Prospective Study of Live Attenuated Vaccines for Patients with Nephrotic Syndrome Receiving Immunosuppressive Agents

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Objective To conduct a prospective study to evaluate the immunogenicity and safety of live attenuated vaccines in patients with nephrotic syndrome receiving immunosuppressive agents.

Study design Patients with nephrotic syndrome receiving immunosuppressive agents with negative or borderline antibody titers (virus-specific IgG levels <4.0) against measles, rubella, varicella, and/or mumps fulfilling the criteria of cellular and humoral immunity were enrolled. Virus-specific IgG levels were measured using an enzyme immunoassay. The primary endpoint was the seroconversion rate (ie, achievement of virus-specific IgG levels ≥4.0) at 2 months after vaccination. Virus-specific IgG levels at 1 year, breakthrough infections (wild-type infections), and adverse events were also evaluated.

Results A total of 116 vaccinations were administered to 60 patients. Seroconversion rates were 95.7% for measles, 100% for rubella, 61.9% for varicella, and 40.0% for mumps. More patients with a borderline antibody titer before vaccination achieved seroconversion than those with negative antibody titer, with statistical significance after varicella and mumps vaccination. The rate of patients who maintained seropositivity at 1 year after vaccination was 83.3% for measles, 94.1% for rubella, 76.7% for varicella, and 20.0% for mumps. No patient experienced breakthrough infection. No serious adverse events, including vaccine-associated infection, were observed.

Conclusion Immunization with live attenuated vaccines may be immunogenic and is apparently safe in our cohort of patients with nephrotic syndrome receiving immunosuppressive agents if their cellular and humoral immunologic measures are within clinically acceptable levels. *(J Pediatr 2017;■■:■■-■■).*

Trial Registration UMIN-CTR UMIN 000007710.

Viral infections, such as measles and varicella, cause serious complications in children receiving immunosuppressive agents. Varicella is especially known to cause fatal, viscerally disseminated infections in patients on immunosuppression. These children have a much higher mortality rate than healthy children.[1-6] There is a 1969 case report of a 4-year-old boy with nephrotic syndrome who died from measles pneumonia during cyclophosphamide treatment.[7] The severity of infection is reportedly less severe in already immunized patients compared with nonimmunized patients.[4] There is also a risk of disease recurrence, such as relapse of nephrotic syndrome, after such viral infections. Therefore, long-lasting protection conferred by vaccination is desirable for these vaccine-preventable diseases.

In Japan, the combined measles and rubella (MR) vaccine is administered routinely at age 1 year and 5-6 years. The varicella vaccine is now also routinely administered twice at age 1 year, although it was voluntary before October 2014. The mumps vaccine is still voluntary. Most children in Japan receive the MR vaccine; however, the rates of varicella and mumps immunization are relatively low.

Live vaccines are generally contraindicated for use in patients receiving immunosuppressive agents, who are considered at greater risk for serious viral infection from the vaccine strains.[8] In Japan, the use of live vaccines is listed as a contraindication on the package insert of every immunosuppressive agent, including cyclosporine, tacrolimus, mycophenolate mofetil, mizoribine, azathioprine, and everolimus. In these patients, administration of live vaccines requires previous discontinuation of immunosuppressive agents, putting them at an unacceptable risk of recurrence of their original disease, such as relapse of nephrotic syndrome. Immunization with live vaccines in selected patients who

EIA	Enzyme immunoassay
MR	Measles and rubella
NCCHD	National Center for Child Health and Development
PHA	Phytohemagglutinin

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demonstrate stable disease activity under immunosuppressive therapy and normal immunologic parameters may be a possible solution to this dilemma.

A number of several case series examining immunization using live attenuated vaccines in patients on immunosuppressive therapy, mainly solid organ transplant recipients, have been published to date.[9-20] No life-threatening adverse events were reported. However, to the best of our knowledge, there are no published data on immunization with live vaccines for patients on immunosuppressive agents for nephrotic syndrome. Therefore, we conducted a prospective study to examine the immunogenicity and safety of live attenuated vaccines for patients with nephrotic syndrome receiving immunosuppressive agents.

Methods

This prospective study was performed between May 2011 and January 2017 at the National Center for Child Health and Development (NCCHD) in Tokyo, Japan. The study was registered under the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: UMIN 000007710). The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the NCCHD (approval no. 452). An intramural committee for live attenuated vaccines for patients receiving immunosuppressive agents, consisting of medical doctors in the Divisions of Infectious Diseases, Immunology, Nephrology and Rheumatology, and Gastroenterology and the Department of General Pediatrics, was established in April 2011 at the NCCHD and since then has been convened once a month to discuss patient eligibility and the monitoring of vaccine safety and immunogenicity. This prospective study of live attenuated vaccines for children with nephrotic syndrome receiving immunosuppressive agents was conducted under the supervision of this committee.

Inclusion criteria for eligible patients are listed in **Table I**. Virus-specific antibody titers were measured using a commercially available enzyme immunoassay (EIA) (Denka Seiken, Tokyo, Japan) for measles, rubella, varicella, and mumps. Negative (−), borderline (±), and positive (+) antibody titers were defined based on EIA measured IgG values of <2.0, 2.0-3.9, and ≥4.0. These cutoff values for IgG levels were determined by the manufacturer based on conversion from international units using World Health Organization standard substances.[26] The conversion formulas were as follows: measles, EIA values × 45 = international values (mIU/mL); rubella, EIA values × 2.3 = international values (IU/mL); varicella, EIA values × 45 = international values (mIU/mL). The relationship between virus-specific antibody titers and clinical efficacy (prevention of infection) suggested for healthy children is shown in **Table II** (available at www.jpeds.com).[27]

We used a freeze-dried live attenuated MR vaccine (Schwartz FF strain for measles and the TO-336 strain for rubella; Takeda, Osaka, Japan), a freeze-dried live attenuated varicella vaccine (Oka strain; Biken, Osaka, Japan), and a freeze-dried live attenuated mumps vaccine. For cases with a history of adverse events due to the MR vaccine, a positive antibody titer for rubella but a negative or borderline titer for measles, we used the freeze-dried live attenuated measles vaccine (Schwartz FF strain; Takeda). For the mumps vaccine, we used the Torii strain (Takeda) until October 2012 and then, because the immunogenicity of that strain proved unsatisfactory in our study, in November 2012 our institute changed to the Hoshino strain (Kitasato Daiichi Sankyo, Saitama, Japan).

Written informed consent was obtained from each patient's guardian for patients aged <15 years, from each patient and his or her guardian for patients aged 15-20 years, or from each patient aged ≥20 years who had achieved remission, was free of relapse of nephrotic syndrome for >6 months, and showed a negative or borderline antibody titer against measles, rubella, varicella, and/or mumps. The following parameters were assessed: CD4 cell count, lymphocyte blast transformation by phytohemagglutinin (PHA), and serum IgG level. In patients with a history of rituximab treatment, CD19 or CD20 cell count was measured as well. If these measurements met the inclusion criteria (**Table I**), the committee members discussed the indications for vaccination. After the committee's approval was obtained, vaccination was administered. Each vaccination was decided as single dose in this study protocol.

Antibody titers were examined at 2 months after vaccination. A positive antibody titer (virus-specific IgG level ≥4.0) was defined as seroconversion (seropositivity; responder), and a borderline or negative antibody titer (virus-specific IgG level <4.0) was defined as a nonresponder. Initial vaccination

Table I. Inclusion criteria for patients with nephrotic syndrome

1. Patients with nephrotic syndrome, aged ≥1 y
2. Negative or borderline antibody titer against 1 or more of measles, rubella, varicella, and mumps
3. Current treatment with 1 or 2 immunosuppressive agents (CsA, Tac, MMF, or MZR)
4. Normal cellular immunity
   $CD4^+$ cells ≥500/mm^3*
   Normal lymphocyte blast transformation by phytohemagglutinin (stimulation index ≥101.6)†
5. Serum IgG level‡ ≥300 mg/dL§
6. Recovery of normal B-cell count in patient with a history of rituximab treatment
7. No steroid use or prednisolone <1 mg/kg/d or <2 mg/kg/2 d
8. Trough levels of Tac¶ <10 ng/mL
9. Trough levels of CsA** <100 ng/mL
10. Remission of nephrotic syndrome for >6 mo
11. Difficulty discontinuing immunosuppressive agents due to relapse of nephrotic syndrome
12. Written informed consent obtained from patients or families

CsA, cyclosporine; *MMF*, mycophenolate mofetil; *MZR*, mizoribine; *Tac*, tacrolimus.
*Cutoff value was adapted from the Centers for Disease Control and Prevention recommendation,[21] which shows the CD4 lymphocyte counts under no evidence of immunosuppression.
†Cutoff value provided by the manufacturer.
‡Serum IgG level assessed as described previously.[22]
§Cutoff value determined as described previously,[23] which shows a 95% range of IgG level of patients aged 1 year.
The criteria in ‡ and § were established in July 2013,when we encountered a renal transplant recipient with chickenpox caused by a varicella vaccine strain, as indicated by her low cellular and humoral immunity (CD4 cell count of 511/mm^3, PHA stimulation index of 91.1, and serum IgG level of 208 mg/dL).
¶Tac level assessed as described previously.[24]
**The method of assessing CsA level was described by Morelle et al.[25].

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