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Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine administered to older infants and children naïve to pneumococcal vaccination

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ABSTRACT

Background: Streptococcus pneumoniae infections are a major cause of morbidity and mortality in children <5 years old worldwide. To increase serotype coverage globally, a 13-valent pneumococcal conjugate vaccine (PCV13) has been developed and approved in many countries worldwide.
Objective: Assess the safety and immunogenicity of PCV13 in healthy older infants and children naïve to previous pneumococcal vaccination.
Methods: This was a phase 3, open-label, multicenter study conducted in Polish children ($N = 354$) who were vaccinated according to 3 age-appropriate catch-up schedules: Group 1 (aged 7 to <12 months) received two PCV13 doses with a booster at 12–16 months of age; Group 2 (aged 12 to <24 months) received two vaccine doses only; and Group 3 (aged 24 to <72 months) received a single dose of PCV13. Statistical analyses were descriptive. The proportion of immunological "responders" achieving serotype-specific antipneumococcal polysaccharide concentrations $\geq$0.35 μg/mL, 1-month after the last dose of vaccine, was determined for each vaccine serotype. In addition, antipolysaccharide immunoglobulin (Ig) G geometric mean concentrations (GMCs) were calculated. Safety assessments included systemic and local reactions, and adverse events.
Results: The proportion of immunological responders was $\geq$88% across groups for all serotypes. Antipolysaccharide IgG GMCs were generally similar across groups. Each schedule elicited immune response levels against all 13 serotypes comparable to or greater than levels previously reported in infants after a 3-dose series. The 3 catch-up schedules had similar tolerability and safety profiles; a trend was present towards greater local tenderness with increasing age and subsequent dose administration.
Conclusions: Immunological responses and safety results support the use of PCV13 for catch-up schedules in older infants and children naïve to pneumococcal vaccination.

Abbreviations: AE, adverse event; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; Ig, immunoglobulin; IPD, invasive pneumococcal disease; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious AE.

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1. Introduction

Streptococcus pneumoniae infections are a major cause of morbidity and mortality worldwide. Globally, pneumococcal disease has been estimated to account for approximately 541,000 deaths annually in children aged <5 years [1]. The 7-valent pneumococcal conjugate vaccine (PCV7), which includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F is effective in preventing invasive pneumococcal disease (IPD) and pneumonia caused by vaccine serotypes in infants and young children. Effectiveness has been demonstrated both for a standard vaccination schedule of 3 doses in the first 6 months of life followed by a toddler dose at 12–15 months of age [2,3], and for a simplified schedule of a 2-dose primary series and a toddler dose at 11–12 months of age [4,5]. Postmarketing surveillance data also indicate that the 3-dose schedule without the toddler dose decreased hospitalization for pneumonia [6]. It has also been shown that in addition to the direct benefits of vaccinated infants and children, the administration of PCV7 has a substantial indirect effect in reducing the incidence of pneumococcal disease in unvaccinated adults, including those aged ≥65 years [7–10]. Given these observations, the World Health Organization has recommended the universal use of PCV7 in infants and children [11].

To increase serotype coverage globally, a 13-valent pneumococcal conjugate vaccine (PCV13) has been developed and approved in many countries worldwide [12]. In addition to the 7 serotypes included in PCV7, PCV13 contains serotypes 1, 3, 5, 6A, 7F, and 19A. As with PCV7, each of the polysaccharides in PCV13 is covalently conjugated to a common carrier protein, CRM_{197}, a nontoxic variant of diphtheria toxin. The serotypes in PCV13 are the 13 most common serotypes causing IPD globally [13]. Serotypes 6A and 19A are particularly important additions, as both are known to mediate a substantial proportion of pneumococcal disease [2,14–16]. Although children aged <2 years are particularly susceptible to pneumococcal disease, older children are also known to be vulnerable. One study found that almost 30% of patients admitted to hospital with systemic pneumococcal disease were aged 2–10 years; a third were aged 5–10 years [17].

This study, conducted in Poland, assessed the immunogenicity of PCV13 in healthy older infants (aged 7 to <12 months or 12 to <24 months) and children (aged 24 to <72 months) naïve to previous pneumococcal vaccination using the catch-up schedule recognized for PCV7. The safety and tolerability of PCV13 was also assessed. These data were submitted to regulatory agencies globally to support licensure in this age group.

2. Methods

2.1. Study design

This phase 3, open-label, multicenter trial was conducted at 9 sites in Poland in accordance with the ethical principles in the Declaration of Helsinki. The protocol was reviewed and approved by the appropriate ethics committee. Written informed consent was obtained from all parents/guardians prior to the subject being enrolled.

2.2. Subjects

Subjects were eligible if they were healthy and aged between 7 months and <72 months (5 years). Subjects were enrolled into 1 of 3 age groups: Group 1 was 7 to <12 months of age; Group 2 was 12 to <24 months of age; and Group 3 was 24 to <72 months of age. The vaccination schedule for each age group was based on the recommended schedule for PCV7 in those subjects not previously vaccinated [18]. Subjects were ineligible if they had been previously vaccinated with a licensed or investigational pneumococcal vaccine or if they had any of the following: contraindication to vaccination; known or suspected immune deficiency or suppression; history of disease caused by *S. pneumoniae*; severe chronic disorder including severe congenital malformation or neurological disorder; history of seizures; received blood products/gammaglobulins within preceding 3 months; were participating in another interventional trial; or were direct descendants of study-site personnel.

2.3. Interventions

The vaccination schedule for each age group was based on the catch-up regimen for PCV7 in older infants and children who are naïve to previous vaccination with a pneumococcal conjugate vaccine [18]. The study schedule for vaccine doses and blood draws is shown in Table 1. Group 1 (aged 7 to <12 months) received 3 doses of PCV13; Group 2 (aged 12 to <24 months) received 2 doses of PCV13; and Group 3 (aged 24 to <72 months) received 1 dose of PCV13. Each dose was 0.5 mL administered by intramuscular injection (needle length 2.5 cm) into the left anterolateral thigh muscle or left deltoid according to local practice. Blood was drawn 28–42 days after the last vaccination in the schedule; for Group 3 blood was also drawn prior to the immunization given the known increase in antipneumococcal antibody titers with age as a result of natural exposure.

2.4. Vaccines

PCV13 contains pneumococcal polysaccharides from PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) as well as serotypes 1, 3, 5, 6A, 7F, and 19A. As with PCV7, each of the polysaccharides is covalently conjugated to CRM_{197}. PCV13 contains 2.2 μg of each polysaccharide, except for 4.4 μg of serotype 6B, in 5 mM succinate buffer with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose. The vaccine used in the study was lot number 7-5093-006A (Wyeth Pharmaceuticals/Pfizer Inc; Collegeville, PA, USA).

2.5. Antipneumococcal immunogenicity assessments

Antipneumococcal immune responses to PCV13 were evaluated before vaccination in Group 3 and 1 month after the final dose in all groups by measuring serotype-specific anticapsular polysaccharide immunoglobulin (Ig) G antibodies. Serotype-specific IgG was measured using the standard pneumococcal anticapsular polysaccharide enzyme-linked immunosorbent assay (ELISA) [19]. The assay measures IgG antibody concentrations in human serum against an international reference serum, 89-SF, which has known and published IgG antibody assignments for each of the 13 serotypes in PCV13 [20]. The reference serum was pre-absorbed with a crude pneumococcal cell-wall extract containing pneumococcal cell-wall polysaccharide, and the clinical test serum and control samples were pre-absorbed with both pneumococcal cell-wall extract and purified serotype 22F polysaccharide to enhance the specificity of the assay by removal of nonspecific antibodies [21,22]. ELISA results are presented by serotype using geometric mean concentrations (GMCs) expressed as μg/mL. In addition, for each serotype immunological responders are defined as those subjects whose post-immunization antipolysaccharide ELISA titers were ≥0.35 μg/mL. This antibody level has been associated with vaccine effectiveness against IPD in infants from earlier studies of pneumococcal conjugate vaccines [23].

The evaluable immunogenicity population was the primary analysis population, comprising eligible subjects who had ≥1 valid and determinate assay result for the proposed analysis, and had no major protocol violations. For the purpose of analysis, the