Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Randomized clinical trial of a single versus a double dose of 13-valent pneumococcal conjugate vaccine in adults 55 through 74 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

Lisa A. Jackson [a,*], Hana M. El Sahly [b], Sarah George [c], Patricia Winokur [d], Kathryn Edwards [e], Rebecca C. Brady [f], Nadine Rouphael [g], Wendy A. Keitel [b], Mark J. Mulligan [g], Robert L. Burton [h], Aya Nakamura [i], Jennifer Ferreria [i], Moon H. Nahm [h]

[a] Kaiser Permanente Washington Health Research Institute, Seattle, WA, United States
[b] Departments of Molecular Virology & Microbiology and Medicine, Baylor College of Medicine, Houston, TX, United States
[c] Division of Infectious Diseases, Allergy, & Immunology, Saint Louis University School of Medicine, and St. Louis VA Medical Center, St. Louis, MO, United States
[d] University of Iowa and Iowa City VA Medical Center, Iowa City, IA, United States
[e] Vanderbilt Vaccine Research Program, Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, United States
[f] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[g] The Hope Clinic of the Emory Vaccine Center, Division of Infectious Diseases, Department of Medicine, School of Medicine, Emory University, Decatur, GA, United States
[h] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States
[i] The Emmes Corporation, Rockville, MD, United States

ARTICLE INFO

Article history:
Received 17 October 2017
Received in revised form 18 December 2017
Accepted 19 December 2017
Available online xxxx

Keyword:
Pneumococcal vaccine

ABSTRACT

Introduction: In older adults, prior administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23) blunts the opsonophagocytic antibody (OPA) response to subsequent administration of 13-valent pneumococcal conjugate vaccine (PCV13). To determine whether a higher dose of PCV13 could mitigate this effect in adults 55 through 74 years of age, we compared OPA responses to a double dose of PCV13 in persons previously vaccinated with PPSV23 with responses to a single dose of PCV13 in previously vaccinated persons, and with a single dose in PPSV23 naïve persons.

Methods: Subjects previously vaccinated with PPSV23 were randomly assigned to receive either a single injection or two concurrent injections of 0.5 mL PCV13. Naïve subjects received a single injection of 0.5 mL PCV13. Serotype-specific OPA responses to 12 of the PCV13 serotypes were assessed on samples collected on Day 29 and Day 181. Comparisons of the OPA titers between study groups were based on the lower bound of the 95% confidence interval of the log geometric mean ratio to define superiority (>1) and non-inferiority (>0.5).

Results: At Day 29, the OPA responses to one dose in previously vaccinated (n = 284) versus one dose in naïve subjects (n = 311) achieved the threshold for non-inferiority for only 3 of the 12 serotypes. In previously vaccinated subjects, responses to a double dose (n = 288) versus a single dose met the threshold for superiority for 7 serotypes. The responses to a double dose in previously vaccinated subjects versus a single dose in naïve subjects met the threshold for non-inferiority for 9 serotypes.

Conclusions: There is a dose response to PCV13 in older adults and the higher response to a double dose in previously vaccinated adults is non-inferior to that of a single dose in naïve adults for 9 of the 12 PCV13 serotypes evaluated.

1. Introduction

In 2014, the Advisory Committee on Immunization Practices (ACIP) modified the longstanding recommendation for routine use of 23 valent pneumococcal polysaccharide vaccine (PPSV23)

* Corresponding author at: KPWHRI, 1730 Minor Avenue, Ste 1600, Seattle, WA 98101, United States.
E-mail address: Jackson.L@ghc.org (L.A. Jackson).

https://doi.org/10.1016/j.vaccine.2017.12.061
0264-410X/

in adults 65 years of age and older to add routine administration of 13 valent pneumococcal conjugate vaccine (PCV13) [1]. This decision was based in part on the results of a landmark randomized placebo controlled trial of PCV13 in approximately 85,000 pneumococcal vaccine naïve, immunocompetent adults 65 years of age and older in the Netherlands (CAPITA trial) [2], which found that PCV13 was effective in reducing the risks of vaccine-type community acquired pneumonia (efficacy 46%) and invasive pneumococcal disease (efficacy 75%).

The 2014 ACIP recommendation specifies that, for immunocompetent adults ≥65 years of age who have not previously received either PPSV23 or PCV13, PCV13 should be given first, followed at least one year later by PPSV23. This sequence is recommended due to the evidence that prior administration of PPSV23 blunts the immune response to subsequent doses of PCVs, including PCV13, in adults [3,4].

For immunocompetent adults ≥65 years who have received PPSV23 but not PCV13, a dose of PCV13 is recommended, to be given at least one year after the most recent dose of PPSV23. For those given the PPSV23-PCV13 sequence, the benefits of PCV13 vaccination observed in the CAPITA population of PPSV23 naïve persons may not be realized, due to the blunting of the immune response to PCV13 induced by the prior PPSV23 vaccination. An estimated 25% of immunocompetent adults 50 through 64 years of age in the United States have an indication for PPSV23 vaccination [5] and so could receive PPSV23 before they are recommended to receive PCV13.

We conducted a large dose ranging study of PCV13 vaccine that enrolled two groups of adults 55 through 74 years of age – those who had received PPSV23 three through seven years prior to enrollment and those who had never received PPSV23. The previously vaccinated subjects were randomized to receive either two 0.5 mL doses of PCV13 given concurrently or a single 0.5 mL dose of PCV13 and the OPA responses to the double dose were compared with the single dose to evaluate a dose effect. The vaccine naïve group received a single 0.5 mL dose of PCV13. The OPA responses to the double dose in the previously vaccinated group were compared with the responses to the single dose in the vaccine naïve group to evaluate the extent to which the higher dose could mitigate the effect of hyporesponsiveness due to prior PPSV23 exposure.

2. Methods

2.1. Vaccine and administration

Each dose of PCV13 (Prevnar 13®, Pfizer, Philadelphia, PA), composed of saccharides 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 (CRM197), was supplied in a single 0.5 mL dose prefilled syringe and was administered by intramuscular injection in the deltoid. Subjects received either one 0.5 mL injection or two 0.5 mL injections, one in each arm, at the enrollment visit.

2.2. Study design

This open-label phase IIb study evaluated medically stable adults 55 through 74 years of age who had either never received PPSV23 or who had previously received exactly one prior dose of PPSV23, which was administered ≥3 and ≤7 years prior to enrollment. Enrollment into both groups was stratified by age group (55 through 64 years and 65 through 74 years) (Supplemental Fig. 1). The presence or absence of prior PPSV23 vaccination may have been presumptively ascertained by subject report but for all sub-

Table 1
Demographic characteristics by study group, all enrolled subjects.

	All subjects (N = 883)	Group I – Naïve, Age 55–64 (N = 164)	Group I – Naïve, Age 65–74 (N = 147)	Group IIA – Previously Vaccinated, Age 55–64 (N = 139)	Group IIA – Previously Vaccinated, Age 65–74 (N = 145)	Group IIB – Previously Vaccinated, Age 55–64 (N = 139)	Group IIB – Previously Vaccinated, Age 65–74 (N = 149)
Gender–n(%)							
Male	371 (42)	36 (22)	77 (52)	52 (37)	76 (52)	59 (42)	71 (48)
Ethnicity–n(%)							
Non-Hispanic	862 (98)	159 (97)	144 (98)	132 (95)	143 (99)	137 (99)	147 (99)
Race–n(%)							
American Indian/Alaskan Native	1 (0)	0	0	0	1 (1)	0	0
Asian	14 (2)	0	2 (1)	1 (1)	5 (3)	4 (3)	2 (1)
Black/African American	61 (7)	8 (5)	4 (3)	18 (13)	6 (4)	17 (12)	8 (5)
White	793 (90)	154 (94)	140 (95)	114 (82)	132 (91)	115 (83)	138 (93)
Multi-Racial	10 (1)	2 (1)	1 (1)	4 (3)	0	2 (1)	1 (1)
Other/Unknown	4 (0)	0	0	2 (1)	1 (1)	1 (1)	0
Age (years)							
Mean (STD)	65.0 (5.3)	59.7 (2.8)	67.6 (2.6)	60.8 (2.7)	70.5 (2.0)	61.0 (2.8)	70.3 (2.0)
Median	65.0	59.6	66.4	61.1	70.5	61.8	70.1
Min, Max	(55, 74)	(55, 64)	(65, 74)	(55, 64)	(65, 74)	(55, 64)	(65, 74)
Time since prior PPSV23 (years)							
Mean (STD)	n/a	n/a	n/a	4.5 (1.2)	4.8 (1.2)	4.7 (1.3)	4.6 (1.1)
Median				4.4	4.4	4.4	4.4
Min, Max				3.0, 7.9	3.0, 7.5	3.0, 7.8	3.0, 7.3

Groups I and IIA received a 0.5 mL dose of PCV13, Group IIB received two 0.5 mL doses of PCV13.

Please cite this article in press as: Jackson LA et al. Randomized clinical trial of a single versus a double dose of 13-valent pneumococcal conjugate vaccine in adults 55 through 74 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.12.061