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Immunogenicity and safety of concomitant MF59-adjuvanted influenza vaccine and 23-valent pneumococcal polysaccharide vaccine administration in older adults

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ABSTRACT

Background: Concomitant administration of influenza and pneumococcal vaccines facilitates their uptake by older adults; however, data on immunogenicity and safety of concomitant administration of adjuvanted trivalent inactivated influenza vaccine (aIIV3) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) have not been reported.
Methods: Subjects aged ≥65 years ($N = 224$) were randomized 1:1:1:1 to receive MF59-aIIV3 alone, MF59-aIIV3 + PPSV23 in contralateral arms, MF59-aIIV3 + PPSV23 in the same arm or PPSV23 alone (Clinical Trial Number – NCT02225327). Hemagglutination inhibition assay and multiplex opsonophagocytic killing assay were used to compare immunogenicity after single or concomitant vaccination.
Results: All groups met immunogenicity criteria for the influenza vaccine in older adults with similar seroconversion rates and geometric mean fold-increases, irrespective of concomitant vaccinations and injection site. For each pneumococcal serotype, opsonic index (OI) increased markedly after the PPSV23 vaccination, irrespective of the concomitant influenza vaccine. All subjects showed an OI ≥ 8 for serotypes 6B, 18C and 19A post-vaccination, with a suggestion that the ipsilateral concomitant vaccination might be associated with higher OIs for some antigens. Local and systemic adverse events were more common in subjects receiving PPSV23 compared to those receiving aIIV3 alone.
Conclusions: No interference was observed with antibody responses to influenza or pneumococcal antigens when aIIV3 and PPSV23 were administered concomitantly.

1. Introduction

Q3 Concomitant administration of the influenza vaccine and the pneumococcal vaccine is an effective way to improve immunization coverage of these recommended vaccines in older adults [1]. Although concomitant administration of the 13-valent pneumococcal conjugate vaccine (PCV13) and conventional trivalent inactivated influenza vaccine (IIV3) has been demonstrated to result in acceptable reactogenicity and immune responses to both sets of antigens, lower responses to PCV13 antigens have been observed compared to separate administration [2–4]. Fewer data are available on concomitant administration of pneumococcal polysaccharide vaccine (PPSV23) and IIV3 [5].

MF59 emulsion-adjuvanted trivalent inactivated influenza vaccine (aIIV3) may provide higher and broader antibody responses than conventional IIV3, resulting in a higher level of clinical

Abbreviations: aIIV3, adjuvanted trivalent inactivated influenza vaccine; IIV3, inactivated trivalent influenza vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; HI, hemagglutination inhibition; GMT, geometric mean titers; CHMP, Committee for Medicinal Products for Human Use; OI, opsonic index; MOPA, multiplex opsonophagocytic killing assay.

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effectiveness [6–10]. The adjuvanted seasonal vaccine is licensed in numerous European, Asian and Latin American countries and in Canada specifically for older adults, for whom the pneumococcal vaccine also may be recommended. As there are currently no published data on concomitant administration of aIIV3 and PPSV23, we assessed the immunogenicity and safety of their concomitant administration compared to administration of them separately. Moreover, as MF59 exerts its adjuvant effect locally when co-administered with an antigen [11,12], we took this opportunity to examine whether ipsilateral administration of the MF59-adjuvanted influenza vaccine with PPSV23 would have a regional adjuvant effect on immune responses to the pneumococcal antigens administered nearby, compared to when the two vaccines were administered contralaterally.

2. Methods

2.1. Study design

From October to November 2013, this single-center, open label randomized trial was conducted (Clinical Trial Number – NCT02225327) at Guro Hospital, Korea University, Seoul, Republic of Korea. Adults aged ≥65 years old were randomized in a 1:1:1:1 ratio to receive: one dose of MF59-aIIV3 only (group 1); MF59-aIIV3 and PPSV23 concomitantly but in different arms (group 2); MF59-aIIV3 and PPSV23 concomitantly and in the same arm, with a ~1-inch distance separating the injections (group 3); or one dose of PPSV23 only (group 4).

Adults aged ≥65 years old who were healthy as well as those with stable underlying diseases (≥6 weeks) were included. Exclusion criteria included: history of *S. pneumonia* infection within the previous 5 years; previous pneumococcal vaccination; previous influenza vaccination within the last 6 months; hypersensitivity to any vaccine component (including eggs); history of Guillain–Barre syndrome; known immunodeficiency or immunosuppressant use; coagulation disorders; administration of blood products or immunoglobulins within the most recent 6 months.

The study was approved by the ethics committee of Korea University Guro Hospital (IRB No. KUGH13169-001) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided written, informed consent before enrollment. Venous blood samples of 10 mL were taken on day 0 and post-vaccination day 30 ± 7.

2.2. Vaccines administered

MF59-adjuvanted trivalent influenza vaccine (Fluad®, Novartis Vaccines and Diagnostics, S.R.L., Siena, Italy) is an inactivated subunit vaccine containing 15 μg HA/strain in each 0.5-mL dose, including three influenza vaccine strains from the 2013–2014 northern hemisphere season: A/California/7/2009 (H1N1) pdm09-like virus, A/Victoria/361/2011 (H3N2)-like virus and B/Massachusetts/2/2012-like virus.

PPSV23 (Prodiax-23®, Merck & Co. Inc., West Point, PA, USA) contained the capsular polysaccharides of 23 *Streptococcus pneumoniae* serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). Each 0.5 mL vial contained 25 μg of purified polysaccharide from each serotype.

2.3. Immunogenicity assessment

Standard microtiter hemagglutination inhibition (HI) assays were performed as previously described [13]. An HI titer of ≥40 was considered a protective level. geometric mean titers (GMT) were measured before and one month post-vaccination. Serologic responses were assessed using criteria of the Committee for Medicinal Products for Human Use (CHMP) for older adults [14]. To confirm protective immunogenicity, at least one of the following three criteria was required for each influenza virus strain: (1) GMT-fold increase >2.0; (2) seroprotection rate >60%; or (3) seroconversion rate >30%. Seroconversion rate was defined as the proportion of subjects with either seroconversion (a change in HI titer from <1:10 to ≥1:40) or a four-fold or more increase in antibody titer.

Representative opsonic indices (OI) of the samples were assessed using the validated multiplex opsonophagocytic killing assay (MOPA) as previously described [15–18]. Target strains STREP5, SPEC6B, OREP18C, and TREP19A (expressing capsule types 5, 6B, 18C and 19A, respectively) were derived from wild-type strains DBL5, BG25-9, GP116, and DS3519-97, respectively, and have been described previously [15]. Each of them was resistant to only one of four antibiotics (streptomycin, spectinomycin, optochin and trimethoprim). The OIs were defined as the serum dilution that kills 50% of bacteria and were determined by linear interpolation. In this study, all sera were diluted 5-fold due to limited sample volumes, hence, the limit of detection was a titer of 20. A detailed protocol is posted online at http://www.vaccine.uab.edu).

2.4. Safety assessment

Solicited local or systemic reactions to the vaccines were monitored using diary cards during the14 days post-vaccination. Participants were asked to record pain, tenderness and redness diameter at both injection sites and systemic symptoms such as headache, malaise, chills, muscle aches, and arthralgia. Severity was recorded according to the Food and Drug Administration Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [19]. Subjects were also asked to record any unsolicited adverse event during the 14 days after vaccination.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 18.0. Descriptive statistics were reported as numbers and percentages of participants. HI antibody titers and OIs were expressed as geometric means with 95% confidence intervals (CI). An analysis of variance (ANOVA) was used to assess variation of GMTs between groups at each time point; multiple comparison tests were performed using Tukey's procedure. Categorical variables were analyzed using a chi-square test (Fisher's exact test was used for <30 samples). Statistical significance was defined as $p < 0.05$.

For GMT ratios, CIs were computed using Student's t test for the mean difference of the measures on the log scale. Non-inferiority was defined as met if the lower limit of the two-sided 95% CI for the GMT ratio [(aIIV3 + PPSV23)/PPSV23 or (aIIV3 + PPSV23)/aIIV3] at one month post-vaccination was >0.5 (2-fold criterion). Results were considered statistically significantly lower, if the upper limit of the 95% CI for the GMT ratio was <1.0.

3. Results

3.1. Baseline characteristics

A total of 224 subjects were randomly assigned in a 1:1:1:1 ratio to one of four vaccination groups: aIIV3 alone (group 1), aIIV3 + PPSV23 in different arms (group 2), aIIV3 + PPSV23 in the same arm (group 3) or PPSV23 alone (group 4) (Fig. 1). A total of 216 subjects (group 1, $N = 56$; group 2, $N = 52$; group 3, $N = 55$; group 4, $N = 53$) were available for the assessment of immunogenicity and safety. Baseline demographics were similar between the study groups (Table 1).

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