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Immunogenicity of 13-valent pneumococcal conjugate vaccine in immunocompetent older adults with stable underlying medical conditions

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Abstract

The 13-valent pneumococcal conjugate vaccine (PCV13) elicits robust functional antibody responses in immunocompetent adults aged ≥50 years, including healthy adults and those considered at risk (ie, stable, chronic cardiovascular disease, pulmonary disease, or diabetes mellitus). This analysis is consistent with data suggesting immunocompetent at-risk populations aged ≥50 years produce functional anti-pneumococcal antibody responses to PCV13 comparable to those not at risk. An OPA titer that correlates with protection has not been defined for adults; however, PCV13 elicits generally higher responses than the 23-valent pneumococcal polysaccharide vaccine (PPSV23) one month after vaccination. PCV13 vaccination of immunocompetent at-risk populations likely results in benefits analogous to those without additional risk.

Keywords: 13-valent pneumococcal conjugate vaccine; at-risk adults; pneumococcal disease; diabetes mellitus; cardiovascular disease; pulmonary disease

Introduction

Streptococcus pneumoniae is a major cause of morbidity and mortality worldwide [1]. Adults ≥50 years of age are at increased risk for developing invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) [2, 3]. In addition, underlying chronic medical conditions such as cardiovascular disease, pulmonary disease, and diabetes mellitus, all of which have been shown to increase the risk for pneumococcal pneumonia, are more prevalent in individuals >50 years of age [4]. An analysis of data from the Active Bacterial Core surveillance system in the United States reported that among cases of IPD in subjects 50 to 64 and ≥65 years of age, there was a disproportionately high frequency of cardiac disease (12% and 37%, respectively), chronic lung disease (21% and 31%), and diabetes (22% and 25%) [5]. Thus, effective strategies to prevent pneumococcal disease in these at-risk individuals are of great importance.

Two previous studies assessed safety and immunogenicity of the 13-valent pneumococcal conjugate vaccine (PCV13) in healthy, pneumococcal vaccine–naive adults 50 to 64 years of age and a third study assessed safety and immunogenicity of PCV13 in adults ≥70 years of age who were previously vaccinated with 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23). All 3 studies allowed enrollment of subjects with stable chronic underlying diseases such as chronic cardiovascular disease, pulmonary disease, or diabetes mellitus. These studies showed that PCV13 elicits robust functional antibody responses in a population that included these at-risk subjects [6-8]. We now report a post hoc analysis of the 3 previously published studies comparing functional antibody responses to PCV13 in at-risk adults ≥50 years of

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age with responses in those considered not at increased risk. In addition, inclusion of PCV13 and PPSV23 study groups in 2 studies permits a similar post hoc comparison of functional antibody responses to vaccination in pneumococcal vaccine–naive at-risk subjects 60 to 64 years of age.

Materials and methods

Study design

At-risk subjects were defined as those diagnosed with stable chronic cardiovascular, pulmonary, liver, or renal disease, or diabetes mellitus (type 1 or 2). Stable disease, which was part of inclusion/exclusion criteria for each study, was defined as not requiring significant change in therapy or hospitalization for worsening disease within 12 weeks before vaccination. The most common diagnoses for cardiovascular disease were coronary artery disease, angina pectoris, and congestive cardiac failure; for pulmonary disease, the most common diagnoses were asthma, chronic obstructive pulmonary disease, and chronic bronchitis.

Functional antibody responses in participants of the 3 previous randomized trials who were vaccinated with PCV13 or PPSV23 have been reported [6-8]. Study 1 enrolled 470 PPSV23-naive adults aged 60 to 64 years (median age, 61 y), 125 of whom were considered to be at risk [6]. Study 2 enrolled 799 PPSV23-naive adults aged 50 to 64 years (cohort 1, 60 to 64 years [median age, 62 y] and cohort 2, 50 to 59 years [median age, 54 y]), 148 of whom were considered to be at risk [7]. Study 3 enrolled 431 adults aged ≥70 years (median age, 76 y) who were vaccinated with PPSV23 ≥5 years before study enrollment, 153 of whom were considered to be at risk [8]. Blood samples in the 3 studies were drawn for immunogenicity analyses before and approximately 1 month after vaccination [6-8].

Vaccines

PCV13 (Prevnar 13/Prevenar 13®, Pfizer Inc) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F individually conjugated to a nontoxic form of diphtheria toxin cross-reactive material 197. Each 0.5-mL dose contains 2.2 µg of each serotype, except type 6B, which is included at 4.4 µg. PPSV23 (Pneumovax 23®, Merck & Company, Inc) consists of a capsular polysaccharide from 12 of the serotypes included in PCV13 (all except 6A), as well as 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F). The vaccine is formulated to contain 25 µg of each of the 23 polysaccharide serotypes per 0.5-mL dose.

Immunogenicity analysis

Opsonophagocytic assay (OPA) geometric mean titers (GMTs) approximately 1 month after PCV13 administration in at-risk subjects ≥50 years of age with cardiovascular disease, pulmonary disease, or diabetes mellitus were descriptively compared with those in subjects without these underlying medical conditions. In addition, in studies 1 and 2, OPA GMTs after PCV13 or PPSV23 vaccination were compared in at-risk subjects 60 to 64 years of age with cardiovascular disease, pulmonary disease, or diabetes mellitus previously naive to pneumococcal vaccination [6, 7]. To increase sample sizes of the at-risk population in these 2 studies, OPA data from study participants were pooled; study 3 was not included in this pooled analysis because adults enrolled into this study differed in age and immunization status [8].

Statistical analysis

OPA GMTs elicited by PCV13 and PPSV23 were calculated for each serotype; comparisons were made between at-risk subjects and subjects not considered at risk. Ratio of GMTs for PCV13 to PPSV23, which included all subjects with a determinate OPA titer to the given serotype, were calculated by back-transforming the mean difference between vaccine groups on the logarithmic scale; confidence intervals (CIs) for the ratio are back-transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures (PCV13 – PPSV23). Geometric mean fold rise (GMFR) was calculated using OPA GMT data for all subjects with available data from both the pre- and postvaccination blood draws; CIs are back-transformations of a CI based on the Student *t* distribution for the mean fold rise. A statistically significantly higher GMT was inferred when the lower limit of the 2-sided 95% CI for the GMFR was >1. Similar criteria were used for GMT ratios.

Results

Baseline characteristics

Mean age across the 3 studies ranged from 54 to 77 years. The majority of subjects in all studies were white and non-Hispanic. The predominant at-risk condition was diabetes in study 1, pulmonary disease in study 2, and cardiovascular disease in study 3. Subjects in the clinical studies were not stratified for risk conditions at enrollment; therefore, number of subjects in the at-risk groups varied, and in some cases, was very low. The percentage of subjects without underlying medical conditions ranged from 65% to 83% across the 3 studies (Supplementary Table). Mean time since prior PPSV23 vaccination in study 3 was 8.4 years (range, 5.0–17.1).

Immunogenicity

Across all 3 studies, OPA GMTs to PCV13 serotypes 1 month after vaccination were comparable in at-risk subjects with stable chronic medical conditions and those without those conditions (Supplementary Figure), despite slight variations between studies, at-risk condition, and serotypes. In a pooled analysis of data from studies 1 and 2 evaluating subjects 60 to 64 years of age previously naive to pneumococcal vaccination who were diagnosed with cardiovascular disease, pulmonary disease, or diabetes mellitus, OPA GMTs increased from before to after PCV13 vaccination for the 12 serotypes common to both vaccines and serotype 6A (Table 1). GMFRs from prevaccination to postvaccination were generally higher among PCV13 than PPSV23 recipients for all serotypes and risk conditions. PCV13 elicited numerically higher OPA GMTs compared with PPSV23 for the majority of serotypes in all at-risk groups. Statistically significantly higher OPA GMTs were observed for 4, 9 and 7 of the 12 common serotypes in subjects with cardiovascular disease, pulmonary disease, or diabetes mellitus, respectively, and in all at-risk groups for serotype 6A, a serotype unique to PCV13 (Table 2).

Table 1 OPA GMTs and GMFRs in PPSV23-naive subjects 60−64 years of age with at-risk conditions in studies 1 and 2 (Cohort 1).

Serotype		*Cardiovascular disease*		*Pulmonary disease*		*Diabetes mellitus*	
		PCV13	*PPSV23*	*PCV13*	*PPSV23*	*PCV13*	*PPSV23*
		n[a]=43−52	*n[a]=32−43*	*n[a]=63−78*	*n[a]=36−47*	*n[a]=84−105*	*n[a]=60−82*
1	Prevaccination GMT	7	9	6	6	6	6
	Postvaccination GMT[b]	139	102	140	61	189	116
	GMFR (95% CI)[c]	20.1 (12.20–33.05)	11.8 (6.93–19.98)	22.7 (14.72–34.91)	10.0 (5.49–18.28)	30.1 (21.58–42.01)	19.9 (13.86–28.42)
3	Prevaccination GMT	5	7	6	6	6	7
	Postvaccination GMT[b]	74	69	67	50	80	84
	GMFR (95% CI)[c]	14.3 (9.44–21.67)	10.3 (6.83–15.65)	10.4 (7.24–14.85)	8.3 (5.43–12.82)	14.2 (10.28–19.67)	11.2 (8.20–15.32)
4	Prevaccination GMT	15	14	16	11	31	12
	Postvaccination GMT[b]	1502	1145	1746	341	2597	639
	GMFR (95% CI)[c]	98.7 (42.34–230.27)	83.8 (30.70–228.68)	109.1 (54.85–217.16)	30.2 (11.23–81.43)	84.0 (44.89–157.13)	52.2 (25.77–105.90)
5	Prevaccination GMT	6	5	6	6	6	7
	Postvaccination GMT[b]	344	152	213	91	251	153
	GMFR (95% CI)[c]	54.2 (30.51–96.29)	31.1 (16.28–59.29)	35.2 (21.91–56.51)	16.4 (8.34–32.35)	44.8 (29.29–68.57)	22.7 (14.43–35.72)
6A[d]	Prevaccination GMT	13	17	25	13	21	14
	Postvaccination GMT[b]	2110	337	1984	98	2104	222
	GMFR (95% CI)[c]	166.8 (80.98–343.75)	20.4 (8.83–47.10)	78.5 (43.37–142.23)	7.6 (3.46–16.62)	98.8 (57.59–169.35)	15.5 (8.73–27.53)
6B	Prevaccination GMT	37	36	40	19	39	32
	Postvaccination GMT[b]	1666	1065	1196	425	1250	711
	GMFR (95% CI)[c]	44.5 (19.03–104.20)	29.7 (12.76–69.35)	30.1 (15.24–59.29)	21.9 (8.93–53.78)	32.1 (17.52–58.94)	22.2 (11.83–41.82)
7F	Prevaccination GMT	8	5	6	7	7	7
	Postvaccination GMT[b]	1146	210	751	224	1155	306
	GMFR (95% CI)[c]	146.6 (65.79–326.66)	40.9 (16.93–98.86)	126.4 (66.82–239.03)	33.3 (13.71–81.06)	163.9 (95.19–282.20)	42.3 (23.00–77.70)
9V	Prevaccination GMT	10	12	17	10	12	12
	Postvaccination GMT[b]	740	190	952	84	768	163
	GMFR (95% CI)[c]	72.8 (32.82–161.65)	15.4 (6.00–39.60)	55.9 (29.29–106.66)	8.3 (3.39–20.52)	62.9 (35.16–112.60)	13.8 (6.45–29.60)
14	Prevaccination GMT	38	39	25	64	27	32
	Postvaccination GMT[b]	853	991	600	442	538	606
	GMFR (95% CI)[c]	22.3 (9.95–49.99)	25.6 (10.50–62.62)	24.1 (12.39–46.79)	6.9 (3.42–14.00)	20.1 (11.22–36.02)	19.1 (10.56–34.59)
18C	Prevaccination GMT	19	28	27	29	20	37
	Postvaccination GMT[b]	2186	1245	1610	616	1716	1001
	GMFR (95% CI)[c]	117.2 (59.00–232.80)	44.3 (21.86–89.58)	60.4 (31.02–117.70)	21.5 (9.13–50.53)	86.7 (51.17–146.86)	27.0 (15.59–46.68)
19A	Prevaccination GMT	21	18	18	20	22	29
	Postvaccination GMT[b]	662	368	558	261	669	364
	GMFR (95% CI)[c]	31.5 (17.82–55.53)	20.4 (11.76–35.25)	30.5 (18.90–49.08)	12.9 (7.19–23.17)	30.4 (20.59–44.80)	12.5 (8.27–18.77)
19F	Prevaccination GMT	22	14	12	11	16	27
	Postvaccination GMT[b]	854	476	407	447	818	647
	GMFR (95% CI)[c]	39.2 (19.65–78.10)	32.9 (14.98–72.15)	32.7 (19.14–55.92)	40.6 (19.06–86.56)	52.2 (32.28–84.46)	24.2 (14.24–41.01)
23F	Prevaccination GMT	6	9	6	5	8	8
	Postvaccination GMT[b]	196	49	264	28	309	40
	GMFR (95% CI)[c]	35.7 (17.29–73.60)	5.8 (3.01–11.00)	47.5 (28.25–79.80)	6.1 (2.86–12.88)	37.9 (22.33–64.33)	5.0 (2.94–8.39)

Abbreviations: GMT=geometric mean titer; GMFR=geometric mean fold rise; OPA=opsonophagocytic assay; PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; [a]Number of subjects with valid and determinate OPA results for the specified serotype at both the prevaccination and the postvaccination blood draws; [b]One month postvaccination; [c]GMFRs were calculated using all subjects with available data from both the prevaccination and the postvaccination blood draws. CIs are back-transformations of a CI based on the Student *t* distribution for the mean fold rise; [d]Serotype 6A is uniquely present in PCV13.

Note: GMTs were calculated using all subjects with available data for both the specified blood draws.

Table 2 Comparison of pneumococcal OPA GMTs for PCV13 relative to PPSV23 in PPSV23-naive subjects 60−64 years of age with at-risk conditions in studies 1 and 2 (Cohort 1).

Serotype		*Cardiovascular disease*		*Pulmonary disease*		*Diabetes mellitus*	
		PCV13	*PPSV23*	*PCV13*	*PPSV23*	*PCV13*	*PPSV23*
		n[a]=47−53	*n[a]=36−44*	*n[a]=69−81*	*n[a]=37−47*	*n[a]=93−110*	*n[a]=69−83*
1	Prevaccination GMT	7	8	6	6	6	6
	Postvaccination GMT[b]	139	102	146	61	189	116
	GMT ratio (95% CI)[c]	1.4 (0.68–2.76)		2.4 (1.19–4.87)		1.6 (1.05–2.54)	
3	Prevaccination GMT	5	7	6	6	6	8
	Postvaccination GMT[b]	74	69	71	50	80	84
	GMT ratio (95% CI)[c]	1.1 (0.62–1.84)		1.4 (0.81–2.49)		1.0 (0.64–1.43)	
4	Prevaccination GMT	14	12	16	11	30	12
	Postvaccination GMT[b]	1633	1181	1888	545	2828	695
	GMT ratio (95% CI)[c]	1.4 (0.55–3.49)		3.5 (1.52–7.87)		4.1 (2.20–7.51)	
5	Prevaccination GMT	7	6	6	5	6	7
	Postvaccination GMT[b]	344	152	213	91	251	153
	GMT ratio (95% CI)[c]	2.3 (0.99–5.15)		2.3 (1.06–5.20)		1.6 (0.89–3.03)	
6A[d]	Prevaccination GMT	13	17	27	14	23	14
	Postvaccination GMT[b]	2195	374	2101	95	2148	221
	GMT ratio (95% CI)[c]	5.9 (2.49–13.81)		22.2 (9.27–53.16)		9.7 (4.82–19.51)	
6B	Prevaccination GMT	34	36	38	23	36	30
	Postvaccination GMT[b]	1651	1052	1314	469	1348	710
	GMT ratio (95% CI)[c]	1.6 (0.69–3.56)		2.8 (1.06–7.36)		1.9 (0.93–3.87)	
7F	Prevaccination GMT	8	6	6	7	8	7
	Postvaccination GMT[b]	1168	257	811	224	1164	324
	GMT ratio (95% CI)[c]	4.5 (1.67–12.34)		3.6 (1.38–9.50)		3.6 (1.80–7.13)	
9V	Prevaccination GMT	10	12	18	11	13	12
	Postvaccination GMT[b]	759	227	888	117	787	156
	GMT ratio (95% CI)[c]	3.3 (1.14–9.84)		7.6 (2.77–20.65)		5.0 (2.33–10.88)	
14	Prevaccination GMT	36	38	24	56	25	33
	Postvaccination GMT[b]	867	971	604	526	612	692
	GMT ratio (95% CI)[c]	0.9 (0.36–2.18)		1.1 (0.46–2.83)		0.9 (0.46–1.72)	
18C	Prevaccination GMT	19	28	26	29	19	37
	Postvaccination GMT[b]	2128	1255	1702	650	1806	1012
	GMT ratio (95% CI)[c]	1.7 (0.85–3.38)		2.6 (1.10–6.26)		1.8 (1.04–3.06)	
19A	Prevaccination GMT	21	19	18	21	23	31
	Postvaccination GMT[b]	669	349	586	274	690	385
	GMT ratio (95% CI)[c]	1.9 (1.09–3.39)		2.1 (1.14–3.99)		1.8 (1.17–2.75)	
19F	Prevaccination GMT	20	15	14	12	15	26
	Postvaccination GMT[b]	835	480	426	523	757	657
	GMT ratio (95% CI)[c]	1.7 (0.78–3.87)		0.8 (0.38–1.74)		1.2 (0.69–1.93)	
23F	Prevaccination GMT	5	8	6	5	8	8
	Postvaccination GMT[b]	210	62	275	30	322	41
	GMT ratio (95% CI)[c]	3.4 (1.17–9.79)		9.3 (3.78–22.77)		7.9 (3.72–16.89)	

Abbreviations: GMT=geometric mean titer; OPA=opsonophagocytic assay; PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; [a]Number of subjects with a valid and determinate OPA result for a specific serotype; [b]One month postvaccination; [c]Ratio of postvaccination GMTs PCV13 to PPSV23 is calculated by back-transforming the mean difference between vaccine groups on the logarithmic scale. CIs for the ratio are back-transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures (postvaccination PCV13 – postvaccination PPSV23); [d]Serotype 6A is uniquely present in PCV13.

Note: GMTs were calculated using all subjects with available data for the specified blood draw.

Discussion

Previous studies have established an increased risk for pneumococcal disease in immunocompetent subjects with underlying chronic diseases [4, 5, 9-12], emphasizing the need for effective preventive strategies for these at-risk populations. Several studies have examined the responses to PCV or PPSV vaccination in at-risk adults [13-19]; to date, no studies specifically examined responses after PCV13 vaccination in at-risk adults. Therefore, in this analysis, we evaluated data from 3 previous studies in immunocompetent PPSV23-naive and PPSV23-preimmunized subjects ≥50 years of age that included a considerable percentage of subjects with stable chronic underlying conditions known to put these subjects at increased risk for pneumococcal disease. An OPA titer that correlates with protection has not been defined for adults.

As shown in this study, PCV13 administered to adults with cardiovascular disease, pulmonary disease, or diabetes mellitus, elicited functional pneumococcal antibody responses that were generally comparable to those of individuals considered not to be at risk, regardless of previous PPSV23 administration. In PPSV23-naive adults 60 to 64 years of age with an at-risk condition, OPA GMTs increased from prevaccination to postvaccination with PCV13 or PPSV23 for the 12 serotypes common to both vaccines and 6A. GMFRs from prevaccination to postvaccination were higher for PCV13 than for PPSV23 with few exceptions. In general, PCV13 elicited higher responses than PPSV23 in these at-risk subjects, a number of which were statistically significant. This is consistent with the higher PCV13 responses observed in the primary studies comprising subjects with and without risk conditions [6, 7].

The limitations of this analysis lie in its descriptive nature and relatively low numbers of some at-risk groups, as subjects in the clinical studies were not stratified for risk conditions at enrollment; this resulted in variable numbers of subjects in each at-risk group, with low representation of some at-risk conditions. Although the original studies assessed antibody responses one year after vaccination, one of the studies evaluated responses in a subset of less than 100 subjects, which limits drawing meaningful conclusions; therefore, one year data were not included in this analysis. However, recent data from the Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) 65 years of age and older in the Netherlands, that included approximately 85,000 subjects, demonstrated that PCV13 compared to placebo is efficacious against vaccine-type CAP, including nonbacteremic CAP, as well as vaccine-type IPD; importantly, this study included immunocompetent subjects with chronic conditions such as cardiovascular disease, pulmonary disease, and diabetes mellitus [20, 21]. Antibody responses were assessed in a subset of subjects at 1, 12 and 24 months after PCV13 vaccination. Consistent with the observations in the present studies, functional antibody responses were similar across all evaluated underlying medical conditions and all serotypes. Furthermore, antibody levels remained above baseline across all evaluated time points [22].

Conclusion

The results presented herein suggest that vaccination of immunocompetent at-risk populations with PCV13 likely results in immunologic benefits analogous to those experienced by populations not at additional risk.

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Conflicts of Interest

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Supplementary data

Supplementary data associated with this article can be found, at http://nobleresearch.org/Doi/10.14312/2053-1273.2015-2. These data include supplementary Table and Figure.

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