



Immunogenicity and safety of SARS-CoV-2 mRNA vaccine in patients with nephrotic syndrome receiving immunosuppressive agents

Koichi Kamei¹ · Masao Ogura¹ · Mai Sato¹ · Kentaro Nishi¹ · Kensuke Shoji² · Takanori Funaki² · Chikara Ogimi² · Shuichi Ito³

Received: 9 April 2022 / Revised: 13 May 2022 / Accepted: 16 May 2022

© The Author(s), under exclusive licence to International Pediatric Nephrology Association 2022

Abstract

Background As there are no large-scale reports of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mRNA vaccination in patients with nephrotic syndrome using immunosuppressive agents, we conducted the prospective study.

Methods SARS-CoV-2 mRNA vaccines were administered to patients with nephrotic syndrome receiving immunosuppressive agents. The titers of SARS-CoV-2 spike protein receptor-binding domain antibodies were measured before and after vaccination. We evaluated factors associated with antibody titers after vaccination and analyzed adverse events.

Results We enrolled 40 patients and evaluated vaccine immunogenicity in 35 of them. Seroconversion (>0.8 U/mL) was achieved in all patients, and the median antibody titer was 598 U/mL (interquartile range, 89–1380 U/mL). Patients using mycophenolate mofetil (MMF) showed lower antibody titers than those who were not (median: 272 U/mL vs. 2660 U/mL, $p=0.0002$), and serum immunoglobulin G (IgG) levels showed a weak linear relationship with antibody titers ($R^2=0.16$). No breakthrough infections were noted. Three patients (7.5%) suffered from a relapse of nephrotic syndrome (2 and 3 days, respectively, after the first dose and 8 days after the second dose), two of whom had a history of relapse within 6 months before the vaccination.

Conclusions The SARS-CoV-2 mRNA vaccine was immunogenic in patients with nephrotic syndrome using immunosuppressive agents, although the use of MMF and low levels of serum IgG were associated with lower antibody titers after vaccination. Patients with high disease activity may experience a relapse of nephrotic syndrome after vaccination.

Keywords SARS-CoV-2 S antibody · Seroconversion · Mycophenolate mofetil · Serum IgG · Relapse · Nephrotic syndrome

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first described in December 2019, leading to a global pandemic of coronavirus disease 2019 (COVID-19). Patients using immunosuppressive agents are at increased risk of mortality from SARS-CoV-2 infection, especially

solid organ transplantation (SOT) recipients, in whom the mortality rate has been reported as 10–30% [1, 2]. On the other hand, relatively favorable outcomes have been reported in children and young adolescents compared with elderly patients [3–5]. The course of SARS-CoV-2 infection in children has been reported as mild, even in those using immunosuppressive agents [6, 7], although further research is necessary.

SARS-CoV-2 mRNA vaccines are highly efficacious and widely recommended to prevent the spread of the COVID-19 pandemic in the general population. Furthermore, vaccines are crucial to prevent severe life-threatening infection in high-risk patients, such as elderly people or patients using immunosuppressive agents. However, a reduced humoral immune response was reported in patients using immunosuppressive agents, especially in SOT recipients, after vaccination [8–15]. Moreover, in some patients, vaccination may

✉ Koichi Kamei
kamei-k@ncchd.go.jp

¹ Division of Nephrology and Rheumatology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan

² Division of Infectious Diseases, National Center for Child Health and Development, Tokyo, Japan

³ Department of Pediatrics, Yokohama City University Hospital, Yokohama, Kanagawa, Japan

be associated with the recurrence of disease activity, such as a flare of rheumatic disease, the aggravation of hematuria and proteinuria in nephritis, or acute rejection in SOT recipients. Thus, the indication for vaccination should be examined carefully for each patient, and the advantage of the prevention of infection must be weighed against the disadvantage of disease recurrence after vaccination.

Because there are no large-scale reports of SARS-CoV-2 vaccination in patients with nephrotic syndrome using immunosuppressive agents, several clinical questions remain unanswered. First, the immune response after vaccination has to be evaluated in this population. The use of immunosuppressive agents decreases humoral response after vaccination, and seroconversion rates in SOT recipients were reported as 30–50% [8–15], which is much lower than those of immunocompetent people. In contrast, the seroconversion rates of patients with rheumatic disease were reported as relatively high (80–90%) [16–18]. Second, factors associated with a low immune response in patients with nephrotic syndrome require evaluation. Third, adverse events after vaccination, such as the relapse of nephrotic syndrome, must be examined. Although relapses of nephrotic syndrome were reported after SARS-CoV-2 mRNA vaccination [19, 20], its incidence is unknown.

Here, we conducted a prospective observational study of SARS-CoV-2 mRNA vaccination of patients with nephrotic syndrome using immunosuppressive agents to evaluate its immunogenicity and safety in this population.

Methods

Study design and patient population

This prospective observational study was performed between April and December 2021 at the National Center for Child Health and Development in Tokyo, Japan. Inclusion criteria for study entry were patients with childhood-onset nephrotic syndrome using immunosuppressive agents who planned to receive a SARS-CoV-2 mRNA vaccine. During the study period, vaccination was approved in Japan for people aged ≥ 12 years. All patients were vaccinated while their nephrotic syndrome was in remission.

Immunosuppressive agents were indicated for steroid-dependent nephrotic syndrome (SDNS), frequently relapsing nephrotic syndrome (FRNS), or steroid-resistant nephrotic syndrome (SRNS). SDNS was defined as two consecutive relapses during steroid therapy or within 14 days after therapy cessation. FRNS was defined as more than two relapses within 6 months after initial remission or more than four relapses within 12 consecutive months. SRNS was defined as the failure to achieve remission despite therapy with prednisolone at 60 mg/m²/day for 4 weeks. All patients

performed a daily urine dipstick test at home to detect proteinuria. Relapse was defined as a morning dipstick test result of 3+ for proteinuria for 3 consecutive days and urinary protein/creatinine ratio > 2.0 g/g confirmed in the laboratory of the hospital. Date of relapse was defined as the first day of these 3 consecutive days. Patients who had a history of SRNS and subsequently suffered from SDNS/FRNS were categorized as SRNS. Previous kidney biopsy data were also collected. Kidney pathologies were categorized as minimal change disease, focal segmental sclerosis, and others. All of them were diagnosed using light microscopy, immunofluorescence, and electron microscopy. Patients with B-cell depletion (defined as CD20 cells comprising $< 1\%$ of the total lymphocyte count) after rituximab treatment were excluded from our study.

Study protocol

After acquiring informed consent from all study participants, the titer of SARS-CoV-2 spike protein receptor-binding domain antibodies (SARS-CoV-2 S antibodies) was determined using the Elecsys Anti-SARS-CoV-2 S semiquantitative immunoassay (Roche, Basel, Switzerland). CD4 cell counts, lymphocyte blast transformation induced by phytohemagglutinin (PHA), and serum immunoglobulin G (IgG) levels were also examined as immunological parameters. The study participants were immunized with either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) SARS-CoV-2 mRNA vaccines, in which the recommended interval between the two doses was 21 and 28 days, respectively. The SARS-CoV-2 S antibody titer was determined between 2 weeks and 3 months after the second dose in all patients. Adverse events observed 1 month after vaccination were evaluated using a questionnaire.

Antibody testing

Patients were tested for SARS-CoV-2 S antibody using the commercially available Elecsys Anti-SARS-CoV-2 S semiquantitative immunoassay. Values < 0.8 U/mL were considered negative. The laboratory that tested our study samples defined ≥ 250 U/mL as evidence of an immune response in infected patients, and a previous study defined a SARS-CoV-2 S antibody titer ≥ 250 U/mL as optimal and < 250 U/mL as suboptimal [21]. We utilized these definitions in our study because our population did not include children aged < 12 years.

Study outcomes

The primary study outcome was the rate of seroconversion after SARS-CoV-2 mRNA vaccination of patients with nephrotic syndrome using immunosuppressive agents. The

secondary outcome was the determination of factors associated with antibody titers after vaccination, which were identified by comparing the characteristics between patients with optimal (≥ 250 U/mL) and suboptimal (< 250 U/mL) titers. These analyses were performed in patients who had received both vaccine doses. We evaluated the clinical efficacy of the vaccination by reviewing the patient's charts for records of breakthrough infection. The observation period ended on January 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 a relapse of nephrotic syndrome after vaccination.

Statistical analysis

Results were expressed as medians with interquartile ranges (IQRs) for continuous variables and as numbers and percentages for categorical variables. Clinical and immunological factors were compared between two groups using the Mann–Whitney U test for continuous variables and the Fisher exact test for categorical variables. p values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP v16.0 (SAS Institute Japan Ltd., Tokyo, Japan).

Results

Patient characteristics

We enrolled 40 patients in this study (Fig. 1). Patient characteristics are shown in Table 1. The median age at

vaccination was 16 years, and 40% of the study population was aged ≥ 18 years. Furthermore, 70% of them were using mycophenolate mofetil (MMF). Most patients (92.5%) received the BNT162b2 vaccine. Although booster vaccination (third vaccine) is recommended and most of the enrolled patients have received it, observation of this study was finished beforehand, as this study did not include the booster vaccination.

Seroconversion rates following vaccination

All patients had < 0.4 U/mL of SARS-CoV-2 S antibody before vaccination. Post-vaccination titers were measured after a median of 47 days (IQR: 30–62) following the second dose (Table 1). The rate of seroconversion was 100%. The median SARS-CoV-2 S antibody titer was 598 U/mL (IQR: 89–1380 U/mL) (Fig. 2). There was no relationship between SARS-CoV-2 S antibody titer and the elapsed time after the second dose.

Comparison between patients with optimal (≥ 250 U/mL) and suboptimal (< 250 U/mL) antibody responses to SARS-CoV-2 mRNA vaccination

We compared the clinical and immunological parameters between patients with optimal (≥ 250 U/mL) and suboptimal (< 250 U/mL) SARS-CoV-2 S antibody titers. The rate of patients with MMF in the optimal titer group was significantly lower than that in the suboptimal titer group (66.7% vs. 100.0%, $p = 0.03$). Actually, patients using MMF showed lower antibody titers than those who were not (median: 272 U/mL vs. 2660 U/mL, $p = 0.0002$) (Fig. 3a). In the immunological parameters, serum IgG levels in the optimal titer

Fig. 1 CONSORT flow diagram of the study population

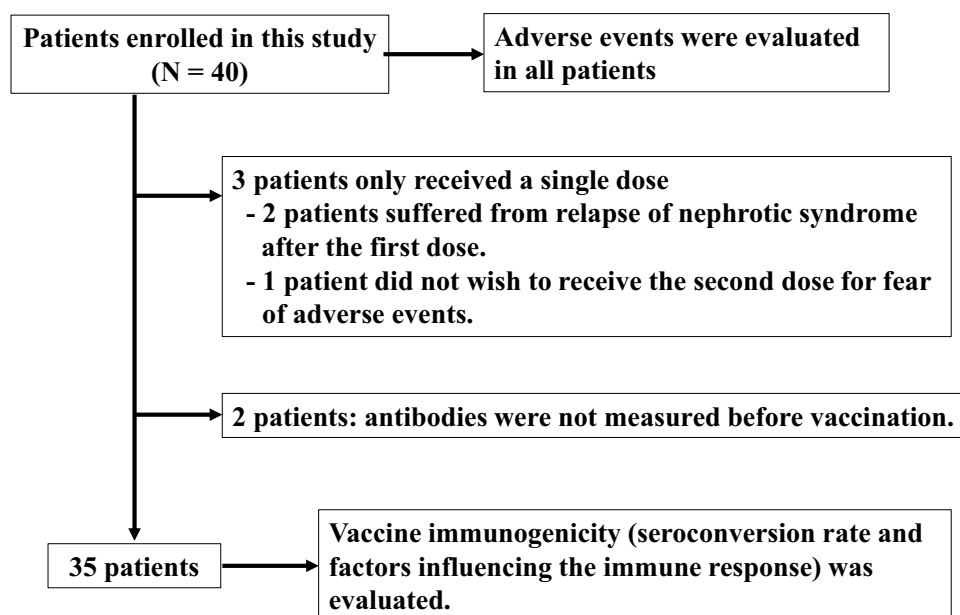


Table 1 Patient characteristics ($N=40$)

Variables	
Male gender	25 (62.5)
Age at onset of nephrotic syndrome (y)	5.8 (2.5–10.8)
Age at vaccination (y)	16.7 (15.4–21.8)
Age \geq 18 y at vaccination	16 (40.0)
Duration between onset and vaccination (y)	11.7 (7.1–15.9)
Kidney biopsy	
Minimal change disease	27 (67.5)
Focal segmental glomerulosclerosis	6 (15.0)
Patients who did not undergo kidney biopsy	7 (17.5)
Type of nephrotic syndrome	
Steroid dependent/frequent relapsing	29 (72.5)
Steroid resistant nephrotic syndrome	11 (27.5)
Past history of rituximab treatment	32 (80.0)
Rituximab treatment within 1 year before vaccination	3 (7.5)
Patients who suffered from relapse within 6 months before vaccination	4 (10.0)
Immunosuppressive agents at vaccination	
MMF	28 (70.0)
Cyclosporin A	8 (20.0)
Mizoribine	2 (5.0)
Cyclosporin A + MMF	1 (2.5)
Tacrolimus + MMF	1 (2.5)
Patients who received steroids at vaccination	0 (0.0)
Serum albumin (g/dL)	4.6 (4.5–4.8)
Lymphocyte count (/mm ³)	1777 (1438–2350)
CD4 + T cell count (/mm ³)	695 (586–860)
Serum IgG (mg/dL)	926 (742–1141)
PHA-SI	259 (202–323)
Number of vaccine doses	
One dose	3 (7.5)
Two doses	37 (92.5)
SARS-CoV-2 vaccine	
Pfizer, BNT162b2	37 (92.5)
Moderna, mRNA-1273	3 (7.5)
Antibody testing after the second dose (days)	47 (30–62)
Observation period after vaccination (days)	165 (145–180)

Values are expressed as numbers (%) or median (IQR)

IQR, interquartile range; MMF, mycophenolate mofetil; IgG, immunoglobulin G;

PHA-SI, phytohemagglutinin-stimulation index; SARS-CoV-2, severe acute respiratory coronavirus type 2

group were significantly higher than those in the suboptimal titer group (median, 1038 mg/dL vs. 767 mg/dL, $p=0.003$). It showed a weak linear relationship with SARS-CoV-2 S antibody titers ($R^2=0.16$) (Fig. 3b). The PHA-stimulation index (PHA-SI) was a statistically significant factor in the comparison between optimal and suboptimal antibody titers (median, 303 vs. 220, $p=0.02$), although it did not show a

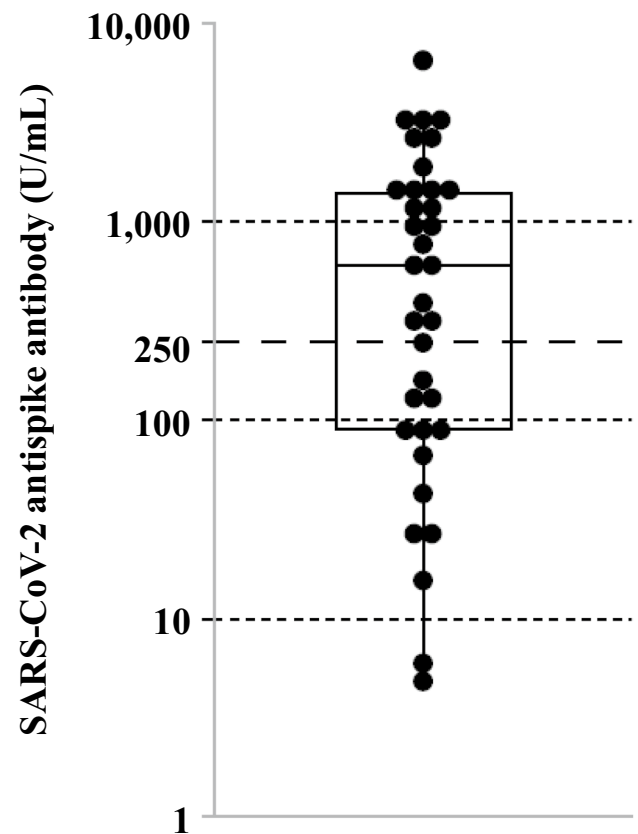


Fig. 2 SARS-CoV-2 S antibody titers after vaccination ($n=35$). Box represents the median and interquartile range (IQR). Median: 598 U/mL, IQR: 89–1380 U/mL, minimum: 5 U/mL; maximum: 6520 U/mL

linear relationship with antibody titers (Fig. 3c). Patients with a history of rituximab tended to show a lower antibody titer after vaccination, although this was not statistically significant. Two patients who received rituximab treatment within 1 year before vaccination (8 and 9 months, respectively) showed suboptimal antibody titers (94.2 U/mL and 82.6 U/mL, respectively).

Breakthrough infection after vaccination during the study period

No patients suffered from breakthrough infection during the observation period after vaccination (median: 165 days, IQR: 145–180).

Adverse events

Table 2 shows the adverse events observed after vaccination. Three patients (7.5%) suffered a relapse of nephrotic syndrome; two occurred after the first dose (2 and 3 days after vaccination, respectively) and one after the second dose

Fig. 3 Factors associated with SARS-CoV-2 S antibody titers after vaccination. **a** Comparison between patients using or not using MMF. **b** Relationship between serum IgG levels and SARS-CoV-2 S antibody titers (SARS-CoV-2 S antibody = $1.65 \times \text{IgG} - 524.2$, $R^2 = 0.16$). **c** Relationship between PHA-SI and SARS-CoV-2 S antibody titers (SARS-CoV-2 S antibody = $-0.75 \times \text{PHA-SI} + 1234.0$, $R^2 = 0.003$). Data in all panels are expressed as median (IQR). SARS-CoV-2 S antibody, severe acute respiratory syndrome coronavirus type 2 spike protein receptor-binding domain antibody; MMF, mycophenolate mofetil; IgG, immunoglobulin G; PHA-SI, phytohemagglutinin-stimulation index

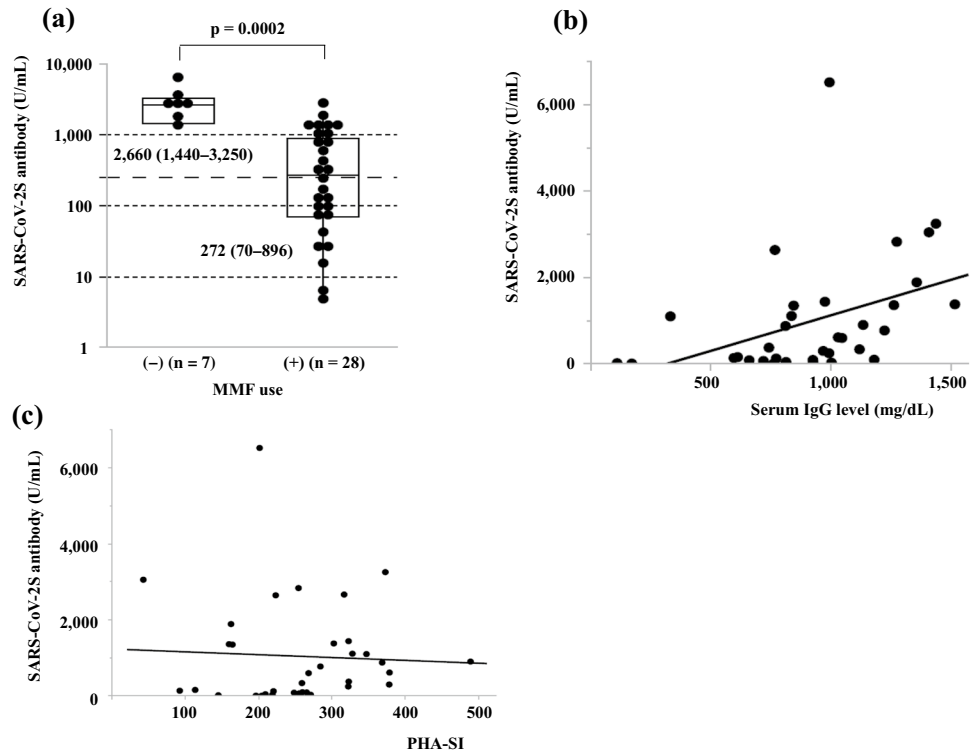


Table 2 Adverse events of SARS-CoV-2 vaccination

Adverse events	First dose (n = 40)	Second dose (n = 37)
Local adverse events		
Pain	29 (72.3)	30 (81.1)
Redness	10 (25.0)	9 (24.3)
Swelling	9 (22.5)	12 (32.4)
Systemic adverse events		
Fever (≥ 37.5 °C)	5 (12.5)	25 (67.6)
Fatigue	8 (20.0)	23 (62.2)
Headache	9 (22.5)	18 (48.6)
Vomiting	0 (0.0)	1 (2.7)
Myalgia	11 (27.5)	11 (29.7)
Arthralgia	1 (2.5)	4 (10.8)
Lower back pain	0 (0.0)	1 (2.7)
Diarrhea	1 (2.5)	0 (0.0)
Dizziness	1 (2.5)	0 (0.0)
Anaphylaxis	0 (0.0)	0 (0.0)
Relapse of nephrotic syndrome	2 (5.0)	1 (2.7)
Transient proteinuria	1 (2.5)	1 (2.7)

Values are expressed as numbers (%)

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

(8 days after vaccination). All three patients achieved remission after steroid treatment. Two (50%) of four patients who experienced a relapse within 6 months before vaccination

suffered from a relapse after vaccination. In contrast, only one (3%) of 36 patients who did not experience a relapse within 6 months before vaccination suffered from a relapse after vaccination ($p = 0.02$). Two patients who suffered from a relapse after the first dose did not receive the second dose, and their antibody titers were < 0.4 U/mL at 21 days after vaccination and 48 U/mL at 90 days after vaccination, respectively. One patient who suffered from a relapse after the second dose had an antibody titer of 3050 U/mL at 56 days after vaccination.

Discussion

We performed a prospective study of SARS-CoV-2 mRNA vaccination in patients with nephrotic syndrome using immunosuppressive agents. All patients achieved seroconversion. The median antibody titer was 598 U/mL despite immunosuppressive treatment, and 60% of patients had an optimal antibody titer (≥ 250 U/mL). However, use of MMF and low levels of serum IgG were associated with lower antibody titers after vaccination. Regarding adverse events, three patients suffered from a relapse of nephrotic syndrome after vaccination.

The SARS-CoV-2 mRNA vaccine elicits a high antibody response in the general population [22, 23]. The median SARS-CoV-2 S antibody titer (measured using the Elecsys immunoassay by Roche) in 103 infection-naïve

healthcare workers was reported as 57 U/mL (range: 2–991 U/mL) after the first dose and 2177 U/mL (range: 108–9545 U/mL) after the second dose [22]. All patients achieved seroconversion after the first dose, and a marked booster effect was observed after the second dose [22]. Another report showed a median SARS-CoV-2 S antibody titer of 1974.5 U/mL after the second dose in 110 healthcare workers [23]. Reduced humoral immune response has been reported in patients using immunosuppressive agents, especially SOT recipients, after vaccination [8–15]. However, patients with nephrotic syndrome using immunosuppressive agents in our study showed a favorable immune response, although their antibody titers (median: 598 U/mL) were lower than those in immunocompetent populations in previous reports [22, 23]. None of the patients in our study experienced a breakthrough infection after vaccination. An adequate serologic response to inactivated influenza vaccines in patients using immunosuppressive agents has been reported in several studies [24–28]. Similarly, our findings indicate that the SARS-CoV-2 mRNA vaccine is immunologically effective in patients with nephrotic syndrome despite using immunosuppressive agents.

Patients in our study using MMF showed lower immunogenicity than those not using MMF. MMF was reported to reduce immunogenicity after vaccination in SOT recipients [8–13]. At our center, most patients using MMF had a history of rituximab treatment. Antibody production after SARS-CoV-2 mRNA vaccination is severely decreased after rituximab treatment, and this low immune response occurs during B-cell depletion (usually 5–6 months after treatment) and also for several months after B-cell recovery [16–18, 29]. Furer et al. reported a seroconversion rate after BNT162b2 mRNA vaccination of 20% within 6 months after rituximab treatment, and this increased to 50% 1 year after rituximab treatment [16]. In our study, a history of rituximab treatment seemed to be a factor of lower immunogenicity, although it was not statistically significant ($p=0.06$). Thus, we cannot completely rule out the possibility that rituximab may lead to a poor immune response in patients with MMF. As most patients with MMF had a history of rituximab treatment, we could not perform a comparison between patients with and without MMF in a group who had no history of rituximab treatment.

The level of serum IgG is a marker of the humoral immune response and B-cell/plasma cell functions, which are generally influenced by MMF and rituximab treatment. Our study revealed that low serum IgG levels were correlated with low antibody titers after vaccination. Relapse did not influence serum IgG levels because all patients underwent vaccination during remission of nephrotic syndrome. No patients showed low levels of serum albumin at vaccination.

After vaccination, three patients (7.5%) suffered from a relapse of nephrotic syndrome, and two showed transient proteinuria after vaccination, which recovered spontaneously. Previous case reports have mentioned that a relapse of nephrotic syndrome might occur after SARS-CoV-2 mRNA vaccination [19, 20]. Relapse of nephrotic syndrome in the 6 months prior to vaccination might be a risk factor of relapse after vaccination, although further evaluation is warranted for confirmation. Relapse of nephrotic syndrome was also reported following influenza vaccination [30–32]. Thus, when SARS-CoV-2 mRNA vaccines are administered to patients with nephrotic syndrome, we must weigh the advantages against the disadvantages of vaccination for each patient and pay attention to the possibility of a relapse, particularly in cases with a history of relapse within 6 months prior to vaccination.

There were several limitations to our study. First, as this was a single-center study, the number of patients was relatively small. Thus, multivariate analysis to evaluate risk factors for a lower humoral response was not performed. Second, although MMF was identified as a factor of a lower humoral response, the confounding effect of rituximab could not be completely ruled out. Thus, larger studies are necessary to evaluate risk factors for lower humoral response in patients with nephrotic syndrome. Third, the immunogenicity examined in this study is limited to the early phase after vaccination. Antibody titers diminish within 3–6 months after vaccination, and booster vaccination is necessary [33–35]. We are conducting a follow-up study to investigate the preservation of antibody titers and the effect of booster vaccinations in this study cohort. Fourth, the population of our study included children and young adolescent patients. The median age was 16.7 years old, which was relatively older than those of the pediatric population at large. Vaccine immunogenicity of pure pediatric patients with nephrotic syndrome using immunosuppressive agents has to be evaluated in the future. Fifth, as this study is only single arm, we could not compare them with the healthy controls.

In conclusion, SARS-CoV-2 mRNA vaccines were immunologically effective in patients with nephrotic syndrome using immunosuppressive agents. All patients achieved seroconversion after vaccination. MMF use and a low level of serum IgG might be risk factors for low antibody titers after vaccination. Since a relapse of nephrotic syndrome can occur, we should be cautious about adverse events such as a relapse, particularly in patients with a history of relapse within 6 months prior to vaccination.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00467-022-05633-y>.

Acknowledgements The authors thank all the participants and physicians in charge for their contributions to this study.

Author contribution All authors were physicians treating the patients in this report. Koichi Kamei conducted the study and prepared the manuscript; Kentaro Nishi, Mai Sato, and Masao Ogura collected the clinical data; Kensuke Shoji, Takanori Funaki, and Chikara Ogimi edited and reviewed the manuscript; and Shuichi Ito oversaw the work and revised the manuscript. All authors read and approved the final manuscript.

Funding This work was funded by grants from the Taiju Life Social Welfare Foundation.

Data availability The data that support the findings of this study are available from the corresponding author, Koichi Kamei, upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval This study was performed in accordance with the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labour and Welfare of Japan. It was also approved by the ethics committee at the National Center for Child Health and Development (no. 2020–359).

Consent to participate and for publication Written informed consent for publication was obtained from the patients' guardians (patients aged < 15 years), from patients and their guardians (patients aged 15–20 years), or from the patients only (patients aged ≥ 20 years) prior to study enrollment.

Conflict of interest Koichi Kamei has received research funding from the Terumo Foundation for Life Sciences and Arts and the Public Foundation of Vaccination Research Center; donations from Chugai Pharmaceutical Co. Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co. Ltd, Teijin Pharma Ltd., Shionogi & Co. Ltd., and Otsuka Pharmaceutical Co. Ltd.; and lecture fees from Tanabe Mitsubishi Pharma Corp., Baxter Ltd., and Zenyaku Kogyo Co., Ltd. All other authors have no potential conflicts of interest to disclose. The first draft of the manuscript was written by Koichi Kamei.

References

- Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E (2021) COVID-19 and solid organ transplantation: a review article. *Transplantation* 105:37–55. <https://doi.org/10.1097/TP.0000000000003523>
- Raja MA, Mendoza MA, Villavicencio A, Anjan S, Reynolds JM, Kittipibul V, Fernandez A, Guerra G, Camargo JF, Simkins J, Morris MI, Abbo LA, Natori Y (2021) COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. *Transplant Rev (Orlando)* 35:100588. <https://doi.org/10.1016/j.trre.2020.100588>
- Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S (2020) Epidemiology of COVID-19 among children in China. *Pediatrics* 145:e20200702. <https://doi.org/10.1542/peds.2020-0702>
- Götzinger F, Santiago-García B, Noguera-Julian A, Lanaspá M, Lancella L, Calò Carducci FI, Gabrovská N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininger U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M, ptbnet COVID-19 Study Group (2020) COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* 4:653–661. [https://doi.org/10.1016/S2352-4642\(20\)30177-2](https://doi.org/10.1016/S2352-4642(20)30177-2)
- Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, Waddington C, Thomas J, Russell S, van der Klis F, Koirala A, Ladhani S, Panovska-Griffiths J, Davies NG, Booy R, Eggo RM (2021) Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. *JAMA Pediatr* 175:143–156. <https://doi.org/10.1001/jamapediatrics.2020.4573>
- Marlais M, Wlodkowski T, Al-Akash S, Ananin P, Bandi VK, Baudouin V, Boyer O, Vásquez L, Govindan S, Hooman N, Ijaz I, Loza R, Melgosa M, Pande N, Pape L, Saha A, Samsonov D, Schreuder MF, Sharma J, Siddiqui S, Sinha R, Stewart H, Tasic V, Tönshoff B, Twombly K, Upadhyay K, Vivarelli M, Weaver DJ, Woroniecki R, Schaefer F, Tullus K (2020) COVID-19 in children treated with immunosuppressive medication for kidney diseases. *Arch Dis Child* 106:798–801. <https://doi.org/10.1136/archdischild-2020-320616>
- Mastrangelo A, Morello W, Vidal E, Guzzo I, Annicchiarico Petruzzelli L, Benetti E, Materassi M, Giordano M, Pasini A, Corrado C, Puccio G, Chimenz R, Pecoraro C, Massella L, Peruzzi L, Montini G, COVID-19 Task Force of the Italian Society of Pediatric Nephrology; COVID-19 TASK FORCE of the Italian Society of Pediatric Nephrology (2021) Impact of COVID-19 pandemic in children with CKD or immunosuppression. *Clin J Am Soc Nephrol* 16:449–451. <https://doi.org/10.2215/CJN.13120820>
- Hod T, Ben-David A, Olmer L, Levy I, Ghinea R, Mor E, Lustig Y, Rahav G (2021) Humoral response of renal transplant recipients to the BNT162b2 SARS-CoV-2 mRNA vaccine using both RBD IgG and neutralizing antibodies. *Transplantation* 105:e234–243. <https://doi.org/10.1097/TP.0000000000003889>
- Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, Katchman E, Halperin T, Turner D, Goykhan Y, Shibolet O, Levy S, Houry I, Baruch R, Katchman H (2021) Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant* 21:2719–2726. <https://doi.org/10.1111/ajt.16615>
- Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, Martzloff J, Perrin P, Moulin B, Fafi-Kremer S, Caillard S (2021) Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int* 99:1498–1500. <https://doi.org/10.1016/j.kint.2021.04.005>
- Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, Tau N, Mashraki T, Neshet E, Rahamimov R (2021) Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect* 27:1173.e1–1173.e4. <https://doi.org/10.1016/j.cmi.2021.04.028>
- Vaiciuniene R, Sitkauskiene B, Bumblyte IA, Dalinkeviciene E, Ziginskiene E, Bagdonas D, Augliene R, Petruliene K, Bagdziuniene I, Skarupskiene I, Stankuviene A, Sauseriene J, Macinskis S, Valius L (2021) Immune response after SARS-CoV-2 vaccination in kidney transplant patients. *Medicina (Kaunas)* 57:1327. <https://doi.org/10.3390/medicina57121327>
- Timmermann L, Globke B, Lurje G, Schmelzle M, Schöning W, Öllinger R, Pratschke J, Eberspächer B, Drosten C, Hofmann J, Eurich D (2021) Humoral immune response following SARS-CoV-2 vaccination in liver transplant recipients. *Vaccines (Basel)* 9:1422. <https://doi.org/10.3390/vaccines9121422>
- Guarino M, Cossiga V, Esposito I, Furno A, Morisco F (2022) Effectiveness of SARS-CoV-2 vaccination in liver transplanted

- patients: the debate is open! *J Hepatol* 76:237–239. <https://doi.org/10.1016/j.jhep.2021.07.034>
15. Marion O, Del Bello A, Abravanel F, Faguer S, Esposito L, Laure Hebral A, Bellière J, Izopet J, Kamar N (2021) Predictive factors for humoral response after 2-dose SARS-CoV-2 vaccine in solid organ transplant patients. *Transplant Direct* 8:e1248. <https://doi.org/10.1097/TXD.0000000000001248>
 16. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, Zisapel M, Elalouf O, Kaufman I, Meidan R, Broyde A, Polachek A, Wollman J, Litinsky I, Meridor K, Nochomovitz H, Silberman A, Rosenberg D, Feld J, Haddad A, Gazzit T, Elias M, Higazi N, Kharouf F, Shefer G, Sharon O, Pel S, Nevo S, Elkayam O (2021) Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 80:1330–1338. <https://doi.org/10.1136/annrheumdis-2021-220647>
 17. Tzioufas AG, Bakasis AD, Goules AV, Bitzogli K, Cinoku II, Chatzis LG, Argyropoulou OD, Venetsanopoulou AI, Mavrommati M, Stergiou IE, Pezoulas V, Voulgari PV, Katsimpari C, Katechis S, Gazi S, Katsifis G, Sfontouris CI, Georgountzos AI, Liossis SN, Papagoras C, Fotiadis DI, Skopouli FN, Vlachoyiannopoulos PG, Moutsopoulos HM (2021) A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with systemic autoimmune and autoinflammatory rheumatic diseases. *J Autoimmun* 125:102743. <https://doi.org/10.1016/j.jaut.2021.102743>
 18. Braun-Moscovici Y, Kaplan M, Braun M, Markovits D, Giryas S, Toledano K, Tavor Y, Dolnikov K, Balbir-Gurman A (2021) Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. *Ann Rheum Dis* 80:1317–1321. <https://doi.org/10.1136/annrheumdis-2021-220503>
 19. Izzedine H, Bonilla M, Jhaveri KD (2021) Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial? *Nephrol Dial Transplant* 36:1565–1569. <https://doi.org/10.1093/ndt/gfab215>
 20. Nakazawa E, Uchimura T, Hirai Y, Togashi H, Oyama Y, Inaba A, Shiga K, Ito S (2021) New-onset pediatric nephrotic syndrome following Pfizer-BioNTech SARS-CoV-2 vaccination: a case report and literature review. *CEN Case Rep* 11:242–246. <https://doi.org/10.1007/s13730-021-00656-0>
 21. Thuluvath PJ, Robarts P, Chauhan M (2021) Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. *J Hepatol* 75:1434–1439. <https://doi.org/10.1016/j.jhep.2021.08.008>
 22. Hirotsu Y, Amemiya K, Sugiura H, Shinohara M, Takatori M, Mochizuki H, Omata M (2021) Robust antibody responses to the BNT162b2 mRNA vaccine occur within a week after the first dose in previously infected individuals and after the second dose in uninfected individuals. *Front Immunol* 12:722766. <https://doi.org/10.3389/fimmu.2021.722766>
 23. Callegaro A, Borleri D, Farina C, Napolitano G, Valenti D, Rizzi M, Maggiolo F (2021) Antibody response to SARS-CoV-2 vaccination is extremely vivacious in subjects with previous SARS-CoV-2 infection. *J Med Virol* 93:4612–4615. <https://doi.org/10.1002/jmv.26982>
 24. Tanaka S, Saikusa T, Katafuchi Y, Ushijima K, Ohtsu Y, Tsumura N, Ito Y (2015) Serologic response after vaccination against influenza (A/H1N1) pdm09 in children with renal disease receiving oral immunosuppressive drugs. *Vaccine* 33:5000–5004. <https://doi.org/10.1016/j.vaccine.2015.06.049>
 25. Poyrazoğlu HM, Düşünsel R, Gündüz Z, Patiroğlu T, Köklü S (2004) Antibody response to influenza A vaccination in children with nephrotic syndrome. *Pediatr Nephrol* 19:57–60. <https://doi.org/10.1007/s00467-003-1301-3>
 26. Campos LM, Silva CA, Aikawa NE, Jesus AA, Moraes JC, Miraglia J, Ishida MA, Bueno C, Pereira RM, Bonfa E (2013) High disease activity: an independent factor for reduced immunogenicity of the pandemic influenza A vaccine in patients with juvenile systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 65:1121–1127. <https://doi.org/10.1002/acr.21948>
 27. Kumar D, Blumberg EA, Danziger-Isakov L, Kotton CN, Halasa NB, Ison MG, Avery RK, Green M, Allen UD, Edwards KM, Miller G, Michaels MG, AST Infectious Diseases Community of Practice (2011) Influenza vaccination in the organ transplant recipient: review and summary recommendations. *Am J Transplant* 11:2020–2030. <https://doi.org/10.1111/j.1600-6143.2011.03753.x>
 28. Gavaldà J, Cabral E, Perez-Romero P, Len O, Aydilto T, Campins M, Quintero J, Peghin M, Nieto J, Charco R, Pahissa A, Cordero E, Spanish Network for the Research in Infectious Diseases (REIPI) (2013) Immunogenicity of pandemic influenza A H1N1/2009 adjuvanted vaccine in pediatric solid organ transplant recipients. *Pediatr Transplant* 17:403–406. <https://doi.org/10.1111/petr.12084>
 29. Mrak D, Tobudic S, Koblichke M, Graninger M, Radner H, Sieghart D, Hofer P, Perkmann T, Haslacher H, Thalhammer R, Winkler S, Blüml S, Stiasny K, Aberle JH, Smolen JS, Heinz LX, Aletaha D, Bonelli M (2021) SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. *Ann Rheum Dis* 80:1345–1350. <https://doi.org/10.1136/annrheumdis-2021-220781>
 30. Fernandes P, Jorge S, Lopes JA (2010) Relapse of nephrotic syndrome following the use of 2009 pandemic influenza A (H1N1) vaccine. *Am J Kidney Dis* 56:185–186. <https://doi.org/10.1053/j.ajkd.2010.04.011>
 31. Ishimori S, Kamei K, Ando T, Yoshikawa T, Kano Y, Nagata H, Saida K, Sato M, Ogura M, Ito S, Ishikura K (2020) Influenza virus vaccination in children with nephrotic syndrome: insignificant risk of relapse. *Clin Exp Nephrol* 24:1069–1076. <https://doi.org/10.1007/s10157-020-01930-8>
 32. Angeletti A, Bruschi M, Bianchin S, Bonato I, Montobbio C, Verina E, Lugani F, Cravedi P, Ghiggeri GM (2021) Vaccines and disease relapses in children with nephrotic syndrome. *Clin J Am Soc Nephrol* 16:937–938. <https://doi.org/10.2215/CJN.01890221>
 33. Favresse J, Bayart JL, Mullier F, Elsen M, Eucher C, Van Eeckhoudt S, Roy T, Wieers G, Laurent C, Dogné JM, Closset M, Dourfils J (2021) Antibody titres decline 3-month post-vaccination with BNT162b2. *Emerg Microbes Infect* 10:1495–1498. <https://doi.org/10.1080/22221751.2021.1953403>
 34. Erice A, Varillas-Delgado D, Caballero C (2022) Decline of antibody titres 3 months after two doses of BNT162b2 in non-immunocompromised adults. *Clin Microbiol Infect* 28:139.e1–e139.e4. <https://doi.org/10.1016/j.cmi.2021.08.023>
 35. Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, Haljasmägi L, Rumm AP, Maruste R, Kärner J, Gerhold JM, Planken A, Ustav M, Kisand K, Peterson P (2021) Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. *Lancet Reg Health Eur* 10:100208. <https://doi.org/10.1016/j.lanpep.2021.100208>

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