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Long-term immunogenicity of influenza vaccine among the elderly: Risk factors for poor immune response and persistence☆

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ABSTRACT

The elderly have been considered as the priority group for influenza vaccination, but their influenza vaccine-induced antibody was believed to decline more rapidly. Long-term immunogenicity of the influenza vaccine among the elderly was evaluated as compared to young adults. Serum hemagglutinin inhibition (HI) titers were determined at pre- and post-vaccination periods (at 1, 6, and 12 months after vaccination). Of the 1018 subjects, 716 (70.3%) were followed up during a 12-month period. Seroprotection rates at 1 month post-vaccination ranged from 70.1% to 90.3% depending on the age group and influenza vaccine virus strain. At 6 months post-vaccination, seroprotection rates for all three strains had declined significantly in adults ≥65 years ($P < 0.01$), but still met the EMEA criteria. Low pre-vaccination HI titer (<1:40) and advanced age were associated with early decline of HI titers, falling below seroprotective levels around 6 months after vaccination.

1. Introduction

Influenza is a major cause of morbidity and mortality among the elderly. Elderly people are at increased risk of death from influenza as a result of pulmonary complications as well as exacerbation of underlying medical conditions. According to a previous report in the 1990s, 90% of the 36,000 annual influenza-associated respiratory- and circulatory-related deaths in the US occurred among persons older than 65 [1]. That is why the Advisory Committee on Immunization Practices (ACIP) strongly recommends that aged persons (more than 50 years old) should be given priority for vaccinations [2].

In the Republic of Korea (ROK), influenza vaccine coverage rates in elderly people have been quite high and are estimated to be 70.0% in the 60–69 age range and 84.8% in people 70 years and older [3]. However, vaccine efficacy among the elderly has been reported to be variable: 23–60% for preventing influenza illness, 30–50% for preventing hospitalization, and 27–75% in reducing mortality from influenza [4–6]. In addition, there have been concerns that influenza vaccine-induced antibodies decline more rapidly in the elderly compared to younger adults [7]. The relatively short duration of antibody persistence after immunization can further decrease the effectiveness of influenza vaccine if exposure to influenza occurs late in the epidemic season.

Decreased serological efficacy of the influenza vaccine among elderly people is assumed due to aging immunity and chronic co-morbidities such as diabetes, liver cirrhosis, malignancies, etc. However, immune senescence is related to the gradual involution of the thymus gland resulting in T-cell insufficiency, while B-cell function remains mostly intact [8]. Therefore, the reason behind decreased serologic response after influenza vaccination in the elderly has been controversial.

In this study, we intended to assess long-term immunogenicity (up to a 12-month period) of influenza vaccine among the elderly compared to younger adults, stratified according to age and the presence of underlying co-morbidities.

2. Materials and methods

2.1. Study design

Between October 2007 and September 2008, we conducted an observational open label multi-center study to assess the immunogenicity of influenza vaccine and its persistence after vaccination in adults 18 years and older. The study was performed at two univer-

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Table 1
Baseline characteristics of per protocol immunogenicity population.

Characteristics	18–49 years old (n = 161)	50–64 years old, healthy (n = 175)	50–64 years old, co-morbid (n = 127)	≥65 years old (n = 253)	P-value
Age, mean ± SD	35.2 ± 7.8	57.6 ± 4.3	58.3 ± 3.9	71.7 ± 4.5	<0.01
Male, no. (%)	22 (13.7)	43 (24.6)	34 (26.8)	82 (32.4)	<0.01
Influenza vaccinees in the previous year, no. (%)	114 (70.8)	118 (67.4)	82 (64.6)	228 (90.1)	<0.01
Co-morbidities, no. (%)	0	0	127 (100)	44 (17.4)	<0.01
Liver cirrhosis	0	0	15 (11.8)	0	
Chronic renal failure	0	0	9 (7.1)	0	
Diabetes	0	0	77 (61.1)	43 (17.0)	
Malignancy	0	0	8 (6.3)	1 (0.4)	
Steroid user	0	0	33 (26.0)	3 (1.2)	

sity hospitals and one public health center located in southwestern Seoul, Korea.

The primary objective of the study was to investigate the immunogenicity of influenza vaccine in short-term (1 month post-vaccination) and long-term (6 months and 12 months post-vaccination) among the elderly compared to younger adults. Each patient was stratified into four groups according to their age and underlying co-morbidities (diabetes, liver cirrhosis, chronic renal failure, malignancy, and chronic steroid use): elderly subjects ≥65 years, subjects aged 50–64 with co-morbidities, subjects aged 50–64 without co-morbidities, and subjects aged 18–49. The secondary objective was to analyze the risk factors for poor immune response after influenza vaccination by measuring seroconversion and immunogenic persistence. In addition, vaccine safety and reactogenicity were assessed.

All subjects enrolled in the study were adults ≥18 years of age without unstable medical diseases. Demographic data for the subjects included in the study are described in Table 1. Exclusion criteria were as follows: contraindication for the influenza vaccine including egg allergy, febrile illness ≥37.5 °C on the day of enrollment, influenza vaccination within the past 6 months, any other vaccination within the past 30 days, chemotherapy for malignancy within the past 30 days, high-dose systemic steroid (prednisone ≥0.5 mg/kg/day) therapy in the past 30 days, treatment with immunoglobulins during the previous 3 months, and any condition which might, in the opinion of the investigator, interfere with the study results.

The study was approved by the ethics committee of each institution involved and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All subjects provided written, informed consent before enrollment.

On day 0, post-vaccination day 30 ± 7, post-vaccination day 180 ± 7, and post-vaccination day 365 ± 7, 10 ml venous blood samples were obtained from each subject.

2.2. Vaccines

The trivalent inactivated split influenza vaccine Vaxigrip® (Sanofi-Pasteur, Seoul, Korea) containing 15 μg of each hemagglutinin antigen was used, which was composed of the following influenza strains: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. This composition was antigenically identical to that of the 06–07 season except for the H1N1 strain (A/New Caledonia/20/99 in 06–07 season).

2.3. Assessment of immunogenicity

Hemagglutination-inhibiting (HI) antibodies were measured by a standard microtiter assay. Sera were pre-treated with receptor-destroying enzyme (RDE) [Sigma, St. Louis, MO, USA (1:5)] for 18 h at 37 °C and then inactivated at 56 °C for 30 min. Serum dilution from 1:10 to 1:20,240 (11 dilution steps) were then prepared in triplicate. The serum HI antibodies were determined using test antigens at a concentration of four hemagglutinating units per 25 μl of virus per assay in a 0.5% (v/v) suspension of washed chicken erythrocytes. The microtiter plates were maintained at room temperature until sedimentation was visible. Serum dilution at which complete inhibition of hemagglutination was achieved was considered as the serum antibody titer. Titer of <1:10 was considered negative and arbitrarily assigned as 1:5. Geometric mean titer (GMT) was determined in pre- and post-vaccination samples. Serologic response, measured by HI antibody titer, was assessed using the criteria of the European Agency for the Evaluation of Medicinal Products (EMEA) as follows: seroprotection rate (the percentage of subjects with a post-vaccination titer ≥1:40), seroconversion rate (either a post-vaccination titer ≥1:40 in subjects with a pre-vaccination titer of <1:10 or a ≥4-fold titer increase in subjects with a pre-vaccination titer of ≥1:10), and GMT fold (GMT ratio of the post-vaccination titer to pre-vaccination titer) [9]. The EMEA definition of seroprotection was used at 1, 6, and 12 months after vaccination to directly compare the immunologic persistence among the three post-vaccination time points. One of the following criteria must be met for the licensure of seasonal influenza vaccine: seroprotection rate >70% for subjects aged 18–60 and >60% for subjects over 60, seroconversion rate >40% for subjects aged 18–60 and >30% for subjects over 60, and GMT fold >2.5 for subjects aged 18–60 and >2.0 for subjects over 60 [9].

2.4. Assessment of safety and reactogenicity

All 1018 subjects were observed for 30 min following vaccine administration to check for immediate local and systemic reactions. Each subject filled out a diary card and recorded any local/systemic reactions on the 3rd and 7th days after vaccination. Local reactions included injection site pain, ecchymosis, swelling, and erythema with the greatest diameter of erythema being measured and recorded for each affected subject. Systemic reactions included fever (axillary temperature ≥37.5 °C), myalgia, fatigue, malaise, syncope, and seizures.

2.5. Statistical methods

All statistical analyses were performed using SPSS version 10.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are reported as the number of subjects and corresponding percentage. HI antibody titers are expressed as geometric mean with 95% confidence interval (CI). Analysis of variance (ANOVA) was used to assess variation of GMTs and GMT folds among different groups for each time point. Seroprotection rate at 1, 6, and 12 months after vaccination were compared by the chi-square test with Bonferroni *post hoc* multiple comparisons correction. To determine the differences between independent groups (good responders versus poor responders after vaccination), categorical variables were analyzed using the chi-