Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Optimizing seroprotection against pneumococcus in children with nephrotic syndrome using the 13-valent pneumococcal conjugate vaccine

Laure F. Pittet MD [a,e,*], Klara M. Posfay-Barbe MD, MS [b], Hassib Chehade MD [c], Christoph Rudin MD [d], Alexandra Wilhelm-Bals MD [c], Maria Rodriguez [e], Claire-Anne Siegrist MD [a,f], Paloma Parvex MD [c]

[a] Department of Pediatrics, Children's Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland
[b] Pediatric Infectious Diseases Unit, Department of Pediatrics, Children's Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland
[c] Romand Unit of Pediatric Nephrology, Department of Pediatrics, University Hospitals of Geneva and Lausanne, Switzerland
[d] Department of Pediatrics, University Hospital of Basel, Basel, Switzerland
[e] Platform of Clinical Research in Pediatrics, Department of Pediatrics, University Hospitals of Geneva, Geneva, Switzerland
[f] Department of Pathology, University of Geneva, Faculty of Medicine and World Health Organization Collaborating Center for Vaccinology and Neonatal Immunology, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 10 December 2015
Received in revised form 12 August 2016
Accepted 15 August 2016
Available online xxxx

Keywords:
Idiopathic nephrotic syndrome (NS)
Immunization
Streptococcus pneumoniae
13-valent pneumococcal conjugate vaccine (PCV13)
Vaccine
Enzyme-linked immunosorbent assay (ELISA)

ABSTRACT

Background: Infections are among the main life-threatening complications in patients with nephrotic syndrome (NS), in particular with *Streptococcus pneumoniae*, the first cause of bacterial peritonitis and sepsis in these patients. This study aims to evaluate the baseline seroprotection of NS patients against *S. pneumoniae*, and immunize them with the 13-valent pneumococcal conjugate vaccine (PCV13) regardless of disease activity and previous immunization history, in order to evaluate the immunogenicity, safety profile, and effect of NS treatment on vaccine responses.
Methods: This multicentre prospective interventional study enrolled 42 children with NS at disease onset or during a regular follow-up appointment. PCV13 was administered at inclusion. Serotype-specific *S. pneumoniae* IgG titer were assessed at baseline, after immunization, and at 1 year follow-up. Vaccine safety was evaluated clinically and by urinary tests.
Results: PCV13 induced high serotype-specific IgG titers that were maintained at high levels one year after vaccination, even in children previously immunized. No serious adverse event occurred and relapse frequency was unchanged.
Conclusion: Given that high IgG titers were achieved and maintained after PCV13 vaccination, and considering the high morbidity related to *S. pneumoniae*, we propose PCV13 (re-)vaccination for all NS patients, irrespective of their previous immunization history, treatment and disease activity.

1. Introduction

Nephrotic syndrome (NS) affects mainly pre-school children with a reported incidence of 2–7 per 100,000 children and is characterized by heavy proteinuria (>1 g/m^2/day or protein/creatinine ratio >200 mg/mmol), hypoalbuminemia (<25 g/l) and the presence of edema [1]. Idiopathic NS is the most frequent cause of NS in children and may present as minimal change disease (MC) or focal glomerulosclerosis (FSGS) according to the histology. Although most patients respond to steroid treatment and therefore do not require renal biopsy, some develop steroid dependency or resistance and consequently a biopsy is performed to specify the

Abbreviations: AIM, alternative immunosuppressive medication; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; FSGS, focal segmental glomerulosclerosis; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; IQR, interquartile range; M, month; MC, minimal change disease; NS, nephrotic syndrome; OPA, opsonophagocytosis assay; OR, odds ratio; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SD, standard deviation.

* Corresponding author at: Département de l'enfant et de l'adolescent, Hôpital des Enfants, Geneva University Hospitals, 6 Rue Willy Donzé, 1211 Geneva 14, Switzerland.
E-mail address: laure.pittet@hcuge.ch (L.F. Pittet).

http://dx.doi.org/10.1016/j.vaccine.2016.08.049
0264-410X/

diagnosis and decide whether additional alternative immunosuppressive medication (AIM) is indicated.

NS is also associated with other life-threatening complications, such as infections [2]. The 1–2% annual incidence of invasive bacterial infection is probably due both to the immunosuppressive regimen and the acquired immune deficiency induced by NS. The latter can be partly explained by lymphocyte dysfunction, urinary loss of immunoglobulins and complement, and edema, which presumably predisposes to the penetration and spread of pathogens [3–5]. Impairment of the complement-dependent opsonization delays the clearance of encapsulated bacteria, such as *Streptococcus pneumoniae*, which is the most common cause of bacterial peritonitis and sepsis in these patients. Peritonitis occurs in 2–6% of patients (all pathogens included) and carries a mortality risk of 1–5% [1,6,7].

Most guidelines recommend pneumococcal immunization for NS patients; using pneumococcal conjugate vaccine (PCV), possibly followed by a dose of a 23-valent pneumococcal polysaccharide vaccine (PPSV23). PPSV23 can only be administered after the age of 2 years. It induces a T-cell-independent response and hence no memory cells. PCV, on the other hand, can be administered to children as young as 2 months and is now included in the routine immunization schedule of most countries. It is more immunogenic, and since it induces a T-cell-dependent response, memory cells are produced [8]. Previous studies have demonstrated the immunogenicity of PPSV23 in NS patients immunized at disease onset, during relapse or in remission [9–13], but only one report is available for the 7-valent PCV (PCV7), which was successfully given to NS patients in remission [14,15]. Concerning the impact of treatment on vaccine responses, a comprehensive review of the studies on PPSV23 showed that seroresponses were not altered by steroid treatment, but one study demonstrated the absence of seroresponse in two children receiving AIM [16]. As for PCV7, Liakou et al. also reported lower seroresponses in patients receiving AIM [14,15]. To our knowledge, no data exist on the immunogenicity of 13-valent PCV (PCV13) in NS patients.

This study has multiple aims: first, to evaluate NS patients' immunity against *S. pneumoniae* and investigate factors associated with seroprotection. Second, to assess PCV13 safety, in terms of local and systemic side effect, as well as the effect of vaccination on NS disease activity, given the concern that vaccination may induce NS relapses. Third, to study the immunogenicity of PCV13 in NS patients by measuring both vaccine responses and maintenance of seroprotection at a 1-year follow-up visit. Finally, to evaluate the effect of NS treatment on vaccine seroresponses.

2. Patients and methods

This multicenter prospective interventional cohort study was conducted between 2011 and 2013 in three Pediatric Centers of Swiss Universities. The parents/guardians of children aged 1 to 18-years-old with NS were approached for participation by pediatric nephrologists during a routine visit, either for disease onset, relapse or regular follow-up. Children were excluded if close follow-up was not possible. Parents of all participants signed an informed consent form at the time of study inclusion. The study was approved by the institutional review boards of all 3 university centers (CER 10-263) and was performed according to the principles of the Declaration of Helsinki.

2.1. PCV13 immunization

PCV13 (Prevenar13®, Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA; part of Pfizer, New York, NY, USA) was administered intramuscularly in the deltoid muscle at inclusion (month 0 [M0]). It contains 2.2 μg of pneumococcal polysaccharide of serotype 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, and 4.4 μg of serotype 6B, conjugated to 32 μg of the diphtheria CRM197 protein.

2.2. Evaluation of S. pneumoniae serotype-specific antibody titers

Blood samples were collected at baseline (M0), after PCV13 immunization (M3, vaccine responses) and at the 1-year follow-up visit (M12, follow-up serology). *S. pneumoniae* serotype-specific IgG titers were assessed using the enzyme-linked immunosorbent assay (ELISA) test for 6 serotypes [17] including 3 serotypes included in all pneumococcal vaccines (serotypes 14, 19F and 23F) and 3 serotypes only included in the PPSV23, but not in PCV13 (serotypes 9N, 11A and 17F). The lowest and highest limits of quantification for this assay are 0.3 mg/L and 5 mg/L, respectively, regardless of the serotype. Titers below or above this limit were reported as a value of 0.15 mg/L (half of the lowest limit) or 7.5 mg/L (1.5 times the highest limit), respectively. Titers higher than 0.3 mg/L were considered to be protective and those higher than 1 mg/L as highly protective, regardless of the serotype.

2.3. Vaccine safety monitoring

All patients were seen clinically at M1, M2, M3, M6 and M12. Disease activity was evaluated clinically and by urinary tests. Abnormal proteinuria levels and relapse were defined as a urinary protein/creatinine ratio of 20 and 200 mg/mmol or more, respectively. Identification of vaccine side-effects was assessed using standardized questions at each visit. Patients or their parents were asked to call the investigators if anything unusual was experienced during the one year follow-up.

Table 1
Children with nephrotic syndrome: characteristics at study inclusion.

		[n] (% patient)
Gender	Female	17 (40%)
Disease subtype	SSNS	39 (93%)
	SDNS	2 (5%)
	SRNS	1 (2%)
Diagnosis	MC	35 (83%)
	FSGS	6 (14%)
	DMP	1 (2%)
Diagnosis confirmed by renal biopsy		17 (40%)
Treatment at inclusion	No treatment	20 (48%)
	Steroids	15 (36%[a])
	AIM	15 (36%[a])
History of pneumococcal vaccine	Any vaccine	27 (64%)
	PCV	22 (81%[b])
	– PCV7 only	16 (73%[c])
	– PCV7 than PCV13	1 (5%[c])
	– PCV13 only	5 (23%[c])
	PPSV23	10 (37%[b])
	Both PPSV23 and PCV	5 (19%[b])
History of pneumococcal disease	Any	6 (14%)
	Pneumonia	5 (12%)
	Peritonitis	1 (2%)

AIM: alternative immunosuppressive medication (cyclosporine, mycophenolate mofetil, tacrolimus); DMP: diffuse mesangial proliferation; FSGS: focal segmental glomerulosclerosis; MC: minimal change disease; n: number of patients; PCV7: 7-valent pneumococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; SDNS: steroid-dependent nephrotic syndrome (defined as a frequency of ⩾4 relapses/year); SRNS: steroid-resistant nephrotic syndrome; SSNS: steroid-sensitive nephrotic syndrome.
[a] Eight patients were treated with both steroids and AIM.
[b] Percentage of patients with a history of pneumococcal vaccine.
[c] Percentage of patients with a history of PCV vaccine.

Please cite this article in press as: Pittet LF et al. Optimizing seroprotection against pneumococcus in children with nephrotic syndrome using the 13-valent pneumococcal conjugate vaccine. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.08.049