Efficacy and safety of the SARS-CoV-2 mRNA vaccine in lung transplant recipients: a possible trigger of rejection

Yasufumi Goda · Daisuke Nakajima · Satona Tanaka · Yoshito Yamada · Yojiro Yutaka · Kohei Unagami · Mikiko Yoshikawa · Hiroto Egawa · Hiroshi Date

Received: 5 April 2022 / Accepted: 16 October 2022 / Published online: 26 October 2022

© The Author(s), under exclusive licence to The Japanese Association for Thoracic Surgery 2022

Abstract
Objective Solid organ transplant recipients have an increased risk of developing severe coronavirus disease 2019 (COVID-19). Although SARS-CoV-2 mRNA vaccination has been strongly recommended for solid organ transplant recipients, its efficacy and safety have remained unknown.

Methods We performed an observational prospective cohort study in 18 lung transplant recipients who received two doses of SARS-CoV-2 mRNA vaccine, including BNT162b2 (n = 17) or mRNA-1273 (n = 1), between June and October 2021. The titers of IgG antibodies against the SARS-CoV-2 spike protein (S-IgG) were measured in serum samples collected before the prime dose, three weeks after the prime dose, and four weeks after the booster dose. Reactogenicity and adverse events were evaluated after vaccination.

Results There were no recipients with previous SARS-CoV-2 infection prior to vaccination. S-IgG levels were elevated in 2/18 (11.1%) recipients after the prime dose and in 5/18 recipients (27.8%) after the booster dose (31.7 ± 30.6 U/ml). The time from transplantation to vaccination tended to be longer in the seropositive group than the seronegative group [7.5 (3.9–10.2) vs 2.8 (1.9–4.0) years, \( p = 0.059 \)]. Maintenance dose of mycophenolate mofetil tended to be lower in the seropositive group than in the seronegative group [500 (250–500) vs 1000 (1000–1000) mg/day, \( p = 0.088 \)]. Regarding the adverse events after vaccination, the development of chronic lung allograft dysfunction (CLAD) or antibody-mediated rejection (AMR) were observed in two seropositive patients.

Conclusions The antibody response to the SARS-CoV-2 mRNA vaccine was quite poor in lung transplant recipients. We experienced cases that developed clinical CLAD or AMR that was likely related to SARS-CoV-2 vaccination.

Keywords Lung transplantation · Coronavirus disease 2019 · SARS-CoV-2 mRNA vaccination

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AMR          | Antibody-mediated rejection |
| BAL          | Bronchoalveolar lavage |
| BALF         | Bronchoalveolar lavage fluid |
| BDLT         | Brain-dead donor lung transplantation |
| BMI          | Body mass index |
| CLAD         | Chronic lung allograft dysfunction |
| COVID-19     | Coronavirus disease 2019 |
| CT           | Computed tomography |
| DSA          | Donor-specific antibody |
| ECLIA        | Electrochemiluminescence immunoassay |
| FEV\(_{1,0}\) | Forced expiratory volume in 1 s |
| FVC          | Forced vital capacity |
| HLA          | Human leukocyte antigen |
| IPF          | Idiopathic pulmonary fibrosis |
| LDLLT        | Living-donor lobar lung transplantation |
| MMF          | Mycophenolate mofetil |
| S-IgG        | IgG antibodies against the SARS-CoV-2 spike protein |
| TLC          | Total lung capacity |

*Daisuke Nakajima
daink@kuhp.kyoto-u.ac.jp

1 Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-Cho, Sakyo-Ku, Kyoto 606-8507, Japan

2 Department of Organ Transplantation, Tokyo Women’s Medical University, Tokyo, Japan

3 Department of Organ Transplantation and General Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

4 Department of Surgery, Institute of Gastroenterology, Tokyo Women’s Medical University, Tokyo, Japan
Introduction

In solid organ transplant recipients, SARS-CoV-2 infection results in more severe COVID-19 in comparison to immunocompetent hosts, with a high mortality rate of 14–46% observed in lung transplant recipients [1–4]. Therefore, the International Society for Heart and Lung Transplantation COVID-19 task force strongly recommended SARS-CoV-2 vaccination in heart and lung transplant recipients [5, 6]. However, lung transplant recipients are usually provided more intensive immunosuppressive therapy in comparison to other solid organ transplant recipients, which could impair their ability to generate an adequate immune response to the SARS-CoV-2 vaccine.

In the present study, we aimed to assess the immunogenicity and adverse events following SARS-CoV-2 vaccination to determine the efficacy and safety of SARS-CoV-2 vaccination in lung transplant recipients.

Patients and methods

Lung transplant recipients managed at Kyoto University, who were ≥ 18 years age, and who underwent transplantation over one year previously were eligible for inclusion in this observational prospective cohort study. Between June and October 2021, 18 lung transplant recipients were enrolled and received two doses of BNT162b2 vaccine (Pfizer-BioNTech) (n = 17) or mRNA-1273 vaccine (Moderna) (n = 1). Serum samples were collected shortly before and three weeks after the initial dose, and four weeks after the second dose. The IgG antibody levels against the SARS-CoV-2 spike protein (S-IgG) were measured in serum samples by an electrochemiluminescence immunoassay (ECLIA) using an Elecsys Anti-SARS-CoV-2 Antigen assay kit (Roche Diagnostics GmbH, Mannheim, Germany). The sensitivity and specificity of this assay are 100% and 99.8%, respectively. Antibody-positive cut-off value as determined by the manufacturer was ≥ 0.8 U/mL [7, 8] Local reactions, including redness, swelling, pain, warm sensation, and stiffness at the injection site, and systemic reactions, including fever, headache, fatigue, myalgia/arthralgia, and others (palpitations, tachypnea, etc.), were examined by the questionnaires during days 0 to 9 after each vaccine dose.

This study was approved by the Institutional Review Board of Kyoto University Hospital (R2971). Written informed consent was obtained from all participants.

The data are presented as the medians and interquartile ranges for continuous variables. The Mann–Whitney U test or unpaired t test were used for the analysis of data between two groups. Categorical data were analyzed by Fisher’s exact test. P values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using GraphPad Prism version 9.0.0 (GraphPad Software, CA, USA).

Results

The clinical characteristics of 18 lung transplant recipients are shown in Table 1. Brain-dead donor lung transplantation (BDLT) was performed for 14 recipients, and living-donor lobar lung transplantation (LDLLT) was performed for 4 recipients. The maintenance immunosuppression regimens consisted of a combination of tacrolimus, mycophenolate mofetil (MMF), and prednisone in most lung transplant cases.

SARS-CoV-2-specific IgG was not detected in any participants prior to the initial dose. The S-IgG levels were slightly increased in 2 of 18 (11.1%) patients at three weeks after the first dose (1.6 ± 1.1 U/ml) and were further increased in 5 of 18 patients (27.8%) at 4 weeks after the second dose (31.7 ± 30.6 U/ml) (Fig. 1). These five patients were defined as the seropositive group. SARS-CoV-2-specific IgG was not detected in 16 patients after the first dose and 13 patients after the second dose. These thirteen patients were defined as the seronegative group.

There was no significant difference in age or transplant type between the groups (Table 1). All seropositive patients were men, whereas 8 of 13 (61.5%) patients in the seronegative group were women (p = 0.036). The seropositive group showed a significantly higher body mass index (BMI) than the seronegative group [21.3 (20.0–23.0) vs. 17.4 (16.0–18.8), p = 0.026]. The period from lung transplantation to vaccination tended to be longer in the seropositive group [7.5 (3.9–10.2) years] in comparison to the seronegative group [2.8 (1.9–4.0) years, p = 0.059]. The dosage MMF administered to the seropositive group [500 (250–500) mg/day] was lower in comparison to the seronegative group [1000 (1000–1000) mg/day, p = 0.088], whereas the tacrolimus trough level and prednisone dosage of the groups were similar.

Regarding the reactogenicity after each vaccine dose, pain at the injection site was found to be the most common local side effect (94.4% after each dose), and fatigue was the most frequently encountered systemic symptom (22.2% after the first dose and 27.8% after the second dose) (Fig. 2). Possible clinical antibody-mediated rejection (AMR) newly developed in one seropositive patient, and chronic lung allograft dysfunction (CLAD) progressed in another seropositive patient after the second dose. In contrast, the development of AMR or CLAD was not observed in the seronegative group.
Case 1: possible clinical AMR and progression of pulmonary fibrosis

The patient was a 62-year-old man who had undergone right unilateral brain-dead donor lung transplantation for idiopathic pulmonary fibrosis (IPF) four years previously; his postoperative course was uneventful. Maintenance immunosuppressive therapy consisted of tacrolimus (trough level: 8–15 ng/ml), MMF (1500 mg/day), and prednisone (6 mg/day [0.1 mg/kg/day]).
infection events, bronchoscopy with bronchoalveolar lavage (BAL) was performed. A bronchoalveolar lavage fluid (BALF) analysis revealed 520 cells/μL (neutrophils [26.0%], lymphocytes [8.0%), macrophages [66.0%], and eosinophils [0%]). No specific bacteria or fungi were cultured in the BALF. A pulmonary function test showed the following results: forced expiratory volume in 1 s (FEV$_{1.0}$), 3.13 L (with a 15% fall from baseline); total lung capacity (TLC), 5.46 L (with a 7% fall from baseline), and FEV$_{1.0}$/forced vital capacity (FVC), 77.7%. Antibody screening test did not show any donor-specific antibody (DSA) at that time. Steroid pulse therapy was conducted, and the administration of inhaled corticosteroid/beta-agonist and azithromycin were initiated for the treatment of possible CLAD. The administration of nintedanib was also started to manage the progression of IPF. Although clinical symptoms of exertional dyspnea and dry cough improved, the patient was finally diagnosed with possible clinical AMR with presence of DSA against human leukocyte antigen (HLA)-C7 (mean fluorescence intensity: 1517) at 22 weeks after the prime dose. DSA has turned negative one month after the initiation of IVIG therapy. A BALF analysis showed 380 cells/μL.

**Case 2: CLAD progression**

The patient was a 64-year-old male who had received bilateral living-donor lobar lung transplantation for IPF 10 years previously. The maintenance immunosuppressive drugs consisted of cyclosporine (trough level: 150–250 ng/ml), MMF (250 mg/day), and prednisone (10 mg [0.2 mg/kg], every other day). At one year after transplantation, the pulmonary function had gradually decreased due to possible clinical AMR with the presence of DSA against HLA-DQ4 (mean fluorescence intensity: 14,990.1) and -DQ8 (mean fluorescence intensity: 11,731.3). Following steroid pulse and IVIG (1 g/kg) therapy, DSA gradually decreased and eventually disappeared eight years after transplantation. The pulmonary function had remained stable with a FEV$_{1.0}$ of 1.9 L since then.

The patient was referred to our outpatient clinic with worsening exertional dyspnea one week after the first dose of SARS-CoV-2 vaccination. S-IgG was not detected three weeks after the prime dose and S-IgG level was 15.2 U/ml four weeks after the second dose. Ground-glass opacities extended in both lower lobes and pleural effusion was increased on the right side on chest CT (Fig. 4). A pulmonary function test showed the following results: FEV$_{1.0}$, 1.67 L (with a 23% decline from baseline), TLC, 3.22 L (with a 15% fall from baseline), and FEV$_{1.0}$/FVC, 92.8%. DSA was not detected. A BALF analysis showed 380 cells/μL.
μL (neutrophils [1.0%], lymphocytes [3.0%], macrophage [96.0%], and eosinophils [0%]), and no specific bacteria and fungi were detected in the BALF culture. The patient was clinically diagnosed with CLAD stage 1, restrictive allograft syndrome phenotype, which was treated by steroid pulse therapy, conversion of cyclosporine to tacrolimus, administration of azithromycin, and home oxygen therapy. However, the patient has gradually been deteriorating with worsening ground-glass opacities on chest CT.

Discussion

The current study evaluated the immune response and adverse events after two-dose SARS-CoV-2 vaccination to determine the efficacy and safety of the vaccine in lung transplant recipients. A significantly reduced humoral immune response was found in lung transplant patients, even after two-dose vaccination, with only 27.8% showing positive S-IgG levels at four weeks after the second dose. This finding is consistent with previous studies that reported a diminished antibody response (0–36%) after the two-dose SARS-CoV-2 mRNA vaccine in lung transplant patients [9–12]. However, in this study, the antibody response increased from 11.1% after the first dose to 27.8% after the second dose, which indicates that booster dose had an accretive, although moderate, effect on antibody production in lung transplant patients. Importantly, early reports provided evidence of an increase in the serologic response after the third dose of SARS-CoV-2 vaccine in solid organ transplant recipients [13, 14]. Furthermore, a recent study reported that lung transplant recipients with no antibody response after two doses of SARS-CoV-2 vaccine showed a cellular response (47%) and humoral response (13%) at three weeks after the third dose, although the effect of the third dose on antibody generation was still moderate [15]. Therefore, considering the increase in seropositivity between the first, second, and third vaccine doses, further studies are needed to elucidate the potential benefits of an additional booster dose on antibody production among immunocompromised organ transplant recipients.

In this study, S-IgG development appeared to be associated with low-dose MMF and a longer time from transplantation to vaccination, which is consistent with previous reports [9, 16, 17]. However, temporary adjustment of immunosuppressive regimens during and/or after vaccination, with a possible increase in the risk of graft rejection, should not be considered in lung transplant recipients. Notably, possible clinical AMR or CLAD progressed in the seropositive patients after two-dose vaccination, and the association between these adverse events and SARS-CoV-2 vaccination should be investigated. Although this seems to be the first report on the progression of clinical AMR and CLAD in post-lung transplant patients following SARS-CoV-2 vaccination. To confirm lung graft rejection, a biopsy of lung tissue needs to be performed. One weak point associated with this paper is due to the fact that we diagnosed both AMR and CLAD progression clinically without performing transbronchial lung biopsies due to the patients’ poor respiratory condition and refusal. However, it is true that the two patients who lived independently and had been stable for many years after undergoing surgery, clearly developed a worsening of their symptoms after receiving the two-dose vaccination including a worsening of their clinical respiratory condition, a deterioration of their pulmonary function and the new appearance of Fig. 4 Time course of the progression of chronic lung allograft rejection (CLAD) after D1 and D2 in case 2. On chest CT a week after D2 (②), ground-glass opacities were extended in both lower lobes and pleural effusion was increased on the right side. These findings were not observed on chest CT six months before vaccination (①). TLC, total lung capacity. FVC, forced vital capacity. FEV1.0, forced expiratory volume in 1 s. BAL, bronchoalveolar lavage. CT, computed tomography. DSA, donor-specific antibody.
anti-HLA antibody production and CLAD development in and B cells, which could be a trigger of donor-specific mRNA vaccine, stimulates robust cellular and humoral responses induced by eliciting CD4+ and CD 8+ T cells and B cells, which could be a trigger of donor-specific anti-HLA antibody production and CLAD development in responders to the SARS-CoV-2 vaccine [21–23].

In the first case, pulmonary fibrosis was also exacerbated in the left native lung with IPF, following the receipt of the second vaccine dose. There have been some case reports on the acute exacerbation of interstitial pneumonia or IPF after SARS-CoV-2 vaccination [24, 25]. The chest CT findings in the left native lung following vaccination were consistent with those observed in previous case reports. Cellular and/or humoral immunologic responses induced by the SARS-CoV-2 vaccine may contribute to the acute exacerbation of IPF [26].

The present study was associated with some limitations, including its small size, the absence of a healthy control group, and the fact we only assessed the S-IgG levels and did not assess neutralizing antibody titers or memory T-cell response. The small sample size might affect the relatively high rate of lung allograft rejection following COVID-19 vaccination in this study. However, despite the small sample size of the present study, which reported preliminary data, it included the important experience of severe adverse events, including clinical AMR and the deterioration of CLAD and IPF, after SARS-CoV-2 vaccination in post-lung transplant patients. Furthermore, despite the absence of a healthy control group, which made true comparison difficult, the robust 100% antibody response rate, observed in clinical trials among the healthy population, was a reasonable benchmark. [27] A recent study suggested that SARS-CoV-2-specific T-cells may be present in some lung transplant recipients despite the lack of antibody response [8, 13].

In conclusion, lung transplant recipients showed a reduced S-IgG antibody response after the completion of a two-dose series of SARS-CoV-2 mRNA vaccine, which indicates that lung transplant recipients will likely remain at risk of developing severe COVID-19, even after SARS-CoV-2 vaccination. However, the true test of the SARS-CoV-2 vaccine is its clinical efficacy in reducing the severity of COVID-19 and associated mortality [27–29]. Therefore, further study is required to determine whether the decreased humoral response after SARS-CoV-2 vaccination that was observed in the present study is truly associated with lower clinical efficacy. Regarding the critical side effects, we experienced seropositive cases that developed clinical AMR and a deterioration of CLAD and IPF that was likely related to the SARS-CoV-2 vaccine. We have now followed these patients for less than 1 year. To really understand the magnitude of these adverse events, it would thus be helpful to have a much longer follow-up of these patients’ courses.

Funding This study was supported by a Grant-in-Aid for Investigation of Promotion of Health Labor Administration (Research Project for Promotion of Policies for Emerging and Re-emerging Infectious Diseases and Immunization) [Principal Investigator: Yoshio Hirota; Grant Number: 20HA2001].

 Declarations
Conflict of interest The authors declare no conflicts of interest in association with the present study.

References
1. Saez-Gimenez B, Berastegui C, Barrecheguren M, et al. COVID-19 in lung transplant recipients: a multicenter study. Am J Transplant. 2021;21:1816–24.
2. Messika J, Eloy P, Roux A, et al. COVID-19 in lung transplant recipients. Transplantation. 2021;105:177–86.
3. Aversa M, Benvenuto L, Anderson M, et al. COVID-19 in lung transplant recipients: a single center case series from New York City. Am J Transplant. 2020;20:3072–80.
4. Kamp JC, Hinrichs JB, Fuge J, Ewen R, Gottlieb J. COVID-19 in lung transplant recipients-risk prediction and outcomes. PLoS ONE. 2021;16:e0257807.
5. Surgery C, Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic. ISHLT 2020: 2–16. Published online.
6. SARS-CoV-2 Vaccination in Heart and Lung Transplantation: Recommendations from the ISHLT COVID-19 Task Force. Accessed April 15, 2021. https://ishlt.org/ishlt/media/Documents/COVID19_Vaccine-Recommendations_3–15–2021.pdf.
7. Uysal EB, Gümiş S, Bektöre B, Bozkurt H, Gözalan A. Evaluation of antibody response after COVID-19 vaccination of healthcare workers. J Med Virol. 2021;94:1060.
8. Kaku N, Nishiuma F, Shigeishi Y, et al. Performance of anti-SARS-CoV-2 antibody testing in asymptomatic or mild COVID-19 patients: a retrospective study in outbreak on a cruise ship. PLoS ONE. 2021;16:e0257452.
9. Hallett AM, Greenberg RS, Boyarsky BJ, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. J Heart Lung Transplant. 2021;40:1579–88.
10. Havlin J, Svoročova M, Dvorackova E, et al. Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients. J Heart Lung Transplant. 2021;40:754–8.
11. Schramm R, Costard-Jackle A, Rivinius R, et al. Poor humoral and T-cell response to two-dose SARS-CoV-2 messenger RNA vaccine BNT162b2 in cardiothoracic transplant recipients. Clin Res Cardiol. 2021;110:1142–9.
12. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA. 2021;325:2204–6.
13. Kamar N, Abravanel F, Marion O, Cout A, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med. 2021;385:661–2.
14. Peled Y, Ram E, Lavee J, et al. Third dose of the BNT162b2 vaccine in heart transplant recipients: immunogenicity and clinical experience. J Heart Lung Transplant. 2022;41:148–57.
15. Havlin J, Skotnicova A, Dvorackova E, et al. Impaired humoral response to third dose of BNT162b2 mRNA COVID-19 vaccine despite detectable spike protein-specific t cells in lung transplant recipients. Transplantation. 2021;106:e183.

16. Aslam S, Danziger-Isakov L, Mehra MR. COVID-19 vaccination immune paresis in heart and lung transplantation. J Heart Lung Transplant. 2021;40:763–6.

17. Kantauskaite M, Müller L, Kolb T, et al. Intensity of mycophenolate mofetil treatment is associated with an impaired immune response to SARS-CoV-2 vaccination in kidney transplant recipients. Am J Transplant. 2022;22:634–9.

18. Del Bello A, Marion O, Delas A, Congy-Jolivet N, Colombat M, Kamar N. Acute rejection after anti-SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant. Kidney Int. 2021;100:238–9.

19. Masset C, Lebot-Bouras S, Branchereau J, Renaudin K, Cantarovich D. Pancreas allograft rejection occurring after ChAdOx1 nCoV-19 vaccine. Diabetes Metab. 2021;48:101303.

20. Vyhmeister R, Enestvedt CK, VanSandt M, Schlansky B. Steroid-resistant acute cellular rejection of the liver after severe acute respiratory syndrome coronavirus 2 mRNA vaccination. Liver Transpl. 2021;27:1339–42.

21. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and Th1 T cell responses. Nature. 2020;586:594–9.

22. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324:782–93.

23. Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to “potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases.” Clin Immunol. 2021;224:108665.

24. Amiya S, Fujimoto J, Matsumoto K, et al. Case report: acute exacerbation of interstitial pneumonia related to messenger RNA COVID-19 vaccination. Int J Infect Dis. 2022;116:255–7.

25. Ghincea A, Ryu C, Herzog EL. An acute exacerbation of idiopathic pulmonary fibrosis after BNT162b2 mRNA COVID-19 vaccination: a case report. Chest. 2022;161:e71–3.

26. Luppi F, Cerri S, Taddei S, Ferrara G, Cottin V. Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. Intern Emerg Med. 2015;10:401–11.

27. Frenchk RJ Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med. 2021;385:239–50.

28. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16.

29. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.