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Vaccination status and immune response to 13-valent pneumococcal conjugate vaccine in asplenic individuals

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ABSTRACT

Overwhelming post-splenectomy infection (OPSI) is immediately life-threatening and vaccination against encapsulated bacteria, in particular pneumococci, decreases its incidence.

First, we investigated the adherence to vaccination guidelines in a retrospective study of the hospital records of splenectomised patients. Second, patients were asked to complete a questionnaire and invited to participate in a study where 12-valent pneumococcal serotype-specific IgG concentrations were determined before and 4 to 6 weeks after vaccination with PCV13.

Of 79 individuals who underwent splenectomy between 2000 and 2012: 81.0% received pneumococcal vaccine, 51.9% received vaccine against *Haemophilus influenzae* type B and 22.8% received meningococcal vaccine. 31 individuals were deceased. 33 individuals completed questionnaires and accepted participation in the second part of the study. The participants consisted of two groups: (1) prior PPV23 ($n = 24$) and (2) prior PPV23 + PCV13 ($n = 9$). In group 1, pre-PCV13 GMC's ≥ 0.35 μg/mL were observed for serotypes 1, 4, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, and GMC's < 0.35 μg/mL for serotypes 3 and 5, significant increases pre- to post-PCV13 were found for serotypes 1, 3, 4, 5, 7F, 18C, 19A, 23F ($p \leq 0.001$) and 19F ($p = 0.01$) and all 12 serotypes-specific GMC were above 0.35 μg/mL after vaccination. Group 2 did not receive vaccine in this study, but blood tests showed all 12 serotype-specific GMC > 0.35 μg/mL.

Adherence to guidelines regarding primary pneumococcal vaccination was adequate but only a minority received the recommended meningococcal vaccination.

High levels of pneumococcal serotype-specific antibodies were observed in the previous PPV23 vaccinated group, and more pronounced in the previous PCV13 group, and our data suggests that PCV13 is immunogenic for serotypes 1, 3, 4, 5, 7F, 18C, 19A, 19F and 23F, if used as a booster dose in asplenic patients with previous PPV23 vaccination.

1. Introduction

Patients who are asplenic or hyposplenic have a greatly increased risk of severe infections with encapsulated bacteria, in particular pneumococci. Overwhelming post-splenectomy infection (OPSI) is a serious disease that can progress to fulminant sepsis and death within less than 24 h [1]. The mortality in OPSI is 50–80% despite antibiotic and intensive care treatment [2]. Pneumococci are responsible for more than 50% of the cases of OPSI [3]. After the introduction of vaccination against encapsulated bacteria in connection with splenectomy, the incidence of OPSI has decreased [4].

In the United States, guidelines from the Centers for Disease Control and Prevention (CDC), published in 1997 and updated in 2010, recommended the use of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in adults with anatomical or functional asplenia and revaccination after 5 years [5]. Whether patients should be recommended pneumococcal polysaccharide vaccine (PPV) or pneumococcal conjugate vaccine (PCV) and the possible benefits of repeated vaccinations is the subject of a current debate [6–8]. Heidelberger et al. demonstrated weaker antibody responses to a second immunization with capsular polysaccharides [9]; however, there has been concern that sensitization may induce immune tolerance [10]. While PPV induces a T-cell independent immune response, the conjugation of a protein to the pneumococcal polysaccharide leads to a T-cell dependent immune response and an immunological memory. In 2012, CDC published new guidelines for the use of PCV13 and PPV23 for adults with

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immunocompromising conditions [11]. Asplenic or immunocompromised persons who are pneumococcal vaccine-naïve should receive one dose of PCV13 followed after at least eight weeks by one dose of PPV23, and persons who have previously received ≥1 dose of PPV23 should be given a PCV13 dose ≥1 year after the last PPV23 dose was received. Furthermore, a second dose of PPV23 should be given at least five years after the first PPV23 dose and no sooner than 8 weeks after PCV13.

Since 1994, the Swedish National Board of Health and Welfare has recommended PPV23 to defined risk groups, including patients with anatomical or functional asplenia [12]. A booster dose is recommended to adults 5 to 10 years after the primary vaccination. The pneumococcal conjugate vaccine was introduced in the Swedish child immunization schedule in 2009 but there are still no official recommendations for the use of PCV in asplenic adults.

PPV23 has been shown to reduce the incidence of invasive pneumococcal disease (IPD) by 50–70% [8]. The immune response to PPV23 is adequate in asplenic patients but suboptimal in patients with immune deficiencies [13,14]. PCV has a protective effect of 90% against invasive pneumococcal disease and the 7-valent pneumococcal conjugate vaccine (PCV7) has a documented adequate immune response in asplenic children [15]. In a study of 111 asplenic adults (median age 54.8 years) who received PCV7, significant increases in serotype-specific IgG geometric mean concentrations were observed pre- to post-PCV7 for the PCV7 serotypes, though concentrations ≥0.35 μg/mL were demonstrated pre-PCV7 in a majority of participants due to prior PPV23 vaccination [16]. Results from this study further showed that, following PCV7, the percentage of asplenic individuals with serotype-specific IgG concentrations ≥1.00 μg/mL increased significantly for serotypes 4, 6B, 9V, 19F, and 23F. PCV13 is identical in formulation for the seven common serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F), but contains six additional antigens: 1, 3, 5, 6A, 19A, and 7F.

The aims of this study were to investigate the adherence to vaccination guidelines as outlined above and to investigate the immunogenicity to PCV13 in splenectomised individuals.

2. Materials and methods

2.1. Study population and data collection

All patients who underwent splenectomy at the Central Hospital Kristianstad, Sweden, during the period January 2000 to October 2012 were identified through the surgical planning database (Orbit), using ICD-10 procedure codes for splenectomy (JMA00) and abdominal splenectomy (JMA10). Further, the date of splenectomy and the underlying diagnosis leading to splenectomy were identified.

All patients received an invitation letter and were asked to complete a questionnaire regarding relevant prior vaccinations, the reason for splenectomy, possible current medications or chronic illnesses affecting the immune system. Additional information regarding the above questions was obtained from the patients' clinical records. Patients were offered individual appointments for information about the study. All patients able to give written, informed consents were eligible for inclusion in the study.

Participants completed all study visits at the Department of Infectious Diseases, Central Hospital Kristianstad, Sweden.

All data were anonymised and stored in a Microsoft Excel file. The study was approved by the regional ethics committee at Lund University, Sweden (Dnr 2013/204).

2.2. Blood specimens and antibody assays

For all participants, blood samples were collected at the time of inclusion in the study (up to two months before vaccination). The subgroup of patients who received PCV13 in this study were instructed to return for a second set of blood samples four to six weeks after vaccination. Sera (0.5 mL) were frozen at −20 °C and subsequently analysed at Statens Serum Institut, Copenhagen, Denmark.

Pneumococcal serotype-specific IgG concentrations were determined for twelve serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) included in both PPV23 and PCV13, using a luminex method based on the procedure described by Lal et al. [17].

2.3. Vaccination

All participants who had neither received PCV13 previously nor PPV23 within the last year, and without contraindications, were vaccinated with one dose PCV13 (Prevenar 13®, Pfizer). Participants with a PPV23 vaccination within the last year also received a dose of PCV13 if ≥2 pneumococcal serotype-specific IgG concentrations were below 0.35 μg/mL. PCV13 was administered as an intramuscular injection in the deltoid muscle.

2.4. Statistical analysis

The age and sex of participants vs non-participants were compared using the Chi square test.

Pneumococcal serotype-specific IgG concentrations were expressed as geometric mean concentrations (GMC) with 95% confidence intervals (CI). IgG concentrations pre- and post-PCV13 were log transformed and significance of changes were analysed using paired T-test. Subgroup analyses were performed using the Wilcoxon matched-pairs signed-rank test. Proportions of subjects with serotype-specific IgG concentrations ≥0.35, 1.00 and 5.00 μg/mL were calculated and the significance of changes pre- to post-PCV13 were tested for each serotype using an exact McNemar's test. Statistical analyses were made using Microsoft Excel 2010 and Stata® 12.0.

3. Results

3.1. Demographics, diagnoses and vaccine coverage of the splenectomy cohort

A total of 78 patients were splenectomised at the Central Hospital Kristianstad between January 2000 and October 2012. At the time of splenectomy, the median age was 61.5 years (range 11–88 years). Thirty-one of the splenectomised individuals were deceased at the start of this study. Five patients (6.4%) had died within 14 days post-splenectomy. Twelve patients had died at the hospital, and the following causes of death were identified in records: pneumonia or sepsis of unknown etiology ($n = 4$), terminal cancer ($n = 3$), haemorrhage ($n = 2$), pneumonia and septic shock caused by non-typeable *Haemophilus influenzae* ($n = 1$), multitrauma ($n = 1$), and cardiac failure ($n = 1$). Nineteen patients had died in a hospice, nursing home or at home, and the final causes of death in this group is unknown to the authors but ten of the patients had been diagnosed with metastatic cancer.

Regarding vaccination against pneumococci, 64 individuals (81.0%) had received at least one dose of PPV23 and 11 (13.9%) had been vaccinated with PCV13. Five patients had received PCV13 as a primary vaccine followed by PPV23 after 8 weeks. Twenty (64.5%) of the deceased patients had received at least one dose of PPV23 and none had received PCV13. Pneumococcal vaccination had been repeated with PPV23 and PCV13 in 17.7% and 7.7%, respectively of