CORRESPONDENCE

Prospective longitudinal study of kinetics of humoral response to one, two, or three doses of SARS-CoV-2 vaccine in hematopoietic cell transplant recipients

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TO THE EDITOR:

Cancer is an established risk factor for poor outcomes with SARS-CoV-2 disease 2019 (COVID-19) [1]. Patients with a hematologic malignancy have increased mortality and rates of decompensation and hospitalization compared to solid tumors [1]. Recipients of hematopoietic cell transplant (HCT) are at a higher risk of severe disease and death from COVID-19 [2]. Although specific biomarkers associated with protection from SARS-CoV-2 infection have yet to be identified, measurement of neutralizing antibody (NAb) activity is generally accepted as a surrogate of vaccine effectiveness [3]. Degree and durability of antibody response to one, two or three doses of SARS-CoV-2 vaccination in HCT recipients is incompletely known and may correlate to infection outcomes. To better understand the protective immunity from COVID-19 vaccines, longitudinal studies are necessary to investigate the kinetics of antibody response after vaccination and effect of individual characteristics on such responses.

METHODS

We conducted a prospective, longitudinal study to evaluate the degree and durability of anti-spike protein receptor binding domain (anti-S RBD) and NAb response to SARS-CoV-2 vaccine in patients with cancer. We here present the HCT cohort. This study was approved by the Institutional Review Board of the University of Kansas Medical Center. Subjects enrolled in this cohort were ≥18 years, recipients of an autologous (auto) or allogeneic (allo) HCT and received, or were planning to receive one of the available vaccines: Comirnaty (Pfizer), AD26.COV2.S (J&J) or Spikevax (Moderna). At study start, unvaccinated patients were eligible. Because of rapid vaccine availability, the protocol was later amended to include partially and fully vaccinated patients. To get a real-world representation of the cancer population, patients with prior COVID-19 were not excluded. Blood specimens were collected before first vaccine dose (B1D), before second dose (B2D), 1 month (1mA2D), 3 months (3mA2D) and 6 months (6mA2D) after the second dose. For AD26.COV2.S, blood collections were 1 month, 2 months, 4 months and 7 months after dosing. Once a third dose was approved for cancer patients, blood was collected 1 month following dosing (1mA3D).

Measurements of anti-S RBD (U/ml) and NAb (neutralization %) were performed using the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay and the SARS-CoV-2 Surrogate Virus Neutralization Test (SVNT) assay (GenScript), respectively. Primary endpoint was geometric mean titers (GMTs) of anti-S RBD antibodies. An analysis was also performed at 1mA2D on the variables of age, donor type, underlying malignancy, HCT comorbidity index, type of graft-versus-host disease (GVHD) prophylaxis, GVHD treatment, and corticosteroid (CS) use.

RESULTS

Between 3/2/2021 and 11/30/2021, 126 patients enrolled, 79% allo-HCT and 21% auto-HCT. Median age was 59.5 (19–78) years, and 56% were male. Of the 118 patients with available pre-enrollment COVID-19 PCR testing data, three had confirmed infection. Median time from transplant to first vaccine dose was 440 days. A total of 312 samples were collected (Fig. 1a). Median time between the second and third vaccine doses was 154 days. GMTs of the anti-S RBD for all patients are shown in Fig. 1a. The proportion of patients with anti-S RBD ≥ 100 U/ml was 13.5%, 13.8%, 65.8%, 74.7%, 72.4% and 90.6% B1D, B2D, 1mA2D, 3mA2D, 6mA2D and 1mA3D respectively. Rate of seropositivity (anti-S RBD ≥ 0.8 U/ml) was 40.5%, 58.6%, 92.4%, 97.5%, 93.1% and 98.1% B1D, B2D, 1mA2D, 3mA2D, 6mA2D and 1mA3D, respectively. Mean percent neutralization by SVNT was 2.6%, 7.5%, 79.0%, 72.3%, 62.5% and 89.4% B1D, B2D, 1mA2D, 3mA2D, 6mA2D and 1mA3D, respectively (Fig. 1b). Correlates of GMTs 1 month after the second dose of vaccine were explored by univariate analysis. Patients aged ≤50 years had a GMT of 677.3 U/ml compared to 226.3 U/ml and 314.9 U/ml in those 51–65 and >65 [GMT ratio 0.33 (95% CI, 0.12–0.97) and 0.46 (95% CI, 0.12–1.82), respectively]. Auto-HCT recipients had higher GMTs compared to allo-HCT [GMT ratio 0.22 (95% CI, 0.1–0.51)]. Time from transplant to initial vaccination >12 months was associated with higher GMTs compared to ≤6 months [GMT ratio 5.98 (95% CI, 2.08–17.2)] (Table 1). Patients on immunosuppressive therapy (IST) during their primary vaccination series had lower GMTs compared to patients not on IST [GMT ratio 0.11 (95% CI, 0.03–0.38)]. Recipients of a mRNA vaccine had higher GMTs than those receiving J&J 1mA2D (Table 1), however GMTs did not significantly differ 3mA2D for Pfizer compared to Moderna or J&J [GMT ratio 2.19 (95% CI, 0.72–6.66) and 2.08 (95% CI, 0.57–7.52) respectively].

DISCUSSION

Our study showed that after two doses of vaccine in HCT recipients, anti-S RBD GMTs peak at 3 months with modest decline at 6 months, whereas NAb activity peaks at 1 month with steady decline around 6 months. It should be noted these numbers represent a noticeable blunted response compared to the general

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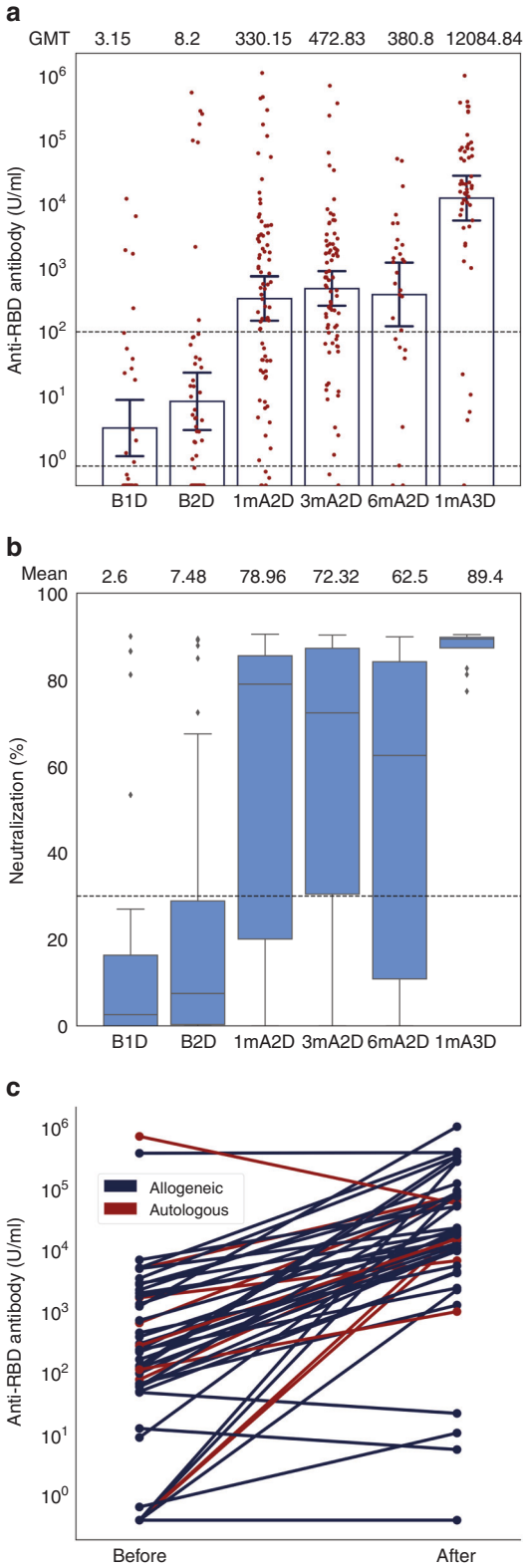

Fig. 1 Anti-Spike Protein Receptor Binding Domain (Anti-S RBD) and Neutralizing Antibody Response to Vaccines. a Anti-S RBD titers for all patients by timepoints. The anti-S RBD antibody titers for all 126 patients. In total, 342 blood samples were collected for antibody testing (37 before first vaccine dose, 58 before second dose, 79 1 month after second dose, 79 3 months after second dose, 29 6 months after second dose and 53 1 month after the third dose). Each dot represents a patient sample. The horizontal axis represents time points for the collection of samples: before first vaccine dose (B1D), before second dose (B2D), 1 month after second dose (1mA2D), 3 months after second dose (3mA2D), 6 months after second dose (6mA2D) and 1 month after the third dose (1mA3D). The lower horizontal dashed line represents seropositivity (0.8 U/ml) and the upper horizontal dashed line, the threshold value of 100 U/ml. The bars represent Geometric Mean Titers (GMTs) with 95% confidence intervals (whiskers). GMTs are also displayed numerically. There is a 36-fold increase in titers one month after the 3rd dose, compared to titers 1 month after completion of the primary vaccination. **b** Neutralization in all patients by timepoints. Box-and-whisker plots of the percent neutralization using the Surrogate Viral Neutralization Test (SVNT). The horizontal axis represents time points for the collection of samples: before first vaccine dose (B1D), before second dose (B2D), 1 month after second dose (1mA2D), 3 months after second dose (3mA2D), 6 months after second dose (6mA2D) and 1 month after the third dose (1mA3D). The whiskers indicate the range, the boxes indicate the interquartile range and the horizontal line within each box indicates the median. The dots represent the outliers. The horizontal dashed line represents threshold of neutralization (30%). Mean percent neutralization was 2.6% B1D, 7.48% B2D, 78.96% 1mA2D, 72.32% 3mA2D, 62.5% 6mA2D and 89.4% 1mA3D. **c** Anti-S RBD titers before and after third dose of a mRNA vaccine. The anti-S RBD antibody titers before and 30 days after receiving a third dose of SARS-CoV-2 vaccine. The "before" are the last antibody titers prior to the third dose. The median time between the second and third vaccine doses was 154 days. Each line represents a patient. Red lines represent auto-HCT and blue lines allo-HCT. In total, 36 out of 53 (68%) patients had anti-RBD above the threshold of 100 U/ml before the third dose compared to 49 out of 53 (92%) after the third dose.

population [4]. Antibody response following a third vaccine dose was pronounced with a >30-fold increase in anti-S RBD titers compared to titers after primary vaccination (Fig. 1a, c) and a 30% increase in neutralization capacity (Fig. 1b). These findings suggest memory B-cells are functional in these subjects as in non-HCT patients [5]. The longitudinal nature of this study demonstrates that low antibody responses early post-vaccination do not always correlate to low titers at later timepoints in terms of robustness of response or rate of surrogate viral neutralization. While this study did not review breakthrough infections or cellular immunity, it should be noted that in the setting of a prolonged pandemic, with knowledge that NAbs can improve infection severity and duration, evidence of sustained antibody response is valuable and has utility for timing of vaccination after HCT [6]. To capture a real-world snapshot of this population, patients with a prior SARS-CoV-2 infection were included. Baseline (pre-vaccination) anti-RBD seropositivity rate was 40%, and 14% of the patients had Neutralization activity of >30%, reflecting differences in the sensitivity of the two assays [7, 8].

We identified several risk factors for poor humoral response to SARS-CoV-2 vaccination, including age >50 years, allo-HCT recipients, vaccination within 1 year since HCT, and GVHD requiring IST. These data demonstrate a common theme that immunosuppression is the major determinant of the immunogenicity of SARS-CoV-2 vaccination whether due to transplant type, time since transplant, or use of IST with or without CS. Allo-HCT patients on high-dose CS or with GVHD have historically been excluded from SARS-CoV-2 vaccination studies, however, this subset of patients represents the most fragile HCT recipients [9, 10]. Patients should be screened for risk factors for poor vaccine response and be followed appropriately. Specifically, those at an elevated risk, i.e., are of older age, recipients of allo-HCT, HCT within 12 months, or on IST including CS [2, 11]. As the vaccines have been shown to have minimal toxicity in this population, they should be offered to all eligible HCT patients

Table 1. Analysis of Demographics, Disease and Treatment Variables Associated with Anti-S RBD Antibody 1 Month After the Second Vaccine Dose.

All patients				
Characteristic	*N* (%)	1 month after 2nd vaccine dose (1mA2D)		
		N at (79)	GMT (95% CI) (U/ml)	GMT ratio (95% CI)
Age (years)				
≤50	32 (25)	23	677.29 (118.93, 3857.24)	Reference
51–65	63 (50)	42	226.29 (77.95, 656.93)	0.33 (0.12, 0.97)
>65	31 (25)	14	314.9 (80.55, 1231.02)	0.46 (0.12, 1.82)
Vaccine				
Pfizer	68 (54)	40	393.22 (142.45, 1085.44)	Reference
Moderna	50 (40)	34	360.33 (88.87, 1461.03)	0.92 (0.23, 3.72)
J&J	6 (5)	5	44.99 (27.19, 74.43)	0.11 (0.07, 0.19)
Sex				
Female	55 (44)	36	319.66 (94.35, 1083.03)	Reference
Male	71 (56)	43	339.2 (117.87, 976.12)	1.06 (0.37, 3.05)
Transplant type				
Autologous	26 (21)	10	1234.72 (113.67, 13412.45)	Reference
Allogeneic	100 (79)	69	272.7 (117.81, 631.28)	0.22 (0.1, 0.51)
Hematologic malignancy[a]				
AML + MDS	66 (52)	47	219.54 (81.49, 591.43)	Reference
Multiple Myeloma	18 (14)	6	2147.72 (161.87, 28497.24)	9.78 (0.74, 129.8)
ALL	13 (10)	11	812.41 (69.52, 9493.75)	3.7 (0.32, 43.24)
CLL + Lymphoma	22 (17)	11	363.32 (38.44, 3433.53)	1.65 (0.18, 15.64)
Donor type[b]				
Matched sibling donor (MSD)	31 (25)	22	395.57 (80.26, 1949.73)	Reference
Haploidentical donor (Haplo)	28 (22)	19	152.05 (41.0, 563.95)	0.38 (0.1, 1.43)
Matched unrelated donor (MUD)	40 (32)	27	332.86 (77.98, 1420.74)	0.84 (0.2, 3.59)
Time to transplant				
≤6 months	31 (25)	23	156.87 (27.86, 883.23)	Reference
6–12 months	25 (20)	22	143.18 (36.03, 569.02)	0.91 (0.23, 3.63)
>12 months	68 (53)	34	937.81 (325.95, 2698.22)	5.98 (2.08, 17.2)
Allogeneic HCT Patients				
Characteristic	*N* (%)	1 month after 2nd vaccine dose (1mA2D)		
		N (69)	GMT (95% CI) (U/ml)	GMT ratio (95% CI)
HCT-Ci score[c]				
0	13 (13)	7	150.82 (21.88, 1039.52)	Reference
1–2	37 (37)	27	336.35 (77.87, 1452.76)	2.23 (0.52, 9.63)
3 or more	46 (46)	32	235.68 (67.64, 821.19)	1.56 (0.45, 5.44)
GVHD prophylaxis (post-HCT cyclophosphamide)				
No	74 (74)	51	354.81 (126.79, 992.89)	Reference
Yes	26 (26)	18	129.37 (33.72, 496.38)	0.36 (0.1, 1.4)
Any GVHD treatment				
No	54 (54)	35	795.16 (274.53, 2303.15)	Reference
Yes	46 (46)	34	90.63 (26.98, 304.42)	0.11 (0.03, 0.38)
GVHD treatment (Tacrolimus)				
No	83 (83)	55	386.87 (151.0, 991.2)	Reference
Yes	17 (17)	14	69.03 (12.15, 392.24)	0.18 (0.03, 1.01)
GVHD treatment (Sirolimus)				
No	98 (98)	67	326.91 (143.22, 746.22)	Reference
Yes	2 (2)	2	0.63 (0.26, 1.52)	0.0 (0.0, 0.0)
GVHD treatment (Ruxolitinib)				
No	86 (86)	58	364.95 (143.89, 925.62)	Reference
Yes	14 (14)	11	58.68 (10.57, 325.77)	0.16 (0.03, 0.89)
GVHD treatment (Corticosteroid)[d]				
No	79 (79)	55	378.1 (156.3, 914.66)	Reference
Yes	21 (21)	14	75.54 (8.41, 678.13)	0.2 (0.02, 1.79)

[a]Myeloproliferative neoplasms (2), Other (3), Hodgkin lymphoma (1) and Non-malignant heme (1) omitted from analysis.
[b]One subject with mismatched unrelated donor (MMUD) omitted from analysis.
[c]Four patients missing HCT-Ci score omitted from analysis.
[d]Defined as prednisone dose of at least 20 mg or equivalent at the time of the 2nd dose of SARS-CoV-2 vaccine.

without contraindications [12]. There are currently no recommendations for anti-S RBD or NAb monitoring and those at risk warrant close surveillance, continued vigilance with social distancing and masks, and aggressive management in case of infection. In conclusion, our study demonstrates that administration of a third mRNA vaccine dose yields a significant increase in anti-S RBD antibodies and neutralization capacity in HCT recipients. Older age, allo-HCT and IST are major determinants of low humoral immunogenicity to SARS-CoV-2 vaccination. More studies are needed to find the threshold of clinical efficacy of anti-S RBD titers and rates of viral neutralization especially in the setting of new variants and antigenic shift.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. The funders had no role in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

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COMPETING INTERESTS

AKG and ZYP are co-founders of Sinochips Diagnostics; PS serves as advisory board member and consultant to Merck, Novartis, Exact Sciences, Seattle Genetics, Immunomedics, Myriad Genetics, AstraZeneca, Puma Biotechnology; JZ served as a scientific advisor/consultant for AstraZeneca, Biodesix, Novocure, Bayer, Daiichi Sankyo, Mirati, Novartis, Cardinal Health, Bristol Myers Squibb, Nexus Health and Sanofi and is on the speakers' bureau for AstraZeneca and MJH Life Sciences and has received research funding from AstraZeneca, Biodesix, Novartis, Genentech/Roche, Mirati, AbbVie and Hengrui Therapeutics; GCD serves on an advisory board for Novartis; JPM serves as advisory board member and consultant to Novartis, Kite Pharmaceuticals, BMS and Allovir; MH received consulting fees from Janssen, Pharmacyclics, Novartis Inc., Kite Pharmaceuticals and TG therapeutics. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

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