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Comparison of the immunogenicity and safety of polysaccharide and protein-conjugated pneumococcal vaccines among the elderly aged 80 years or older in Japan: An open-labeled randomized study

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ABSTRACT

An open-labeled randomized study was conducted to compare the immunogenicity and safety of polysaccharide (PPV23) or protein-conjugated pneumococcal vaccine (PCV7) among the elderly aged 80 years or older. A total of 105 nursing home residents were enrolled in this study. We analyzed the geometric mean concentration (GMC) of serotype-specific immunoglobulin G (IgG) and the geometric mean titer (GMT) of the opsonization index (OI) for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The GMCs of serotype-specific IgG and the GMTs of the OI significantly increased one month after vaccination in both groups for all seven serotypes evaluated. In the PCV7 group, study subjects with serotypes 4, 9V, 18C, and 23F exhibited statistically significant elevations in both serotype-specific IgGs and OIs compared to those of the PPV23 group. Both vaccines were tolerated without any severe adverse events, and no differences in systemic adverse events were observed between the two groups, although adverse reactions such as redness and localized swelling were more common in the PCV7 group. Our data demonstrated that the GMCs of serotype-specific IgG and the GMTs of the OI were higher in the PCV7 group compared to those in the PPV23 group. Our study also confirmed the safety of both the PCV7 and PPV23 vaccines in elderly people aged 80 years or older.

1. Introduction

Streptococcus pneumoniae infection is a major cause of mortality and morbidity worldwide among the elderly. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is widely recommended for administration to those who are at a high risk of *S. pneumoniae* infection, such as elderly people and splenectomy patients [1]. However, owing to the purified free polysaccharides that comprise its surface capsule, PPV23 does not elicit T cell-dependent immune responses and is a poor inducer of immunologic memory. Furthermore, vaccine-induced antibody titers may achieve insufficient levels and decrease annually, particularly 5 years after vaccination [2].

The conjugation of the capsular polysaccharide to a diphtheria protein stimulates not only B-cell immune response but also T cell-dependent immune responses and enhanced memory response at the time of boosting [3]. Therefore, pneumococcal conjugate vaccines produce superior immune responses, particularly in infants. For this reason, the heptavalent pneumococcal conjugate vaccine (PCV7) was licensed in 2000 in the United States and in 2009 in Japan. PCV7 also produces better immune responses than PPV23 in groups at higher risk of developing invasive pneumococcal diseases

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and pneumococcal pneumonia, such as individuals with HIV [4] or chronic obstructive pulmonary disease [5].

In healthy elderly people 50–80 years old, Goldblatt et al. [6] reported that PCV7 produced superior immunogenicity compared with PPV23. In recent years, the increasing number of elderly people over 80 years old hospitalized for pneumococcal pneumonia has been reported [7]. While pneumococcal vaccination is strongly recommended for this population, no data are currently available for comparison of the immunogenicity and safety between PCV7 and PPV23 for this age group. Therefore, we performed this prospective study to clarify these unknown aspects.

2. Materials and methods

2.1. Study subjects

The present study was a randomized, open-label study designed to compare the immunogenicity and safety of PCV7 (Prevenar; Pfizer) with those of PPV23 (Pneumovax; MSD). Data were collected between April 2011 and December 2012 from participants who were 80 years or older and had never received pneumococcal vaccinations. None of the participants had any documented history of pneumococcal infection. They were selected from five different nursing homes around Tokyo and were randomly assigned to either the PPV23 group or the PCV7 group using the sealed envelope system with a 1:1 allocation ratio. A total of 105 participants were enrolled in this study, and all participants provided written informed consent.

In addition, subjects were excluded if they had a history of any streptococcal vaccination, a history of anaphylactic reaction to diphtheria toxin, or symptoms of fever on the day of vaccination.

We set the sample size on the basis of a study by Goldblatt et al. [6] on the comparison of immunogenicity between PCV7 and PPV23 among adults aged 50–80 years. They assigned 33–60 subjects to a subgroup of one arm and showed higher geometric mean concentrations (GMCs) of serotype-specific IgG response in several serotypes.

This study was reviewed and approved by the Research Ethics Committee of Keio University School of Medicine (2010-231-2) and by the Research Ethics Committee of Kitasato University Kitasato Institute Hospital (1108-02). This trial was registered with the UMIN Clinical Trials Registry (UMIN000006132).

2.2. Vaccines

The PCV7 used in this study is currently licensed only for pediatric use in Japan. PCV7 contains polysaccharides of pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which are conjugated to the protein carrier CRM197, a nontoxic variant of the diphtheria toxin. Each serotype-specific polysaccharide is conjugated separately prior to formulation as a multivalent vaccine. The vaccine contains aluminum phosphate as an adjuvant.

PPV23 contains a mixture of purified capsular polysaccharides from 23 different serotypes of *S. pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. This vaccine is adjuvant-free.

Each participant received 0.5 mL of either PPV23 or PCV7 via subcutaneous injection. PPV23 and PCV7 were dispensed and administered by members who were not blinded and not involved in subsequent data analysis.

2.3. Samples

Blood samples (10 mL) were drawn from all the subjects on the day of vaccination and approximately one month after vaccination. Sera were separated by centrifugation (3500 rpm, 15 min, 4 °C) and stored at −80 °C.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Anti-pneumococcal immunoglobulin G (IgG) antibodies were measured by World Health Organization (WHO)-approved ELISA, using standard reference serum (89-SF or 007sp) and C-polysaccharide and 22F polysaccharide absorption, as previously reported [8,9]. The levels of serotype-specific IgGs for seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) were determined in both vaccination groups according to the WHO protocol (a detailed version of the protocol is available at http://www.vaccine.uab.edu/ELISAProtocol(89SF).pdf). These serotypes are covered by PCV7.

2.5. Multiplexed opsonophagocytic killing assay

A multiplexed opsonophagocytic killing assay for seven serotypes, 4, 6B, 9V, 14, 18C, 19F, and 23F, based on antibiotic-resistant strain target bacteria, was performed at the Research Institute for Microbial Diseases, Osaka University, as previously described [10]. The quality control serum used in each assay was prepared from the pooled sera of adults vaccinated with PPV23 or PCV7. The opsonization index (OI) was defined as the serum dilution capable of killing 50% of the bacteria, which was determined by using opsotiter3 software according to the WHO protocol (a detailed version of this protocol is available at www.vaccine.uab.edu/UAB-MOPA.pdf) [11]. Laboratory analysis, ELISA, and a multiplexed opsonophagocytic killing assay were performed by members who were blinded to vaccine allocation.

2.6. Adverse reactions

All patients were observed daily by medical staff to monitor body temperature and any local or systemic reactions, starting from the day of vaccination to day 7. Injections were graded based on the occurrence of several possible adverse events as follows: grade I (the reaction was present but easily tolerated), grade II (the reaction interfered with normal activity), and grade III (the reaction was severe or incapacitating).

2.7. Statistical analysis

Average antibody concentrations and the increases from baseline were expressed as geometric means. Differences in the GMCs of serotype-specific IgG and the geometric mean titers (GMTs) of the OI were assessed by the Wilcoxon matched-pairs signed-ranks test. For multiple comparisons, we calculated Bonferroni-adjusted P values. The frequencies of adverse reactions were compared between vaccinations by the Fisher exact test. Differences with $P < 0.05$ were considered to be statistically significant. Data analysis was performed by members who were blinded to vaccine allocation.

3. Results

3.1. Participant characteristics

Overall, 623 eligible participants were reviewed in the 5 nursing homes (Fig. 1). One hundred and five participants were enrolled in this study after they provided written informed consent. Five subjects were subsequently dropped from the study prior to vaccination (2 subjects were hospitalized, 2 subjects left the nursing home, and 1 subject died). Consequently, 100 subjects were vaccinated (Table 1); of these, 49 received PPV23 and 51 received PCV7. The mean ages at enrollment were 88.3 years for the PPV23 group and 87.7 years for the PCV7 group, with 45 subjects in their