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Original Research

A Phase I/II Randomized Trial of Higher Dose mRNA-1273 Boosters in Lung Transplant Recipients

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Abstract

Higher-dose mRNA booster vaccines have not been well studied for transplant recipients. This study evaluated the safety, reactogenicity and immunogenicity of higher dose mRNA-1273 booster vaccines among lung transplant recipients (LTRs). This phase 1/2 open-label randomized clinical trial of higher-dose mRNA-1273 booster vaccination enrolled nineteen adult LTRs into the 50 µg (n = 8) vs. 100 µg (n = 11) groups before enrollment was terminated due to the availability of the bivalent mRNA-1273.222 vaccine. Local and systemic reactogenicity was predominantly mild or moderate in severity for both dose groups, mostly limited to pain at the injection site, fatigue and headache. Humoral and cellular immune responses were weak. Overall, 75% and 64% of the 50 µg and 100 µg groups had detectable neutralizing antibodies on Day 30 (vs. 63% and 55% on Day 1), respectively. On Day 30, 50% and 55% had detectable spike-specific $CD4^+$ IFNγ responses (vs. 29% and 36% on Day 1), and 50% and 36% had detectable $CD8^+$ IFNγ responses (vs. 29% and 45% on Day 1) for the two groups, respectively. LTRs have reactogenicity and immune responses that are attenuated compared with the non-immunocompromised population. Administration of higher doses in solid organ transplant patients may be warranted. Clinical trial NCT05280158.

Keywords

SARS-CoV-2 vaccine; immune response; reactogenicity; lung transplantation; high dose vaccine; humoral immunogenicity; cellular immunogenicity

1. Introduction

Overall coronavirus disease 2019 (COVID-19) mortality has decreased since the start of the pandemic due to improvements in treatment, as well as infection and vaccine-induced immunity. Solid organ transplant recipients (SOTRs), however, remain at high risk for poor outcomes after SARS-CoV-2 infection despite receiving intensive vaccination regimens.

Lung transplant recipients (LTRs) in particular have fared poorly with the worst COVID-19 outcomes among SOTRs [1-3]. Due to the allograft's exposure to the external environment and active immune surveillance, LTRs generally require higher levels of immunosuppression than recipients of other types of solid organ transplants. Lung transplantation is also unique among the

solid organ transplants due to direct infection and injury of the allograft by SARS-CoV-2. A prospective multicenter cohort study of 509 SOTRs with COVID-19 between March 2020 to November 2021 found that LTRs (n = 48) had the highest mortality at 31%, compared to kidney (15%), heart (4%), liver (11%), and kidney-pancreas (12%) transplant recipients ($p < 0.02$) [4]. A retrospective single center cohort study of LTRs reported mortality rates of 34% (11 of 32 LTRs), 17% (8 of 47), and 12% (12 of 98) during the alpha, delta and omicron surges respectively [5].

In August 2021, the U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for the use of the mRNA-1273 as a third "primary" dose at 100 μgs for immunocompromised individuals. Starting October 2021, subsequent "booster" doses were granted EUA at 50 μgs for both immunocompromised and immunocompetent individuals. However, compared with immunocompetent participants, SOTRs have attenuated humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination. Studies have reported anti-SARS-CoV-2 IgG antibody detection after the second mRNA vaccine dose in only 34-54% of SOTRs [6-8] and less than 20% of LTRs [9-11]. Third dose vaccines appeared to improve humoral [12-14] and cellular [6, 12, 15] responses for solid organ recipients, but has not been studied specifically for LTRs.

Dose selection for the mRNA-1273 and the bivalent mRNA-1273.222 vaccines were based in part on phase 1 dose-escalation trials that demonstrated a dose-dependent increase in immunogenicity, but also dose-dependent reactogenicity [15-17]. Although one trial evaluated 40 older adults (age >70 years) [15], these dose-finding studies excluded SOTRs and the immunosuppressed. Given the expected differences in vaccine-induced reactogenicity and immunogenicity, dose-finding trials specific for SOTRs are warranted. This phase 1/2 study evaluated the safety, reactogenicity and immunogenicity of higher doses of the mRNA-1273 vaccine given as a booster (fourth or fifth) dose among LTRs.

2. Materials and Methods

With IRB approval (IRB#22-000192), we conducted a phase I/II open-label randomized clinical trial to determine the safety, reactogenicity and immunogenicity of higher dose (100 or 200 μg) mRNA-1273 booster vaccination among LTRs at the University of California, Los Angeles. Informed consent was obtained from all study participants. LTRs 18 years or older who previously received at least three doses of the mRNA-1273 or BNT162b2 vaccines were eligible. Participants were required to receive standard immunosuppression with a corticosteroid (minimum prednisone 5 mg), calcineurin inhibitor (tacrolimus), and an antimetabolite (minimum mycophenolate mofetil 250 mg twice daily or mycophenolate sodium 180 mg twice daily). Those with known prior SARS-CoV-2 infections and receipt of COVID-19 monoclonal antibodies (Evusheld) were excluded.

Sixty participants were scheduled to receive one of three booster vaccine doses (50, 100, or 200 μg) with a dose-escalation design. The first cohort was randomized to the 100 μg or 50 μg dose with 2:1 ratio. The second cohort was scheduled for randomization to the 200 μg or 50 μg dose with a 2:1 ratio. However, study enrollment was terminated after enrollment of 19 participants into the first cohort due to the availability of the bivalent mRNA-1273.222 booster. Subject randomization was performed by a statistician using a RedCap database.

2.1 Vaccine

mRNA-1273 doses were provided by Moderna in multi-dose vials at a concentration of 0.2 mg per milliliter.

2.2 Procedures

In-person study visits occurred on Days 1, 7 and 30. Telephone visits occurred on Days 3, 90 and 180. A daily diary was used to record local and systemic adverse reactions (ARs) based on the FDA Toxicity Grade Scale through Day 7. Unsolicited adverse events (AEs) reports were assessed at all study visits by structured interview and medical chart review through Day 28. Serious adverse events (SAE, Appendix 1) and Adverse Events of Special Interest (AESI, Appendix 2) were reported and assessed through Day 180.

Humoral immunogenicity was measured by the PhenoSense pseudovirus neutralization assay, using a lentiviral vector pseudotyped with SARS-CoV-2 D614G spike protein as previously described [18, 19] (Appendix 3). A detectable anti-SARS-CoV-2 neutralizing antibody (nAb) was defined as a nAb titer greater than three times titer of the specificity (false positive) control measured for each sample. Cellular immunogenicity against SARS-CoV-2 spike protein was measured by flow cytometry with ICS for IFNγ, IL-2 and TNFα as previously described with a 0.01% limit of detection [20] (Appendix 3).

2.3 Endpoints

The primary endpoint was safety and reactogenicity measured by the frequency, intensity and grade of solicited local and systemic ARs through Day 7, unsolicited adverse events (AEs) through Day 28, serious AEs (SAEs), and adverse events of special interest (AESIs) through Day 180. The secondary endpoints were humoral and cellular immunogenicity measured on Day 30.

2.4 Statistical Analysis

Descriptive statistics were used to summarize the frequency and grade of AEs. nAbs on Day 30 and the change between Days 1 (pre-vaccine) and 30 were compared between dose groups using T-tests with a two-sided $p < 0.05$ significance. The frequency of IFNγ, IL-2 or TNFα responses by ICS on Day 30 and the change between Days 1 and 30 were compared between the dose groups using Fisher's exact tests. nAbs and ICS results below the limit of detection were considered at the lower limit.

2.5 Ethics Statement

This study was approved by the UCLA's Institutional Review Board #22-000192 on 2/25/22 and adheres to OBM Transplantation's Research and Publication Ethics Guidelines. Informed consent was obtained from all participants.

3. Results

Between March 18, 2022 and October 3, 2022, 19 participants were enrolled in the 100 μg (n = 11) and 50 μg (n = 8) groups. The target study enrollment was not achieved due to study pause

resulting in recruitment challenges, and the availability and preferential use of the bivalent vaccine in the study population. The study pause occurred due to protocol deviation (no safety issues), after an error in the allocation order of study vaccine occurred at the study site where the first two participants enrolled received 100 µg doses instead of the 50 µg doses as specified in the protocol. This resulted in a protocol amendment ultimately delaying enrollment in the 200 µg dose group.

Baseline characteristics were similar between the two study groups with respect to gender, age, and time from transplant (Table 1). The proportion of white participants was higher in the 100 µg group (73%) compared with the 50 µg group (38%). The proportion of participants with a pre-transplant diagnosis of idiopathic pulmonary fibrosis (IPF) was higher in the 50 µg group (63%), compared with the 100 µg group (27%). There were no participants with a history of receiving anti-B cell therapies. Most participants received their fifth dose as part of this study in both the 50 µg (75%) and 100 µg (82%) groups. Similarly, most participants in the 50 µg and 100 µg groups received prior vaccination with Moderna vaccine only: 75% and 82%, respectively. Participants received their prior Moderna and Pfizer vaccines at the standard doses approved by EUA.

Table 1 Participant Characteristics at Enrollment.

Characteristic	**50 µg Dose** (n = 8)		**100 µg Dose** (n = 11)	
Sex				
Female	2	25%	4	36%
Male	6	75%	7	64%
Age (mean years)	62		62	
Race/Ethnicity				
Asian	1	13%		
Black				
Hispanic	3	38%	3	27%
Pacific Islander	1	13%		
White	3	38%	8	73%
Single Lung Transplant	25%		45%	
Time from Transplant (mean years)	4.5		4.3	
Pre-Transplant Diagnosis [1]				
IPF	5	63%	3	27%
CTD-ILD	1	13%	3	27%
HP	1	13%	2	18%
COPD/Emphysema			2	18%
CPFE			1	9%
Pulmonary Hypertension	1	13%		
Mean Prednisone dose (mgs) [2]	5.63		6.64	
Mean Tacrolimus dose (mgs) [2]	4.31		2.49	
Median mycophenolate mofetil dose (mgs) [2]	1000		1125	
Median mycophenolate sodium dose (mgs) [2]	720		1080	
Study vaccine was 5th dose	6	75%	9	82%
Prior vaccines were Moderna only	6	75%	9	82%

[1] IPF = idiopathic pulmonary fibrosis, CTD-ILD = connective tissue disease associated ILD, HP = hypersensitivity pneumonitis, COPD = chronic obstructive pulmonary disease, CPFE = combined pulmonary fibrosis and emphysema. [2] Total daily dose.

3.1 Frequency of Adverse Events

There were no SAEs or AESIs related to the study vaccine in either dose group. Two participants experienced SAEs that were unrelated to the study vaccine (Appendix 1). Solicited local and systemic ARs were mostly mild or moderate in intensity for both groups. Local ARs were reported in 88% (7/8) and 82% (9/11) of the 50 µg and 100 µg groups, respectively (Figure 1). With the exception of one participant in the 100 µg group who experienced grade 2 injection site swelling, the local ARs were mild and limited to pain at the injection site. There was no grade 3 local ARs reported in either group.

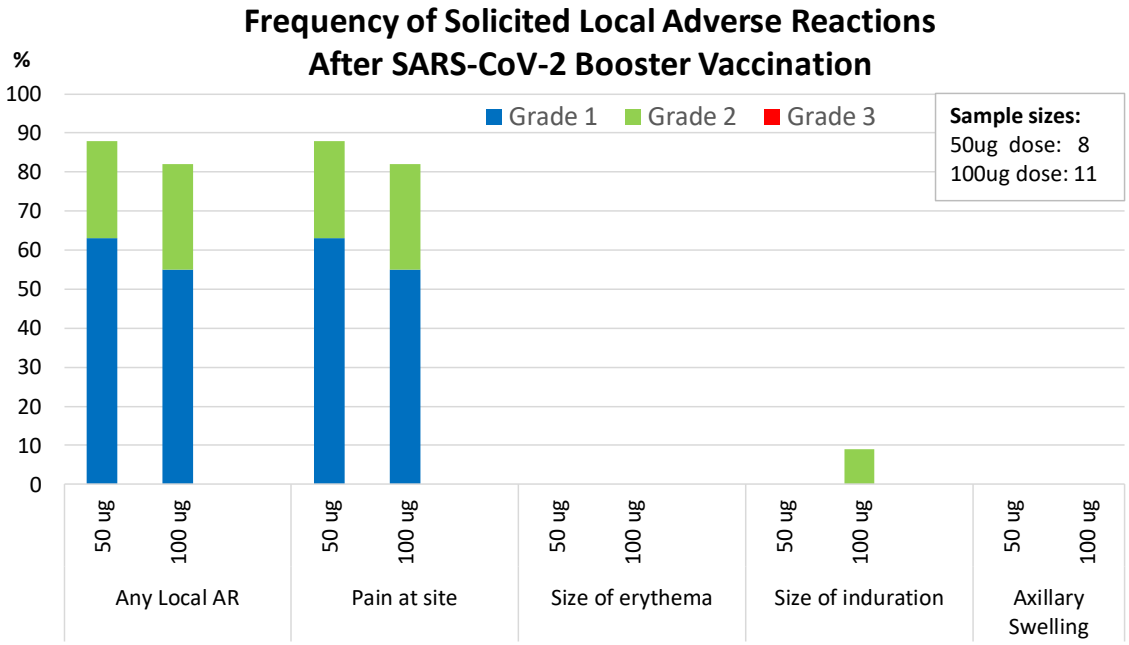

Figure 1 Frequency of solicited local adverse reactions after mRNA-1273 vaccination based on the FDA Toxicity Grading Scale.

Systemic ARs were reported in 50% (4/8) and 27% (3/11) of the 50 µg and 100 µg groups, respectively (Figure 2). The most common systemic AR was fatigue reported in 50% and 18%, followed by headache reported in 25% and 27% in the 50 µg and 100 µg groups, respectively. Myalgia, arthralgia, chills and nausea were less commonly reported with frequencies <15% in both the 50 µg and 100 µg groups. There were no episodes of fever reported in either dose group. Most of the reported systemic ARs were grades 1-2, with the exception of fatigue, headache and nausea/vomiting. Grade 3 fatigue was reported in 13% and 9% of the 50 µg and 100 µg groups, respectively. The only other grade 3 ARs reported were grade 3 headache in 13% of the 50 µg group and grade 3 nausea/vomiting in 13% of the 50 µg group. With the exception of one participant in the 100 µg group who had grade 2 injection site pain on Day 4, all other ARs occurred in the first three days post-vaccination.

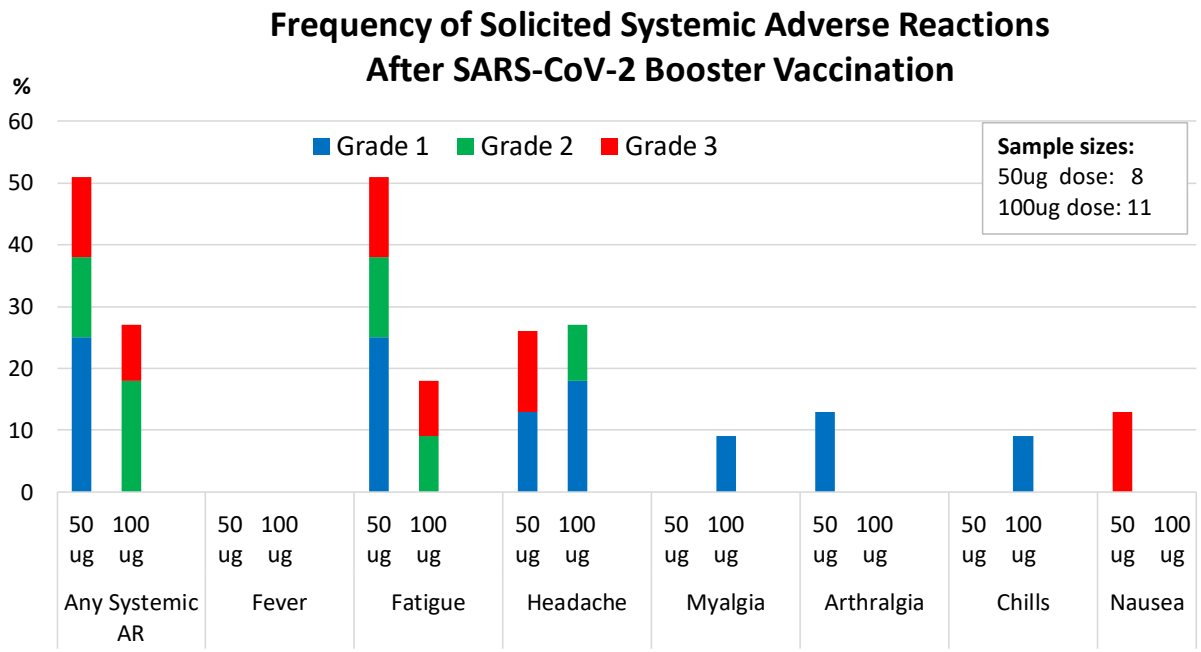

Figure 2 Frequency of solicited sytemic adverse reactions after mRNA-1273 vaccination based on the FDA Toxicity Grading Scale.

3.2 Humoral Immunogenicity

Humoral immunogenicity was measured by a pseudovirus neutralization assay using a lentivirus pseudotyped for the D614G spike protein on Day 1 (pre-vaccine) and Day 30. For the D614G pseudovirus, 63% and 55% of the 50 µg and 100 µg groups had detectable ID50 nAb titers on Day 1, respectively (Figure S1). On Day 30, these proportions remained overall unchanged at 75% and 64% for the 50 µg and 100 µg groups. The median nAb titers on Day 1 prior to vaccination was similar for the 50 µg and 100 µg groups at 4260 and 6514, respectively (Table 2). Table 2 describes the nAb titers on Day 1 and 30 for each participant with relevant clinical data. nAb titers were overall unchanged between Day 1 and Day 30 for both groups with a median change of -1221 and 0 for the 50 µg and 100 µg groups, respectively.

Table 2 Day 30 Immune Response by Participant.

Participant	Age	Years Since Tx	Dose Number	Mixed Dose [1]	Day 1 NAb [2]	Day 30 NAb [2]	Day 1 Dectable $CD4^{+}$ [3]	Day 30 Dectable $CD4^{+}$ [3]	Day 1 Dectable $CD8^{+}$ [3]	Day 30 Dectable $CD8^{+}$ [3]
50 mcg Dose:										
1	65	3.9	4	0	118	830	0		0	
2	54	2.8	4	0	57		1	0	0	1
3	48	10.2	5	0	17670	7619	0	1	0	0
4	76	4.3	5	1	40	40	0	1	0	0
5	62	5.0	5	0	8299	5436	1	1	0	0
6	66	1.8	5	0	30788	46022	0	1	0	0
7	60	5.7	5	1	220	4175	0	0	0	0

8	61	2.2	5	0	9613	6813	0	1	1	0
Median or %:	**61.5**	**4.5**		**25%**	**4260**	**5436**	**25%**	**71%**	**13%**	**13%**
100 mcg Dose:										
9	71	3.5	4	0	113	40	0	0	0	0
10	60	2.6	4	0	113	40	0	0	0	0
11	65	1.8	5	0	112	71	1	0	1	0
12	71	12.0	5	1	10906	7800	1	1	1	1
13	61	2.8	5	0	8018	5405	1	0	0	0
14	70	2.6	5	0	43	166	0	0	0	1
15	41	6.2	5	0	6514	5293	0	1	0	0
16	71	2.1	5	0	14825	7340	1	1	0	0
17	69	7.8	5	1	14414	9791	0	1	0	0
18	60	2.2	5	0	14347	7630	0	0	0	0
19	48	4.0	5	0	40	158	1	1	0	1
Median or %:	**65.0**	**4.3**		**18%**	**6514**	**5293**	**45%**	**45%**	**18%**	**27%**

[1] Mixed dose = Prior receipt of both Moderna and Pfizer vaccine doses; [2] Pseudovirus neutralization assay responses against D614G; [3] Intracellular staining results for IFNγ, IL-2 or TNFα.

3.3 Cellular Immunogenicity

Spike-specific $CD4^+$/$CD8^+$ T cell responses were evaluated by flow cytometry with intracellular staining for IFNγ, IL-2 and TNFα on Day 1 (pre-vaccine) and Day 30. For the $CD4^+$ compartment, spike-specific responses by intracellular IFNγ staining on Days 1 and 30 were only detectable (>0.01%) in 29% and 50% for the 50 μg group, and 45% and 55% for the 100 μg group, respectively (Figure S2). Detectable spike-specific IL-2 responses on Days 1 and 30 were: 29% and 63% for the 50 μg group, and 64% and 64% for the 100 μg group respectively. Detectable spike-specific TNFα responses on Days 1 and 30 were: 57% and 57% for the 50 μg group, and 36% and 36% for the 100 μg group, respectively. The change in the frequency of detectable spike-specific responses by IFNγ, IL-2 or TNFα between Days 1 and 30 was not significant for either dose group, but the analysis was underpowered to detect these differences.

For the $CD8^+$ compartment, spike-specific responses by intracellular IFNγ on Days 1 and 30 were detectable in 14% and 50% for the 50 μg group, and 45% and 36% for the 100 μg group, respectively (Figure S3). Detectable spike-specific IL-2 responses on Days 1 and 30 were: 14% and 38% for the 50 μg group, and 36% and 36% for the 100 μg group respectively. Detectable spike-specific TNFα responses on Days 1 and 30 were: 14% and 25% for the 50 μg group, and 9% and 27% for the 100 μg group, respectively. The change in the frequency of detectable responses by IFNγ, IL-2 or TNFα between Days 1 and 30 was not significant for either dose group, but the analysis was limited by sample size.

4. Discussion

This randomized open-label phase 1-2 open-label trial evaluated the safety, reactogenicity and immunogenicity of higher dose mRNA-1273 booster vaccination among LTRs aged 18 years or older.

Trial enrollment was terminated early due to the availability of the bivalent mRNA-1273.222 booster in September 2022, but we report the results from the 19 LTRs who received either the 50 μg or 100 μg mRNA-1273 booster doses.

Local and systemic ARs were mostly mild to moderate at both dose groups. For comparison purposes, we reference the frequency of local and systemic ARs from two previous clinical trials evaluating the 50 μg (P201, n = 167) and 100 μg (P205, n = 303) doses of mRNA-1273 as a third dose (first booster) among non-immunocompromised adults [21]. With the exception of pain at the injection site, the reported frequency of local and systemic ARs in the current study were lower than reported in the P201 and P205 studies of the 50 μg and 100 μg mRNA-1273 booster dose.

Pain at the injection site was the most common local AR and reported with a similar frequency across these studies: 80% and 89% in the P201 and P205 studies, and 88% and 82% in the 50 μg and 100 μg groups of the current study. The size of erythema (4% and 9%), size of induration (5% and 13%), and axillary swelling (20% and 29%) were reported at higher frequencies in the P201 and P205 studies, compared with the size of erythema (0% and 0%), size of induration (0% and 9%), and axillary swelling (0% and 0%) reported for the 50 μg and 100 μg groups in the current study, respectively. Similarly, systemic ARs were reported at higher frequencies in the P201 and P205 studies compared with the current study. The overall frequency of systemic ARs was 75% and 86% in the P201 and P205 studies, compared with 50% and 27% for the 50 μg and 100 μg groups in the current study, respectively. Fatigue (59% and 73%), headache (55% and 62%), myalgia (49% and 68%), arthralgia (41% and 49%), chills (35% and 44%), fever (7% and 14%) and nausea (11% and 20%) were reported at higher frequencies in the P201 and P205 studies, compared with fatigue (50% and 18%), headache (25% and 27%), myalgia (0% and 9%), arthralgia (13% and 0%), chills (0% and 9%), fever (0% and 0%), and nausea (13% and 0%) reported for the 50 μg and 100 μg groups in the current study, respectively.

This decreased reactogenicity observed among lung transplant recipients in the current study is consistent with our understanding of immunosuppressive medications and adaptive immune responses. Since lung transplant recipients receive immunosuppressive medications dosed to minimize immune responses against the lung allograft, we would expect attenuation of immune responses (both reactogenicity and immunogenicity) against vaccines as well. The initial phase 1 dose-escalation study of mRNA-1273 evaluated the 25 μg, 100 μg, and 250 μg doses for 15 non-immunocompromised participants in each group [16]. After the second dose, they found higher anti-S-protein antibody levels with higher vaccine doses. However, systemic ARs were also more common with higher vaccine doses, particularly at the 250 μg dose with three participants (21%) reporting at least one severe AR. These systemic ARs were considered dose-limiting for the non-immunocompromised population. The current study suggests that LTRs have significantly less reactogenicity and may tolerate higher doses with minimal adverse events.

Several studies have evaluated the safety and reactogenicity of SARS-CoV-2 mRNA vaccines among SOTRs, which have included LTRs [6, 12, 22, 23]. Hall et al. randomized 120 SOTRs to a third 100 μg dose of mRNA-1273 vs placebo, and reported local and systemic ARs in the treatment group that were only mildly increased over the placebo group [12]. Similar to the current study, the most common ARs were pain at the injection site (77%), followed by fatigue (50%), myalgia (23%), headache (18%), swelling (15%) and arthralgia (12%), with other ARs reported in less than 10% of participants. These AR were limited to grades 1 and 2 on the FDA Toxicity Grading Scale. The frequency of local and systemic ARs reported among the immunocompromised in these studies are

in sharp contrast to the higher frequencies reported in the P201 and P205 studies involving non-immunosuppressed participants. A few case reports suggested a potential for SARS-CoV-2 mRNA vaccines inducing acute allograft rejection [14, 24, 25]. However, these reports have been rare despite the large number of vaccine doses administered to SOTRs and no clear associations have been established. Episodes of myocarditis and pericarditis among SOTRs have been reported to vaccine safety reporting databases in the United States and Europe, but not at a higher rate than for the general population [26]. Taken together, these data support the safety and decreased reactogenicity after the SARS-CoV-2 mRNA vaccines among SOTRs, compared to non-immunosuppressed individuals.

Despite receiving at least three prior SARS-CoV-2 mRNA vaccine doses, only 63% and 55% of the 50 μg and 100 μg groups had a detectable ID50 nAb titer on day 1. There was limited additional increase in neutralizing antibody response after the study dose, with only 63% and 75% of the two groups with a detectable titer on Day 30, respectively. In comparison, an evaluation of 30 non-immunosuppressed participant by our group using the same PhenoSense neutralization assay found that 90% had detectable nAbs after the first vaccine dose, and 100% after the second dose [19]. The attenuated humoral immune responses observed in the current study is comparable to prior studies of humoral immunogenicity in SOTRs reporting anti-spike IgG antibody detection in only 34-54% after the second vaccine dose [7, 8, 12], with even lower responses reported for LTRs [9-11].

Similarly, cellular immune responses were weak for both dose groups in the current study with Day 30 spike-specific $CD4^+$ IFNγ responses observed in only 50% and 55% of the 50ug and100 μg groups, respectively. Day 30 spike-specific $CD8^+$ IFNγ responses were detectable in only 50% and 36% of the 50 μg and 100 μg groups. Intracellular staining for IL-2 and TNFα showed a similar low frequency of spike-specific responses. Cellular responses by intracellular staining has not been well studied for LTRs, and differences in laboratory techniques make direct comparisons across studies difficult. However, the weak $CD4^+$ and $CD8^+$ responses observed in the current study is consistent with prior studies. In a randomized trial of a third dose mRNA-1273 vaccine in SOTRs, Hall et al. detected a spike-specific IFNγ and IL-2 polyfunctional response in 0.04% and 0.01% of $CD4^+$ cells for the vaccine (n = 31) and placebo (n = 31) groups respectively, with a minimal $CD8^+$ response detected for both groups [12]. In comparison, a phase 1 study evaluating the safety and immunogenicity of mRNA-1273 priming doses among older non-immunocompromised participants found more robust responses after a two dose 100 μg priming series [15]. $CD4^+$ responses by IFNγ intracellular staining increased from 0.001% to 0.164%, and $CD8^+$ responses increased from 0.001% to 0.126% between the pre-vaccine and post-vaccine (14 days after the second vaccine dose) respectively, among ten participants aged over 70 years. These findings indicate that many LTRs continue to have weak humoral and cellular anti-SARS-CoV-2 immune responses compared with the non-immunocompromised population.

The major limitation of this study is the small sample size of both vaccine dose groups. This limited our ability to perform statistical comparisons of reactogenicity and immunogenicity between the two dose groups. It also precluded statistical adjustment for relevant factors including: vaccine dose, prior vaccine types and immunosuppressive dosing. The strength of this study is the conceptual novelty of a randomized trial evaluating higher mRNA-1273 doses among SOTRs which has not been previously reported.

In summary, this randomized open-label trial evaluated the safety, reactogenicity and immunogenicity of the standard 50 μg vs 100 μg booster dose of the mRNA-1273 vaccine among

LTRs. The study was terminated early due to the availability of the bivalent mRNA-1273.222 booster, but the results suggest the following: 1) LTRs have less reactogenicity to mRNA-1273 vaccination compared with non-immunocompromised individuals due to their immunosuppressive medications, 2) Spike-specific humoral and cellular immune responses remain weak in LTRs compared with non-immunosuppressed individuals, and 3) These spike-specific humoral and cellular responses remained weak with the 100 µg dose. The results of this study suggest that higher doses of SARS-CoV-2 mRNA vaccines (e.g. 200 µg) could be evaluated in LTRs given the lower reactogenicity and room for improved immunogenicity observed in this study.

Abbreviations

AE	Adverse Events
AESI	Adverse Events of Special Interest
AR	Adverse Reactions
CD4	Helper T Cell
CD8	Cytotoxic T Cell
COVID-19	Coronavirus Disease 2019
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
IFNγ	Interferon-Gamma
IL-2	Interleukin-2
ICS	Intracellular Staining
IgG	Immunoglobulin G
IPF	Idiopathic Pulmonary Fibrosis
LTR	Lung Transplant Recipient
mRNA	Messanger Ribonucleic Acid
mg	Milligram
nAb	Neutralizing Antibody
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOTR	Solid Organ Transplant Recipient
TNFα	Tumor Necrosis Factor Alpha
µg	microgram

Author Contributions

All authors contributed to the design of the study and collection of the data. MYS, JLC, AR, MF, AR, AD, RS, OOA, GT, JMS, PTG, OEB, AM, RMB, MHK, CJP, YL, TW, AF, BL, ZE, KA, JMM, AA, DMS, DE, JAB, OOY and SSW contributed to the development of the study design and protocol, subject recruitment, sample and data collection, and analysis plan. MYS, OOY, SSW and DE performed the data analysis. MYS, FJI, CJP, YL, TW and OOY performed the laboratory analysis. All authors contributed to the interpretation of the data. MYS, JAB, OOY and SSW drafted the manuscript. All authors critically revised the manuscript and approved the final version for submission.

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Competing Interests

AF, BL, ZE, KA and JMM are employees of Moderna, Inc. and may hold stock/stock options in the company. Moderna, Inc had no impact on the results or outcomes of the study. All other authors do not have potential conflicts of interest to disclose.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Supplemental Materials

1. Figure S1: Neutralizing antibody titers measured by the D614G SARS-CoV-2 pseudovirus neutralization assay.
2. Figure S2: $CD4^+$ response after spike protein peptide pool stimulation measured by flow cytometry with intracellular staining for IFNγ, IL-2 and TNFα.
3. Figure S3: $CD8^+$ response after spike protein peptide pool stimulation measured by flow cytometry with intracellular staining for IFNγ, IL-2 and TNFα.
4. Appendix 1: Serious Adverse Experiences (SAEs) Unrelated to Study Vaccine.
5. Appendix 2: Adverse Events of Special Interest (AESI) Terms.
6. Appendix 3: Immunogenicity Assays [18-20, 27].

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