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ABSTRACT

Background. There are insufficient reports on the immunogenicity and safety of the COVID-19 vaccination after lung transplantation in Korea.

Methods. Between April and September 2021, lung transplant recipients (n = 52) and healthy controls (n = 22) underwent vaccination. The levels of antibodies were assessed prospectively at 4 weeks after priming and second dose.

Results. Of a total of 52 lung transplant recipients, there were 84.6% nonresponders, 15.4% second-dose responders, and 0% primary dose responders. Among healthy controls, 63.6% were priming responders, and 18.2% were second-dose responders, and 18.2% were nonresponders. Compared with the control group, lung recipients were less likely to develop antibodies ($P < .001$). Antibody formation tended to be higher in recipients more than 1 year after transplantation (0 vs 20.5%, $P = .076$). No major safety events were reported, and the adverse symptoms were mild and consistent with those of the general population. In a multivariate regression analysis, mycophenolic acid levels (µg/mL) (odds ratio 0.25, $P = .005$) and tacrolimus level (ng/mL) (odds ratio 0.65, $P = .035$) were significantly associated with antibody formation.

Conclusions. The immunogenicity of the second dose of COVID-19 vaccination with various combinations was substantially low in lung transplants. A booster of the COVID-19 vaccine is warranted in lung transplants, especially a year later.

LUNG transplant recipients are at a high risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. SARS-CoV-2 vaccination may reduce the morbidity and mortality of COVID-19 in lung transplant recipients [2]. Currently, the International Society for Heart and Lung Transplantation guidelines strongly recommend SARS-CoV-2 vaccination in transplant candidates and recipients [3]. There is a paucity of literature regarding the efficacy of SARS-CoV-2 vaccination in lung transplantation recipients. In a previous study, solid organ transplant recipients who received 2 doses of the BNT162b2 (Pfizer/BioNTech) or mRNA1273 (Moderna) vaccine showed dramatically reduced humoral response, with only 15% of individuals developing antispike antibodies after dose 1 (D1), 46% of individuals developing no antibodies, and 39% of individuals developing antibodies only after dose 2 (D2) [4]. However, lung transplant recipients show a diminished antibody response after vaccination [5]. Only 9% of the individuals

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were priming dose responders, 27% were second-dose responders, and 64% were nonresponders after messenger RNA (mRNA) vaccination [5]. In Korea, 1 human adenovirus vector-based vaccine and 2 SARS-CoV-2 mRNA vaccines were previously available; several solid organ transplant recipients have received human adenovirus vector-based vaccines. While the coronavirus pandemic is expected to continue, the data specifically received human adenovirus vector-based vaccines. While the coronavirus pandemic is expected to continue, the data specifically

MATERIALS AND METHODS

Study Population

The study population consisted of 2 cohorts, SARS-CoV-2 infection-naive healthy controls (n = 22) and lung transplant recipients (n = 52) (Fig 1). We prospectively enrolled patients aged >18 years who underwent lung transplantation between 2016 and 2020 and completed a 2-dose vaccine course between April and September 2021 after informed consent was obtained. The data on age, sex, body mass index, transplant date, medications, other immune conditions, allergies, and vaccination information were collected. For comparison, we retrospectively conducted antibody tests on healthy controls who received a 2-dose vaccination course. Blood was collected from healthy controls in a Pusan National University Yangsan Hospital biobank after obtaining informed consent. The biobank provided well-banked samples and clinical data were collected. The study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (05-2021-151).

Blood Specimen Collection and Testing

The samples were collected 4 weeks after D1 and 4 weeks after D2 in lung transplant recipients and healthy controls. Antibody tests for SARS-CoV-2 were performed using the quantitative Elecsys Anti-SARS-CoV-2 S assay (Elecsys Anti-S; Roche Diagnostics, Mannheim, Germany) with a Cobas 8000 e801 unit (Roche Diagnostics). The Elecsys anti-S assay uses a recombinant protein representing the receptor binding domain of the S antigen, which favors the quantitative determination of high-affinity antibodies against SARS-CoV-2. The results are reported as the concentration of antibodies with a measurement range of 0.4 to 250 U/mL; samples with values above the measuring range were diluted 10-fold. The values <0.8 U/mL were interpreted as nonreactive (negative) and ≥0.8 U/mL as reactive (positive).

Antibody Response After SARS-CoV-2 Vaccination

The participants were divided into 3 categories according to the immunosassay results. Those who developed positive results after both doses (1 and 2, D1, D2) were classified as priming dose responders. Those who failed to develop antibodies after both doses were classified as nonresponders. If an individual failed to develop antibodies after D1, but subsequently did so after D2, they were classified as second-dose responders.

Reactogenicity and Adverse Events After SARS-CoV2 Vaccination

The questionnaires were distributed to the participants 7 days after D1 and D2. After each dose, the participants were asked if they had received new diagnoses of COVID-19, other infections, acute rejection, or neurologic illness, and if so, whether they required hospitalization, intensive care unit management, or mechanical ventilation. Local symptoms, including pain, redness, and swelling, as well as systemic adverse reactions, including fever, fatigue, headache, chills, vomiting, diarrhea, and myalgia, were resolved. The incidence of COVID-19 infection was followed after vaccination in patients and controls. The median follow-up period was 343 days (interquartile range [IQR] 308.3-478 days).

Statistical Analysis

Continuous variables are presented as the median and IQR, and categorical variables are presented as counts and percentages. The χ² or Fisher’s exact test or Mann–Whitney test was used for categorical and continuous variables, respectively. Univariate and multivariate regression analyses were performed. The statistical significance was set at P ≤ .05. Statistical analyses were conducted using IBM SPSS Statistics v25.

RESULTS

Study Population Demographics and Clinical Characteristics

No patient had a prior polymerase chain reaction that confirmed the diagnosis of COVID-19. Among lung transplant recipients, the median age was 60 years (IQR 53-66 years), and 65.4% were men (Table 1). The median body mass index was 21.7 (IQR 19.6-24.9). The median age tended to be lower in the healthy control group than that in the lung transplant group (60 vs 36 years, P = .060).

The median time since transplant was 525.5 days (IQR 267-881.5 days). The most common maintenance immunosuppressive regimen was a combination of tacrolimus, mycophenolate, and prednisone (82.7%). There was a significant difference in the vaccine type between the 2 groups (P < .001). Notably, 34 individuals (65.4%) received the ChAdOx1 vaccine, 10 individuals (19.2%) received the BNT162b2 vaccine, and 8 individuals (15.4%) received the mRNA-1273 vaccine for D1. Additionally, 29 individuals (55.8%) received the ChAdOx1 vaccine, 15 individuals (28.8%) received the BNT162b2 vaccine, and 8 individuals (15.4%) received the mRNA-1273 vaccine for D2. The healthy control group received the BNT162b2 vaccine for both D1 and D2 (100%).

The median vaccine dosing interval was 76 days (42-77 days) for the lung transplant recipients and 55.5 days (53.8-56 days) for the healthy controls (P < .001).

Immunogenicity After Each SARS-CoV-2 Vaccine Dose

Among a total of 52 lung recipients, 15.4% were second-dose responders, 84.6% were nonresponders, and none were priming responders. Among healthy controls, 63.6% were priming responders, 18.2% were second-dose responders, and 18.2% were nonresponders. The median antibody titers were significantly different between lung transplant recipients and controls (D1
Table 1. Demographic and Clinical Characteristics of Lung Transplant Recipients Who Completed a 2-Dose SARS-CoV-2 Vaccine Series

| LT Recipients (n = 52) | Healthy control (n = 22) | P |
|------------------------|--------------------------|---|
| **Age**                | 60 [53-66]               | 36 [29-59.5] | .060 |
| **Male**               | 34 (65.4)                | 13 (59.1) | .607 |
| **BMI, kg/m²**         | 21.7 [19.6-24.9]         | 21.5 [20.0-23.4] | .758 |
| **Days from transplant to priming vaccine** | 525.5 [267-881.5] | |
| Maintenance immunosuppression | Tacrolimus | 52 (100) |
|                        | Mycophenolate | 45 (86.5) |
|                        | Corticosteroids | 52 (100) |
|                        | Sirolimus | 4 (7.7) |
|                        | Azathioprine | 4 (7.7) |
|                        | Everolimus | 1 (1.9) |
| Maintenance immunosuppression combination | Quadruple (Tacrolimus, sirolimus, mycophenolate, prednisone) | 4 (7.7) |
|                        | Quadruple (Tacrolimus, everolimus, azathioprine, prednisone) | 1 (1.9) |
|                        | Triple (Tacrolimus, mycophenolate, prednisone) | 43 (82.7) |
|                        | Triple (Tacrolimus, azathioprine, prednisone) | 3 (5.8) |
|                        | Dual (Tacrolimus, steroid) | 3 (5.8) |
| **Vaccine type-priming/booster** | Oxford AstraZeneca/Oxford AstraZeneca | 29 (55.8) | 0 | <.001 |
|                        | Oxford AstraZeneca/Pfizer-BioNTech | 5 (9.6) | 0 |
|                        | Pfizer-BioNTech/Pfizer-BioNTech | 10 (19.2) | 22 (100) |
|                        | Moderna/Moderna | 8 (15.4) | 0 |

Data are presented as median [interquartile range] or N (percentage). BMI, body mass index; LT, lung transplant.

In lung transplant recipients, no significant differences were observed with respect to the age, sex, or time since transplantation (Table 2). Antibody formation tended to be higher in recipients more than 1 year after transplantation (0 vs 20.5%, P = .076). The antibody titer according to the time since transplant are presented in Fig 3. The median D2 antibody level was 1.4 (0.9-6.3) for second-dose responders and 0 U/mL (IQR 0-0 U/mL) for nonresponders. No association was observed between the vaccine type and antibody response. The rates of usage of antimetabolite agents were significantly lower in the second-dose responders compared with nonresponders (75% vs 97.7%, P = .011). The median tacrolimus level was significantly lower in the second-dose responders (7.2 vs 11 ng/mL, P = .003). In addition, the median mycophenolic acid level was significantly lower in the second-dose responders (1.2 vs 3.3 μg/mL, P = .006).

**Fig 1.** Patient enrollment. Among 52 lung recipients, 15.4% were second-dose responders, 84.6% were nonresponders, and none were priming responders.

**Fig 2.** 2021 April – May Covid 19 vaccination N=74

**2021 April – May Covid 19 vaccination N=74**

- **Lung transplantation N=52**
  - After 4 weeks of first vaccination
    - Antibody test (+), 0%
  - After 4 weeks of second vaccination
    - Antibody test (+), 15.4%

- **Control N=22**
  - After 4 weeks of first vaccination
    - Antibody test (+), 63.6%
  - After 4 weeks of second vaccination
    - Antibody test (+), 81.8%

ChAdOx1/ChAdOx1 4/29, 13.8%  
ChAdOx1/BNT162b2 1/5, 20%  
BNT162b2/BNT162b2 2/10, 20%  
mRNA-1273/mRNA-1273 1/8, 12.5%

BNT162b2/BNT162b2 18/22, 81.8%
Factors Associated With Antibody Formation in Lung Transplant Recipients

In a univariate regression analysis, antimetabolite agents (odds ratio [OR] 0.07, 95% confidence interval [CI] 0.01-0.89, P = .041), mycophenolic acid level (μg/mL) (OR 0.31, 95% CI 0.15-0.66, P = .002), and tacrolimus level (ng/mL) (OR 0.75, 95% CI 0.58-0.97, P = .027) were significantly associated with antibody formation (Table 3). The time since transplantation (more than 1.5 years) (OR 6.39, 95% CI 0.73-56.38, P = .095) tended to be associated with antibody formation. In a multivariate regression analysis, mycophenolic acid levels (μg/mL) (OR 0.25, 95% CI 0.10-0.66, P = .005) and tacrolimus level (ng/mL) (OR 0.65, 95% CI 0.43-0.97, P = .035) were significantly associated with antibody formation.

COVID-19 Infection After Vaccination

A total of 11 patients developed COVID-19 infection after vaccination. Seven patients (13.5%) were lung transplant patients and 4 (18.2%) were healthy controls (P = .602). In lung transplant recipients, 2 patients were second-dose responders and 5 patients were nonresponders. The median time from vaccination to COVID-19 infection was longer in second-dose responders than in nonresponders (221 vs

Table 2. Demographic and Clinical Characteristics of Lung Transplant Recipients According to Antibody Response

| Variables                        | Second-dose Responders (n = 8) | Nonresponders (n = 44) | P     |
|----------------------------------|---------------------------------|------------------------|-------|
| Age                              | 61 [50.5-68.8]                  | 60 [53.5-66]           | .812  |
| Sex                              | 5 (62.5)                        | 29 (65.9)              | .852  |
| Days from transplant to booster vaccine | 869.5 [593-1178.3]              | 559.5 [290.3-954]      | .769  |
| Days from transplant to booster vaccine |                      |                        | .342  |
| 3-6 mo                           | 0                               | 1 (2.3)                |       |
| 6 mo to 1 y                      | 0                               | 12 (27.3)              |       |
| 1-2 y                            | 3 (37.5)                        | 14 (31.8)              |       |
| >2 y                             | 5 (62.5)                        | 17 (38.6)              |       |
| Includes antimetabolites maintenance immunosuppression | 6 (75)                        | 43 (97.7)              | .011  |
| Tacrolimus level, ng/mL          | 7.2 [6.1-8.8]                   | 11 [9–13]              | .002  |
| Tacrolimus level, ng/mL          |                                 | .011                   |
| >10                              | 0                               | 25 (56.8)              |       |
| 8-10                             | 3 (37.5)                        | 9 (20.5)               |       |
| ≤8                               | 5 (62.5)                        | 10 (22.7)              |       |
| Mycophenolic acid level, μg/mL   | 1.2 [0.2-1.8]                   | 3.3 [2.6-4.6]          | .006  |
| Mycophenolic acid level, μg/mL   |                                 | <.001                  |
| >3.5                             | 0                               | 17 (38.6)              |       |
| 2-3.5                            | 1 (12.5)                        | 22 (50.0)              |       |
| ≤2                               | 7 (87.5)                        | 5 (11.4)               |       |
| Vaccine types-priming/booster    |                                 |                        | .950  |
| Oxford AstraZeneca/Oxford AstraZeneca | 4 (50)                        | 25 (56.8)              |       |
| Oxford AstraZeneca/Pfizer-BioNTech | 1 (12.5)                        | 4 (9.1)                |       |
| Pfizer-BioNTech/Pfizer-BioNTech | 2 (25)                          | 8 (18.2)               |       |
| Moderna/Moderna                  | 1 (12.5)                        | 7 (15.9)               |       |
| COVID-19 infection               | 2 (25)                          | 5 (11.4)               | .299  |
| Time from vaccine to COVID-19 infection | 221 (204)                   | 182 [138-204]          | .053  |

Data presented as median [interquartile range] or N (percentage).
182 days, \( P = .053 \). None of the patients required oxygen therapy or developed pneumonia.

Reactogenicity After Each SARS-CoV-2 Vaccine Dose

Myalgia was most commonly reported reaction (48.1% after D1, 22.2% after D2), and pain at the injection site was the second-most commonly reported reaction after vaccination (14.8% after D1, 44.4% after D2), followed by fatigue (7.4% after D1, 16.7% after D2), fever (7.4% after D1, 5.6% after D2), and headache (3.7% after D1, 5.6% after D2) (Fig 4). Severe symptoms were absent, and no major safety events, such as acute rejection, new neurologic illness, or anaphylaxis were reported.

DISCUSSION

In this study of 52 lung transplant recipients who were administered 2 doses of SARS-CoV-2 vaccines, we found dramatically diminished antibody responses compared with healthy controls. Only 15.4% developed antibodies after the second dose (second-dose responders), and 84.6% failed to develop antibodies at all (nonresponders). A small number of lung transplant recipients showed reactogenicity to various SARS-CoV-2 vaccine regimens. No major safety events were reported, and adverse symptoms were mild and consistent with those of the general population. With the second dose of SARS-COV-2 vaccination, lung transplant recipients experience an attenuated humeral response, which may be suboptimal.

These findings are consistent with published reports of diminished antibody responses in lung transplant recipients after administration of SARS-CoV-2 mRNA and human adenovirus vector-based vaccines [5–9]. In a recent study, 53% of heart and lung transplant recipients received human adenovirus vector-based vaccines [5]. The seroconversion rate of human adenovirus vector-based vaccines was lower than BNT1262b2 (10% vs 44%, \( P = .03 \)). There were no significant differences in the median anti-S levels (0.56 vs 2.28 binding antibody U/mL, \( P = .183 \)) or T-cell response (23% vs 19%, \( P = .58 \)) between transplant recipients who received BNT162b compared with ChAdOx110. In this study, 29 patients received 2 doses of human adenovirus vector-based vaccines, and only 13.8% of subjects showed antibody formation after a second shot. This may be one of the reasons for the very low seroconversion rate in our lung transplant cohort. Even though we did not check the T-cell response, this implies that the second dose of SARS-CoV-2 vaccination might be suboptimal in this population.

Another reason for the suboptimal seroconversion rate is that most lung transplants in this cohort were within 1 year after lung transplantation, which were under high levels of immunosuppression compared with populations in other studies [10]. Antimetabolic agent use was also associated with lower immunogenicity, as in a previous study [4,11]. In particular, in a multivariate regression analysis, mycophenolic acid levels (\( \mu g/mL \)) and tacrolimus level were significantly associated with antibody formation. This suggests 2 points of view regarding SARS-CoV-2 vaccination in lung transplants. First, the booster dose of SARS-CoV-2 vaccine can be suboptimal for 1 year after lung transplantation. An additional booster is needed to achieve optimal protective effect against SARS-CoV-2 vaccination. Second, it may be necessary to withhold or lower the level of immune suppressant before vaccination.

Currently, SARS-CoV-2 mRNA, human adenovirus vector-based, and protein-based vaccines are available. In these data, 2 doses of SARS-CoV-2 vaccination did not achieve an acceptable level of antibody response irrespective of the regimen or combination of available vaccines. Given the evidence regarding vaccination in lung transplantation, third shots are warranted, especially within a year after lung transplantation [12,13]. Additionally, human adenovirus vector-based vaccines are relatively unacceptable for inducing humoral immunogenicity.

Table 3. Factors Associated With Antibody Formation in Lung Transplant Recipients

|                      | Univariate Analysis |                      | Multivariate Analysis |
|----------------------|---------------------|----------------------|----------------------|
|                      | OR (95% CI)         | \( P \)              | OR (95% CI)         | \( P \)              |
| Antimetabolic agent  | 0.07 (0.01-0.89)    | .041                 |                      |                     |
| Mycophenolic acid level (\( \mu g/mL \)) | 0.31 (0.15-0.66)  | .002                 | 0.25 (0.10-0.66)    | .005                 |
| Tacrolimus level (ng/mL) | 0.75 (0.58-0.97) | .027                 | 0.65 (0.43-0.97)    | .035                 |
| Time since transplantation (more than 1.5 y) | 6.39 (0.73-56.38) | .995                 |                      |                     |

CI, confidence interval; OR, odds ratio.
This study has several limitations as a pilot trial to examine the immunogenicity of 2 doses of SARS-CoV-2 vaccination. The number of populations was limited, regimens were heterogeneous, and there were differences in the duration between vaccination doses. Nevertheless, this has meaningful points regarding SARS-CoV-2 vaccination in lung transplant recipients under high immunosuppressive agents. An additional booster is required during the first year of transplantation under relatively high immunosuppressant use, and may require stopping or reducing the administration of antimeatabolic agents before vaccination.

In conclusion, this study confirmed attenuated responses to ChAdOx1, BNT162b2, and mRNA-1273 vaccines in lung transplant recipients. In particular, depending on the amount of immunosuppressants used and the transplant period, they may have an immunologic disadvantage and are unlikely to produce robust humoral or cellular immune responses to SARS-CoV-2. Further studies are required to evaluate vaccine immunogenicity and efficacy after each booster dose in this cohort.

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