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Safety and Tolerability of SARS-CoV2 Emergency-Use Authorized Vaccines for Allogeneic Hematopoietic Stem Cell Transplant Recipients

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ABSTRACT

The safety and efficacy of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) emergency-use authorized (EUA) vaccines have been confirmed in the general population. However, there are no data on its safety and tolerability or efficacy in recipients of allogeneic hematopoietic stem cell transplant (HCT). We performed this study to identify the incidence of adverse events following SARS-CoV2 EUA vaccines, the incidence of new-onset graft-versus-host disease (GVHD) or worsening of existing GVHD after EUA vaccine administration, and the incidence SARS-CoV2 positivity in vaccinated HCT patients. We retrospectively reviewed 113 HCT patients who received at least one dose of EUA vaccine to describe the safety and tolerability, any impact on GVHD, and the incidence of SARS-CoV2 PCR positivity after vaccination. Patients received either Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines. Patients were included if they were 18 years or older and had received at least one dose of vaccine in the post-HCT setting. Most patients presented with myalgias/arthralgias (first dose, 7.7%; second dose, 14.6%), fatigue (first dose, 15.4%; second dose, 29.2%), and injection site pain (first dose, 40.4%; second dose, 43.8%). Other side-effects experienced by patients included nausea, vomiting, diarrhea, headache, and injection-site rash and swelling. Liver function abnormalities occurred in 18.6% of patients. Neutropenia, thrombocytopenia, and lymphopenia occurred in 13.3%, 11.5%, and 8.8% of patients, respectively. Forty percent of patients had active chronic GVHD at the time of vaccination, and worsening chronic GVHD occurred in 3.5% of the patients. New chronic GVHD developed in 9.7% of patients after vaccination. The SARS-CoV2 EUA vaccines were well tolerated in allogeneic HCT recipients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is a novel coronavirus emerging from Wuhan, China, that can cause severe respiratory illness and a myriad of other complications now referred to as COVID-19. This disease was declared a pandemic by the World Health Organization in March 2020 and has affected hundreds of millions of people worldwide [1]. COVID-19 clinical presentations can vary greatly among patients, and those who are at highest risk for severe illness that could lead to hospitalization and/or death include older age, obesity, diabetes, and an immunocompromised state, among other conditions [2].

Since December 2020, three vaccines have been approved under an Emergency Use Authorization (EUA) protocol in the United States: Pfizer-BioNTech COVID-19 (BNT162b2) messenger RNA (mRNA) vaccine, Moderna COVID-19 (mRNA-1273) mRNA vaccine, and Johnson & Johnson/Janssen (Ad26.COV2.S) adenovirus vaccine.

The Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 vaccines are both formulated as a lipid nanoparticle-encapsulated mRNA encoding the SARS-CoV2 prefusion-stabilized full-length spike protein. Both mRNA vaccines are a two-dose series separated by 21 days or 28 days, depending on which vaccine is administered. Both the Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 vaccines had greater than 90% efficacy with tolerable safety profiles [3-7]. Among BNT162b2 recipients, 26.7% reported adverse events compared with 12.2% of those receiving a placebo; these adverse events included local injection site reactions, pyrexia, fatigue, chills,

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myalgia/arthralgia, nausea, and headache [3-5,8]. Similarly, mRNA-1273 had higher solicited adverse events compared with placebo with grade 3 or 4 systemic adverse events occurring in 15.8% of recipients after the second dose of vaccine, with manifestations like those reported for BNT162b2 [6-8]. These two EUA vaccines in registration clinical trials had very low rates of serious adverse effects.

Cancer is a risk factor for developing severe COVID-19, which can be attributed to immunosuppression from the underlying disease and/or therapeutic interventions for treating the cancer [9]. In particular, among patients with hematologic malignancy and hematopoietic stem cell transplant (HCT) recipients, the mortality from COVID-19 is significantly higher than in the general population [10-12]. The risk of increased mortality can be due to various factors, such as type of hematologic malignancy, chemotherapy regimens used, neutropenia, lymphopenia, type of conditioning regimen used in preparation for HCT, ongoing immunosuppressive medications for the prevention of graft-versus-host disease (GVHD), or active treatment of GVHD after HCT [13,14]. None of the clinical trials of SARS-CoV2 EUA vaccines included immunocompromised patients, specifically HCT recipients [3-7]. Prevention of COVID-19 in HCT recipients is the key intervention and requires a multifaceted approach. The best intervention would be vaccinating healthy caregivers, but that was not a reality due to the initial vaccine shortage during the pandemic. Furthermore, the National Comprehensive Cancer Network, American Society for Transplantation and Cellular Therapy, and American Society of Hematology have recommended vaccinating allogeneic HCT patients based on specific guidance relating to time from HCT and other factors. The decision making is complex when compared with the general population, as the provider must balance the patient's higher risk for severe COVID-19 due to immunosuppressed state against the likelihood of a poor vaccine response [15,16]. Currently, there is no information on the safety of EUA vaccines in HCT patients and the potential impact on GVHD.

Given the lack of safety and tolerability data in the HCT population, we performed this study to identify the incidence of adverse events following SARS-CoV2 EUA vaccines. We also reviewed the incidence of new-onset GVHD or worsening of existing GVHD after EUA vaccine administration and the incidence of SARS-CoV2 positivity in vaccinated HCT patients.

MATERIALS AND METHODS

Study Design

This retrospective study was performed at City of Hope National Medical Center, which collected data from electronic medical records to identify HCT patients who received at least a dose of SARS-CoV2 EUA vaccine between December 2020 and April 2021. Patients at our institution during the study period could only receive the Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines. Inclusion criteria included patients 18 years of age or older and who had received at least one dose of vaccine in the post-HCT setting. There were no exclusion criteria. Additional details about potential side-effects following vaccination were gathered by voluntary COVID-19 vaccine surveys (see Supplementary Figure S1) offered to patients by their physicians that were entered into the patients' medical records. Patients were required to have at least one physician follow-up assessment after a minimum of 1 week following the first dose of vaccine; in addition, only physician assessments within 40 days after receiving their last dose of vaccine were included in the analysis. The initial follow-up period was intended to be 30 days, but due to the retrospective nature of this study it had to be extended to 40 days to ensure adequate capture of physician assessments following vaccination. This study was approved by an institutional review board.

Endpoints and Definitions

The primary endpoint was the incidence of patient-reported and clinical laboratory adverse events from the BNT162b2 or mRNA-1273 vaccines up to 40 days after the final vaccine dose. Patient-reported adverse events required documentation by a physician of vaccine tolerability or a response to a voluntary COVID-19 survey from the patient to be considered evaluable. The incidence rate was reported based on the vaccination dose received by the patient. The severity of patient-reported adverse events (e.g., fevers, myalgias) could not be graded by Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, due to insufficient details regarding severity in the physician documentation to appropriately grade these adverse events. As a result, patient-reported adverse events were reported as incidence rates. Baseline laboratory parameters such as white blood cell count, absolute neutrophil count, absolute lymphocyte count, platelets, eosinophils, serum creatinine, and liver function tests were collected. Abnormalities in laboratory parameters following vaccination were documented, and severity was graded using CTCAE v5.0 for newly developed abnormalities or worsening of severity from baseline after vaccination; the highest grade was used for analysis. Grading for acute GVHD using the Mount Sinai Acute GVHD International Consortium criteria or for chronic GVHD using the National Institutes of Health consensus criteria was not consistently available in physician documentation. Therefore, the incidence of new or worsening of GVHD was determined based on documentation in the electronic medical record of an intervention for GVHD, such as increasing the dose of current GVHD medications not due to subtherapeutic levels or initiation of a medication to treat GVHD. The onset of new or worsening GVHD was required to have occurred within 40 days of receiving the last vaccine dose to be included in the study results. Clinical laboratory adverse event and GVHD incidences were reported as cumulative rates. The incidence of positive SARS-CoV2 viral infection, symptomatic COVID-19 infection, and/or COVID-19 complications following vaccination was collected throughout the study period with frequency of testing based on institutional policies and physician discretion. A SARS-CoV2 test was deemed positive if a nasal swab, nasopharyngeal swab, or saliva tested positive for SARS-CoV2 via nucleic acid amplification, or antigen test [17,18].

RESULTS

Patient Characteristics

There were 113 patients who met inclusion criteria with baseline characteristics summarized in Table 1. Eight patients

Table 1
Baseline Characteristics of Patients Included in Analysis

Characteristic	Value
Age at vaccination (yr), median (range)	66.5 (22-77)
Days after transplant at vaccination, median (range)	588 (100-11,004)
Vaccine received, *n* (%)	
BNT162b2 (Pfizer-BioNTech)	49 (43.4)
mRNA-1273 (Moderna)	64 (56.6)
Sex, *n* (%)	
Male	78 (69.0)
Female	35 (31.0)
Primary diagnosis at HCT, *n* (%)	
Acute myeloid leukemia	51 (45.1)
Acute lymphocytic leukemia	9 (8.0)
Myelodysplastic syndromes	20 (17.7)
Myelofibrosis	18 (15.9)
Other	15 (13.3)
Donor type, *n* (%)	
Matched related	26 (23.0)
Matched unrelated	53 (46.9)
Mismatch unrelated	15 (13.3)
Haploidentical	19 (16.8)
Immunosuppressant for GVHD, *n* (%)	
Yes	74 (65.5)
No	39 (34.5)
Corticosteroid use for GVHD, *n* (%)	15 (13.3)
Prior COVID-19 positive test, *n* (%)	4 (3.5)
Completed patient survey to assess tolerability, *n* (%)	36 (31.9)
Time to survey response after first dose (d), median (range)	35 (2-108)

did not have a documented second dose in the electronic medical record and as a result were only followed for 40 days after the first vaccine dose. Median age at vaccination was 66.5 years (range, 22-77), with a median of 588 days (range, 100-11,004) post-HCT at the time of vaccination. Patients received either the BNT162b2 (43.4%) or mRNA-1273 (56.6%) vaccine. At the time of the first dose of the vaccine, 65% of patients were on immunosuppressants for the prevention or treatment of GVHD, with 13.3% of those patients on a corticosteroid at a median dose of 5 mg/day (range, 1.25-30). Four patients had a history of positive SARS-CoV2 test via PCR prior to vaccination. Of the four patients with a positive test, two tested negative by PCR prior to vaccination, and the status of the other two was not known. Median follow-up for patients who received both vaccines was 49 days (range, 12-70), with a median of two physician assessments (range, 1-13) to evaluate for safety.

Patient-Reported Adverse Effects

Only 36 of the 113 patients (31.9%) responded to the survey to assess adverse effects after vaccination was completed. The median time to survey response from the first dose of vaccine received was 35 days (range, 2-108). In addition to these 36 patients, physician documentation of patient-reported adverse events occurred in 16 patients during their first dose and 12 patients during the second dose of vaccine, which resulted in 52 and 48 patients being evaluable, respectively. As summarized in Table 2, the major adverse events experienced by patients were myalgias, arthralgias, fatigue, and injection site pain. Due to varying physician practices and inconsistent frequency of laboratory monitoring, resolution times of toxicities may have been overestimated and are not presented here. Rates of myalgia and arthralgia from the first dose and the second dose of vaccine were reported to be 7.7% and 14.6%, respectively. There was a difference in rate of fatigue between the first and second dose, with the incidence of fatigue being 13.8% higher after the second dose. Injection site pain after the first and second doses occurred in 40.4% and 43.82% of the patients, respectively, which was much lower than reported with the registration trial for BNT162b2 (71%-83% for the first dose and 66%-78% for the second, depending on age) and mRNA-1273 (83.7% for the first dose and 88.2% for the second dose) [3-7]. Other side-effects experienced by patients included nausea, vomiting, diarrhea, headache, and injection-site rash and swelling. One patient had axillary lymphadenopathy on the arm of the injection site, and another patient experienced increased blood pressure and tachycardia shortly after receiving the vaccine.

Table 2
Patient-Reported Adverse Effects After **COVID-19** Vaccination

	n (%)	
	First Dose (*N* = 113)	Second Dose (*N* = 105)
Evaluable patients, *n* (%)	52 (46.0)	48 (45.7)
Fever		
Yes	1 (2.0)	2 (4.2)
No	51 (98.0)	46 (95.8)
Chills		
Yes	2 (3.8)	2 (4.2)
No	50 (96.2)	46 (95.8)
Myalgias/arthralgias		
Yes	4 (7.7)	7 (14.6)
No	48 (92.3)	41 (85.4)
Fatigue		
Yes	8 (15.4)	14 (29.2)
No	44 (84.6)	34 (70.8)
Injection site pain		
Yes	21 (40.4)	21 (43.8)
No	31 (59.6)	27 (56.2)
Other symptoms		
Yes	8 (15.4)*	8 (16.7)†
No	44 (84.6)	40 (83.3)

* Included nausea, vomiting, diarrhea, headache, and rash, as well as a patient developing pneumonia.

† Included nausea, vomiting, diarrhea, gastrointestinal upset, injection site rash and swelling, axillary lymphadenopathy, headache, and change in taste, as well as a patient who had hypertension/tachycardia.

Clinical Laboratory Adverse Effects

The cumulative incidence rates of clinical laboratory adverse events for all patients who received at least one dose of vaccine are summarized in Table 3. As mentioned previously, eight patients received only one dose of vaccine and had

Table 3
Clinical Laboratory Adverse Effects After COVID-19 Vaccination

Adverse Effect	Incidence
Hepatic impairment, *n* (%)	21 (18.6)
Grade 1	16 (14.2)
Grade 2*	3 (2.6)
Grade 3	1 (0.9)
Grade 4*	1 (0.9)
Time to evaluation of hepatic impairment (d), median (range)	26 (3-66)
Neutropenia,† *n* (%)	15 (13.3)
Grade 1	6 (5.3)
Grade 2	5 (4.5)
Grade 3	0 (0)
Grade 4†	4 (3.5)
Time to evaluation of neutropenia (d), median (range)	20.5 (3-49)
Thrombocytopenia, *n* (%)	13 (11.5)
Grade 1	6 (5.3)
Grade 2	3 (2.6)
Grade 3‡	2 (1.8)
Grade 4‡	2 (1.8)
Time to evaluation of thrombocytopenia (d), median (range)	34 (6-66)
Lymphopenia, *n* (%)	10 (8.8)
Grade 1	3 (2.7)
Grade 2	3 (2.7)
Grade 3§	4 (3.5)
Grade 4§	0 (0)
Time to evaluation of lymphopenia (d), median (range)	19.5 (10-55)
Eosinophilia, *n* (%)	5 (4.4)
Time to evaluation of eosinophilia (d), median (range)	28 (13-58)

* Two out of the three patients with grade 2 hepatic impairment had baseline grade 1 hepatic impairment. The patient with grade 4 hepatic impairment had baseline grade 1 hepatic impairment prior to receiving the vaccine and had recently been started on azole for antifungal prophylaxis.

† Five patients were actively on chemotherapy, and three patients experienced grade 4 neutropenia.

‡ Two patients were actively on chemotherapy; one patient experienced grade 3 and another experienced grade 4 thrombocytopenia. One patient had baseline grade 2, and another had baseline grade 3 thrombocytopenia prior to receiving vaccine.

§ All patients with grade 3 and 4 lymphopenia had baseline lymphopenia prior to receiving the vaccine.

Table 4
Summary of Reported Cases of New or Worsening GVHD Incidences After Vaccination

	Active GVHD Prior Vaccine (Location)	Onset After Vaccination (d)	Worse/New	Location	Intervention
67-yr-old male; MDS s/p MUD day +1041	No	3	New	Skin	Started prednisone 40 mg daily, mycophenolate, and sirolimus
73-yr-old male; AML s/p MUD day +346	Yes (GI)	11	Worse	GI	Started prednisone 60 mg daily × 1 week
70-yr-old male; myelofibrosis s/p MUD day +622	Yes (oral)	21	Worse	Oral	Increased tacrolimus dose and frequency of dexamethasone oral rinses
42-yr-old female; MDS s/p haplo day +744	Yes (skin)	10	New	Oral	Started prednisone 40 mg daily and resumed tacrolimus
68-yr-old male; ALL s/p MUD day +2358	Yes (skin/GI/eye)	30	New	Lung	Started methylprednisolone 1 mg/kg/d and ruxolitinib; transitioned from steroid to etanercept
49-yr-old male; myelofibrosis s/p MUD day +1098	Yes (skin/joints)	21	New/worse	Skin/joints/GI	Enrolled in GVHD investigational protocol
74-yr-old male; myelofibrosis s/p MUD day +313	No	31	New	Skin/oral	Started prednisone 40 mg daily, ruxolitinib, and dexamethasone rinses
65-yr-old female; MDS s/p MMUD day +323	No	39	New	Skin/oral/eye	Started prednisone 30 mg twice a day; restarted tacrolimus and increased sirolimus dose
65-yr-old female; T cell LGL s/p haplo day +459	No	55	New	Skin	Started triamcinolone 0.5% ointment
66-yr-old male; AML s/p MRD day +194	No	34	New	Eye	Started prednisolone 1% eye drops
77-yr-old male; myelofibrosis s/p MUD day +1669	No	31	New	Skin	Started triamcinolone 0.1% ointment
71-yr-old male; MDS s/p MUD day +216	Yes (skin/oral/eye)	44	New/worse	GI/oral/eye	Started prednisone 30 mg daily, budesonide, and tacrolimus; eye plugs placed
75-yr-old female; AML s/p MUD day +160	Yes (oral/eye)	48	New	GI	Switched from dexamethasone rinses to budesonide

MDS indicates myelodysplastic syndromes; MUD, matched unrelated donor; s/p, status post; AML, acute myeloid leukemia; GI, gastrointestinal; ALL, acute lymphocytic leukemia; MMUD, mismatched unrelated donor; haplo, haploidentical; LGL, large granular lymphocytic leukemia; MRD, matched related donor.

no documented second dose in the electronic medical record. Hepatic impairment was observed in 21 of 113 patients (18.6%), with a median of 26 days (range, 3-66) to evaluation of adverse events, which were defined as an elevation in bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) after the first vaccination. One patient with baseline grade 1 hepatic impairment who had recently started on an azole for antifungal prophylaxis experienced a grade 4 increase in AST and grade 3 increase in ALT, which occurred 26 days after his only dose of vaccine; the levels returned to baseline approximately 1 week later after discontinuation of the azole. Another patient experienced a grade 3 increase in both ALT and AST that occurred 4 days after the second dose of vaccine. This patient was initiated on prednisone and ruxolitinib for new-onset GVHD of the skin and mouth on evaluation, and eventually liver toxicity resolved within a month. The incidence rates for neutropenia, thrombocytopenia, and lymphopenia were 13.3%, 11.5%, and 8.8%, respectively. Seven patients who experienced bone marrow suppression were actively being treated with chemotherapy at the time; six of the patients were being treated for relapse, and one was on maintenance post-HCT. Five patients experienced eosinophilia while being vaccinated, with one patient requiring urgent care for the treatment of pneumonia at the time of eosinophilia.

Impact on GVHD

Prior to the first dose of vaccine, baseline chronic GVHD was present in 39.8%, mostly with skin (68.9%) and oral (37.8%) involvement. Table 4 provides a summary of all of the cases of new or worsening GVHD after vaccination. New chronic GVHD developed in 9.7% of patients, and worsening chronic GVHD occurred in 3.5% of patients; two patients experienced both new and worsening of GVHD symptoms. One patient with a previous history of chronic GVHD of the eyes, skin, and gut required hospitalization for approximately 18 days after his only dose of BNT162b2; his suspected GVHD of the lung was treated with the initiation of etanercept. All of these patients with new or worsening chronic GVHD symptoms are currently well controlled, with symptoms either improving or being resolved in subsequent follow-up assessments.

DISCUSSION

Both mRNA vaccines, BNT162b2 and mRNA-1273, were found to be safe and efficacious in the general population. The major adverse effects reported in the phase II/III study by Polack et al. [3] among patients who experienced an adverse event with BNT162b2 were injection site pain (66%-83%), fatigue (34%-59%), headache (25%-52%), fever (1%-16%), chills (6%-35%), and muscle pain (14%-29%), and they depended on a patient's age and whether or not they occurred after the first or second dose [4,5]. Similarly, in a Phase III study, Baden et al. [6] reported that the mRNA-1273 vaccine resulted in high injection site pain (74%-90.1%), fatigue (33.3%-67.6%), headache (24.5%-62.8%), fevers (0.3%-17.4%), chills (5.4%-48.3%), and myalgias (6.1%-23.7%), based on criteria similar to those for the BNT162b2 population [7]. Significantly worse adverse events were reported after the second dose for each of the vaccines. Our safety results in the allogeneic transplant patient population are comparable to the safety results found in the clinical studies submitted to the US Food and Drug Administration for emergency use authorization for both vaccines. Unfortunately, our data did not include Ad26.COV2.S, which does not allow us to make any conclusions regarding the safety of this vaccine in this specific population. Only two patients

tested positive for SARS-CoV2 by PCR after receiving the vaccine, which was believed to be due to viral shedding, as these patients had a prior history of SARS-CoV2 infection and were asymptomatic, requiring no hospitalization. The adverse events reported in BNT162b2 and mRNA-1273 registration trials remained the prominent ones in our study, with a caveat that they occurred at lower rates. This could be due to a low survey response rate and possibly recall bias from the patients who did complete the survey, which was not in real time, as patients tend to only report more severe adverse events to physicians unless in a clinical trial setting. Another potential explanation of lower incidence rates of adverse events could be an impaired immune response to the vaccine in the HCT population, as a significant proportion of vaccine recipients had active chronic GVHD. The required uptake of mRNA from BNT162b2 or mRNA-1273 by dendritic cells to encode for the necessary spike protein and ability to mobilize adaptive immunity via T cells and B cell lymphocytes toward COVID-19 might be suboptimal in HCT patients, as immune function might not normalize until a year after HCT and might further be delayed by GVHD and its treatment [19,20].

Approximately 12% of patients in our study had worsening of baseline chronic GVHD or development of new-onset chronic GVHD after vaccination. Currently, there are very few studies evaluating the relationship between vaccines and the incidence of GVHD. A study published by Natori et al. [21] reported an incidence of new or worsening GVHD in approximately 26% of patients who received the influenza vaccine but did not have a comparator group. Baumrin et al. [22] analyzed the effect of the recombinant zoster vaccine on GVHD incidence and observed no significant difference. We also observed a few cases of eosinophilia and hepatic impairment that occurred after the vaccination; however, it is difficult to ascribe causality to the vaccines due to the retrospective nature of this study. Messenger RNA vaccines can be highly immunogenic, and in the clinical trials younger populations had more robust immune responses, as suggested by higher rates of adverse events, and the same biologic effect can be seen in our HCT patients. However, with ongoing immunosuppression and high incidence of chronic GVHD, the rates of some adverse effects were less in our patients. Because of the high immunogenicity from the vaccines, activation of inflammatory pathways might lead to immune-related adverse events even in this immunocompromised patient population.

Our study had several limitations. It is retrospective in nature and had a small sample size. A low survey response rate due to its voluntary nature, recall bias, and the use of physician documentation when survey responses were unavailable were also limitations to obtaining detailed descriptions of patient-solicited local and systemic adverse events. In addition, the smaller than expected sample size might have impacted patient-reported outcomes, which could have led to a lower solicited adverse event rate compared with published studies. Laboratory results were not collected at consistent time frames, and the frequency of collection was driven by the patient's overall clinical management rather than routine monitoring relative to vaccination. With a median of only two physician assessments to evaluate for adverse events, this could have potentially affected the results regarding the incidence of laboratory adverse events and the time to onset of clinical laboratory adverse events relative to vaccination. However, our results do provide some clarity regarding the safety and tolerability of mRNA EUA vaccines in HCT patients. More comprehensive studies are needed regarding the safety of SARS-CoV2 vaccines in the HCT population, especially from the standpoint of predicting the risk of GVHD, whether new-onset or worsening of baseline GVHD, with these novel vaccines using mRNA, as well as how to provide patient education regarding the risks. Of further importance is assessing immunogenicity of vaccines when given early after HCT or later, especially in the context of existing guidelines for vaccinating HCT patients including SARS-CoV2 in the setting of the pandemic [23-25]. Our study provides much-needed preliminary data indicating that both EUA mRNA vaccines are safe and well tolerated in allogeneic HCT populations, despite some major limitations of our study.

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SUPPLEMENTARY MATERIALS

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