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# Serologic response after vaccination against influenza (A/H1N1)pdm09 in children with renal disease receiving oral immunosuppressive drugs

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ABSTRACT

A limited number of reports are available regarding the effect of the influenza vaccine in pediatric patients receiving steroid and immunosuppressant therapy. The influenza A(H1N1)pdm09 vaccine was administered to 15 children with renal disease who were receiving steroid and immunosuppressant therapy (treatment group) and 23 children with who were not receiving these drugs (non-treatment group). Titer transition of the hemagglutination inhibition antibody was compared between the 2 groups immediately before vaccination and 4 weeks and 6 months after vaccination. Multivariate analysis showed a significant correlation between geometric mean titer, SCR, and SPR with age, while no correlation was observed between treatment with immunosuppressant therapy and efficacy. No serious adverse reactions occurred after vaccination.

This strain is not present in existing influenza vaccines, and A(H1N1)pdm09HA vaccination was administered alone in 2009. The children in this study had not previously been exposed to this strain. Therefore, we evaluated the effect of the A(H1N1)pdm09HA vaccine without the effects of vaccination or past infection with A(H1N1)pdm09HA or A(H3N2) vaccination in the previous year.



## 1. Introduction

The Advisory Committee on Immunization Practices recommends that patients with chronic renal disease should receive vaccination to prevent worsening of the underlying disease due to influenza A(H1N1)pdm09 infection [1]. While a number of studies have investigated vaccination in adult renal transplant recipients, only a limited number studies have evaluated the efficacy and safety of vaccination in pediatric renal transplant recipients [2], particularly there are no studies by pediatric non-transplant patient in those receiving immunosuppressant therapy.

In Japan, immunosuppressant and steroid therapy is used to treat frequently relapsing nephrotic syndrome, IgA nephropathy, and other common renal diseases in children on the basis of disease severity. There is growing concern that acquisition of the influenza antibody may be affected during steroid pulse therapy or long-term daily steroid treatment (≥2 mg/kg/day or ≥20 mg/day) [3]. In the field of transplantation, the effects of vaccine are reportedly different depending on the type and dose of immunosuppressants and steroids used to treat renal diseases [4–11]. There is no consensus regarding adverse reactions and worsening of the underlying disease associated with vaccination in pediatric patients with renal disease. It is also controversial whether vaccination induces recurrence of frequently relapsing nephrotic syndrome [12,13] and whether inactivated influenza vaccine is involved in rejection reactions in pediatric organ transplant recipients [14,15].

A(H1N1)pdm09 vaccination was not actively administered to children due to the concern of adverse reactions. However, vaccination is now recommended for designated individuals with underlying renal disease due to the risk of developing severe renal disease in influenza A(H1N1)pdm09 infection [1]. Therefore, it is important to understand the efficacy and safety of vaccination in pediatric patients with renal disease on immunosuppressant and steroid therapy as well as independent background factors involved in antibody induction.

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## 2. Materials and methods

### 2.1. Study design

This prospective study was conducted in pediatric patients with renal disease who visited the Department of Pediatrics and Child Health, Kurume University Medical Center on an outpatient basis. The study subjects comprised 15 children concomitantly receiving steroid and immunosuppressant therapy (treatment group) and 23 children (6 Bronchial asthma with no treatment and 17 health) not receiving steroid and immunosuppressant therapy (non-treatment group). Children who had already acquired influenza A(H1N1)pdm09 infection during the same season were excluded from participation in the study.

In November 2009, the influenza HA vaccine (lot No. HP01A, BIKEN) A/California/7/2009 strain was administered to all patients. Children aged <1 year were vaccinated twice with 0.1 mL of vaccine, children aged between 2 and −6 years were vaccinated twice with 0.2 mL of vaccine, children aged between 6 and −13 years were vaccinated twice in the left and right arms with 0.3 mL of vaccine, and children aged ≥13 years were vaccinated once with 0.5 mL of vaccine. The interval between the first and second vaccinations was 4 weeks.

At the time of vaccination, the subject's baseline demographic data were collected using physician- and self-administered questionnaires. Patient serum samples were collected 3 times, including immediately before vaccination (S0), immediately before the second vaccination, which was 4 weeks after the initial vaccination (S1), and 6 months after vaccination (S2). All samples were collectively subjected to titer measurement of hemagglutination inhibition reaction (HI) antibody at the Surveillance Center of Research Institute for Microbial Diseases, Osaka University, and vaccine efficacy was evaluated based on the criteria of the European Medicines Evaluation Agency (EMA).

Additionally, follow-up visits were conducted for 24 weeks using postcards (once every week) to monitor the occurrence of adverse events potentially related to vaccination; worsening of the underlying disease; symptoms such as fever, nasal discharge/congestion, pharyngeal pain, and cough/sputum; visit to a medical institution; results of a rapid diagnostic kit; and hospitalization.

**Table 1**
Clinical background of the study population.

| | Immunosuppressant | |
|---|---|---|
| | Yes ($n$ = 15) | No ($n$ = 23) |
| Sex (male (%)) | 53.3 | 65.2 |
| Age (mean (SD)) | 11.8 (4.0) | 4.8 (2.9) |
| Frequently relapsing nephrotic syndrome | 9 | 0 |
| Systemic lupus erythematosus | 5 | 0 |
| IgA nephropathy | 1 | 0 |

### 2.2. Statistical analysis

When calculating indicators of immunogenicity, geometric mean fold rise (GMFR), seroconversion rate (SCR), seroprotection rate (SPR), and geometric mean titer (GMT), 1:5 was used for HI titers <1:10. HI titers were logarithm-transformed for evaluation. SCR, SPR, GMT, and 95% confidence intervals were calculated according to the level of influential factors, and a two-sided test was used with a significance level set at 0.05. Univariate and multivariate logistic regression analyses were conducted for SCR and SPR, and univariate and multivariate regression analyses were conducted for GMT. SPSS and Microsoft Excel were used for statistical analyses.

This study was approved by the Ethics Committee of Kurume University, and prior written consent was obtained from the legal guardians of the subjects to participate in the study.

## 3. Results

### 3.1. Subject demographics

The underlying diseases in the 15 children in the treatment group included frequently relapsing nephrotic syndrome in 9 children, systemic lupus erythematosus in 5 children, and IgA nephropathy in 1 child. 6 Bronchial asthma with no treatment and 17healh were the underlying disease in the 23 children in the non-treatment group.

Mean and median ages of children not receiving immunosuppressant therapy were 4.8 years and 4 years, respectively, and 15 children receiving concomitant steroid and immunosuppressant therapy (Table 1) had a mean age of 11.8 years and a median age of 12 years. Prednisolone was administered at a

**Table 2**
geometric mean titer response After Vaccination in age and sex and pre HI titer.

| | Immuno-suppressant | | Geometric mean titer | | |
|---|---|---|---|---|---|
| | | | Time of blood sampling | | |
| | | | S0 (shortly before) | S1 (4 weeks after) | S2 (6 months after) |
| Age (year) | | | | | |
| 1–5 | Yes | 1 | 5 | 20 | 80 |
| | No | 18 | 5.4 | 14.7 | 22.3 |
| 6–10 | Yes | 4 | 5.0 | 28.3 | 14.1 |
| | No | 4 | 7.1 | 80.0 | 20.0 |
| 11–18 | Yes | 10 | 7.1 | 246.6 | 100.8 |
| | No | 1 | 5 | 80 | – |
| Sex | | | | | |
| Male | Yes | 8 | 7.1 | 95.1 | 14.1 |
| | No | 15 | 5.7 | 15.9 | 17.6 |
| Female | Yes | 7 | 5.5 | 121.3 | 95.1 |
| | No | 8 | 5.5 | 36.7 | 31.7 |
| Pre HI titer | | | | | |
| <10 | Yes | 13 | 5 | 100.8 | 34.8 |
| | No | 20 | 5 | 17.4 | 19.0 |
| ≧10 | Yes | 2 | 28.3 | 160 | 320 |
| | No | 3 | 12.6 | 80 | 40 |

dose of <20 mg/day (0.14 mg/kg/d) in 14 children and ≥20 mg/day (0.50 mg/kg/d) in 4 children, with a mean dose of 9.3 mg/day (0.22 mg/kg/d). Prednisolone was the sole steroid used in this study, and immunosuppressants used included cyclosporin (CsA) in 10 children (mean dose at the time of vaccination, 3.28 mg/kg/day; mean blood concentration at the time of vaccination C0 (medicine Blood concentration before internal use), 90.88; mean treatment duration before vaccination, 29.3 months), tacrolimus (Tac) in 3 children (mean dose at the time of vaccination, 0.09 mg/kg/day; mean blood concentration at the time of vaccination C12 (medicine Blood concentration 12 h after internal use), 3.53; mean treatment duration before vaccination, 7.3 months), mizoribine (MZB) in 3 children (mean dose at the time of vaccination, 4.81 mg/kg/2d; mean blood concentration at the time of vaccination C2, 2.96; mean treatment duration before vaccination, 11.6 months), and a combination of CsA and MZB in 1 child.

Serum samples were collected from 38 children immediately before vaccination, 36 children 4 weeks after vaccination, and 23 children 6 months after vaccination; the pre-vaccination antibody titer was <1:10 in 89.5% of the subjects. Follow-up visits using postcards did not identify any patients with positive influenza rapid test results or suspected latent infection with at least a 4-fold increase in antibody titer after the pandemic compared with those patients after vaccination.

### 3.2. Antibody titer

(i) Geometric mean titer and geometric mean fold rise

Table 2 shows the time profile of GMT according to age, sex, and pre-vaccination antibody titer. Showing a higher GMT in older age groups. Analyses according to sex and pre-vaccination antibody titer revealed no apparent differences in GMT after vaccination. The children were divided into 2 groups according to whether they were receiving immunosuppressant therapy to generate a time profile of GMT and GMFR (Table 3). GMFR increased by at least 2.5-fold in the 2 groups at both time points of 4 weeks and 6 months after vaccination, satisfying the criteria of EMA regardless of whether children were receiving immunosuppressant therapy.

(ii) Seroconversion rate: Proportion of children with an at least 4-fold increase in antibody titer after vaccination.

Both groups met the criterion for EMA, an SCR >40%, at 4 weeks after vaccination (Table 3).

(iii) Seroprotection rate: Proportion of children showing an increase to 40 or higher. This number exceeded 50%, the criterion for EMA, in the treatment group at 4 weeks after vaccination, demonstrating a statistically significant increase in antibody titer (Table 3).

### 3.3. Impact of steroid and immunosuppressant therapy on geometric mean time (regression analysis)

While univariate analysis showed ($P$ = .000) for immunosuppressant treatment and age, multivariate analysis showed a regression coefficient of 0.01 ($P$ = .001) only for age, leading to the conclusion that age is a significant relative factor for increased GMT in treatment group and non-treatment group (Table 4). The higher age of the treatment group may have resulted in the age appearing to be a relative factor in univariate analysis.

### 3.4. Impact of steroid and immunosuppressant therapy on seroconversion rate (logistic regression analysis)

Based on the results of multivariate analysis, the odds ratio for age was found to be 1.78 ($P$ = 0.008), demonstrating a significant correlation between SCR and age in treatment group and

**Table 3**
Immune response among immunosuppressant and nonimmunosuppressant.

| Immuno-suppressant | Geometric mean titer | | | Geometric mean fold rise | | Seroconversion rate | | Seroprotection rate | |
|---|---|---|---|---|---|---|---|---|---|
| | S0 (95%CI) | S1 (95%CI) | S2 (95%CI) | S1/S0 (95%CI) | S2/S0 (95%CI) | S1 (95%CI) | S2 (95%CI) | S1 (95%CI) | S2 (95%CI) |
| Yes ($n$ = 15) | 6.3 (4.9–6.5) | 104.4 (40.0–272.9) | 50.4 (8.2–311.3) | 16.9 (6.0–47.4) | 9.0 (1.7–48.4) | 69.2 (38.6–90.9) | 66.7 (22.3–95.7) | 76.9 (46.2–95.0) | 66.7 (22.3–95.7) |
| No ($n$ = 23) | 5.6 (4.2–9.4) | 21.2 (12.5–36.0) | 21.7 (12.6–37.5) | 3.8 (2.3–6.1) | 3.7 (2.2–6.2) | 43.5 (23.2–65.5) | 35.3 (14.2–61.7) | 43.5 (23.2–65.5) | 35.3 (14.2–61.7) |

**Table 4**
Assessment of impact of steroid and immunosuppressant on geometric mean titer (regression analysis).

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Regression coefficient | *P* | Regression coefficient | *P* |
| Immunosuppressant | 0.692 | 0.002 | 0.079 | 0.822 |
| Age | 0.107 | <0.001 | 0.100 | 0.001 |
| Sex | 0.293 | 0.214 | 0.193 | 0.310 |
| Prevaccination titer | 0.010 | 0.254 | 0.007 | 0.376 |

non-treatment group (Table 5). No significant correlation was observed between treatment, sex, and pre-vaccination antibody titer and SCR.

### 3.5. Impact of steroid and immunosuppressant therapy on SPR (logistic regression analysis)

Based on the results of multivariate analysis, the odds ratio for age was 1.82 ($P = 0.008$), demonstrating a significant correlation between SPR and age in treatment group and non-treatment group (Table 5). No significant correlation was observed between treatment and sex and SPR.

### 3.6. Adverse reactions after vaccination

Adverse reactions were monitored for 24 weeks after vaccination using postcards. No serious adverse reactions were reported. Furthermore, no children experienced worsening of the underlying disease after vaccination.

## 4. Discussion

For studies examining the influenza vaccine, infection and vaccination in the previous year affects the vaccine during the following year, complicating the study. In our study, children were exposed to the A(H1N1)pdm09 strain for the first time because the strain is not included in existing trivalent influenza vaccines. GMT at pre-vaccination antibody titer was lower than 40 in this study.

Multivariate analyses in our study deemed GMT, SCR, SPR, and age to be relevant factors. As with the non-treatment group, the treatment group met the criteria of EMA for all GMFR, SCR, and SPR, showing no correlation between treatment and vaccine efficacy. The impacts of immunosuppressant therapy on antibody titer were not evaluated due to the sample size in this study. These results demonstrate the usefulness of the influenza A(H1N1)pdm09 vaccine in the treatment group.

Effectiveness of the existing influenza vaccine is predominantly influenced by age, immunologic status, and history of infection of vaccinated individuals.

In terms of age, efficacy of existing influenza vaccines in healthy adult ranges between 43% and 58%[16]. The efficacy in children ranges between 44% and 49% in the age group of 1–5 years, 74–76% in the age group of 6–10 years, and 70–81% in the age group of 11–15 years, indicating a different effect depending on age [17]. This study also showed that an increase in GMT at 4 weeks after vaccination with increasing age; these values were 15.0, 47.6, and 217.8 in children aged 1–5, 6–10, and 11–18 years, respectively. Multivariate analyses results also demonstrated a significant difference in both SCR and SPR according to age, with odds ratios of 1.78 and 1.82, respectively.

Several studies have examined the impacts of steroid and immunosuppressant therapy on acquisition of antibody after vaccination for various drugs and underlying diseases. Concerns arise regarding the efficacy of inactivated vaccines when prednisolone at ≥2 mg/kg/day or ≥20 mg/day is used daily, and 1 report found that alternate-day administration does not affect antibody acquisition [3]. The mean dose of prednisolone in this study was 9.3 mg/day given every other day, which was considered to not affect antibody acquisition. Of the 4 children using ≥20 mg/day prednisolone daily at the time of vaccination, 4 children showed increase in S1 antibody titer. A comparison of steroid/immunosuppressant and immunosuppressant groups following pediatric renal transplant and a control group of healthy children showed a difference in GMT according to vaccine type, but showed no difference in SPR, revealing no influence on vaccine effectiveness. These results were also assumed to be due to the low dose of prednisolone used in this study (3.6 mg/m$^2$/day; 2.9–5.4 mg/m$^2$/day) [2]. Based on these reports, we successfully demonstrated that prednisolone at a dose of less than 2 mg/kg or 20 mg/day does not influence influenza vaccine effectiveness. Ulinski et al. [18] administered pneumococcal vaccination when minimal lesion nephrotic syndrome recurred and reported that no significant difference between a group of patients who simultaneously initiated daily use of prednisolone 60 mg/m$^2$ and a group of patients who received low-dose prednisolone (≤15 mg/m$^2$ given every other day) after remission. Further studies of the efficacy of vaccination when prednisolone is administered at ≥2 mg/kg/day or ≥20 mg/day should be conducted.

Several studies have been conducted to examine the relationship between immunosuppressant therapy and vaccination. Salles et al. [4] conducted a study in 69 renal transplant recipients to compare antibody acquisition after influenza vaccination between a mycophenolate mofetil (MMF) group and an azathioprine (Aza) group and revealed lower antibody acquisition in the MMF group. Other reports have stated that MMF used for transplantation therapy impaired antibody acquisition after influenza vaccination [5–7]. In our study, 4 children used MZB, which has a

**Table 5**
Assessment of impact of steroid and immunosuppressant on seroconversion rate and seroprotection rate (logistic regression analysis).

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | OR | *P* | OR | *P* |
| Immuno-supressant | Seroconversion rate | 2.924 | 0.144 | 0.692 | 0.854 |
| | Seroprotection rate | 4.333 | 0.060 | 0.918 | 0.966 |
| Age | Seroconversion rate | 1.421 | <0.001 | 1.782 | 0.008 |
| | Seroprotection rate | 1.552 | 0.002 | 1.822 | 0.008 |
| Sex | Seroconversion rate | 0.342 | 0.214 | 0.294 | 0.262 |
| | Seroprotection rate | 0.407 | 0.219 | 0.291 | 0.266 |
| Prevaccination titer | Seroconversion rate | 0.977 | 0.504 | 0.959 | 0.265 |
| | Seroprotection rate | – | – | – | – |

similar mechanism to MMF, and no impact on antibody acquisition was observed in all 4 children. Additionally, there is no consensus regarding the impact of calcineurin inhibitors, CsA, Tac, and sirolimus (Sir). While CsA was reported to reduce the effect of the vaccine [8], and since there were no significant differences in the effect of the vaccine with CsA and Sir [9], antibody acquisition for all influenza H1N1, H3N2, and B are more favorable with Sir, and there was no impact of Sir on antibody acquisition between patients on Sir and healthy subjects, resulting in no clear conclusion [10]. In our study, 7 of 10 children who received CsA were not affected. The 3 children with impaired antibody acquisition were aged 3, 9, and 11 years, indicating that the lower age of the 3-year-old child and cause is unknown in the 9-year-old child may have influenced these results. The antibody titer of the 11-year-old child was 1:80 before vaccination and 1:160 4 weeks after vaccination. This patient was asymptomatic, had no latent infection with a less than 4-fold increase in antibody titer, and did not meet efficacy criteria. A previous report examining Tac showed a reduced effect of the vaccine in 53 renal transplant recipients within 6 months of transplantation as compared to 106 healthy control subjects [11]. In our study, 3 patients used Tac; 2 of these patients were unaffected and 1 did not undergo measurement. GMT GMFR SCR SPR are higher in immunosuppressant groups of Table 3, the reason is because immunosuppressant groups is older.

In transplantation therapy, immunosuppressants are often used at high doses and in various combinations. The results of our study may be affected by immunosuppressants used at therapeutic doses for nephritis. Therefore, the effect of the influenza vaccine can be maintained in patients with nephritis receiving therapeutic doses of immunosuppressants that are lower than those used in transplantation therapy.

## 5. Conclusions

In 2009, a vaccination program was launched against the influenza A(H1N1)pdm09 strain, which is not included in existing influenza vaccines; the children in this study were exposed to this strain for the first time. Nevertheless, antibody acquisition after vaccination was favorable, and no adverse events occurred in pediatric patients with renal disease receiving concomitant steroid and immunosuppressant therapy. The impact of age on antibody acquisition was more prominent than that of medications used in the study. Influenza A(H1N1)pdm09 vaccination can be recommended for patients receiving steroid and immunosuppressant therapy.

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