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Pneumococcal conjugate vaccine triggers a better immune response than pneumococcal polysaccharide vaccine in patients with chronic lymphocytic leukemia A randomized study by the Swedish CLL group

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ABSTRACT

Aim: To determine if patients with untreated chronic lymphocytic leukemia (CLL) benefit from vaccination with a 13-valent pneumococcal conjugated vaccine (PCV13), Prevenar13®, compared to a 23-valent pneumococcal polysaccharide vaccine (PPSV23), Pneumovax®, in terms of immune response.
Background: *Streptococcus pneumoniae* causes substantial morbidity in patients with CLL, a group known to respond poorly to polysaccharide vaccines. Comparative studies with conjugated vaccines are lacking.
Methods: 128 treatment naïve CLL patients from eight hematology clinics in Sweden were randomized to vaccination with PCV13 (n = 63) or PPSV23 (n = 65) after stratification by IgG level and CLL clinical stage (Rai). Blood samples for evaluation of immune response were obtained at baseline, and at one and six months after vaccination. Analyses for each of the 12 pneumococcal serotypes common for PCV13 and PPSV23 were performed by opsonophagocytic assay (OPA) and enzyme-linked immunosorbent assay (ELISA).
Results: PCV13 elicited a superior immune response than PPSV23 in 10/12 serotypes one month after vaccination and in 5/12 serotypes six months after vaccination, measured as OPA geometric mean titers (GMTs). Geometric mean concentrations of serotype-specific IgG antibodies elicited by PCV13 as measured by ELISA, were higher than those elicited by PPSV23 in half of the common serotypes, both after one and six months. PPSV23 did not trigger a better immune response than PCV13 for any of the serotypes, regardless of analysis method or time point of analysis. Negative predictive factors for vaccination response were hypogammaglobulinemia and long disease duration. Both vaccines were well tolerated.
Conclusions: In patients with previously untreated CLL, the efficacy of PCV13 in terms of immune response is superior to PPSV23 for most serotypes common for the two vaccines. We therefore propose that PCV13 should be included in vaccination programs against *Streptococcus pneumoniae* for CLL patients and administered as early as possible during the course of the disease.

1. Introduction

Patients with chronic lymphocytic leukemia (CLL) have an increased risk of infection due to predisposing factors such as hypogammaglobulinemia, T- and NK-cell dysfunction and complement defects [1,2]. Moreover, the short- and long-term side effects of different treatment modalities, such as chemotherapy and monoclonal antibodies, add further to infection susceptibility [1–6]. Infections caused by *Streptococcus pneumoniae* are a major cause of morbidity and mortality in CLL-patients, which makes prevention essential [7–9].

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Vaccination is a straightforward option to increase immunity and prevent infection. However, patients with CLL are known to respond inadequately to polysaccharide vaccines, which are T-cell independent, with immunization response rates in unselected CLL-patients varying from 0 to 22% in different studies [6,7,10–12]. Reasons for the low response rates are multifactorial and include impaired humoral immunity (due to a lack of functional B-cells) and defect T-cell function [11,13,14]. It has been proposed that treatment naïve patients at an early stage of disease respond better to vaccination [15].

Conjugation of the polysaccharide with a protein carrier (protein-conjugate vaccines) renders a T-cell dependent, memory inducing vaccine [8,14–16]. Pneumococcal conjugate vaccines (PCVs) were first approved for infants and are globally recommended as routine childhood immunization [16–20]. They also improve immune response to bacteria and induce an immunological memory in the elderly [14,15]. PCVs have dramatically decreased the incidence of invasive pneumococcal disease caused by the included serotypes, but a shift in the distribution of disease causing serotypes has followed [17,18,20–22]. One study, using the 7-valent PCV, suggested that a conjugate vaccine renders a higher immune response than polysaccharide vaccines in patients with CLL, reporting a response rate of 20–47%, depending on serotype [14]. However, there are no randomized studies comparing the two different types of pneumococcal vaccines in CLL patients and no consensus regarding vaccination recommendations [14,23,24].

The aim for the present study was to determine if untreated patients with CLL benefit from vaccination with a 13-valent pneumococcal conjugated vaccine (PCV13), Prevenar13®, compared with a 23-valent capsular polysaccharide vaccine (PPSV23), Pneumovax®, in terms of immune response.

2. Methods

2.1. Patient selection

Treatment naïve CLL patients, 18 years or older in all clinical stages (Rai 0-IV), from eight hematology units in Sweden, were enrolled prospectively in the study between September 2013 to June 2015. An informed consent was required from all patients and physical examination and blood chemistry was performed to evaluate WHO performance status and Rai stage. Major exclusion criteria were: previous vaccination with a pneumococcal vaccine within 5 years, symptomatic disease and/or intention to start treatment with chemotherapy and/or monoclonal antibodies within one month, other active malignancy, allergic reaction to a vaccine in the past, neutropenia (absolute neutrophil count (ANC) $<0.5 \times 10^9$/L), ongoing infection, positive Direct Antiglobulin Test (DAT) or known previous or ongoing hemolysis.

2.2. Study design

The study was designed as a two armed, randomized, non-blinded trial. After informed consent, patients were randomized at the enrollment visit using a randomized block design with equal probability to receive PCV13 or PPSV23. Because of expectation of lower immunization response in patients with low serum IgG levels and clinically advanced disease, patients were stratified by IgG levels (normal or below normal range according to the local laboratory) and CLL stage (using the Rai clinical staging system, stage 0-I-II or stage III-IV). Blood samples for immunogenicity analyses were obtained immediately before vaccination and after one and six months, respectively (Fig. 1).

The study was performed according to the International Conference on Harmonisation's Guidelines for Good Clinical Practice and the ethical principles outlined by the Declaration of Helsinki. The Ethics committee in Stockholm and the Medical Product Agency of Sweden approved the protocol. An independent contract research organization (Karolinska Trial Alliance) monitored the study. The study is registered at www.clinicaltrials.gov (NCT01892618).

2.3. Vaccines and administration

PCV13 (Prevenar13®, Pfizer; Lot Numbers F81998, G67365, J42115) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F individually conjugated to a nontoxic mutant form of diphtheria toxin cross-reactive material 197 (CRM197) protein, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate, per 0.5 mL dose. The vaccine contains

2.2 μg of each saccharide, except for 4.4 μg of 6B, per 0.5 mL dose, and is supplied in single-dose syringes without preservatives and stored at 2–8 °C.

PPSV23 (Pneumovax 23®, Sanofi Pasteur MSD; Lot Numbers H011754, J009828, K021211) consists of purified capsular polysaccharides from 12 of the serotypes included in PCV13 (except 6A), as well as 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F). The vaccine contains 25 μg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine and contains phenol as a preservative and stored at 2–8 °C [22].

Vaccines were administered by intramuscular injection in the deltoid using 23G 25 mm needles.

2.4. Study objectives

2.4.1. Immunogenicity

Study objectives were to compare immune response after vaccination for the 12 pneumococcal serotypes common for PCV13 and PPSV23, in terms of OPA titers and serotype-specific IgG antibodies measured by ELISA.

2.4.2. Primary study objectives

Primary study objectives were to compare responses at one month after vaccination; 1. To compare OPA geometric mean titers (GMTs) for each serotype. 2. To compare the proportion of patients with positive immunological responses defined as a post vaccination OPA titer $\geq$ assay LLOQ in at least 8 of the 12 serotypes common for PCV13 and PPSV23, in the two vaccination groups, according to pre-defined response criteria. Lower limit of quantification (LLOQs) for OPA determined from assay validation experiments (serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:113; serotype 9V, 1:141; serotype l4, 1:35; serotype 18C, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13).

2.4.3. Secondary study objectives

Secondary study objectives were: 1. To compare immune response in terms of OPA titers six months after vaccination, using the same means of comparison as for the primary end point. 2. To compare ELISA geometric mean concentrations (GMCs) for each serotype measured one and six months after vaccination.

2.5. Laboratory methods

2.5.1. General aspects

Blood samples for immunogenicity analyses were centrifuged within 45 min from drawing of the blood and plasma was collected and frozen in labeled vials to minimum −20 °C at the local site. After study completion, all samples were sent to Pfizer's Vaccine

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