Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Safety and immunogenicity of the Cuban heptavalent pneumococcal conjugate vaccine in healthy infants. Results from a double-blind randomized control trial Phase I

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ARTICLE INFO

Article history:
Received 12 July 2017
Received in revised form 3 May 2018
Accepted 4 May 2018
Available online xxxx

Keywords:
Pneumococcal conjugate vaccine
Immunogenicity
Safety
Infant
Clinical trial
Cuban

ABSTRACT

Background: Cuba has a new pneumococcal conjugate vaccine candidate (PCV7-TT). This study evaluates the safety and immunogenicity in healthy infants using 2p+1 vaccination schedule.
Methods: A phase I, controlled, randomized and double blind clinical trial was designed. 30 unvaccinated healthy infants were included. 20 subjects were assigned to study group (PCV7-TT) and 10 to control group (Synflorix®) to receive the vaccines at 7, 8 months of age (primary series) and 11 months (booster dose). Blood samples were collected 30 days after second dose and post booster for antibodies measure analysis by ELISA and OPA. The statistics analysis included the frequency of occurrence for adverse events and the immune response. Non-parametric tests were used to compare the immune response. The clinical trial was published in the Cuban Public Register of Clinical Trials with code RPCEC00000173 available at http://registroclinico.sld.cu.
Results: Overall, the safety profile of PCV7-TT was similar to Synflorix®. Local reactions were predominant and systemic events were mild in severity. Swelling and redness were frequently associated with PCV7-TT mainly after the first dose (50% and 40% respectively). 15% and 10% of subject reported severe swelling after first dose with PCV7-TT and after second dose with Synflorix®. Mild fever (≥38–≤39), vomiting and sleep disturb were the systemic events reported. 100% of infants achieved pneumococcal IgG antibody concentrations ≥0.35 μg/ml after booster dose for serotypes 1, 14, 18C and 19F in each vaccine group. For serotypes 5, 6B and 23F, more than 80% infants vaccinated with Synflorix® or PCV7-TT

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https://doi.org/10.1016/j.vaccine.2018.05.027
0264-410X/

achieved protective IgG GMC $\geq$ 0.35 μg/ml after booster dose. OPA proportion's responders to the seven common serotypes were 89.5% or more after the primary dose and 100% after booster dose in vaccinated with PCV7-TT.

Conclusions: The Cuban PCV7-TT is safe, well tolerated and immunogenic in healthy infants.

1. Introduction

Streptococcus pneumoniae is responsible for pneumococcal invasive disease (IPD), causing significant morbidity and mortality worldwide [1]. Prevention of pneumococcal infection through vaccination remains the best strategy to reduce the incidence of IPD. The pneumococcal conjugate vaccines (PCVs) have been shown to be highly immunogenic, safe, well tolerated and effective in reducing invasive and noninvasive pneumococcal diseases in vaccinated children [2]. Besides their direct effects in infants, PCVs have a substantial indirect effects, resulting in the reduction of disease burden among unvaccinated adults and toddlers [3,4]. Available evidences from various countries have shown that PCVs can be administrated concurrently with other vaccines that are typically recommended during the first year of life [5,6].

Baseline data in Cuba previous 2014 about pneumococcal serotype distribution is really limited and based mainly in meningeal isolations. The first study exploring the prevalence of NP colonization in children was conducted and published in 2017 [7].

To date Cuba and many other low-income countries have not yet introduced pneumococcal vaccination into their national immunization programs due to their elevated costs. Indeed, despite significant global efforts to facilitate vaccine procurement through different advantageous financial mechanisms, the introduction of these complex and relatively expensive vaccines has been lengthy worldwide [8]. In 2007, Cuba initiated the development of a seven-valent tetanus toxoid conjugated PCV (PCV7-TT), the first in a subsequent series of more complex PCVs. PCV7-TT was developed bearing in mind the following criteria: (a) to include seven serotypes, learning from Prevnar-7 that the impact of PCV could be high if the selected serotypes match with the current epidemiology; (b) to use tetanus toxoid conjugates to increase the immunogenicity induced against the serogroups 19 and 6 through 19F and 6B conjugates; and (c) to reduce the time of pharmaceutical development by reducing the complexity of the vaccine and making it available as soon as possible. The final composition of this vaccine consists of 2 μg of PS from serotypes 1, 5, 14, 18C, 19F, 23F and 4 μg of 6B, all conjugated to tetanus toxoid and adsorbed on aluminum phosphate [9]. The vaccine is currently in late clinical development [10,11] before the introduction in Cuba in 2019. The seven serotypes contained in the new vaccine candidate representing 49.9% of total IPD in Cuba in 2009 [12] and 42.3% in 2014 [13]. Expected potential cross protection effect for 6A and 19A, the serotype coverage will raises more than 70%.

We expect that the Cuban PCV7-TT may represent an appealing option for countries that have not yet introduced PCV considering its price. Indeed, the seven prevalent serotypes included in the vaccine account for over 60% of isolated serotypes worldwide [14]. In the present article, we provide the first evidences of safety and immunogenicity of PCV7-TT in infants aged 7–11 months, who have not been previously vaccinated against pneumococcal diseases.

2. Methods

2.1. Study design and ethical considerations

A phase I, parallel, controlled, randomized and double blind clinical trial was designed with the primary objective to assess the safety of PCV7-TT in infants, using a two primary doses plus a booster (2p+1) schedule administrated at 7, 8 and 11 months of age. The secondary objective was to evaluate the immunogenicity of the PCV7-TT among the same study population.

The study protocol was reviewed and approved by the Ethics Committee of the Children University Hospital "Juan Manuel Márquez" in Havana, Cuba. The clinical trial was authorized by the Cuban National Regulatory Agency according the Good Clinical Practice (GCP) Cuban guidance [15], and published in the Cuban Public Register of Clinical Trials with the code RPCEC00000173 (a protocol summary is available at http://registroclinico.sld.cu). It was conducted in accordance with the code of Ethic of the World Medical Association for experiments in human beings [16].

2.2. Informed consent

Written informed consent was obtained from the parents or legally acceptable representative of each infant before enrollment. Physicians explained in details the benefits and risk of the study and parent's voluntary decided about the enrollment of their infant.

2.3. Enrollment and selection criteria

As PCV7-TT had not been previously evaluated in this population, 30 healthy infants from 38 eligible infants were randomized to the study and control groups. They were 7-months-old residents of Havana, who had not been previously vaccinated against pneumococcal disease and were enrolled upon parents' informed consent.

2.4. Inclusion criteria

We included healthy 7-months-old infants born at least at 36 weeks of gestation, weighing more than 2500 g at birth, presenting adequate nutritional condition and having completed the vaccination schedule during their first semester of life.

2.5. Exclusion criteria

Infants were excluded if they had history of chronic diseases, immunomodulator treatment, any hypersensitivity reaction following a previous vaccination, prior vaccination against *S. pneumoniae*, or acute illness at the moment of vaccination. Infants were also excluded if another vaccine had been administered, or planned, from 30 days before and up to 30 days after the administration of a study vaccine dose.

2.6. Vaccines, target groups and schedule

Eligible participants were randomly assigned in a 2:1 ratio to receive PCV7-TT or Synflorix® at 7, 8 months of age (primary dose) and 11 months (booster dose), based on a random assignment schedule prepared by the sponsor. All participants, study staff, and those assessing the outcomes were blinded to the group assignment. The intervals between consecutive primary vaccination doses were 30 days and 90 days between primary schedule and booster dose. We generated a random list using the R software

Please cite this article in press as: Pérez A et al. Safety and immunogenicity of the Cuban heptavalent pneumococcal conjugate vaccine in healthy infants. Results from a double-blind randomized control trial Phase I. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.027