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Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in ⩾60-year-old adults

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ABSTRACT

Background: Concomitant administration of influenza and pneumococcal vaccines could be an efficient strategy to increase vaccine uptake among older adults. Nevertheless, immune interference and safety issues have been a concern when more than one vaccines are administered at the same time.
Methods: Subjects aged ⩾60 years were randomized in a 1:1:1 ratio to receive MF59-adjuvanted trivalent inactivated influenza vaccine (MF59-aTIV) + 13-valent pneumococcal conjugate vaccine (PCV13) (Group 1), PCV13 alone (Group 2), or MF59-aTIV alone (Group 3). Hemagglutination inhibition (HI) and opsonophagocytic activity (OPA) assays were used to compare immunogenicity after single or concomitant vaccination.
Results: A total of 1149 subjects (Group 1, N = 373; Group 2, N = 394; Group 3, N = 382) were available for the assessment of immunogenicity and safety. All groups met immunogenicity criteria for the influenza vaccine in older adults with similar seroprotection rates, seroconversion rates, and geometric mean titer (GMT) fold-increases, irrespective of concomitant vaccination. For each pneumococcal serotype, OPA titers increased markedly after the PCV13 vaccination, irrespective of the concomitant influenza vaccination. After concomitant administration, the non-inferiority criteria of GMT ratios were met for all three influenza subtypes and 13 pneumococcal serotypes. No vaccine-related serious adverse events occurred.
Conclusions: Concomitant MF59-aTIV and PCV13 administration showed no interference with antibody response and showed good safety profiles.
Conclusions: (Clinical Trial Number – NCT02215863).

1. Introduction

Although highly recommended by advisory committees, the pneumococcal vaccination rate remains quite low compared to influenza vaccination in older adults [1,2]. In light of this low rate, the concomitant administration of influenza and pneumococcal vaccines could be an effective strategy to enhance vaccine uptake rates during early influenza season [2].

In a recent report, concomitant administration of MF59-adjuvanted trivalent inactivated influenza vaccine (MF59-aTIV) and 23-valent polysaccharide vaccine (PPSV23) showed no immunological interference and good safety profiles [3]. In addition to the polysaccharide vaccine, the US Food and Drug Administration (FDA) approved a 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of pneumonia and invasive pneumococcal disease (IPD) in adults in 2012 [4]. However, there are concerns about the unpredictability and complexity of immune interference when multivalent conjugate vaccines are co-administered with other vaccines [5]. The likelihood of immune interference may increase proportionally to the dosages of co-administered vaccine antigen and carrier protein. Actually, concomitant administration of PCV13 and unadjuvanted influenza vaccine showed acceptable immune responses to both sets of antigens, but lower responses to PCV13 antigens compared to separate administration [6–8]. Although the clinical significance of this

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reduction is unclear, the immune response of concomitant PCV13 administration needs to be further assessed with diverse influenza vaccines specific for older adults, including MF59-aTIV, intradermal (ID) vaccine (Intanza15®, Sanofi Pasteur) and high-dose influenza vaccine (Fluzone® High-Dose, Sanofi Pasteur).

As for the elderly, low efficacy (9–60%) has been considered as a weak point of conventional influenza vaccines [9–11]. Improved vaccine efficacy would be beneficial substantially in older adults, better averting influenza-related hospitalization [12]. Although not conclusively claimed in the recent FDA approval, MF59-aTIV vaccine may provide superior immunogenicity compared to the conventional unadjuvanted influenza vaccine, resulting in better clinical effectiveness [13–17]. It is not clear whether MF59 may enhance the immune response to co-administered vaccine antigens or not. In this study, we assessed the immunogenicity and safety of concomitant administration of MF59-aTIV and PCV13 in older adults.

2. Methods

2.1. Study design

This multi-center, open label randomized trial was conducted (Clinical Trial Number – NCT02215863) at four university hospitals, Korea University Guro Hospital, Korea University Ansan Hospital, Hallym University Gangnam Sacred Hospital and Catholic University St. Vincent's Hospital from November 2014 to February 2015. Adults ⩾60 years of age were randomized in a 1:1:1 ratio to receive MF59-aTIV + PCV13 (Group 1), PCV13 alone (Group 2), or MF59-aTIV alone (Group 3). The block randomization method was used.

The primary immunogenicity objective of the study was to demonstrate that immune responses to influenza antigens 1 month after vaccination in Group 1 (concomitant administration) were non-inferior to those in Group 3 (MF59-aTIV alone). Secondary immunogenicity objectives were to demonstrate that the immune responses to PCV13 serotypes in Group 1 were not inferior to those in Group 2 (PCV13 alone) 1 month after vaccination. The safety profile of PCV13 + MF59-aTIV compared with that of each agent alone was also assessed.

Healthy adults ⩾60 years of age with stable underlying diseases (⩾6 weeks) were included. Exclusion criteria included a history of *S. pneumoniae* 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-Barré syndrome, known immunodeficiency or immunosuppressant use, coagulation disorders, and/or the administration of blood products or immunoglobulins within the most recent 6 months.

The study was approved by the ethics committee of each university hospital (Korea University Guro Hospital (IRB No. KUGH13217), Korea University Ansan Hospital (AS14080), Hallym University Gangnam Sacred Hospital (314069) and Catholic University St. Vincent's Hospital (VC14MIMV0193) 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 collected on day 0 and post-vaccination day 28 ± 7.

2.2. Vaccines

The 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, containing three influenza vaccine strains from the 2014–2015 northern hemisphere season: A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, and B/Massachusetts/2/2012-like virus.

The PCV13 (Prevenar-13®, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., New York, USA) vaccine contains polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}). The vaccine is formulated to contain 2.2 μg of each saccharide, except for 4.4 μg of 6B per 0.5-mL dose. The vaccine also contains 0.125 mg aluminum as aluminum phosphate per 0.5 mL dose.

2.3. Immunogenicity assessment

The immune responses to the three antigens in MF59-aTIV were compared between Group 1 and Group 3 at one month after administration of MF59-aTIV using a standard hemagglutination inhibition (HI) assay as previously described [18]. An HI titer ⩾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 [19]. 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%.

The opsonophagocytic activity (OPA) assay procedures were based on previously described methods [20]. GMTs to the 13 pneumococcal serotypes were quantified using serotype-specific OPAs. Titers were defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria. Titers below the lower limit of quantitation were set to a value of 1:4. All assays were performed in clinical trial assay testing laboratories owned by Pfizer using fully validated procedures.

As for both HI and OPA assays, laboratory personnel remained blinded at all times.

2.4. Safety assessment

Solicited local or systemic reactions to the vaccines were monitored using diary cards during the 14 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 [21]. Subjects were also asked to record any unsolicited adverse events during the 14 days after vaccination.

2.5. Statistical analysis

Assuming an immune response rate (⩾4-fold increase in HI assay titers) of 50%, it was projected that 393 subjects per evaluable group would provide at least 80% power to declare a non-inferior MF59-aTIV immune response in Group 1 (concomitant administration) compared to Group 3 (MF59-aTIV alone) in older adults ⩾60 years of age. Considering a dropout rate of approximately 5% in each group, an enrollment of 1239 subjects (413 subjects per group) was planned.

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). Student's *t*-tests were used to assess variation of GMTs between two groups at each time point, and Chi-square tests (Fisher's exact test was used for