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Journal of Infection and Chemotherapy 28 (2022) 1153–1158

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Efficacy and safety of mRNA SARS-CoV-2 vaccines in lung transplant recipients

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ARTICLE INFO

Keywords:
Lung transplantation
COVID-19
SARS-CoV-2
Vaccine
mRNA
Japan

ABSTRACT

Background: To date, reports addressing the antibody response following mRNA SARS-CoV-2 vaccination in lung transplant (LTX) recipients are limited. Thus, the aim of this clinical study was to investigate the efficacy and safety of the vaccines in LTX recipients compared to controls.

Methods: An open-label, nonrandomized prospective study was conducted at Tohoku University Hospital. LTX recipients and controls who received either the BNT162b2 vaccine or the mRNA-1273 vaccine were recruited, and SARS-CoV-2 IgG was measured before and after vaccination. The adverse events were reviewed. Predictors of negative serology after vaccination were evaluated with logistic regression.

Results: Forty-one LTX recipients and 24 controls were analyzed. Although all controls had a positive antibody response to a SARS-CoV-2 mRNA vaccine, antibody response was found in 24.4% of LTX recipients ($p < .0001$). The amount of SARS-CoV-2 IgG following the 2nd dose significantly climbed to 6557 AU/mL in controls, whereas the increase in IgG in LTX recipients was 8.3 AU/mL ($p < .0001$). Fewer LTX recipients developed systemic fever than controls ($p < .0001$) despite equivalent overall adverse event percentages in both groups. A higher plasma concentration of mycophenolate was a significant predictor of negative serology ($p = .032$).

Conclusions: An impaired antibody response to mRNA vaccines was significantly found in LTX recipients compared to controls and was associated with the plasma concentration of mycophenolate. While repeating mRNA vaccination may be one of the strategies to improve antibody response given the safety of the vaccines, emerging data on humoral immune responses based on immunosuppression regimens in LTX recipients should be studied (jRCT1021210009).

1. Introduction

The coronavirus disease (COVID-19) pandemic continues to impose a substantial burden on health-care workers and patients with underlying conditions, for whom mRNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines represent a crucial tool in fighting the pandemic. Immunocompromised patients were shown to have a higher risk of intensive care unit and hospital mortality due to COVID-19 [1]. Among those immunocompromised patients, solid organ transplant (SOT) recipients showed the least seroconversion after the 2nd dose of an mRNA vaccine [2]. Additionally, lung transplant (LTX) recipients were at the greatest risk for mortality among patients who underwent SOT [3]. To date, reports addressing the antibody response following mRNA vaccination in LTX recipients are limited. Controlled trials with mRNA vaccines were arduous due to a lack of control groups, as inoculations with the vaccine series occurred on a worldwide scale after FDA approval, and healthy individuals were already vaccinated when the mRNA vaccine was ready for SOT recipients. Thus, the aim of this clinical study was to investigate the efficacy and safety of mRNA SARS-CoV-2 vaccines in LTX recipients compared to controls.

Abbreviations: Confidence intervals, CIs; Coronavirus disease, COVID-19; Interquartile range, IQR; Lung transplantation, LTX; Odds ratios, ORs; Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; Solid organ transplant, SOT.

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https://doi.org/10.1016/j.jiac.2022.04.019
Received 21 March 2022; Received in revised form 15 April 2022; Accepted 19 April 2022
Available online 17 May 2022

2. Patients and methods

2.1. Study design and patient population

An open-label, nonrandomized prospective study was conducted at Tohoku University Hospital (TUH), Sendai, Japan, and Tohoku Kosai Hospital (TKH), Sendai, Japan. The study protocol was approved by the institutional review boards at both Tohoku University Hospital (2021-1-142) and Tohoku Kosai Hospital (kkrtohoku-202107resp_S1_01). Written informed consent was obtained from all participants prior to entering into the study (Fig. 1). The study was registered at the Japan Registry of Clinical Trials (jRCT1021210009) and afterward started recruiting on June 4th, 2021, and follow-up ended on December 28, 2021.

The primary objective was to evaluate humoral immune responses in LTX recipients who received the mRNA SARS-CoV-2 vaccines. The secondary objectives were to assess the vaccine safety in LTX recipients and analyze the predictors of negative serology after vaccination.

The inclusion criteria for the study were an age of 20 or above and no history of reverse transcription polymerase chain reaction (RT–PCR)-confirmed SARS-CoV-2 infection or positive serology for SARS-CoV-2 IgG prior to vaccination. The study group included LTX recipients who were 6 months out from transplantation and followed at TUH. LTX indications [4], immunosuppression [5], histocompatibility testing [6], antimicrobial prophylaxis [7] and overall management [8] after transplantation have been previously described. Plasma mycophenolate concentration was measured based on the 12-h area under the concentration-time curve (AUC0-12) by a three time-point (C1, C4, and C8) sampling strategy [9]. The control group, composed of health-care workers at TUH and patients who were routinely followed in the respiratory clinic at TKH, was selected from among individuals without any histories of transplantation or immunosuppressive therapy, including corticosteroids.

2.2. mRNA SARS-CoV-2 vaccines and laboratory tests for serology

All participants received either the BNT162b2 vaccine (Pfizer Inc.) at Day 0 and Day 21 or the mRNA-1273 vaccine (Takeda/Moderna) at Day 0 and Day 28 as recommended by the Japanese Ministry of Health, Labour and Welfare. No LTX recipient adjusted immunosuppression around the time of vaccination. Blood samples were collected before the 1st dose and between 4 and 8 weeks after the 2nd dose, when clinical data and adverse events were reviewed by coauthors. SARS-CoV-2 IgG II Quant (Abbott, Tokyo) was used to measure IgG titers to the receptor binding domain (RBD) of the SARS-CoV-2 spike S1 subunit (SARS-CoV-2 IgG). A titer ≥50 AU/mL was considered positive per the manufacturer's threshold. Undetectable IgG (<6.8 AU/mL) was calculated as 1.0 AU/mL for the statistical analysis.

2.3. Adverse events

Questionnaires were administered to all participants to report adverse events within 7 days after each dose of the vaccines. The adverse events were divided into local (pain, redness, swelling) and systemic symptoms (fever, fatigue, headache, chills, nausea, diarrhea, myalgia, arthralgia) and ranked on a scale of 1–5: 1 = no, 2 = mild, 3 = moderate, 4 = severe and 5 = life-threatening symptoms. Moderate symptoms (scale of 3) were defined when symptoms interfered with daily activities. Fever was graded as no fever (<37.5 °C), mild (37.5–38.4 °C), moderate (38.5–39.4 °C), severe (39.5–40.4 °C), or life-threatening (>40.5 °C). The table of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 was modified for the clinical study [10]. Medical charts were also reviewed for acute cellular or antibody-mediated rejection, a >10% irreversible drop in graft function, and newly diagnosed COVID-19 after vaccination.

2.4. Statistical analysis

Data for LTX recipients and controls or positive and negative serologies are shown as percentages or medians (interquartile range [IQR]). Differences between groups were compared with the chi-square or Fisher's exact tests for categorical variables and Mann–Whitney tests for continuous variables. Differences in SARS-CoV-2 IgG across groups were compared by the Mann–Whitney *U* test. Univariate and multivariate analyses were performed with a logistic regression for negative serology as the outcome. Clinically important variables (age and sex) and presumed predictors (time since transplantation, vaccine type and plasma concentration of tacrolimus and mycophenolate) were selected for analysis. Odds ratios (ORs) are presented with their 95% confidence intervals (CIs). Statistical significance was set at $p < .05$. Statistical analyses and graph generation were performed using GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [11].

3. Results

3.1. Clinical characteristics of participants and serology following mRNA SARS-CoV-2 vaccines

Forty-five LTX recipients were recruited into the study groups, and 27 non-transplanted individuals were recruited into the control group, of whom 41 and 24 were analyzed, respectively (Fig. 1). While the clinical characteristics in both groups were similar in terms of the median age, male sex proportion and number of days from the 2nd vaccine to blood collection (**Table 1**), LTX recipients received more BMT162b2 vaccines (34/41, 82.9%) than controls (p = .021). All participants in both groups demonstrated negative serology prior to mRNA vaccination

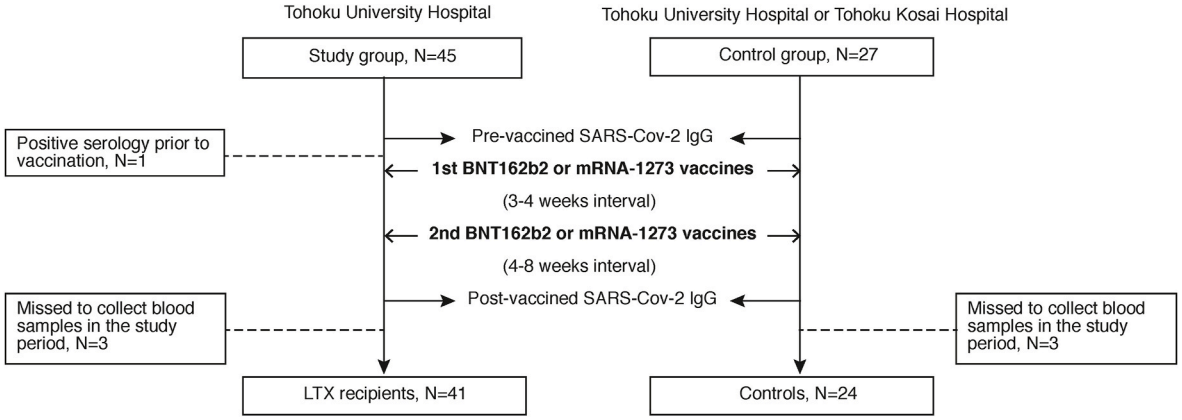

Fig. 1. Study flowchart LTX, lung transplant.

Table 1
Clinical characteristics of participants in the study.

	LTX recipients, N = 41	Controls, N = 24	*p value*
Age, median (IQR)	51 (40–58)	47 (40–56)	0.644
Sex, N (%)			0.797
Female	23 (56.1%)	12 (50.0%)	
Male	18 (43.9%)	12 (50.0%)	
Days from 2nd vaccine to blood collection, median (IQR)	41 (35–52)	42 (35–56)	0.944
Vaccine, N (%)			0.021
Pfizer BNT162b2	34 (82.9%)	13 (54.2%)	
Takeda/Moderna mRNA-1273	7 (17.1%)	11 (45.8%)	
SARS-Cov-2 IgG before vaccination, N (%)			0.999
Positive	0 (0%)	0 (0%)	
Negative	41 (100%)	24 (100%)	
SARS-Cov-2 IgG after 2nd vaccine, N (%)			<.0001
Positive	10 (24.4%)	24 (100%)	
Negative	31 (75.6%)	0 (0%)	

IQR, interquartile range; and LTX, lung transplant.

(p = .999). Although all controls had a positive antibody response to SARS-CoV-2 mRNA vaccines (24/24, 100%), immunoreactivity was found in only 10/41 (24.4%) LTX recipients (p < .0001). The SARS-CoV-2 IgG titers in LTX recipients and controls before the 1st dose and after the 2nd dose are illustrated in Fig. 2. SARS-CoV-2 IgG prior to the 1st dose was undetectable in both groups (p = .549). However, the amount of SARS-CoV-2 IgG following the 2nd dose significantly climbed to 6557 (IQR 3545–10530) AU/mL in controls, whereas the increase in IgG in LTX recipients was only 8.3 (IQR 1.0–41.3) AU/mL (p < .0001).

3.2. Adverse events after each dose of the mRNA SARS-CoV-2 vaccines

Vaccination-site local pain was the most frequent adverse event after the 1st dose of the mRNA SARS-CoV-2 vaccines in both groups (51.2% in LTX recipients and 45.8% in controls) (Fig. 3). While the most common adverse event after the 2nd dose was vaccination-site local pain, seen in 41.5% of LTX recipients, that of controls was systemic fever, found in 62.5%. Fewer LTX recipients than controls developed systemic fever (p < .0001). No participants reported experiencing any life-threatening adverse events (rank scale of 5) during the study period. In addition, no LTX recipients developed acute cellular or antibody-mediated rejection, a >10% irreversible drop in graft function, or newly

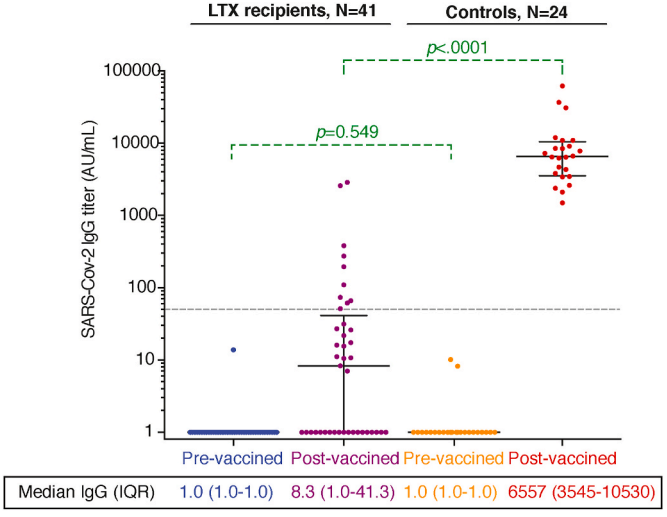

Fig. 2. The trends in SARS-CoV-2 IgG before and after mRNA vaccination in LTR recipients (N = 41) and controls (N = 24) IQR, interquartile range; and LTX, lung transplant.

diagnosed COVID-19 after vaccination.

3.3. Clinical predictors of negative serology following the mRNA SARS-CoV-2 vaccines in LTX recipients

The characteristics and laboratory data of patients with positive and negative serology (N = 10 and 31, respectively) are shown in Table 2. LTX recipients with negative serology were significantly older, with a median age of 52 years [vs. 39 years in those with positive serology] (p = .021), and had more use of mycophenolate at 1000 mg [vs. use at 500 mg in those with positive serology] (p = .039), accompanied by a significantly higher concentration of mycophenolate, with a median AUC of 48.5 μg h/mL [vs. a median AUC of 24.0 in those with positive serology] (p = .008). Male sex, LTX indication, years since lung transplantation, vaccine type and C0 tacrolimus were not different between those with positive and negative serology responses. In the multivariate regression model (**Table 3**), age was not a remarkable predictor of negative serology, with an OR of 1.11 (95% CI 0.99–1.24), yet a high plasma concentration of mycophenolate demonstrated a significant relationship with negative serology, with an OR of 1.10 (95% CI 1.10–1.20).

4. Discussion

Our study presented a weakened antibody response following a two-dose mRNA vaccine regimen in LTX recipients compared to controls (24.4% vs. 100%, $p < .0001$) and substantially lower SARS-CoV-2 IgG titers in the LTX recipients than in controls (8.3 AU/mL vs. 6557 UA/mL, $p < .0001$). Based on the current evidence [12,13], a two-dose mRNA vaccine regimen is effective to minimize COVID-19 in the non-transplanted population and can lead to a humoral immune response with high IgG titers that is similar to those of individuals who were infected with SARS-CoV-2 [14,15]. Similar outcomes were reported from other LTX centers: Narasimhan et al. in Dallas, Texas, indicated that a two-dose mRNA vaccine regimen elicited SARS-CoV-2 IgG in 24.6% of LTX recipients [16]; Shostak et al. in Petah Tikva, Israel, at 18.5% [17] and Hallett et al. at 35.9% [18]. Urgent discussion is needed to determine whether severe COVID-19 is preventable with such inadequate efficacy in LTX recipients who are at greater risk for mortality from COVID-19 [19].

Intriguingly, a small proportion of LTX recipients experienced systemic fever after each dose of the vaccine, which was consistent with previous reports where few LTX recipients became feverish following vaccine series [18,20]. On the other hand, the Japanese controls in our study had more episodes of systemic fever than the recipients (62.5% vs. 4.9%, p < .0001). Systemic fever, especially after the 2nd dose, is common in the Japanese population; 44.1% of health-care workers had body temperatures ≥38.0 °C [21], and approximately 40% of participants in different placebo-controlled studies developed fever [22]. Chapin-Bardales et al. presented that 8.6% and 29.5% of vaccinated US citizens developed fever following the 1st and 2nd doses of mRNA vaccines, respectively [23]. In light of the facts that no life-threatening events, any forms of acute rejection, or irreversible drops in lung function were found and the chances are small that LTX recipients suffer from fever after vaccine series [17,18], mRNA vaccines could be safely administrable to LTX recipients.

Given the limited immunogenicity and good tolerance of a two-dose mRNA vaccine regimen in LTX recipients, repeating SARS-CoV-2 vaccination is one of the strategies to improve the humoral immune response in this population. Hall et al., in Toronto, Canada, demonstrated that the 3rd dose of booster mRNA-1273 vaccine led to substantial immunoreactivity in solid organ transplant (SOT) recipients compared to placebo (55% vs. 18%), and Massa et al., in Nice, France, showed that a three-dose BNT162b2 vaccine regimen changed the seroconversion rate from 44.3% after the 2nd dose to 62.4% after the 3rd dose in kidney transplant recipients who were on a similar

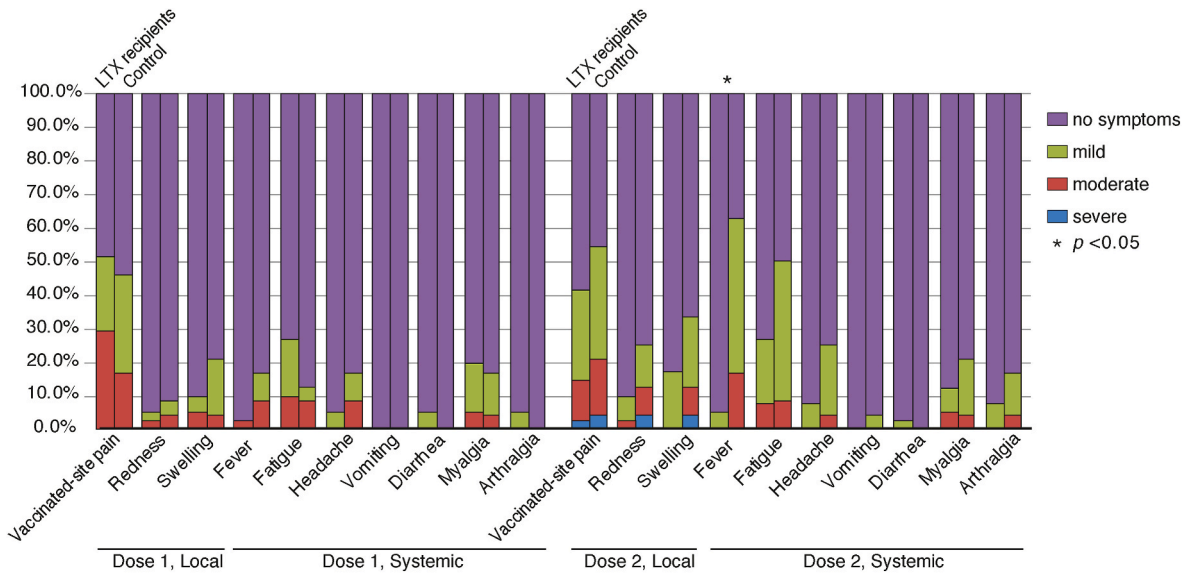

Fig. 3. Percentages of various adverse events occurring in LTX recipients (N = 41) and controls (N = 24) LTX, lung transplant.

Table 2
Clinical characteristics of LTX recipients after the 2nd dose of mRNA SARS-CoV-2 vaccines.

	Positive serology, N = 10	Negative serology, N = 31	*p value*
Age, median (IQR)	39 (37–49)	52 (46–58)	0.021
Sex, N (%)			0.725
Female	5 (50%)	18 (58.1%)	
Male	5 (50%)	13 (41.9%)	
LTX indication, N (%)			0.294
Obstructive	2 (20%)	13 (41.9%)	
Vascular	5 (50%)	7 (22.6%)	
Suppurative	0 (0%)	4 (12.9%)	
Fibrosis	3 (30%)	6 (19.4%)	
Allogeneic	0 (0%)	1 (3.2%)	
Years since lung transplantation, median (IQR)	6 (5–11)	4 (2–10)	0.338
Vaccine, N (%)			0.332
Pfizer BNT162b2	7 (70%)	27 (87.1%)	
Takeda/Moderna mRNA-1273	3 (30%)	4 (12.9%)	
Days from 2nd vaccine to blood collection, median (IQR)	41 (31–50)	41 (34–55)	0.574
Tacrolimus, N (%)§	10 (100%)	30 (96.8%)	0.999
Tacrolimus C0, ng/mL, median (IQR)	8 (6.75–9.75)	8 (6.75–10.0)	0.624
Mycophenolate mofetil, N (%)¶	9 (90%)	29 (93.5%)	0.999
AUC 0–12, μg·h/mL, median (IQR)	24.0 (15.3–39.8)	48.0 (34.5–63.0)	0.008
mg/day, median (IQR)	500 (250–750)	1000 (500–1000)	0.039
Prednisolone, N (%)	10 (100%)	31 (100%)	0.999
mg/day, median (IQR)	5 (5–5)	5 (5–5)	0.309
Sirolimus, N (%)	2 (20%)	3 (9.7%)	0.580

AUC, area under the plasma concentration time curve; C0, trough concentration; IQR, interquartile range; and LTX, lung transplant.
§ One patient on cyclosporine with negative serology was excluded from the analysis.
¶No patients were on azathioprine in the study.

immunosuppression regimen as the LTX recipients in our study [24]. Although a three-dose mRNA vaccine regimen is likely effective for seroconversion in SOT recipients, their antibody responses are not equivalent to those of healthy controls who received a two-dose vaccine regimen. There remains a challenge to explore how often mRNA vaccines should be administered to SOT recipients, e.g., an annual shot or each time a new variant of SARS-CoV-2 is identified.

Table 3
Logistic regression model evaluating clinical predictors of negative serology to mRNA SARS-CoV-2 vaccines in LTX recipients.

	Univariate		Multivariate	
	p value	OR (95% CI)	*p value*	OR (95% CI)
Age[a]	0.032	1.10 (1.01–1.20)	0.060	1.11 (0.99–1.24)
Male sex (vs. female)	0.656	0.72 (0.17–3.02)	0.711	1.50 (0.18–12.6)
AUC of mycophenolate[a]	0.023	1.09 (1.01–1.17)	0.032	1.10 (1.01–1.20)
C0 of tacrolimus[a]	0.508	0.89 (0.64–1.25)		
Vaccine type, BNT162b2 (vs. mRNA-1273)	0.224	2.89 (0.52–16.0)		
Years since transplantation[a]	0.556	0.96 (0.83–1.11)		

AUC, area under the plasma concentration time curve; CI, confidence interval; C0, trough concentration; and OR, odds ratio.
[a] Continuous variables.

The use of mycophenolate has been a known predictor of an impaired humoral immune response following mRNA vaccination in SOT recipients [2,20,25]. Daily use of mycophenolate was associated with negative serology; in addition, our study newly demonstrated that the plasma concentration (AUC 0–12) of mycophenolate was dose-dependently associated with negative serology after a two-dose mRNA vaccine regimen (OR of 1.10, 95% CI of 1.01–1.20). Kantauskaite et al., in Düsseldorf, Germany, also demonstrated a negative correlation between the C0 level of mycophenolate and antibody titers in kidney transplant recipients [26]. It is hard to define which mechanisms of mycophenolate prevent an antibody response in SOT recipients. Perhaps a temporary dose reduction in or the cessation of mycophenolate prior to mRNA vaccine administration may be considered to enable adequate immunization in selected SOT recipients as long as they have stable allograft function. On the other hand, although a wide variability of antibody response to other inactivated vaccines, such as influenza and *Streptococcus pneumoniae* vaccines, was observed in SOT recipients, the immunoreactivity, which ranged from 15% to 90%, was generally lower than that in healthy individuals [27,28]. Despite current guidelines that recommend administering several vaccines after organ transplantation, the humoral immune response and clinical efficacy of these vaccines are

mostly unknown. Emerging data on antibody response based on immunosuppression regimens in SOT recipients should be studied in future trials.

The limitations of the present study arise from the small sample size. As the statistical analysis with multivariable regression was not powered, the conclusions on the association of the plasma concentration of mycophenolate with a reduced antibody response should be interpreted with caution. However, as recent reports focusing on the interrelation of mycophenolate to the antibody response showed similar outcomes [2,20,25,26], the plasma concentration of mycophenolate is likely a key factor impairing antibody development following mRNA vaccination in SOT recipients. Nevertheless, an additional study with a large sample size is required. Another limitation is that the T cell response following mRNA vaccination was not measured in this study. Recent reports have shown that the specific T cell immune response was diminished in SOT recipients compared to controls [29] or was significantly reduced in those with negative serology compared to those with positive serology [20,24,30]. Interestingly, an anti-spike-specific T cell response after mRNA SARS-CoV-2 vaccination was detected in one-third of LTX recipients, even in those with no detectable humoral immune response [31]. Thus, at least some of the patients with no antibody response after vaccination might have some extent of T cell response and thus a clinical benefit to prevent severe COVID-19. However, this needs to be studied with a variety of immunological assays, such as assays for specific $CD4^+$ and $CD8^+$ T cell responses [20,31], anti-spike-RBD ± neutralizing antibodies [20,24] and the complement system [32]. Despite these limitations, this is the first report that showed an impaired antibody response to SARS-CoV-2 mRNA vaccines in Japanese LTX recipients. We plan further study to see the humoral and cellular immune response to SARS-CoV-2 mRNA vaccines after third and fourth vaccination.

5. Conclusion

In conclusion, a significantly impaired antibody response to mRNA vaccines was found in LTX recipients compared to controls and was associated with the plasma concentration of mycophenolate. While repeating mRNA vaccination may be one of the strategies to improve immunoreactivity, emerging data on the humoral immune response based on immunosuppression regimens in LTX recipients should be studied in future trials.

Funding

This work was supported in part by Program Supporting Activities to Prevent Healthcare Collapse Due to COVID-19 from the Yahoo Japan Foundation (WF25646271), Grant-in-Aid for Scientific Research C from the Japan Society for the Promotion of Science (20K08509), the Clinical Research Promotion Program for Young Investigators of Tohoku University Hospital and the Takeda Science Foundation (The visionary research/Hop).

Ethics approval and consent to participate

The study protocol was approved by the institutional review boards at both Tohoku University Hospital (2021-1-142) and Tohoku Kosai Hospital (kkrtohoku-202107resp_S1_01). Written informed consent was obtained from all participants prior to entering into the study.

Consent for publication

Not applicable.

Authors' contributions

TH is the guarantor of this manuscript, is responsible for statistical analysis and has full access to all of the data in the study. MA, TW, YW, HN, HO and HN gathered information from the medical charts and the database and contributed to the data analysis and interpretation. YO had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript.

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