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Revaccination with 23-valent pneumococcal polysaccharide vaccine in the Japanese elderly is well tolerated and elicits immune responses

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ABSTRACT

Background: Following primary vaccination of adults ⩾65 years of age with 23-valent pneumococcal polysaccharide vaccine (PPSV23), immune responses increase and thereafter appear to decrease over time. With increased life expectancy worldwide, revaccination with PPSV23 may be required for continued protection of the elderly population against pneumococcal disease. The present study evaluated the immunogenicity and safety of revaccination with PPSV23 in the Japanese elderly.

Methods: Depending on prior history of PPSV23 vaccination, adults aged ⩾70 years were given a first dose (primary group; $N = 81$) or second dose (revaccination group; $N = 161$, at least 5 years after first dose) of PPSV23 intramuscularly. Subjects were matched for gender, age, and number and type of comorbidity across both groups. Blood samples were collected before and 4 weeks postvaccination to measure serotype-specific immunoglobulin G (IgG) concentrations and opsonophagocytic killing activity (OPA) antibody titers to serotypes included in the vaccine. Injection-site and systemic adverse events (AEs) were collected for 14 days postvaccination.

Results: Baseline serotype-specific IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) were generally higher in subjects with a prior history of PPSV23 vaccination than in PPSV23-naïve subjects. The levels of IgG GMCs and OPA GMTs after revaccination were generally comparable to those observed after primary vaccination. Incidences of systemic AEs were comparable between the 2 groups. Although incidences of injection-site AEs were higher following revaccination than primary vaccination, the difference was not clinically significant as most AEs were mild to moderate in intensity and resolved within 5 days after revaccination without treatment.

Conclusion: Revaccination with PPSV23 was well tolerated and associated with increases in serotype-specific IgG concentrations and OPA titers in the elderly who received a prior PPSV23 dose at least 5 years before. Revaccination with PPSV23 can be safely implemented in the elderly for continued prevention against pneumococcal disease.

Clinical trial registry number: NCT02260882

1. Introduction

Worldwide, adults ⩾65 years of age are at high risk for pneumococcal disease. The risk is further increased for those with underlying illnesses such as chronic heart disease, chronic lung disease, and diabetes mellitus [1,2]. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been developed by Merck & Co., Inc., Kenilworth, NJ and contains capsular polysaccharides from 23 pneumococcal capsular types of *Streptococcus pneumoniae*. Several observational and clinical studies have demonstrated the effectiveness of PPSV23 in the prevention of pneumococcal disease

Abbreviations: AE, adverse event; CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold rise; GMT, geometric mean titer; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; MOPA, multiplexed OPA; OPA, opsonophagocytic killing activity; Pn ECL, pneumococcal electrochemiluminescence; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

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in adults including the elderly population [3–10], and PPSV23 is indicated for the prevention of pneumococcal disease in adults ⩾50 years of age in many countries worldwide. In 2012–2013, serotypes most frequently associated with invasive pneumococcal disease (IPD) in Japanese adults included serotypes 3 (18.5%), 22F (7.9%), 14 (7.5%), 19A (7.5%), 6C (7.5%), and to a lesser extend serotypes 6B, 10A and 23F. Based on these results, the coverage rate afforded by PPSV23 for all IPD cases was 72.2% [11]. In October 2014, Japan introduced PPSV23 in the national immunization program for the prevention of pneumococcal disease for elderly individuals aged ⩾65 years. Recently a 13-valent pneumococcal conjugate vaccine (PCV13) was approved in Japan for the prevention of pneumococcal disease in adults aged ⩾65 years, but it is not included in the national immunization program.

Following PPSV23 vaccination, serotype-specific immunoglobulin G (IgG) concentrations and opsonophagocytic killing activity (OPA) titers increase and then decline over time, though these generally remain above pre-vaccination levels after 5 years [12–14]. Since decreases in serotype-specific IgG concentrations and OPA titers may lead to an increased risk of pneumococcal disease, revaccination may be required in order to provide continued protection with increasing age.

Over the past 40 years, Japan has become an ageing society; in 2010, the average life expectancy after the age of 65 was 18.74 and 23.80 years for men and women, respectively [15]. The need for revaccination with PPSV23 in the Japanese elderly individuals is expected to increase in the near future. PPSV23 revaccination in adults aged ⩾65 years who received their first dose of PPSV23 at least 5 years before is recommended by the Japanese Association for Infectious Diseases [16]. Ohshima et al. evaluated the safety and immunogenicity of a second dose of PPSV23 in 40 elderly patients with chronic lung disease [17]. The present study was conducted in order to confirm the acceptable safety and immunogenicity profiles of PPSV23 revaccination in a large cohort of the Japanese elderly subjects, and to provide further evidence of the value of revaccination in clinical practice.

2. Methods

2.1. Overall study design

This was a non-randomized, open-label, multicenter study conducted at 5 sites (3 general hospitals and 2 clinics) between November 2014 and May 2015 to evaluate the immunogenicity and safety of revaccination with PPSV23 in the Japanese elderly population. Subjects were enrolled into one of the following groups in a 2:1 ratio: revaccination group (subjects who had a confirmed record of prior PPSV23 vaccination at least 5 years before study enrollment) or primary vaccination group (subjects with no prior history of PPSV23 vaccination). Characteristics such as age, gender and number and type of comorbidity (i.e., chronic heart disease: hypertension, angina pectoris and atrial fibrillation; chronic lung disease: asthma, chronic bronchitis and chronic obstructive pulmonary disease; diabetes mellitus) were matched between the two groups. Immunocompromised subjects, those receiving immunosuppressive therapy such as systemic corticosteroids, those with a history of vaccination with pneumococcal conjugate vaccine, those with a history of pneumococcal disease (positive culture from blood or other normally sterile site) and those who were febrile (defined as an oral temperature ⩾37.5 °C) within 24 h before PPSV23 vaccination were excluded from the study.

PPSV23 (Pneumovax®NP, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ) contains 25 μg of each capsular polysaccharide of the 23 types of pneumococci per vial (0.5 mL) and was supplied by each study site. PPSV23 was injected intramuscularly, and the site of injection was recorded.

2.2. Study objectives

The primary immunogenicity objective was to demonstrate that serotype-specific IgG GMCs to serotypes 3, 6B, and 23F measured 4 weeks after revaccination with PPSV23 were statistically greater than those measured immediately before revaccination (baseline); these serotypes were selected because they were most prevalent in Japanese adults with IPD, associated with 16.4% (serotype 3), 14.9% (serotype 6B), and 7.6% (serotype 23F) of all IPD cases during 2010–2011 [11]. Overall, serotype-specific IgG GMCs to 14 serotypes and serotype-specific OPA GMTs to 6 serotypes were measured immediately before and after primary vaccination or revaccination with PPSV23. The safety objective was to assess injection-site and systemic adverse events (AEs) after vaccination with PPSV23 in the primary vaccination and revaccination groups.

2.3. Measurements

Blood samples were collected before and 4 weeks following vaccination with PPSV23, and serum samples were stored at −20 °C until used for testing. For serotype-specific IgG, antibody concentrations of 14 serotypes included in PPSV23 (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) were measured using pneumococcal electrochemiluminescence (Pn ECL) assay [18]. Moreover, IgG concentration for serotype 6A, which is not included in PPSV23, was measured to assess possible cross-reactivity afforded by an immune response to serotype 6B, which is included in PPSV23. OPA was measured for 6 serotypes (3, 4, 6B, 14, 22F, and 23F) using multiplexed OPA (MOPA) assay [19]. The Pn ECL and OPA testing were performed at PPD Vaccines and Biologics Laboratory (Wayne, PA, USA) and at the University of Alabama (Birmingham, AL, USA), respectively.

Injection-site and systemic AEs occurring within 14 days postvaccination were collected. Deaths and other vaccine-related serious adverse events (SAEs) were recorded throughout the study. All subjects were asked to record any injection-site reaction and daily body temperature (oral method) in a vaccine diary for 5 consecutive days postvaccination. Causal relationship between the reported AEs and receipt of PPSV23 was assessed by the study investigators.

2.4. Statistical analysis

For the analyses of immunogenicity in the revaccination group, a one-sample *t*-distribution was used to obtain the mean and 95% confidence interval (CI) of changes in IgG GMCs from baseline (before revaccination) to 4 weeks after revaccination. Subsequently, the mean and 95% CI were back transformed to calculate the corresponding point estimate and 95% CI for geometric mean fold rise (GMFR). The statistical success criterion for demonstrating greater IgG GMCs at 4 weeks after vaccination was that the lower bound of the two-sided 95% CI for GMFR was >1.0 for all three serotypes (3, 6B, and 23F). For immunogenicity analyses for other serotypes in the primary vaccination and revaccination groups, IgG GMCs and OPA GMTs were calculated in a similar manner at baseline and 4 weeks after vaccination.

The safety was evaluated based on solicited injection-site AEs (pain, erythema, and swelling) occurring from Days 1 to 5 after vaccination, fever (⩾37.5 °C, oral temperature) occurring from Days 1 to 5 after vaccination, and any other injection site and systemic AEs occurring from Days 1 to 14 after vaccination.

2.5. Ethical conduct

The present study was conducted in accordance with the principles of Good Clinical Practice. The protocol and informed