Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immunogenicity and safety of a second administration of 13-valent pneumococcal conjugate vaccine 5 years after initial vaccination in adults 50 years and older

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ARTICLE INFO

Article history:
Received 30 October 2015
Received in revised form 24 March 2016
Accepted 27 April 2016
Available online xxx

Keywords:
Adults
PCV13
Pneumococcal conjugate vaccine
Revaccination
Recall responses

ABSTRACT

Background: Vaccination effectively reduces invasive disease and pneumonia caused by *Streptococcus pneumoniae*. However, waning antibody titers and the ability of revaccination to boost titers in older adults have been concerns. A study to describe antibody persistence after vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) and response to revaccination 5 years after the initial dose was conducted.

Methods: Pneumococcal vaccine–naive subjects aged 50–59 years were randomized and vaccinated with PCV13 plus trivalent inactivated influenza vaccine concomitantly or 1 month apart, then revaccinated with PCV13 five years later. Antipneumococcal polysaccharide opsonophagocytic activity (OPA) geometric mean titers (GMTs) and immunoglobulin G (IgG) geometric mean concentrations (GMCs) were determined before and approximately 1 month after each vaccination. Targeted local reactions and systemic events were collected for 14 days, adverse events (AEs) for 1 month, and serious AEs (SAEs) for 6 months after each vaccination.

Results: Of 1116 randomized subjects, 727 were revaccinated at year 5. Between the time of initial vaccination and revaccination, OPA GMTs and IgG GMCs declined but remained higher than levels before initial vaccination for 12 of the 13 vaccine serotypes. One month after revaccination, OPA GMTs and IgG GMCs were comparable with, or higher than, levels observed 1 month after initial vaccination for most vaccine serotypes. Local reactions were mostly mild. AEs were reported by <5% and SAEs by <1% of subjects at 1 and 6 months after revaccination, respectively. No SAEs were vaccine-related.

Conclusions: Revaccination of adults ≥50 years with PCV13 five years after primary vaccination was safe and immunogenic. Additionally, antibody titers were maintained for at least 5 years after vaccination. The vaccine stimulated a memory response as shown by enhanced responses that were maintained or enhanced by revaccination.

ClinicalTrials.gov registration: NCT00521586.

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http://dx.doi.org/10.1016/j.vaccine.2016.04.093
0264-410X/

1. Introduction

Adults aged ≥50 years are at an increased risk for invasive pneumococcal disease (IPD) and pneumonia caused by *Streptococcus pneumoniae* [1,2], with associated mortality positively correlated with advanced age [3,4]. Pneumococcal conjugate vaccines (PCVs), which contain capsular polysaccharide antigens from *S pneumoniae* linked to carrier proteins, elicit T cell-dependent immune responses [5] and are effective in reducing the occurrence of IPD, otitis media and pneumonia in infants [6–8]. Recently, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended 13-valent PCV (PCV13) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) for routine use in pneumococcal vaccine-naive adults ≥65 years of age in the United States [9]. This recommendation is based on immunogenicity studies demonstrating an improved response to serotypes common to both vaccines when PCV is given first [9]. It is also supported by data in adults ≥65 years of age from the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), which demonstrated a vaccine efficacy for PCV13 of 45.6%, 45.0%, and 75.0% against first episodes of confirmed vaccine-type community-acquired pneumonia, confirmed nonbacteremic and noninvasive vaccine-type community-acquired pneumonia, and vaccine-type IPD, respectively [10]. Vaccine efficacy persisted throughout the 4-year follow-up period of the study with no sign of waning.

The current study evaluated the immunogenicity and safety of 2 doses of PCV13 administered at a 5-year interval in adults 50 years of age and older. The first part of the study evaluated the immunogenicity, safety, and tolerability of PCV13 coadministered with trivalent inactivated influenza vaccine (TIV) in adults 50–59 years of age; these results were previously reported [11]. The study demonstrated that anticapsular immune responses, measured as serotype-specific pneumococcal opsonophagocytic activity (OPA) titers and immunoglobulin G (IgG) concentrations, in subjects who were administered PCV13 concomitantly with TIV were noninferior to responses in subjects administered PCV13 alone, although immune responses were lower after concomitant administration of the 2 vaccines compared with administration of PCV13 alone [11]. The current analysis presents the second part of this study, which examines the persistence of circulating antibody after PCV13 vaccination and the immunogenicity, safety, and tolerability of a second dose of PCV13 administered 5 years after the initial vaccination, evaluating an extended interval between PCV13 vaccinations compared with what has been previously reported [12]. This study was performed as part of the development program for PCV13 in adults 50 years of age and older.

2. Materials and methods

2.1. Study design

This was a Phase 3, randomized, double-blind trial conducted at 34 sites in the United States to evaluate levels of antipneumococcal antibody elicited by PCV13 before and for the ensuing 5 years after the initial PCV13 vaccination as well as to evaluate the immune response 1 month after revaccination at year 5 by serotype-specific OPA titers and IgG concentrations. Receipt of the first dose of PCV13 occurred between September 2007 and November 2008, with the last subject visit after administration of the second PCV13 dose occurring in December 2013.

The final protocol, any amendments, and the informed consent form were reviewed and approved by the institutional review boards and/or independent ethics committees for each of the investigational centers participating in the study. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. Written informed consent was obtained from all subjects before enrollment in the study and before performance of any study-related procedures.

2.2. Participants

Subjects, 50–59 years of age at the time of enrollment, who were naive to pneumococcal vaccine and determined to be eligible on the basis of medical history, physical examination, and clinical judgment, were included. Subjects with stable underlying diseases were included. Key exclusion criteria included history of severe adverse reaction associated with a vaccine, history of Guillain-Barré syndrome, and vaccination with TIV or a diphtheria-containing vaccine within 6 months before pneumococcal vaccine administration. In addition, individuals with known or suspected immunodeficiency and those with serious chronic disorders were excluded [11]. Subjects were 55–65 years of age at the time of revaccination with PCV13.

2.3. Interventions

Subjects were initially vaccinated with PCV13 and TIV for the 2007/2008 season either concomitantly (Group 1) or 1 month apart with TIV being administered first (Group 2) [11]. Subjects in both groups were revaccinated with PCV13 five years later (Fig. 1). Vaccines were administered intramuscularly in the deltoid muscle. Blood samples were obtained before and approximately 1 month after each vaccination and yearly during years 1–4.

2.4. Vaccines administered

PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxoid CRM_{197}. The vaccine is formulated to contain 4.4 μg of 6B and 2.2 μg of each of the other 12 saccharides. Each 0.5-mL dose is formulated with 5.0 mM succinate buffer, pH 5.8, 0.85% sodium chloride, and 0.02% polysorbate 80 and contains 0.125 mg aluminum as aluminum phosphate.

2.5. Immunogenicity assessments

Opsonophagocytic and enzyme-linked immunosorbent assays were performed to measure serotype-specific, pneumococcal functional OPA titers and anticapsular IgG concentrations elicited by the PCV13 serotypes. Serology testing was performed on all subjects at year 5. Additionally, from the overall study group, a subset of 200 randomly chosen subjects was selected for yearly serology testing from year 1 through 4 (100 subjects in each group). The all-available immunogenicity population was the population for immunogenicity analyses and included subjects who had ≥1 valid and determinate assay result.

2.6. Safety assessments

Local reactions at the injection site (redness, swelling, pain, and limitation of arm movement) and systemic events were assessed

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AE, adverse event; CAPiTA, Community-Acquired Pneumonia immunization Trial in Adults; CI, confidence interval; CRM_{197}, cross-reactive material 197; GMC, geometric mean concentration; GMFR, geometric mean fold rise; GMT, geometric mean titer; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SAEs, serious adverse events; TIV, trivalent inactivated influenza vaccine.

Please cite this article in press as: Frenck Jr. RW, et al. Immunogenicity and safety of a second administration of 13-valent pneumococcal conjugate vaccine 5 years after initial vaccination in adults 50 years and older. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.093