Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Safety and immunogenicity of a trivalent recombinant PcpA, PhtD, and PlyD1 pneumococcal protein vaccine in adults, toddlers, and infants: A phase I randomized controlled study

W. Abdullah Brooks[a,b], Lee-Jah Chang[c], Xiaohua Sheng[c], Robert Hopfer[c,*], on behalf of the PPR02 Study Team[1]

[a] International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh
[b] Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[c] Sanofi Pasteur, Swiftwater, PA, USA

ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 15 June 2015
Accepted 19 June 2015
Available online xxx

Clinical trial registry number:
WHO Universal Trial Number
U1111-1117-7316

Keywords:
Streptococcus pneumoniae
Pneumococcal vaccine
Infants
Phase I clinical trials

ABSTRACT

Background: Pneumococcal protein vaccines (PPrVs) may provide improved protection over currently available polysaccharide and conjugated polysaccharide vaccines. Here, we examined the safety and immunogenicity of a trivalent recombinant PPrV containing PcpA, PhtD, and PlyD1.
Methods: This was a phase I, single-center, randomized, observer-blind study with safety review between cohorts. Adults (18–50 years; $n=30$) and then toddlers (12–13 months; $n=30$) were randomized 2:1 to receive aluminum-adjuvanted trivalent PPrV (PPrV + adj) containing 50 μg per antigen or placebo. Infants (42–49 days; $n=220$) were next randomized to be injected at 6, 10, and 14 weeks of age with 10 μg PPrV + adj or placebo ($n=60$; 2:1); 25 μg PPrV + adj, 25 μg unadjuvanted PPrV, or placebo ($n=100$; 2:2:1); and 50 μg PPrV + adj or placebo ($n=60$; 2:1). Solicited reactions were recorded for 7 days and unsolicited adverse events for 30 days after each vaccination. Concentrations of antibodies to the three vaccine antigens were measured by enzyme-linked immunosorbent assay.
Results: Tenderness/pain was the most frequent injection-site reaction. Abnormal crying and irritability (infants), loss of appetite (toddlers), and headache, malaise, and myalgia (adults) were the most frequent systemic reactions. Reactions were mostly mild or moderate, resolved within 3 days, were not adjuvant- or dose-dependent, and were not increased by repeated vaccination. No immediate adverse events, hypersensitivity reactions, or treatment-related serious adverse events were reported. In all PPrV + adj cohorts, at least 75% of subjects had a ≥2-fold increase in all three antibody concentrations. In infants, antibody concentrations were higher with PPrV + adj than with unadjuvanted PPrV, higher with three than two vaccinations, and similar at the different vaccine doses.
Conclusions: The candidate trivalent PPrV was safe and immunogenic in adults, toddlers, and infants. Addition of aluminum adjuvant improved immunogenicity in infants without changing the safety profile.

Abbreviation: AE, adverse event; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; EU, ELISA units; GMC, geometric mean antibody concentration; PcpA, pneumococcal choline-binding protein A; PhtD, pneumococcal histidine triad protein D; PlyD1, detoxified Ply derivative; PPrV, pneumococcal protein vaccine; PPrV + adj, aluminum-adjuvanted candidate trivalent pneumococcal vaccine; SAE, serious adverse event.

* Corresponding author. Tel.: +1 570 957 2633; fax: +1 570 957 4287.
E-mail address: robert.hopfer@sanofipasteur.com (R. Hopfer).

[1] The PPR02 Study Team included Guy de Bruyn (Sanofi Pasteur, Swiftwater, PA, USA); Monica Bologa (Sanofi Pasteur, Toronto, ON, Canada); Josemund Menezes (Sanofi Pasteur, Mumbai, India); Daniel Kirby, Xavier Da Costa, David Neveu, and Sanjay Gurunathan (Sanofi Pasteur, Swiftwater, PA, USA);and Doli Goswami, Sultana Yeasmin, Nasrin Parvin, Moshtaq Ahmed, Kamrun Nahar, and Mohammed Ziaur Rahman (International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh).

http://dx.doi.org/10.1016/j.vaccine.2015.06.078
0264-410X/

1. Introduction

Streptococcus pneumoniae is a major cause of illness worldwide and a leading cause of morbidity and mortality in persons of all ages [1,2]. According to the World Health Organization, pneumococcal disease causes 1.6 million deaths per year, 0.7 to 1 million of which are in children <5 years of age [3,4]. Most of these deaths are in low- and middle-income countries.

Pneumococcal polysaccharide vaccines (PPVs), the first vaccines developed against *S. pneumoniae*, contain capsular polysaccharides from the most common serotypes. PPVs are effective at preventing pneumococcal disease in elderly and immunocompromised non-elderly adults, but they are not effective in children <2 years of age and have little effect on nasopharyngeal carriage [3]. This led to the development of pneumococcal conjugate vaccines (PCVs), which are immunogenic in children <2 years of age, reduce nasopharyngeal carriage of vaccine serotypes, induce herd protection, and have improved efficacy in immunocompromised individuals. The inclusion of these vaccines in public immunization programs has significantly reduced rates of pneumococcal infection. Although the current vaccines, PPV23 and PCV13, contain polysaccharides from the most common serotypes, their effectiveness can be limited by differences between circulating and vaccine serotypes and in some countries, their cost can be a limiting factor [3,5]. Furthermore, serotype replacement may reduce their effectiveness and is a concern for their continued use [6].

Pneumococcal protein vaccines (PPrVs) based on serotype-independent antigens are being investigated because they may be simpler to produce than PPVs or PCVs, may protect against more serotypes, and may avoid the problem of serotype replacement [3]. Several pneumococcal proteins are being considered as candidate antigens for a PPrV. In particular, phase I clinical trials have shown that pneumococcal choline-binding protein A (PcpA), polyhistidine triad protein D (PhtD), and pneumolysin can be safely administered and are immunogenic in healthy adults [7–11].

Combining all three antigens in a single vaccine might provide better protection against pneumococcal disease than monovalent or bivalent combinations. In preclinical studies, an aluminum-adjuvanted PPrV containing PcpA, PhtD, and a detoxified pneumolysin derivative (PlyD1) protected infant mice against an intranasal challenge with a lethal dose of *S. pneumoniae* [12]. Here we report the results of a phase I trial evaluating the safety and immunogenicity of a candidate PPrV containing PcpA, PhtD, and PlyD1 in adults, toddlers, and infants.

2. Participants and methods

2.1. Study design and objectives

This was a phase I, single-center, randomized, placebo-controlled, observer-blind study (WHO Universal Trial Number U1111-1117-7316) examining the safety (primary objective) and immunogenicity (secondary objective) of a candidate trivalent PPrV containing PcpA, PhtD, and PlyD1 in healthy infants, toddlers, and adults. The study was conducted between September 27, 2011 and June 4, 2013 at the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh. The study protocol was approved by the Research Review and Ethical Review Committees of the International Centre for Diarrhoeal Disease Research, and the study was conducted in accordance with the Edinburgh revision of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, the applicable national and local requirements regarding ethical committee review, and national laws. All adults and parents or legal representatives of all children in the study provided written informed consent.

2.2. Vaccine candidates

Recombinant PlyD1, PhtD, and PcpA were expressed in *Escherichia coli* as soluble proteins and purified by column chromatography [13]. PlyD1 is a highly detoxified variant of Ply generated by site-directed mutagenesis and differs from the wild-type form by three amino acid substitutions (T65C, G293C, C428A). PhtD was the full-length protein without the signal sequence, and PcpA was the full-length protein lacking the choline-binding domain cloned from strain 14453 (serotype 6B) of *S. pneumoniae*. The candidate trivalent PPrV was a suspension of PcpA, PhtD, and PlyD1 and was prepared as one unadjuvanted and three adjuvanted (PPrV + adj) formulations. The three PPrV + adj formulations contained 0.28 mg of elemental aluminum (phosphate-treated aluminum hydroxide) and 10, 25, or 50 μg of each antigen in 0.5 ml Tris-buffered saline (10 mM Tris, pH 7.4, 150 mM NaCl). The unadjuvanted PPrV contained 25 μg per antigen in 0.5 ml Tris-buffered saline. All vaccines were prepared in single-use vials. The placebo was Tris-buffered saline.

2.3. Subjects

Healthy adults 18–50 years of age, toddlers 12–13 months of age, and infants 42–49 days of age were recruited for this study. Infants and toddlers had to be born at full term (≥37 weeks) and weigh ≥60% of the median weight for Bangladesh as measured by the weight-for-age index. Subjects were excluded if they had received any vaccine within 4 weeks of the first trial vaccination, had previously been vaccinated against *S. pneumoniae*, or had a history of pneumococcal infection (within the previous 5 years for adults). Women of childbearing age were screened with a urine pregnancy test (QuikVue hCG®, Quidel, San Diego, CA, USA). Women could not be pregnant or breastfeeding and had to be either using effective birth control or not be of childbearing potential. Additional exclusion criteria are described in the Supplemental information.

2.4. Study conduct

A total of 30 adults, 30 toddlers, and 220 infants were planned. The trial included one cohort each for adults and toddlers and three ascending-dose cohorts for infants (Fig. 1). Progression from one cohort to the next required a satisfactory review of 7-day safety data. Alert thresholds for the safety review included any vaccine-related serious adverse events (SAEs) and >15% of vaccine-exposed subjects reporting grade 3 fever.

Subjects in the first two cohorts (adults [cohort 1] and toddlers [cohort 2]) were randomized 2:1 to receive a single injection of 50 μg PPrV + adj or placebo (day 0). In the remaining three cohorts, infants received three injections at 6, 10, and 14 weeks of age: cohort 3 ($n = 60$) was randomized 2:1 to receive 10 μg PPrV + adj or placebo; cohort 4 ($n = 100$) was randomized 2:2:1 to receive 25 μg PPrV + adj, 25 μg unadjuvanted PPrV, or placebo; and cohort 5 ($n = 60$) was randomized 2:1 to receive 50 μg PPrV + adj or placebo. Study treatments were administered by intramuscular injection in the deltoid region of the arm (adults) or in the vastus lateralis (toddlers and infants), opposite the limb used for blood sampling.

Infants also received the standard-of-care childhood vaccines administered in the limb opposite the one used for study treatments. Standard-of-care vaccines were provided by the World Health Organization Expanded Program for Immunization and included the following: purified diphtheria toxoid/purified tetanus toxoid/inactivated whole-cell pertussis/*Haemophilus* b oligosaccharide/purified hepatitis B surface antigen vaccine; oral poliomyelitis vaccine; and Bacillus Calmette-Guérin vaccine for infants who did not receive it at birth.

Please cite this article in press as: Brooks WA, et al. Safety and immunogenicity of a trivalent recombinant PcpA, PhtD, and PlyD1 pneumococcal protein vaccine in adults, toddlers, and infants: A phase I randomized controlled study. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.06.078