglobulin G) antibody responses. Patient demographics and disease characteristics were collected. Antibody responses were measured using the Abbott Alinity m SARS-CoV-2 quantitative IgG spike protein serology assay, which is a chemiluminescent microparticle immunoassay that detects IgG antibodies to SARS-CoV-2 (Narasimhan et al., 2021; Mullen, 2021). We collected data on B and T lymphocyte recovery using IgG as a surrogate marker for B-cell recovery, absolute CD4 counts, donor types, presence or absence of active chronic GVHD, immunosuppressant use, and previously known COVID-19 infection. Positive antibody responses were defined as > 50 arbitrary units (AU)/mL. Additionally, a cutoff of 4,160 AU/mL has been correlated with a 0.95 probability of a high titer plaque reduction neutralization test at 1:250 dilution in BNT162b2 (Pfizer-BioNTech) patients (Ebinger et al., 2021) in prior viral strains. We also examined the number of allo-HSCT recipients who achieved this conservative threshold. This study was approved by the Institutional Review Board.

RESULTS

A total of 75 allo-HSCT recipients were included in this study. The median age of patients at the time of antibody testing was 55 years (range: 27–76 years), and 48% were female (36/75). The majority of patients (80%; 60/75) received the BNT162b2 vaccine, and 17.3% (13 patients) received the Moderna vaccine at their respective recommended intervals of 21 and 28 days, while one patient received Pfizer for dose one and Moderna for dose two (Table 1). One patient only received one dose of Moderna vaccination. The antibody levels were measured at least 14 days after vaccination (median: 110 days, range: 14–222 days).

Positive vaccine responses, defined as > 50 AU/mL, were found in 96% (72/75) of patients. These patients were immune reconstituted in large part, with a median IgG level of 890 mg/dL (range: 361–2,156) and a median absolute CD4 count of 424.5 cells/μL (range: 167–1,149). Generally accepted goals for B cell and T cell recovery are IgG > 400 and CD4 > 200 cells/μL, respectively. Two patients obtained vaccination independently without immune reconstitution. Of the 75 patients evaluated, at least 6.7% (5/75) of patients had known, lab-detected COVID-19 infection prior to receiving vaccination. Interestingly, in those infected prior to vaccination, the median antibody response was 43,322 AU/mL (range: 24,559–57,371.9), 15.7 fold higher than the median of 2,748.8 AU/mL (range: < 7–91,818) in the remaining patients. Of the 72 patients who had positive antibody responses > 50 AU/mL, 36.1% (26/72) had active GVHD, and 30.5% (22/72) were on one or more systemic immunosuppressive medications at the time of antibody testing. Immunosuppressive medications included ruxolitinib (Jakafi), sirolimus, tacrolimus, prednisone, methylprednisolone, mycophenolate mofetil, and ibrutinib (Imbruvica).

Additionally, of the 72 patients with positive antibody response, two were on antileukemic therapy with azacitidine and venetoclax (Venclexta) for

Table 1. Patient Characteristics

	n	%
Total	75	100.0
Donor type		
Matched unrelated	37	49.3
Matched related	23	30.7
Mismatched related (haplo-identical)	12	16.0
Mismatched unrelated	2	2.7
Double cord	1	1.3
Gender		
Female	36	48.0
Male	39	52.0
GVHD		
Acute	1	1.3
Chronic	26	34.6
Systemic immune suppression		
Yes	22	29.3
No	53	70.7
Vaccine received		
Pfizer 2 doses	60	17.3
Moderna 2 doses	13	80.0
Pfizer 1 dose/ Moderna 1 dose	1	1.3
One Moderna only	1	1.3
Known COVID-19 prior to vaccine		
Yes	5	6.7
No	70	93.3

relapsed disease. Antibody testing was performed a median of 110 days after the second dose of the mRNA vaccine (range: 14–222 days). The median time from allo-HSCT to checking the anti-spike IgG antibody was 1,098 days (approximately 3 years) post transplant (range: 176–9,160 days). Although the overwhelming response was positive at 96% being over the arbitrary cutoff of 50 AU/mL, only 48% of the patients had IgG spike protein quantitative values above the neutralizing antibody level 4,160 AU/mL referenced previously (Table 2). The widely variable nature of the responses detailed in Figure 1 underscores the need for ongoing antibody testing to further characterize the responses over time. One patient experienced a severe adverse event after the second dose of vaccination, with grade 4 acute GVHD of the liver in the setting of donor lymphocyte infusion; it is unclear whether it was definitively related to the vaccine.

DISCUSSION

Generally, post allo-HSCT vaccination guidelines advise the initiation of a reimmunization series at least 6 months after transplant, and also when IgG levels are > 400 and CD4 counts are > 200 cells/μL. We held to these recommendations when discussing COVID-19 immunizations with our patients, prioritizing COVID-19 vaccines ahead of other vaccines wherever possible. Antibody responses were seen in the vast majority of patients, even in the setting of active chronic GVHD and systemic immunosuppressive therapy. These data contrast reports of inadequate responses in solid organ transplantation patients and underscore the need for additional studies in various subsets of patients for further characterization of responses.

Of the three patients (4%) who were nonresponders to mRNA vaccination, one had inadequate IgG level < 400 and CD4 count < 200 cells/μL, and the other two had normal IgG and CD4. One of the nonresponders had active chronic GVHD at the time of antibody testing, although none of the three patients were on systemic immunosuppression. At this time, there are emerging data regarding BNT162b2 vaccination (Redjoul et al., 2021; Canti et al., 2021; Atanackovic et al., 2021) and emerging studies with cohorts like ours that include both BNT162b2 and Moderna vaccination as well (Mamez et al., 2021; Morsink et al., 2022).

Our study demonstrates the efficacy of SARS-CoV-2 mRNA vaccinations in immune reconstituted allo-HSCT recipients, even in the presence of active chronic GVHD and systemic immunosuppression, and supports immunizing these patients. Despite largely favorable response to vaccination, the range and wide variability of antibody titers indicate the need for repeat antibody testing at regular intervals. Those below the neutralizing threshold of 4,160 AU/mL may be the most likely to benefit from additional doses of vaccination at this time. As all patients who had both a history of COVID-19 infection and two doses of mRNA vaccine had significantly higher levels of antibody titers, these patients are less likely to need additional doses of the vaccine at this time, and

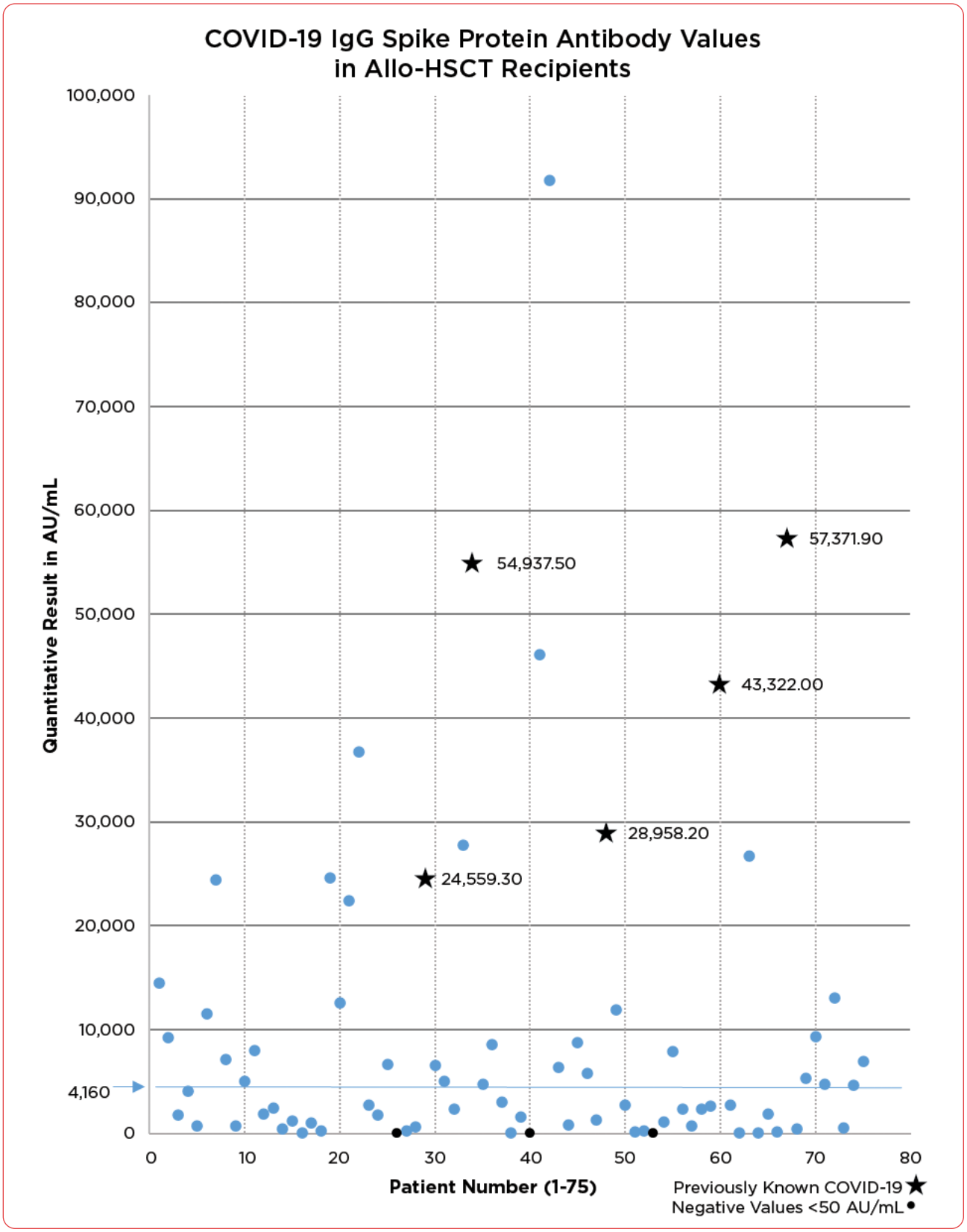

Figure 1. COVID-19 IgG spike protein antibody values in allo-HSCT recipients.

Table 2. IgG Spike Antibody Results

IgG spike range	*n*
0–50 = negative	3
51–1,000	17
1,001–4,500	19
> 4,500	36
Total	75

optimal timing of additional doses of vaccine may be better guided by data concerning quantitative antibody responses. Seven of our 75 patients had additional antibody testing after the initial testing, and all of those patients had a decline in their levels over time. As third and fourth doses of mRNA vaccinations have recently been approved, several of the patients have begun to receive boosters. We are in the process of gathering additional data regarding this. Early analysis of available data at our institution is promising regarding a significant improvement in immune response. Due to the incidence of our patients with grade 4 acute GVHD following immunization in the setting of donor lymphocyte infusion, we advise caution with recent donor lymphocyte infusion. Additional data will be forthcoming, but we encourage clinical trials and study in this area for patients with preexisting GVHD or known risk factors for GVHD, as additional cautions may be needed for this subset of allo-HSCT recipients.

Individualized data for the patients involved has helped to guide recommendations and individual choice regarding risk and mitigation strategies such as masking and social distancing. Although encouraging, our study is limited by a small number of patients, and thus results should be validated in larger clinical trials.

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Disclosure

The authors have no conflicts of interest to disclose.

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