Vaccine 32 (2014) 1181–1186

Contents lists available at ScienceDirect

Vaccine

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

Sustained functional serotype-specific antibody after primary and secondary vaccinations with a pneumococcal polysaccharide vaccine in elderly patients with chronic lung disease

Nobuharu Ohshima[a], Hideaki Nagai[b], Hirotoshi Matsui[b], Shunsuke Akashi[b], Tomohiko Makino[c], Yukihiro Akeda[d], Kazunori Oishi[c,*]

[a] Department of Allergy, National Hospital Organization Tokyo National Hospital, Japan
[b] Center for Pulmonary Diseases, National Hospital Organization Tokyo National Hospital, Japan
[c] Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Japan
[d] International Research Center for Infectious Diseases, Research Institute for Microbial Diseases, Osaka University, Japan

ARTICLE INFO

Article history:
Received 13 July 2013
Received in revised form
18 September 2013
Accepted 24 September 2013
Available online 9 October 2013

Keywords:
Serotype-specific IgG
Opsonophagocytic activity
Pneumococcal polysaccharide vaccine
Revaccination

ABSTRACT

An observational study was conducted to determine immunogenicity before and after primary and secondary vaccinations with 23-valent pneumococcal polysaccharide vaccine in a cohort of 40 elderly patients with chronic lung diseases. Safety of this vaccine was also compared between primary and secondary vaccination. We analyzed serotype-specific immunoglobulin G (IgG) and the opsonization index (OI) for serotypes 6B, 14, 19F, and 23F and compared adverse local and systemic reactions. The levels of serotype-specific IgG and the OIs significantly increased 1 month after primary and secondary vaccinations. Peak levels of IgG after secondary vaccination were 5–20% lower than those after primary vaccination, while serotype-specific OIs after secondary vaccination were comparable with those after primary vaccination. The levels of serotype-specific IgG required for 50% killing significantly decreased 1 month after vaccination. These values for serotypes 14, 19F, and 23F were slightly elevated immediately before secondary vaccination, but those for serotype 6B did not change. After secondary vaccination, these values declined slightly for serotypes 14, 19F, and 23F and remained low for serotype 6B. Although self-limited local and systemic reactions were more frequent after secondary vaccination compared with primary vaccination, no serious systemic reaction was found after either vaccination. Our data suggest a sustained functional serotype-specific IgG after primary and secondary vaccination and confirmed the safety of secondary vaccination among elderly individuals with chronic lung disease.

1. Introduction

Streptococcus pneumoniae is a leading human pathogen that causes a variety of diseases, such as invasive pneumococcal disease (IPD) and non-bacteremic pneumonia, in children and adults. The rates of IPD are highest among children under 5 years of age and among adults who are older than 65 years of age [1–3]. Community-acquired pneumonia (CAP), which is most likely to be caused by *S. pneumoniae*, and the incidence of pneumococcal CAP is also high among the elderly [3–5].

The efficacy, immunogenicity, and safety of the 23-valent pneumococcal polysaccharide vaccine (PPV23; Pneumovax®, Merck Sharp & Dohme) has been extensively studied in adults [6,7]. Although *S. pneumoniae* is commonly responsible for 8–25% of exacerbation in patients with chronic lung diseases such as chronic obstructive pulmonary disease, the immunogenicity studies of PPV23 in this population are scarce [8–12]. Consistent results from observational studies have demonstrated that PPV23 reduces the risk of IPD in immunocompetent older adults. Recent studies from Japan reported that PPV23 prevented pneumococcal pneumonia and reduced the death rate due to pneumococcal pneumonia among nursing home inhabitants in Japan and that PPV23 was effective for all-cause pneumonia for study subjects older than 75 years of age after routine immunization with the influenza vaccine [13,14]. As the percentage of the elderly population (aged 65 years and over) is 23.1% in Japan [15], the demand for receiving PPV23 revaccination 5 years or more after primary vaccination is increasing. The US Advisory Committee on Immunization Practices recommends a single revaccination for persons at increased risk, including adults ≥65-years old who had received their first vaccination ≥5 years previously and were less than 65 years old at the time of their first vaccination in 1997 [16]. Revaccination with

* Corresponding author. Tel.: +81 3 5285 1111; fax: +81 3 5285 1129.
E-mail address: oishik@nih.go.jp (K. Oishi).

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.09.060

PPV23 was contraindicated in Japan until October 2009 [17], but revaccination has been approved for adults who had received their first dose of PPV23 more than 5 years previously.

Jackson et al. reported that secondary vaccination with PPV23 induced local reactions more frequently than primary vaccination, but that these reactions were not serious and resolved within 3 days [18]. In addition, two recent studies from the United States demonstrated comparable functional antibody responses between primary and secondary vaccination in adults older than 65 years of age [19,20]. Hammitt et al. also demonstrated that repeat revaccination with PPV23, administered 6 years or more after the prior dose, was immunogenic and generally tolerated [21]. Furthermore, IgG concentrations were found to exceed vaccine-naïve levels for seven of eight serotypes tested 10 years after the first or second doses of PPV23 [22]. In this study, we examined the immunogenicity and safety of PPV23 in a cohort of patients with chronic lung disease (CLD) who were followed up through the time of primary to secondary vaccination at a single institution and report on the sustained and functional serotype-specific antibodies raised by primary and secondary vaccinations with PPV23.

2. Materials and methods

2.1. Study subjects

Between October 2001 and November 2002, 101 patients with CLD who were 65 years of age or older received primary vaccination with PPV23 at our outpatient clinic. Serum samples from these study subjects had been acquired before and 1 month after primary vaccination and had been preserved for antibody titer analyses [23]. Of 101 patients, 30 patients died and 31 patients were lost for follow-up at our outpatient clinic until September 2009. All patients provided written informed consent.

This study was reviewed and approved by the ethics committee of the National Hospital Organization, Tokyo National Hospital, and was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Samples

Blood samples were drawn from 40 study subjects before and 1 month after secondary vaccination with PPV23. Sera were separated by centrifugation and stored at −80 °C until used.

The levels of serotype-specific immunoglobulin G (IgG) and the opsonization index (OI) were measured in the serum samples obtained before and 1 month after primary vaccination and before and 1 month after secondary vaccination.

2.3. ELISA

Antipneumococcal IgG antibodies were measured with the World Health Organization (WHO)-approved ELISA methodology, using standard reference serum (89-SF or 007sp) and C-polysaccharide and 22F polysaccharide absorptions, as previously described [24,25]. The levels of serotype-specific IgG for four serotypes, 6B, 14, 19F, and 23F, were determined according to the WHO protocol (a detailed protocol is available at www.vaccine.uab.edu/ELISAProtocol [89SF]). These four serotypes are commonly found in adult patients with CAP in Japan [5].

2.4. Multiplexed opsonophagocytic killing assay

A multiplexed opsonophagocytic killing assay (MOPA) for the four serotypes, based on antibiotic-resistant target bacteria, was performed at the Research Institute for Microbial Diseases, Osaka University, as previously described [26]. The quality control serum was prepared from the pooled sera of adults vaccinated with PPV23 and was used in each assay. The OI was defined as the serum dilution that killed 50% of bacteria, and the OI was determined using opsotiter3 software according to the WHO protocol (a detailed protocol is available at www.vaccine.uab.edu/UAB-MOPA). Functional activity of serotype-specific IgG was expressed as the concentration of IgG required for 50% killing of the pneumococcal strain by dividing the IgG concentration of a test sample by the OI [27].

Table 1
Baseline characteristics of 40 patients with chronic pulmonary diseases.

Characteristics	Values
Male sex: No. (%)	18 (45)
Mean age: years of age (SD)	77 (6.1)
65–69 years of age: No. (%)	4 (0.1)
70–79 years of age: No. (%)	22 (55)
≧80 years of age: No. (%)	14 (35)
Comorbid illness: No. (%)	
Sequela of pulmonary tuberculosis	13 (33)
Bronchiectasis	7 (18)
Asthma	7 (18)
Nontuberculous mycobacterial infection	6 (15)
Aspergillosis	3 (8)
Chronic obstructive pulmonary disease	3 (8)
Interstitial pneumonia	1 (3)
Home oxygen therapy: No. (%)	15 (38)
Mean time to revaccination: months (SD)	91 (3.7)

SD, standard deviation.

2.5. Adverse reactions

Subjects were provided a diary to record their body temperature and any local or systemic reactions that occurred from the day of secondary vaccination to day 14. They were instructed to assess the maximal diameter of any redness or swelling at the site of injection; this was expressed as mild for a maximum diameter of 1–5 cm, as moderate for a maximum diameter ≧5 cm, and as severe for a maximum diameter ≧10 cm. A systemic symptom was considered mild when the subjects felt a certain symptom but had no difficulty in daily life. A physical examination with an interview was conducted to record the condition of the study subject on the day of secondary vaccination and 14 days after. Data of adverse reactions after primary vaccination were used for comparison with those after secondary vaccination [23].

2.6. Statistical analysis

Average antibody concentrations and increases were expressed as geometric means. Differences in the geometric mean concentrations (GMCs) of serotype-specific IgG, the OIs, or the IgG required for 50% killing were assessed by the Wilcoxon matched-pairs signed-ranks test. The frequencies of adverse reactions were compared between primary and secondary vaccinations by the Student *t*-test. Differences with a P value <0.05 were considered to be statistically significant.

3. Results

The subject patient group comprised 18 males and 22 females, and all of them were Japanese (Table 1). Four subjects were in their 60s, 22 in their 70s, and 14 in their 80s; the mean age was 77 years. The mean interval between primary and secondary vaccinations was 7 years and 7 months. Their comorbid illnesses included sequelae of pulmonary tuberculosis (33%), bronchiectasis (18%), bronchial asthma (18%), nontuberculous mycobacterial infection