Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Immune response to pneumococcal conjugate vaccine in patients with systemic vasculitis receiving standard of care therapy

Per Nived [a,b,*], Johanna Nagel [a], Tore Saxne [a], Pierre Geborek [a], Göran Jönsson [c], Lillemor Skattum [d], Meliha C. Kapetanovic [a]

[a] Department of Clinical Sciences Lund, Section of Rheumatology, Lund University, Skåne University Hospital, SE-221 85 Lund, Sweden
[b] Department of Infectious Diseases, Central Hospital Kristianstad, J A Hedlunds väg 5, SE-291 85 Kristianstad, Sweden
[c] Department of Clinical Sciences Lund, Section of Infectious Diseases, Lund University, Skåne University Hospital, SE-221 85 Lund, Sweden
[d] Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, and Clinical Immunology and Transfusion Medicine, Region Skåne, Sweden

ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 10 May 2017
Accepted 16 May 2017
Available online xxxx

Keywords:
Systemic vasculitis
Pneumococcal vaccination
Pneumococcal conjugate vaccine

ABSTRACT

Aim: To study the effect of standard of care therapy on antibody response and functionality following immunization with 13-valent pneumococcal conjugate vaccine (PCV13) in patients with primary systemic vasculitis compared to healthy controls.
Methods: 49 patients with vasculitis and 49 controls received a single dose (0.5 ml) PCV13 intramuscularly. Ongoing treatments: azathioprine (AZA; $n = 11$), cyclophosphamide (CYC; $n = 6$), methotrexate (MTX; $n = 9$), rituximab (n = 3); anti-TNF ($n = 2$), mycophenolate mofetil ($n = 2$), prednisolone alone ($n = 15$) and no active treatment ($n = 2$). Specific antibody concentrations for serotypes 6B and 23F were determined using ELISA and opsonophagocytic activity (OPA) assay (23F) was performed, on serum samples taken immediately before and 4–6 weeks after vaccination. Proportion of individuals with putative protective antibody concentration (≥1.0 μg/mL) and positive antibody response (≥2-fold increase from prevaccination concentration) for both serotypes were calculated and groups were compared.
Results: At baseline, 6 patients (12%) and 12 controls (24%) had protective antibody levels for both serotypes. After vaccination, antibodies increased for both serotypes in patients and controls ($p < 0.001$), 32 patients (65%) and 35 controls (71%) reached protective level for 6B, and 32 patients (65%) and 37 controls (76%) for 23 F. Compared to controls, patients had lower prevaccination geometric mean concentration (23F, $p = 0.01$) and a numerical trend towards lower prevaccination level (6B) and postvaccination levels (both serotypes). Patients with prednisolone alone had lower prevaccination OPA ($p < 0.01$) compared to controls. OPA increased after vaccination in both patients and controls ($p < 0.001$), but improvement was better in controls ($p = 0.001$). AZA, CYC or MTX, but not prednisolone alone, tended towards a lower proportion of patients reaching protective antibody levels ($p = 0.06$), compared to controls.
Conclusions: Pneumococcal conjugate vaccine was safe and immunogenic in patients with established vasculitis. Treatment with DMARDs, mostly AZA, CYC and MTX but not systemic prednisolone may impair antibody response.
Trial registration. ClinicalTrials.gov Identifier: NCT02240888. Registered 4 September, 2014

1. Introduction

Modern immunosuppressive therapy greatly improves the survival of patients with systemic vasculitis, but comes at the expense of potentially serious infectious complications [1]. Infection is the most common cause of death within the first year of diagnosis in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and remains a major cause of both mortality and morbidity several years after disease onset [2–4]. Vaccines play an important role in

Abbreviations: PPV23, pneumococcal polysaccharide vaccine; PCV7, pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease; ANCA, antineutrophil cytoplasmic antibody; PR3-ANCA, ANCA directed against proteinase 3; MPO-ANCA, ANCA directed against myeloperoxidase; P-ANCA, perinuclear/nuclear staining; GMC, geometric mean Ab concentrations; ARR, antibody response ratio; ELISA, enzyme-linked immunosorbent assay; OPA, opsonophagocytic activity; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate; AZA, azathioprine; CYC, cyclophosphamide; anti-TNF, tumour necrosis factor inhibitors.

* Corresponding author at: Department of Infectious Diseases, Central Hospital Kristianstad, J A Hedlunds väg 5, SE-291 85 Kristianstad, Sweden.
E-mail address: per.nived@med.lu.se (P. Nived).

http://dx.doi.org/10.1016/j.vaccine.2017.05.044
0264-410X/

the prevention of such infections, but there is concern that immunosuppressive therapy may lead to impaired immune responses. *Streptococcus pneumoniae* (pneumococcus) is one of the leading vaccine-preventable causes of serious infections, e.g. pneumonia, sepsis and meningitis. Invasive pneumococcal disease (IPD) is defined as an infection confirmed by the isolation of pneumococci from a normally sterile site (e.g. the bloodstream). Immunocompromised patients have both increased incidence and mortality of IPD, compared to healthy controls [5,6], and in a recent study from Canada, persons immunocompromised by underlying disease or treatment comprised 28% of all IPD cases [7]. Elevated risks of IPD have been demonstrated in patients previously hospitalized with immune-mediated diseases, for example a 5 times greater risk in patients with polyarteritis nodosa than an age-matched healthy population [8]. In patients with giant cell arteritis, the rate of severe infections during the first year after diagnosis was doubled, compared to an age and sex-matched general population, and a prednisolone dose of >10 mg/day after 1 year of treatment was associated with increased infection-related mortality (hazard ratio 4.6) [9].

Twenty-three-valent pneumococcal polysaccharide vaccine (PPV23) consists of capsular polysaccharides of 23 common IPD-causing serotypes, and in pneumococcal conjugate vaccines (PCVs) a subset of these (e.g. 13 serotypes in PCV13) have been covalently linked to a carrier protein, consisting of a non-toxic mutant of the diphtheria toxin. In contrast to the T cell-independent reactions caused by pneumococcal polysaccharide vaccine (PPV), PCV has been demonstrated to elicit T cell-dependent immune reactions stimulating the proliferation of memory B cells, thus improving immunological memory [10]. In a large trial from the Netherlands, immunocompetent adults (≥65 years of age) received either PCV13 or placebo and a 75% efficacy of PCV13 in preventing IPD was shown [11]. Little is known about the immunogenicity and efficacy of pneumococcal vaccination using pneumococcal conjugate vaccine in immunocompromised persons. Randomized trials of HIV-infected patients in Malawi and Uganda, have indicated that PCV7, but not PPV23, was effective in preventing IPD [12,13]. In the United States, the Centers for Disease Control and Prevention (CDC) recommends that adults with immunocompromising conditions, asplenia, cochlear implants and cerebrospinal fluid leaks, receive immunization with a dose of PCV13, followed in at least 8 weeks by a dose of PPV23 [14].

Our group have previously reported that antibody responses to PPV23 [15] and 7-valent pneumococcal conjugate vaccine (PCV7) [16] are impaired in chronic arthritis patients during treatment with methotrexate (MTX), but not with tumour necrosis factor (TNF) inhibitor monotherapy. We did not observe any difference in the immunogenicity of PCV7 compared to PPV23, in patients with rheumatoid arthritis treated with immunomodulating drugs [17]. Morgan et al. recently reported that patients with systemic vasculitis were safely vaccinated with PCV7, but vaccine responses were highly variable with a median antibody response rate of 46% of patients responding to each antigen, using the threshold 0.35 μg/mL [18]. To date there is little knowledge regarding the immunogenicity of PCV13 in individuals with systemic vasculitis. The aim of this study was to investigate the effect of standard of care therapy on antibody (Ab) response following immunization using 13-valent pneumococcal conjugate vaccine (PCV13) in patients with systemic vasculitis compared to healthy controls.

2. Material and methods

2.1. Patient inclusion

Adult patients who had established systemic vasculitis diagnoses and were regularly monitored at the Department of Rheumatology in Lund and Malmö at Skåne University Hospital were eligible for this study. Patients had to fulfil the American College of Rheumatology criteria for different systemic vasculitides [19]. Ongoing treatment at the time of vaccination was noted as a basis for later patient stratification. Patients were excluded from the study if anti-rheumatic treatment had been changed within 4 weeks before and 6 weeks after vaccination, if they had been previously vaccinated with PPV23 within 1 year, had a history of allergic reaction at previous vaccinations, were pregnant, or had an ongoing infection. Healthy control subjects were recruited from the staff and relatives at the department of Rheumatology in Lund.

2.2. Vaccination protocol

All participants received a single 0.5 mL dose of PCV13 (Prevenar 13®, Pfizer) administered as an intramuscular injection in the deltoid muscle by a rheumatology nurse. At the time of vaccination, a clinical examination was performed by a rheumatologist and data were collected on disease and treatment characteristics and previous vaccinations using a structured protocol. All patients were encouraged to monitor and report possible adverse or unexpected effects of the vaccination, as well as changes in rheumatic disease. Adverse events (AEs) and adverse drug reactions (ADRs) were recorded according to the Guideline for Good Clinical Practice and Clinical Safety Data Management [20].

2.3. Pneumococcal serotype-specific IgG measurement

Serum samples were collected immediately before and 4–6 weeks after vaccination. Serotype-specific IgG antibody concentrations for pneumococcal serotypes 6B and 23F, both included in PCV13, were quantified using enzyme-linked immunosorbent assay (ELISA) meeting World Health Organization (WHO) standard, described previously [21]. The method was executed with two minor modifications. In short, ELISA plates were coated with 1 μg pneumococcal capsular polysaccharides (PS) 6B or 23F. In order to diminish nonspecific binding to capsular PS, dilutions of human sera were absorbed with pneumococcal cell wall PS, and then added to the ELISA plates. In contrast to the WHO protocol, 22F PS was not used for absorption. Goat anti-human IgG antibodies, conjugated with alkaline phosphatase, followed by addition of the substrate, nitrophenyl phosphate, were used for the detection of serotype-specific antibodies (anti-6B and anti-23F IgG). The optical density, proportional to the amount of anti-6B and anti-23F IgG present in the serum, was measured with an ELISA plate reader at 405 nm. The assay was calibrated with international reference serum 89SF, that was kindly provided by Dr. C. Frasch, Bethesda, MD, USA [22]. This is also a modification to the latest WHO protocol which utilizes reference serum 007sp [21]. The lower limit of detection was 0.01 mg/L.

2.4. Opsonophagocytic activity (OPA) assay

OPA assay was performed for pneumococcal serotype 23F. The method has been described by Martinez et al. [23] and was executed with some modifications. The analysis was conducted with samples from 48 systemic vasculitis patients, and 36 healthy controls included in this study.

Pneumococci of serotype 23F obtained from Statens Serum Institut in Copenhagen, were cultured, killed by addition of glutaraldehyde and subsequently frozen in aliquots as described previously [24]. Killed bacteria were thawed and incubated for 20–30 min in the dark with FITC (fluorescein isothiocyanate; F7250, Sigma-Aldrich, St. Louis, MO, USA) in sodium carbonate buffer, subsequently washed 3 times in VBS-CaMg (veronal-buffered saline with 0.15 mM Ca^{2+} and 0.5 mM Mg^{2+}).

Please cite this article in press as: Nived P et al. Immune response to pneumococcal conjugate vaccine in patients with systemic vasculitis receiving standard of care therapy. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.05.044