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Original Article

Immunogenicity and safety of SARS-CoV-2 vaccine with immunosuppressive agents

Short running title: SARS-CoV-2 vaccine in immunosuppressants

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Abstract

Background

We conducted a prospective study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccination of children and adolescents who were taking immunosuppressive agents.

Methods

Two doses of SARS-CoV-2 mRNA vaccine were administered to patients taking immunosuppressive agents. Titers of SARS-CoV-2 spike protein receptor-binding domain antibodies were measured before and after vaccination. Vaccine failure was defined as a postvaccination antibody titer of <0.8 U/mL. Seroconversion rates, factors associated with antibody titers after vaccination, clinical effectiveness against breakthrough infection, and adverse events were evaluated.

Results

A total of 42 patients (median age, 18.1 years) were enrolled. Immunogenicity was measured in 34. The median SARS-CoV-2 spike antibody titer was 329 U/mL (interquartile range [IQR] 50–812 U/mL). Seroconversion (≥0.8 U/mL) was achieved in 29 patients (85%), whereas vaccine failure was diagnosed in 5 (15%). All patients with vaccine failure were recipients of solid organ transplants (SOTs) and were taking two immunosuppressants. The median antibody titer in SOT recipients (57 U/mL) was significantly lower than that in nonrecipients (653 U/mL, $p = 0.0002$), and that of patients taking two immunosuppressive agents (93 U/mL) was lower than that of patients taking one (506 U/mL, $p = 0.003$). Breakthrough infection occurred in three patients (7%). Adverse events were nonspecific, and no flares of primary disease or acute rejection in SOT recipients occurred.

Conclusions

SARS-CoV-2 mRNA vaccine was immunogenic in children and adolescents taking immunosuppressive agents, although SOT recipients and patients taking two immunosuppressive agents tended to show lower postvaccination antibody titers.

Keywords

adolescents, children, immunosuppressive agents, SARS-CoV-2 mRNA vaccine, solid organ transplant recipients

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reportedly carries high risk for mortality in patients taking immunosuppressive agents, especially among solid organ transplant (SOT) recipients. Patients treated with immunosuppressants account for 10–30% of deaths.[1,2] Outcomes of this disease have been more favorable in children and young adolescents than in older patients,[3-5] even among pediatric patients who take immunosuppressive agents.[6,7] However, further research is necessary.

SARS-CoV-2 messenger RNA (mRNA) vaccines are effective in preventing the spread of COVID-19 in the general population. However, a reduced humoral immune response after vaccination was reported in patients taking immunosuppressive agents, especially in adult SOT recipients[8-12], i.e., 30–50%, which is much lower than those in immunocompetent people (nearly 100%). On the other hand, the seroconversion rates among patients with rheumatic disease were reported as relatively high (80–90%).[13-15] Few studies of SARS-CoV-2 mRNA vaccines in children or young adolescents taking immunosuppressive agents have been performed.[16-18]

We conducted a prospective study of SARS-CoV-2 mRNA vaccination in children and young adolescents who took immunosuppressive agents to evaluate the immunogenicity and safety of the vaccine in such patients.

Methods

Study design and patient population

This prospective observational study was performed between April 2021 and March 2022. During the study period, we experienced fourth, fifth and sixth COVID-19 epidemic waves. In the forth, fifth and sixth waves, the predominant variant strains were the Alfa, Delta and Omicron variants. The study included patients taking immunosuppressive

agents who were scheduled to receive a SARS-CoV-2 mRNA vaccine in the Division of Nephrology and Rheumatology at the National Center for Child Health and Development, Tokyo, Japan. During this study period, a SARS-CoV-2 mRNA vaccine was approved in Japan for people aged ≥12 years. All patients were vaccinated while their preexisting disease activity was stable.

Study protocol

After obtaining informed consent from study participants or their guardians, we measured the antibody titer of SARS-CoV-2 spike protein receptor-binding domain antibodies (SARS-CoV-2 spike antibodies). $CD4^+$ T cell counts, lymphocyte blast transformation induced by phytohemagglutinin, and serum immunoglobulin G (IgG) levels were also evaluated as immunological parameters. The study participants were immunized with either BNT162b2 (Pfizer-BioNTech, Cambridge, MA, USA) or mRNA-1273 (Moderna, Cambridge, MA, USA) SARS-CoV-2 mRNA vaccines, for which the recommended intervals between the two doses were 21 and 28 days, respectively. For each patient, both doses were from the same manufacturer. The SARS-CoV-2 spike antibody titer was examined between 2 weeks and 3 months after the second dose in all patients. To evaluate adverse events observed within 1 month after vaccination, we administered a questionnaire (Table 1).

Consent to participate and for publication

Written informed consent to participate and for publication of data was obtained from the guardians of patients aged <15 years, from 15- to 20-year-old patients and their guardians, and from patients aged ≥20 years before study enrollment.

Antibody testing

To measure SARS-CoV-2 spike antibody titers, we used the commercially available Elecsys Anti-SARS-CoV-2 S semiquantitative immunoassay (Roche, Basel, Switzerland). Values of <0.8 U/mL were considered negative, based on the manufacturer's definition. Immunogenicity was evaluated in patients with negative titers (<0.8 U/mL) before vaccination. Antibody titers of ≥0.8 U/mL after vaccination indicated seropositivity. Antibody titers of <0.8 U/mL after vaccination indicated vaccine failure.

Study outcomes

The primary outcome of the study was the seroconversion rate after SARS-CoV-2 mRNA vaccination. To identify factors associated with antibody titers after vaccination, we compared the characteristics of two groups: patients with positive titers (≥0.8 U/mL) and those with negative titers (<0.8 U/mL). We evaluated the clinical efficacy of the vaccination by reviewing patients' charts for records of breakthrough infection. Breakthrough infection is defined as SARS-CoV-2 disease which accompanied with symptoms (fever, cough, etc) and positive SARS-CoV-2 virus proved by antigen test or polymerase chain reaction. The observation period ended on March 31, 2022. We also examined the frequency of local adverse events (pain, redness, and swelling) and systemic adverse events (fever, fatigue, headache, and vomiting), as well as the incidence of an exacerbation of primary disease after vaccination.

Statistical analysis

Results were calculated as medians with interquartile ranges (IQRs) for continuous variables and as numbers with percentages for categorical variables. To compare clinical and immunological factors between the two groups, we used the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant. All statistical analyses were performed with JMP 16.0 (SAS Institute Japan Ltd., Tokyo, Japan).

Ethics approval

This study was performed in accordance with the Declaration of Helsinki and with ethical guidelines issued by the Ministry of Health, Labor, and Welfare of Japan. This study was approved by the ethics committee of the National Center for Child Health and Development, Tokyo, Japan (no. 2020-359).

Results

Patient characteristics

Of the 42 patients enrolled in this study (Fig. 1), 8 were excluded from the seroconversion analysis: 2 whose antibody titers were positive before vaccination (probably because of asymptomatic infection beforehand) and 6 whose antibody titers were not measured before vaccination. Vaccine immunogenicity was evaluated in the remaining 34 patients. Adverse events were evaluated in all patients except one whose responses to a questionnaire were lost. Table 2 lists the patient characteristics. The median age at vaccination was 18.1 years, and almost half the study participants were ≥18 years of age. The primary diseases or conditions for which all 42 patients were taking immunosuppressants were solid organ transplantation in 15 (35.7%), rheumatic disease in 25 (59.5%), and kidney disease in 2 (4.8%). Eighteen patients (42.9%) were taking two immunosuppressive agents, and 21 (50%) were taking steroids. All patients completed two doses of vaccination; 37 (88.1%) received the BNT162b2 vaccine.

Seroconversion rates after vaccination

All 34 patients included in the seroconversion analysis had SARS-CoV-2 spike antibody titers of <0.4 U/mL before vaccination. Twenty-nine patients (85%) achieved seroconversion (Table 2). Vaccine failure was diagnosed in five

patients (15%), whose antibody titers were <0.4 U/mL after vaccination. Three of these five patients were using tacrolimus and The median SARS-CoV-2 spike antibody titer was 329 U/mL (IQR, 50–812 U/mL; Fig. 2a). Fig. 2b depicts the relationship between the SARS-CoV-2 spike antibody titer and the elapsed time after the second dose.

Comparison between patients with positive and negative antibody responses to SARS-CoV-2 mRNA vaccination

We compared clinical and immunological parameters of patients with positive SARS-CoV-2 spike antibody titers (≥0.8 U/mL) with those of patients with negative titers (<0.8 U/mL; Table 3). Receipt of SOTs ($p = 0.01$) and use of two immunosuppressive agents ($p = 0.047$) were associated with negative antibody titers. All five patients with vaccine failure were SOT recipients and were taking two immunosuppressive agents (three were taking tacrolimus and mycophenolate mofetil [MMF] and two were taking MMF and everolimus). The median antibody titer of SOT recipients (57 U/mL) was significantly lower than that of the other patients (653 U/mL; $p = 0.0002$; Fig. 3a). The median antibody titer of patients taking two immunosuppressive agents (93 U/mL) was also significantly lower than that of patients taking only one (506 U/mL; $p = 0.003$; Fig. 3b). Of the 15 SOT recipients, all were taking two immunosuppressive agents; in contrast, only 3 of 19 SOT nonrecipients (16%) were taking two immunosuppressive agents ($p < 0.0001$). Median antibody titers of non-SOT patients taking one and two immunosuppressive agents were 964 U/ml and 916 U/ml, respectively ($p = 0.56$).

Immunological parameters, such as serum IgG levels, $CD4^+$ T cell counts, and phytohemagglutinin-stimulation index, were not related to the rate of seropositivity.

Breakthrough infection after vaccination during the study period

Of the original 42 patients, 3 (7%) experienced breakthrough infection 152, 227, and 247 days, respectively, after the second dose. All three patients had rheumatic disease (systemic lupus erythematosus, dermatomyositis, and antineutrophil cytoplasmic antibody vasculitis), and their SARS-CoV-2 spike antibody titers were positive (216, 6780, and 24.2 U/mL) after vaccination. One patient was taking two immunosuppressive agents (tacrolimus and MMF) for systemic lupus erythematosus, and the other two were taking one immunosuppressive agent (MMF). All three patients had a mild course of breakthrough infection and recovered without specific intervention. Breakthrough infection did not occur in the five patients with vaccine failure during the observation period.

Adverse events

We gathered questionnaires from 41 patients (Table 4). One patient filled out the questionnaire only after the second dose, and so adverse events after the first dose were evaluated in 40 patients. Adverse events were nonspecific. No patients experienced exacerbation of primary disease, such as flare of rheumatic disease or glomerulonephritis in patients with rheumatic disease, and no SOT recipients experienced acute rejection.

Discussion

In our prospective study of SARS-CoV-2 mRNA vaccination in patients taking immunosuppressive agents, the immunosuppressant treatment was mainly for solid organ transplantation and rheumatic disease. Most patients achieved seroconversion, and those who did not were SOT recipients taking two immunosuppressive agents. SOT recipients and patients taking two immunosuppressive agents had significantly lower antibody titers than did other patients. Breakthrough infection occurred in three patients whose antibody titers were positive after vaccination. Adverse events were similar to those in the general population after vaccination. In healthy Japanese people, the frequency of fever was

reported as 14% and 33% after the first and second doses, respectively. No patients experienced exacerbation of primary disease, such as flare of rheumatic disease, and no SOT recipients experienced acute rejection.

Reduced humoral immune response has been reported in SOT recipients after vaccination.[8-12] However, according to several reports, young patients showed relatively better responses to vaccination than did older patients.[9,10] In two reports of children or young adolescent SOT recipients, immunological response after SARS-CoV-2 mRNA vaccination was evaluated.[16,17] In evaluating immunogenicity in 38 vaccinated kidney transplant recipients aged 18.6 ± 2.8 years, Haskin et al. showed that the seroconversion rate was 63%, which was much lower than that in nonrecipients infected with SARS-CoV-2.[16] In 25 young kidney transplant recipients (median age, 19 years) who received two vaccinations, Crane et al. demonstrated a seroconversion rate of 52%.[17] Although the immunoassay of the antibody titers of these two reports (SARS-CoV-2 spike protein measured by Abbott assay) differed from ours, their seroconversion rate, i.e., 10 (67%) of 15 patients, was similar to our results. Use of rituximab and MMF was related to poor immune response.[8-12] In our study population, no patients had received recent rituximab treatment, and none were in a condition of B-cell depletion at the time of SARS-CoV-2 mRNA vaccination. However, MMF was taken by most SOT recipients (13 of 15). We could not evaluate the risk factors for vaccine failure in recipients, as the study population was small.

Rates of seroconversion in patients with rheumatic disease have been reported as 80–90%.[13-15] Rituximab is reportedly associated with poor immune response after vaccination in patients with rheumatic disease,[13,19] but no patients in our study population had taken rituximab for rheumatic disease. To date, the evaluation of immunogenicity in children or adolescent patients with rheumatic disease has not been reported. Of our 25 patients with rheumatic disease, all (100%) exhibited seroconversion after the two doses of vaccine, and no patients experienced flares of the primary disease after vaccination.

Of our study population, SOT recipients showed poorer immune responses than did SOT nonrecipients (most of whom had rheumatic disease). Vaccine failure occurred only in SOT recipients. One possible reason is the number of immunosuppressive agents, as all SOT recipients were taking two immunosuppressive agents. In fact, most SOT nonrecipients were taking only one immunosuppressive agent. However, immunological parameters, such as serum IgG levels, $CD4^+$ T cell counts, and phytohemagglutinin-stimulation index, did not differ between SOT recipients and nonrecipients. These parameters were also not associated with the rate of seropositivity. The reasons for poor immunological response in SOT recipients need to be further evaluated.

Breakthrough infection occurred in three patients during the observation period, although their antibody titers were positive after the vaccination. The clinical courses of infection were mild. It is possible that antibody titers were diminished several months after vaccination, as the breakthrough infections occurred 5–8 months after the second dose. We did not evaluate the antibody levels just before the breakthrough infections. Follow-up studies are intended to investigate the durability of antibody titers and the effect of booster vaccinations in this study cohort.

Our study had several limitations. First, because it was a single-center study, the number of patients was relatively small; thus, multivariable analysis of risk factors for vaccine failure could not be performed. Second, the antibody measured in this study was SARS-CoV-2 spike antibody, not a neutralizing antibody, which provides direct protection against the virus. However, SARS-CoV-2 spike antibody titers as measured with the Elecsys Anti-SARS-CoV-2 S semiquantitative immunoassay proved to be well correlated with neutralizing antibody titers. Third, cellular immunity (T cell immunity against SARS-CoV-2) could not be analyzed. Fourth, flare of underlying disease and clinical effectiveness could not be fully evaluated due to a relatively small study population. Fifth, it is possible that some antibody seropositive individuals had been infected in the study period as we experienced the SARS-CoV-2 virus epidemic waves. We cannot distinguish whether positive SARS-CoV-2 spike antibody titers were due to vaccination or infection.

In conclusion, SARS-CoV-2 mRNA vaccines were immunologically effective in children and adolescents taking immunosuppressive agents. Most patients achieved seroconversion after vaccination. SOT recipients taking two immunosuppressive agents were more likely than other patients to exhibit vaccine failure after vaccination.

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Author's contributions

K.K. designed and conducted the study and prepared the manuscript; M.O., M.S., and K.N. collected the clinical data; K.S., T.F., and C.O. edited and reviewed the manuscript; and S.I. oversaw the work and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Questionnaire administered after SARS-CoV-2 vaccination

Vaccines: Pfizer, Moderna, Others ( )		
Please circle the applicable answers.		
1. Date of the first dose:_____		
Local adverse events		
Pain	No	Yes
Redness	No	Yes
Swelling	No	Yes
Systemic adverse events		
Fever (≥37.5°C)	No	Yes (Maximum: °C)
Fatigue	No	Yes
Headache	No	Yes
Vomiting	No	Yes
Myalgia	No	Yes
Arthralgia	No	Yes
Anaphylaxis	No	Yes (Details:)
2. Date of the second dose:_____		
Local adverse events		
Pain	No	Yes
Redness	No	Yes
Swelling	No	Yes
Systemic adverse events		
Fever (≥37.5°C)	No	Yes (Maximum: °C)
Fatigue	No	Yes
Headache	No	Yes
Vomiting	No	Yes
Myalgia	No	Yes
Arthralgia	No	Yes
Anaphylaxis	No	Yes (Details:)
If you suffered from other adverse events within 1 month after vaccination, please provide the details in the space below.		

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 Patient characteristics ($N = 42$)

Characteristics	Value†
Male gender	14 (33.3)
Age at vaccination (years)	18.1 (15.2–23.7)
Number of patients aged ≥18 y at vaccination	22 (52.4)
Primary disease or condition	
SOT	15 (35.7)
Kidney transplant	14 (33.3)
Liver transplant	1 (2.4)
Rheumatic disease	25 (59.5)
Systemic lupus erythematosus	11 (26.2)
Juvenile idiopathic arthritis	4 (9.5)
ANCA vasculitis	2 (4.8)
Systemic sclerosis	2 (4.8)
Dermatomyositis	2 (4.8)
Mixed connective tissue disease	2 (4.8)
Takayasu arthritis	1 (2.4)
Antiphospholipid antibody syndrome	1 (2.4)
Kidney disease	2 (4.8)
IgA glomerulonephritis	1 (2.4)
Membranous nephropathy	1 (2.4)
Number of patients taking immunosuppressive agents at the time of vaccination	
Two immunosuppressive agents	18 (42.9)
Tacrolimus + MMF	8 (19.0)
MMF + everolimus	7 (16.7)
Cyclosporine + everolimus	1 (2.4)
Cyclosporine + mizoribine	1 (2.4)
Tacrolimus + methotrexate	1 (2.4)
One immunosuppressive agent	24 (57.1)
MMF	17 (40.5)
Methotrexate	4 (9.5)
Tacrolimus	1 (2.4)
Mizoribine	1 (2.4)
Azathioprine	1 (2.4)
Number of patients receiving steroid treatment at time of vaccination	21 (50.0%)
Lymphocyte count (per mm^3)	1877 (1236–2276)
$CD4^+$ T cell count (permm^3)	729 (552–1032)
Serum IgG level (mg/dL)	1207 (1009–1478)
PHA-SI	230 (120–324)
Number of vaccine doses	
One dose	0 (0.0)
Two doses	42 (100.0)
SARS-CoV-2 vaccine	
Pfizer, BNT162b2	37 (88.1)
Moderna, mRNA-1273	5 (11.9)
Observation period after vaccination (days)	225 (192–238)

†Values are expressed as numbers and percentages or as medians and interquartile ranges.

ANCA, antineutrophil cytoplasmic antibody; IgA, immunoglobulin A; IgG, immunoglobulin G; MMF, mycophenolate mofetil; mRNA, messenger RNA; PHA-SI, phytohemagglutinin-stimulation index; SARS-CoV-2, severe acute respiratory coronavirus type 2; SOT, solid organ transplant.

Table 3 Comparison between patients with positive (≥0.8 U/mL) and negative (<0.8 U/mL) antibody responses to SARS-CoV-2 vaccination ($N = 34$)

Characteristic	Antibody response†		*p* value
	Positive ($N = 29$)	Negative ($N = 5$)	
Male gender	10 (34.5)	3 (60.0)	0.35
Age at vaccination (years)	18.1 (15.5–25.4)	17.9 (14.7–21.8)	0.73
Number of patients aged ≥18 years at vaccination	15 (51.7)	2 (40.0)	1.00
Duration between onset and vaccination (years)	12.4 (4.5–16.1)	11.7 (8.4–16.0)	0.75
SOT status			0.01
Recipients	10 (34.5)	5 (100.0)	
Nonrecipients	19 (65.5)	0 (0.0)	
Two immunosuppressive agents at vaccination	13 (44.8)	5 (100.0)	0.047
Calcineurin inhibitors use at vaccination	8 (27.6)	3 (60.0)	0.30
Cyclosporine use at vaccination	1 (3.5)	0 (7.1)	0.20
Tacrolimus use at vaccination	7 (24.1)	3 (60.0)	0.14
Number of patients taking antimetabolic agents at time of vaccination	25 (86.2)	5 (100.0)	1.00
MMF	23 (79.3)	5 (100.0)	0.56
Mizoribine	1 (3.5)	0 (0.0)	1.00
Azathioprine	1 (3.5)	0 (0.0)	1.00
Number of patients taking everolimus at time of vaccination	6 (20.7)	2 (40.0)	0.57
Number of patients taking methotrexate at time of vaccination	3 (10.3)	0 (0.0)	1.00
Number of patients taking steroids at time of vaccination	15 (51.7)	5 (100.0)	0.06
Lymphocyte count (per mm^3)	1905 (1273–2321)	1908 (1003–2129)	0.56
$CD4^+$ T cell count (per mm^3)	732 (523–1,511)	698 (416–930)	0.56
Serum IgG (mg/dL)	1229 (1,077–1,271)	482 (418–1352)	0.09
PHA-SI	220 (116–330)	151 (94–309)	0.59
SARS-CoV-2 vaccine			1.00
Pfizer, BNT162b2	25 (86.2)	5 (100.0)	
Moderna, mRNA-1273	4 (13.8)	0 (0.00)	
Interval between the second vaccine dose and antibody testing (days)	44 (27–69)	31 (30–44)	0.36

†Values are expressed as numbers and percentages or as medians and interquartile ranges.

IgG, immunoglobulin G; MMF, mycophenolate mofetil; mRNA, messenger RNA; PHA-SI, phytohemagglutinin-stimulation index; SARS-CoV-2, severe acute respiratory coronavirus type 2; SOT, solid organ transplantation.

Table 4 Adverse events after SARS-CoV-2 vaccination

Adverse events	Dose†	
	First (*N* = 40)	Second (*N* = 41)
Local adverse events		
Pain	27 (67.5)	30 (73.2)
Redness	8 (20.0)	10 (24.4)
Swelling	12 (30.0)	16 (39.0)
Systemic adverse events		
Fever (≥37.5°C)	6 (15.0)	20 (48.8)
Fatigue	15 (37.5)	25 (61.0)
Headache	8 (20.0)	16 (39.0)
Vomiting	1 (2.5)	2 (4.9)
Myalgia	12 (30.0)	17 (41.5)
Arthralgia	4 (10.0)	9 (22.0)
Anaphylaxis	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	1 (2.4)

†Values are expressed as numbers and percentages.

SARS-CoV-2, severe acute respiratory coronavirus type 2.

Figure legends

Fig. 1. Flow diagram of the study population.

Fig. 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S antibody titers after vaccination (*N*= 34).

(a) SARS-CoV-2 S antibody titers after vaccination. Box represents the median (329 U/mL) and interquartile range (50–812 U/mL; minimum, <0.4 U/mL; maximum, 6780 U/mL).

(b) Time elapsed between the second dose and testing of SARS-CoV-2 S antibody titers.

Fig. 3. Factors associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 S) antibody titers after vaccination.

(a) Comparison between solid organ transplant (SOT) recipients and nonrecipients.

(b) Comparison between patients taking two immunosuppressants (ISs) and those taking one ISs.

All data are expressed as medians (interquartile ranges).

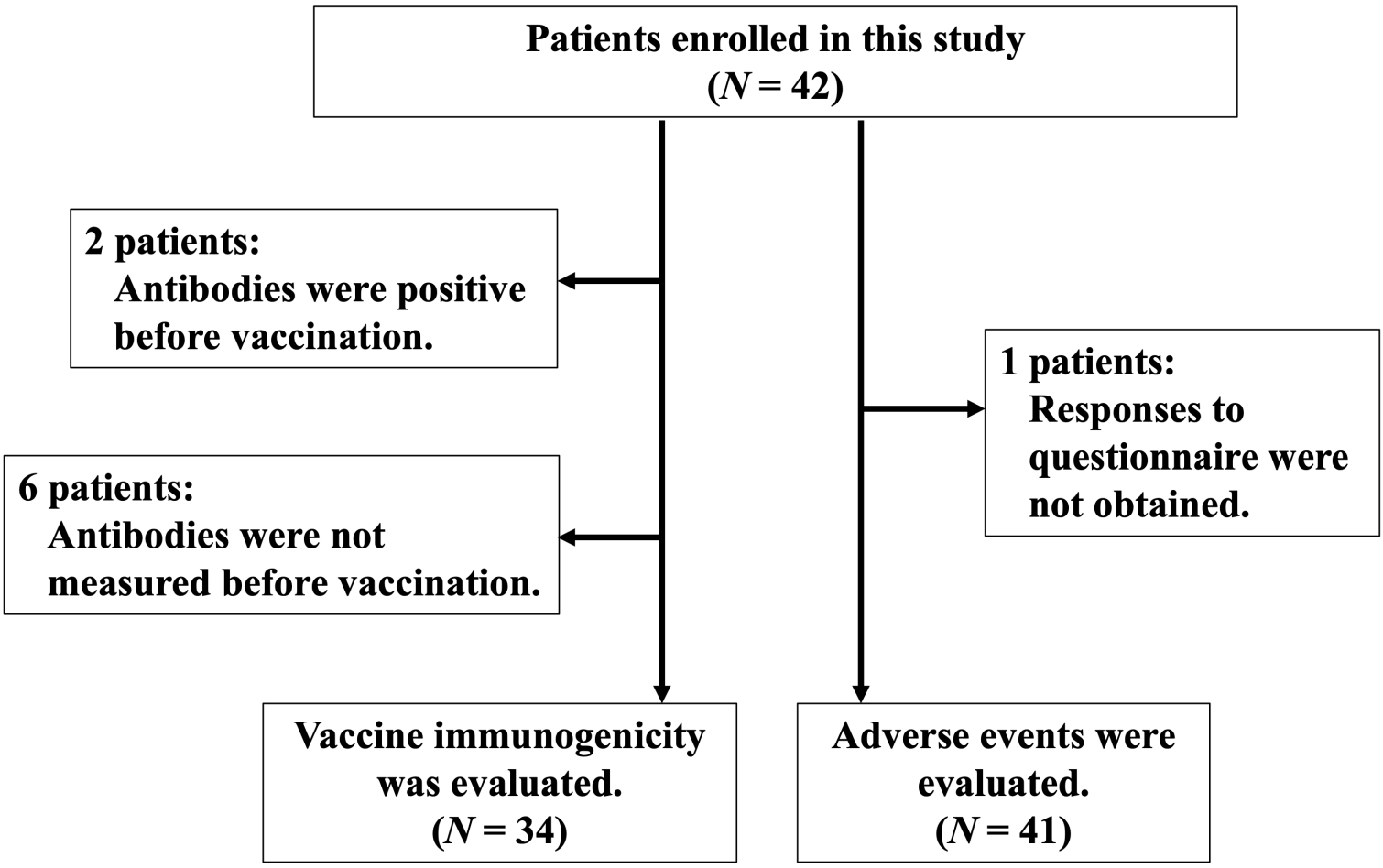

Figure 1

PED_15331_Figures 1.tiff

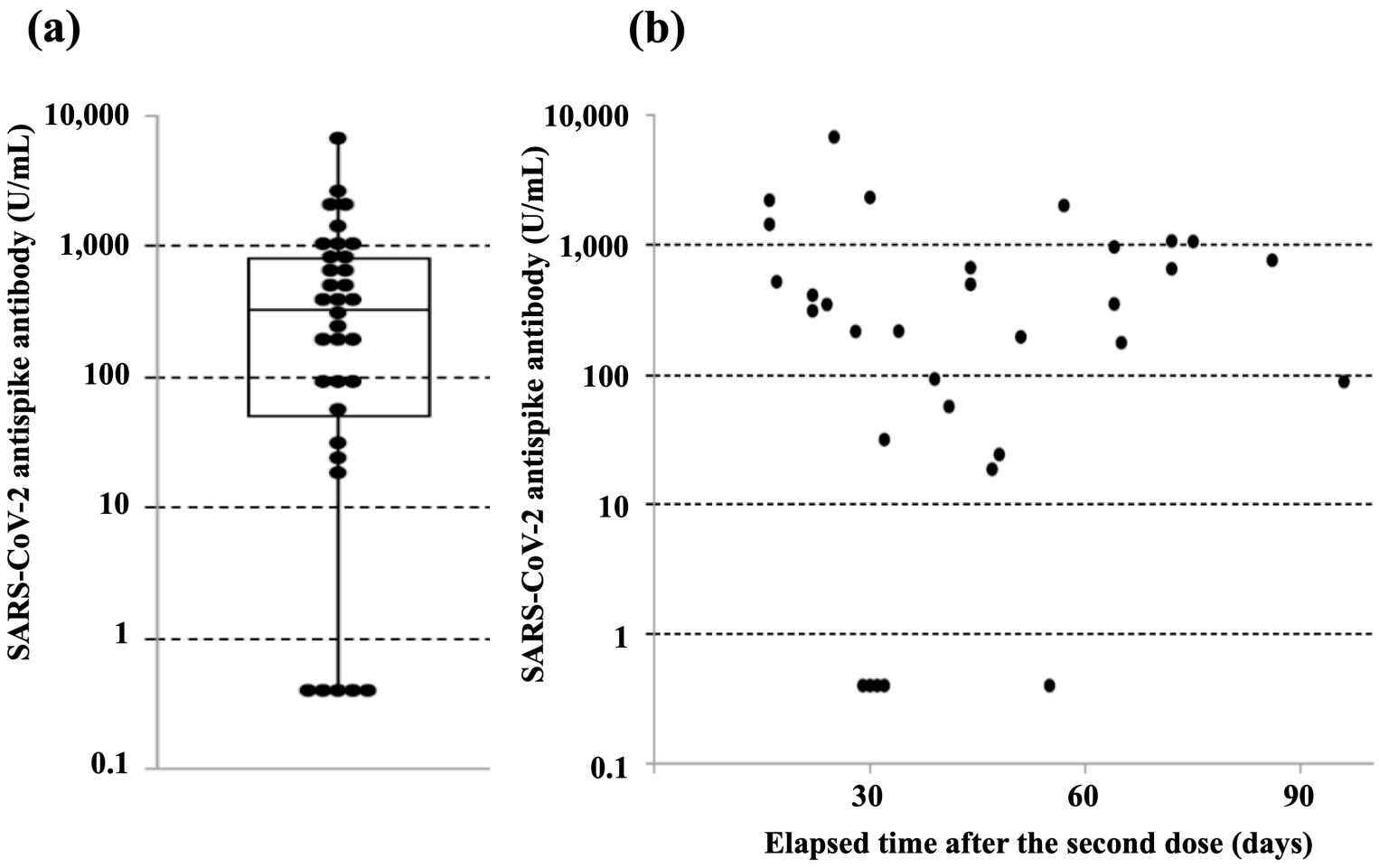

Figure 2

PED_15331_Figures 2.tiff

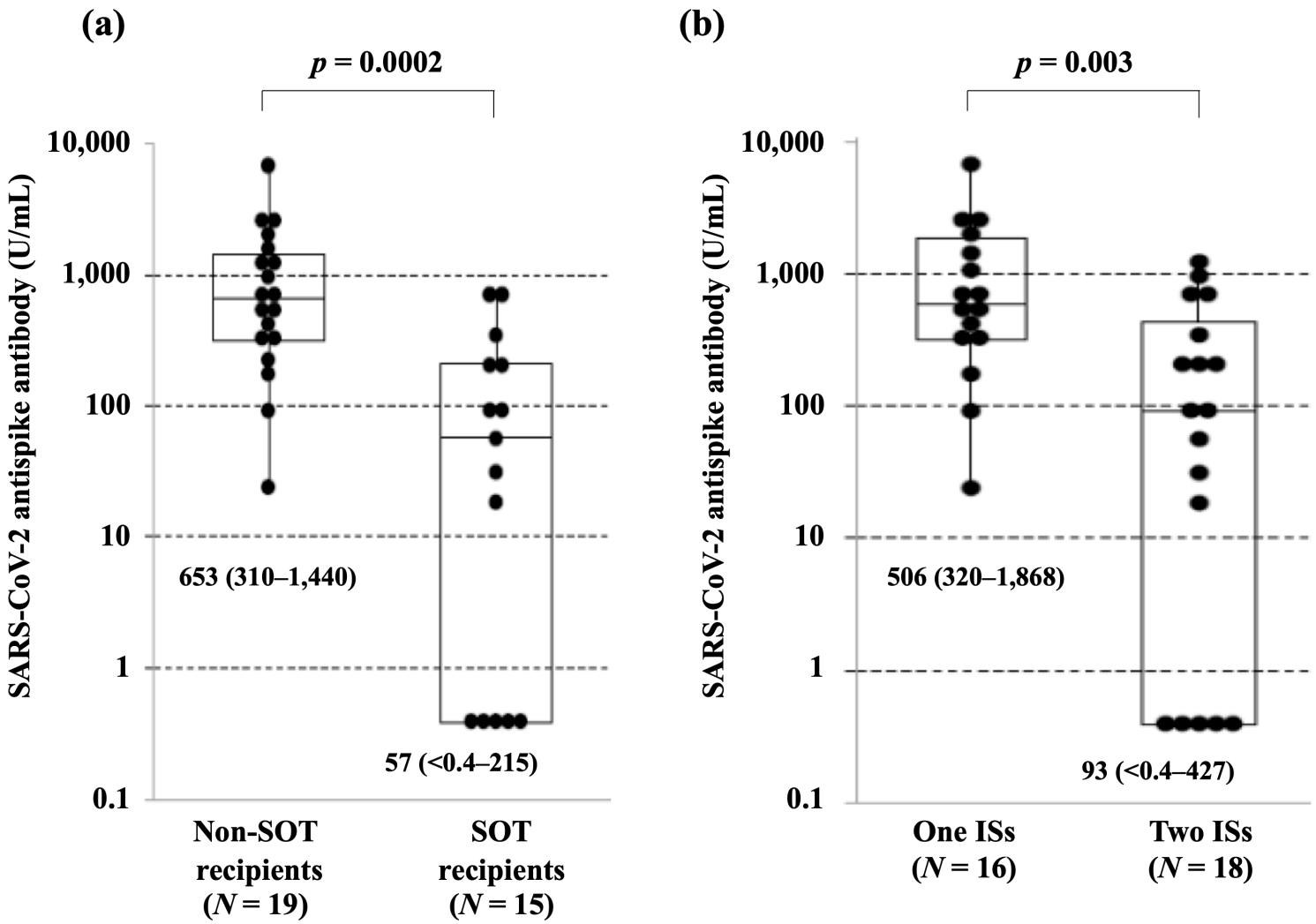

Figure 3

PED_15331_Figures 3.tiff