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Brief Article

Serologic Responses following a Single Dose of SARS-CoV-2 Vaccination in Allogeneic Stem Cell Transplantation Recipients



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Immunocompromised individuals were not included in formal trials of SARS-CoV-2 mRNA vaccines. Subsequent studies in patients with hematologic malignancies and solid organ transplantation recipients suggest inferior responses to vaccination. We determined antibody responses to a single dose of vaccines in one of the most vulnerable patient groups, allogeneic hematopoietic cell transplantation (allo-HCT) recipients. Pfizer-BioNTech (PB) or AstraZeneca (AZ) SARS-CoV-2 vaccines were administered at least 3 months post-transplantation to 55 adult allo-HCT recipients. We found that older age and concurrent use of immunosuppressive medications were significantly associated with lack of antibody response to vaccination. Only 21% of patients on systemic immunosuppression mounted a response, compared with 58% of patients not on immunosuppression ($P = .006$). We also show that responses to the AZ vaccine may be superior to responses to the PB vaccine in this cohort. These findings highlight the need for novel immunogenic vaccine formulations and schedules in these highest-risk patients, as well as continued public health safety measures to protect the most vulnerable members of our society.

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INTRODUCTION

Patients with cancer who develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have higher rates of hospitalization, intensive care admission, invasive ventilation and increased mortality compared with infected patients without cancer [1–3]. Patients with hematologic malignancies and allogeneic hematopoietic cell transplantation (allo-HCT) recipients are particularly vulnerable populations. A recent meta-analysis of >3000 patients with COVID-19 with an underlying hematologic malignancy showed a mortality rate of 34%, 3 times the average rate in the general population [4]. Registry data from the European Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplantation Research demonstrate mortality rates of 30% and 22%, respectively in allo-HCT recipients with a confirmed diagnosis of COVID-19 [5,6]. These findings highlight the need to urgently assess vaccine efficacy and durability in these patients.

To date, most allo-HCT recipients in the United Kingdom have been vaccinated with the PfizerBiontech BNT162b2 vaccine (PB) or the AstraZeneca ChAdOx1 nCoV-19 vaccine (AZ).

Both vaccines generate neutralizing antibodies against the viral S protein, preventing viral entry into host cells [7–9]. The PB vaccine administered as a 2-dose regimen given 21 days apart has demonstrated an efficacy of 52% after the first dose and 95% after the booster dose [7]. Two doses of the PB vaccine elicited strong antiviral CD4⁺ and CD8⁺ responses and high levels of neutralizing antibodies [8]. An interim analysis of 4 randomized controlled trials of the AZ vaccine demonstrated an overall vaccine efficacy of 62.1% in those who received 2 standard doses 4 weeks apart.⁹ Following 1 dose of the AZ vaccine, >95% of participants have detectable antibodies directed against the S protein at day +28, which is further increased following the second dose [10,11]. The UK Joint Committee of Vaccination and Immunisation has recommended that delivery of first vaccine doses be prioritized over second doses; thus, the majority of second vaccine doses in the UK have been delayed to 12 weeks [12]. Current European and US transplant guidelines recommend that COVID-19 vaccination can be administered as early as 3 months after allo-HCT [13–15].

Vaccine efficacy in individuals with hematologic malignancies and those receiving immunosuppressive medications is unknown, because these patients were excluded from the original trials of the PB and AZ vaccines [7–11]. The primary goal of this retrospective analysis was to assess serologic responses to single doses of the PB and AZ vaccines in allo-HCT recipients vaccinated at >3 months post-transplantation.

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RESULTS

Characteristics of the 55 patients included in the analysis are presented in Table 1. The median patient age was 50 years. Acute myelogenous leukemia (41.8%) and acute lymphoblastic leukemia (23.6%) were the most common indications for transplantation. More than two-thirds of the patients (70.9%) had received reduced-intensity conditioning, the majority with T cell depletion with alemtuzumab (54.5%) or antithymocyte globulin (10.9%). Forty-one patients had active graft-versus-host disease, and 29 were on systemic immunosuppression at the time of vaccination. The median time from allo-HCT to vaccination was 460 days (range, 108 to 4533 days). Twenty-two patients underwent COVID-19 antibody testing before vaccination, all of whom had a negative result. Two of these 22 patients had previous PCR-confirmed SARS-CoV-2 infection but undetectable antibodies before vaccination.

Twenty-one patients (38.2%) had a documented positive IgG antibody response following vaccination. In univariate analysis, vaccine nonresponders were more likely to be older

(median age, 51 versus 29 years; $P = .033$) and more likely to be receiving systemic immunosuppression ($P = .0062$). Patients who had acute graft-versus-host disease (6 of 55) appeared to be nonresponders, and, given the small numbers, showed a statistical trend only ($P = .072$). We saw higher rates of seroconversion in AZ vaccine recipients compared with PB vaccine recipients (50% versus 19%; $P = .021$). In addition, there was a trend toward lower lymphocyte counts in nonresponders. Of the 8 patients who received their first vaccine dose within 3 to 6 months post-allo-HCT, only 1 had detectable antibodies post-dose.

Of the 2 patients who had had COVID previously, 1 had COVID before transplantation and had mounted a SARS-CoV-2 IgG antibody response, although this response may have been transient, as the patient was subsequently negative 7 days later (prevaccination) and has remained negative since. Of note, this was this patient's second allo-HCT, following a first transplantation in 2012. The second patient was at 2 years post-transplantation when COVID occurred. At that point, the patient was receiving venetoclax and azacytidine for relapsed

Table 1
Characteristics of Vaccine Responders and Nonresponders Using the Ortho Clinical Diagnostic Anti-SARS-Cov-2 IgG Immunoassay to Assess Response

Characteristic	All (N = 55)	Antibody-Positive after First Vaccine (N = 21)	Antibody- Negative after First Vaccine (N = 34)	P Value
Age, yr, median (range)	50 (18-73)	29 (18-73)	51 (23-73)	.038*
Sex, n (%)				
Male	34 (61.8)	13 (61.9)	21 (61.8)	.991
Female	21 (38.2)	8 (38.1)	13 (38.2)	
Diagnosis, n (%)				.302
Acute lymphoblastic leukemia	13 (23.6)	6 (28.6)	7 (20.6)	
Acute myelogenous leukemia	23 (41.8)	9 (42.9)	14 (41.2)	
Aplastic anemia	2 (3.6)	2 (9.5)	0	
Myelodysplastic syndrome	7 (12.7)	1 (4.8)	6 (17.6)	
Non-Hodgkin lymphoma	7 (12.7)	3 (14.2)	4 (11.8)	
Hodgkin lymphoma	2 (3.6)	0	2 (5.9)	
Myelofibrosis	1 (1.8)	0	1 (2.9)	
Donor type, n (%)				.766
Sibling	9 (16.4)	2	7	
Matched unrelated	35 (63.6)	14	21	
Umbilical cord	7 (12.7)	3	4	
Haploidentical	4 (7.3)	2	2	
Conditioning, n (%)				.248
Full-intensity conditioning	16 (29.1)	8 (39.1)	8 (23.5)	
Reduced-intensity conditioning	39 (70.9)	13 (61.9)	26 (76.5)	
T cell depletion, n (%)				.899
Campath	30 (54.5)	11 (52.3)	19 (55.9)	
Antithymocyte globulin	6 (10.9)	2 (9.5)	4 (11.8)	
None	19 (34.5)	8 (38.1)	11 (32.4)	
Acute GVHD, n (%)	6	0	6 (17.6)	.072
Chronic GVHD, n (%)	35	11 (52.3)	24 (70.5)	.173
Immune suppression at vaccination, n (%)				.0062
On immune suppression	29	6 (28.6)	23 (67.6)	
No immune suppression	26	15 (57.7)	11 (42.3)	
Time to vaccination post-HCT, n (%)				.136
3-6 mo	8	1 (4.7)	7 (20.5)	
>6 months	47	20 (95.2)	27 (79.4)	
Time from vaccine to antibody assessment, d, median (range)	42.1 (14-84)	35 (14-74)	46.5 (14-84)	.226
Lymphocyte count at time of vaccination, $\times 10^9/L$, median	1.18	1.33	1.11	.062
Type of vaccine, n				.021*
PB	21	4	17	
AZ	34	17	17	
Rituximab within last 12 mo, n				.191
Yes	10	2	8	
No	45	19	26	

GVHD indicates graft-versus-host disease.

Table 2
Multivariate Analysis of Variables Affecting the Likelihood of a Positive Serologic Response to Vaccination in Allograft Recipients

Variable	OR	SE	z-Score	P Value	95% CI
Older age (continuous)	0.96	0.192	-1.96	.05	0.92-0.99
Presence of acute GVHD	1	–	–	–	–
Not on immunosuppression	6.21	4.52	2.51	.012	1.48-25.8
AZ versus PB vaccine	3.73	2.93	1.68	.093	0.80-17.35
Higher median lymphocyte count	1.40	0.53	0.90	.370	0.67-2.93

disease. This patient developed antibodies postinfection, and these have remained.

Following multivariate analysis (Table 2), older age and concurrent use of immunosuppression remained significantly associated with nonresponse to first dose of vaccination. No postvaccination adverse events of significance have been reported in this cohort. With regular PCR screening for asymptomatic infection, we have not detected any COVID-19-positive patients from this cohort.

DISCUSSION

In this study of allo-HCT recipients, just over one-third mounted an IgG antibody response to a single dose of the COVID-19 vaccine, showing lower response rates than those reported in original studies of PB and AZ COVID-19 vaccines [7-11]. These findings are in keeping with other analyses of SARS-CoV-2 vaccination in immunosuppressed individuals. One study showed that 13% of patients with hematologic malignancies had an antibody response following the first PB vaccine dose [16], and another study of recipients of solid organ transplants found a response rate of 17% to the PB and mRNA-1273 Moderna vaccines [17]. In comparison, out of 177 staff members tested here, 175 (98%) tested positive for SARS-CoV-2 IgG following a single vaccine dose. Unfortunately, the vaccination and or antibody status of our donors is unknown, because these data are not routinely collected either here or at donor collection centers. Of the sibling donors in our cohort, only 1 had donated within the previous 12 months, prior to COVID vaccination. There was no known evidence that this patient had COVID previously, and antibody testing was not available at that point. The patient was COVID PCR-negative at the time of donation.

Older patients and patients taking systemic immunosuppression, who are most vulnerable to severe COVID-19 disease, are also significantly less likely to mount an IgG response to vaccination, with only 21% of patients on systemic immunosuppression responding. Our findings also suggest that responses to the AZ vaccine may be superior to responses to PB in this group, although confirmation is needed because this association was only a statistical trend in multivariate analysis, and the number of patients assessed was small.

Limitations of this study include the relatively small patient cohort and convenience sampling. This is an interim analysis, and further response assessment after administration of second vaccine doses is planned. In addition, owing to a lack of neutralization assays and cellular immune responses, we are unable to comment on whether the SARS-CoV-2 IgG antibody levels that we have detected are functional antibodies.

The lower response rates seen in allo-HCT recipients after the first dose of vaccine supports delivery of the PB vaccine in immunocompromised individuals according to the originally published schedule, whereas there is some evidence to support a delayed second dose at 8 to 12 weeks in recipients of the AZ vaccine [9]. More detailed analyses including

cell-mediated responses are needed to confirm the optimal timing and schedules for these and emerging SARS-CoV-2 vaccines to best protect allo-HCT recipients and other immunocompromised individuals. Vaccination of household contacts and healthcare workers and the need for continued shielding at times of high community prevalence may be necessary to protect these patients in conjunction with vaccination. Repeated booster doses with serial monitoring for vaccine response in initial nonresponders also may be required. Access to revaccination for allo-HCT recipients who have received COVID-19 vaccination before transplantation is a priority, as post-transplantation, these patients would be considered vaccine-naïve.

These findings highlight the need for novel immunogenic vaccine formulations and schedules in these highest-risk patients, as well as continued public health safety measures to protect the most vulnerable members of our society. It is essential to include older individuals and patients with underlying cancer diagnosis and/or those on immunosuppression in prospective vaccine studies to fully inform global vaccination strategies against COVID-19.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jctc.2021.07.011.

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