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Immunogenicity and safety of a trivalent inactivated 2010–2011 influenza vaccine in Taiwan infants aged 6–12 months

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ABSTRACT

This prospective study aimed to investigate the immune responses and safety of an influenza vaccine in vaccine-naïve infants aged 6–12 months, and was conducted from November 2010 to May 2011. Fifty-nine infants aged 6–12 months received two doses of trivalent inactivated influenza vaccine 4 weeks apart. Hemagglutination inhibition titers were measured 4 weeks after the two doses of study vaccine. Based on the assumption that a hemagglutination inhibition titer of 1:40 or greater against the antigen would be protective in adults, two doses of the study vaccine generated a protective immune response of 63.2% against influenza A(H1N1), 82.5% against influenza A(H3N2) and 38.6% against influenza B viruses in infants aged 6–12 months. The geometric mean fold rises against influenza type A and B viruses also met the European Medicines Agency criteria for flu vaccines. The solicited events within 7 days after vaccination were mild in intensity. No deaths or adverse events such as optic neuritis, cranial neuropathy, and brachial neuropathy or Guillain-Barre syndrome were reported. Two doses of inactivated influenza vaccine were well tolerated and induced a protective immune response against influenza in infants aged 6–12 months.

1. Introduction

Annual influenza vaccination is the most effective method to prevent influenza virus infections and complications [1,2]. Influenza vaccine for young children showed two doses are better than one dose in effectiveness study [3,4]. However, only limited data are available on immune responses to demonstrate the difference of immunogenicity between one and two doses in influenza-naïve infants. We therefore conducted this multicenter, prospective study to determine the immunogenicity and safety of a trivalent inactivated flu vaccine in infants aged 6–12 months.

2. Participants and methods

2.1. Study design

This was a prospective study to evaluate the immunogenicity and safety of a trivalent inactivated 2010–2011 influenza vaccine (AdimFlu-S®, manufactured by Adimmune Corp., Taichung, Taiwan) in infants aged 6–12 months. It was conducted at three medical centers in Taiwan, including China Medical University Hospital, National Taiwan University Hospital, and Chi Mei Medical Center from November 2010 to May 2011 under the approval of Institutional Review Board (IRB) in each center.

All participants received 2 doses of 0.25 mL (7.5 mcg HA per strain) of vaccine separated by 4 weeks. Safety outcomes included immediate reactions at the time of vaccination, solicited local and systemic reactions within 7 days after each vaccination, unsolicited adverse events, and serious adverse events. Sera prepared from blood samples were collected from each infant immediately prior

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to, and 4 weeks after each vaccination. Anti-hemagglutinin (HA) antibody titers were determined using the World Health Organization hemagglutination inhibition reference technique. The analysis was laboratory-blinded. All participants were followed up either by clinical visits or telephone contact for 6 months after the first vaccination.

2.2. Vaccine

The study vaccine was the inactivated split influenza vaccine 2010–2011, licensed in Taiwan under the name AdimFlu-S. It was a sterile suspension without adjuvant prepared from influenza viruses propagated in chicken embryos. For the 2010–2011 seasons, each milliliter of vaccine contained HA of the following three strains: 30 μg A/California/7/2009 (H1N1), 30 μg A/Perth/16/2009 (H3N2), and 30 μg B/Brisbane/60/2008.

2.3. Immunogenicity

The serum samples were tested at the Adimmune Corporation designated central laboratory. Antibody responses were detected by hemagglutination inhibition (HAI) assay with turkey erythrocytes using standard methods, and the HAI assays were performed in duplicate for each sample. All assays were validated according to international standards.

2.4. Safety

Safety data consisted of reactogenicity, serious and non-serious adverse events (AEs) reported by the parents or guardians or observed by the investigator throughout the study. Vital signs were recorded and physical examinations were performed at each clinic visit.

Reactogenicity, defined as pre-specified adverse events including systemic and local solicited events, was recorded by the parents or guardians of the infants on diary cards (a grid of check boxes for each event and each day) for 7 days after each vaccination. With regards to the long-term safety of the study vaccine, all participants were followed up for 6 months after each vaccination. A serious AE (SAE) was defined as an AE that met any of the following criteria: fatal or life-threatening, permanently disabling, requiring or prolonging inpatient hospitalization, congenital anomaly, cancer, and overdose. Investigators were required to promptly report all SAEs.

2.5. Statistical analysis

Data pertaining to demographics and baseline characteristics (i.e. age, sex, weight, height, systolic blood pressure, diastolic blood pressure, pulse rate, and body mass index) were summarized, if applicable. Individual subject listing of demographics and baseline characteristics were also presented.

The immunogenicity of the study vaccine was evaluated. An anti-hemagglutinin antibody titer of <1:10 was considered to be 1:5 for data analysis. The immune responses to the three vaccine viral strains were assessed by calculation of the geometric mean titers (GMT) of anti-HA antibodies, geometric means of post- to pre-vaccination antibody titer ratios (with 95% confidence intervals [CI]), seroprotection rates (percentage of subjects with a titer ≥1:40 on day 28), seroconversion rates (percentage of subjects with a pre-vaccination titer <1:10 achieving a titer ≥1:40 or significant increases in anti-HA levels at least a four-fold rise for seropositive subjects before vaccination. All analyses were repeated for each strain. The protection or conversion rates were summarized for the subjects receiving a specified dose of the vaccine with 95% CI. GMT and 95% CI were computed by taking the exponent of the mean and of the lower and upper limits of the 95% CI of the $\log_{10}$-transformed titers. While there are no published criteria for children younger than 18 years of age, a HAI titer of 1:40 or greater was assumed to be protective against influenza infection.

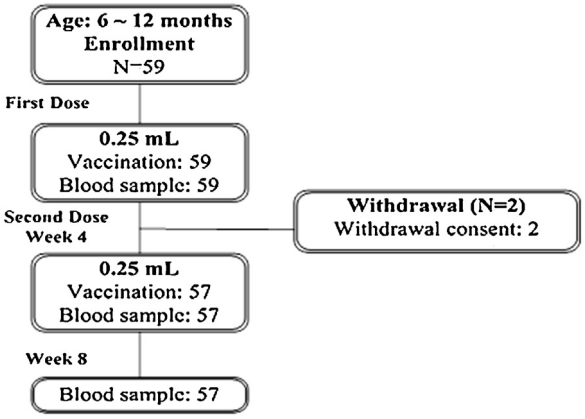

Fig. 1. Dose administration and immunogenicity analysis in the study.

The safety endpoints were the frequency, duration, and intensity of solicited adverse events during the 7 days after the vaccination and the incidence of SAEs and AEs of special interest during the study period. These safety endpoints were evaluated for all of the enrolled subjects. The percentage of subjects with post-vaccination reactions was based on the frequency and the intensity/severity of the reported responses after the vaccination.

3. Results

3.1. Study participants

A total of fifty-nine subjects were enrolled in the study, 32 (54.2%) of whom were boys and 27 (45.8%) girls. The mean age of the subjects was 8.1 ± 1.7 months. The mean weight and the mean height of the subjects at enrolment was 8.38 ± 1.22 kg and 68.34 ± 3.89 cm, respectively. Two subjects withdrew after one dose of vaccination as the parents were unwilling to continue. Fig. 1 shows the enrolment and outcomes of the study.

3.2. Safety

Solicited local events that occurred during the 7 days after each vaccination are summarized in Table 1. Among the enrolled subjects, 15 (25.4%) had at least one solicited local event after first vaccination and five (8.8%) had at least one solicited local event after the second vaccination. Overall, 17 (28.8%) subjects reported at least one solicited local event after the vaccination. The most commonly reported solicited local event after the vaccination was redness (14 subjects, 23.7%) followed by swelling (six subjects, 10.2%), soreness/pain (five subjects, 8.5%) and ecchymosis (three subjects, 5.1%). The intensities of the solicited local events within 7 days after receiving the study vaccine were mild, except for one case whose swelling was reported to be moderate in intensity. The solicited systemic events that occurred during the 7 days after each vaccine are summarized in Table 2.

Overall, 35 (59.3%) subjects reported at least one solicited systemic event after the vaccination. The most commonly reported solicited systemic event after the vaccination was cough (29 subjects, 49.2%) followed by nasal congestion (24 subjects, 40.7%), malaise (14 subjects, 23.7%) and sore throat (13 subjects, 22.0%). Nine (15.3%) subjects had a fever after a vaccination. All of the reported solicited systemic events were generally mild to moderate in intensity. No deaths were reported in this study. Six subjects reported a total of nine SAEs that lead to hospitalization.