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Pneumococcal vaccination in patients with systemic lupus erythematosus: A multicenter placebo-controlled randomized double-blind study

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ABSTRACT

Background: Invasive pneumococcal disease and respiratory tract infections are both frequent and severe in patients with systemic lupus erythematosus (SLE). This study aimed to compare the immunological efficacy and safety of pneumococcal vaccination with the 23-valent polysaccharide (PPS) vaccine alone to a sequential immunization with the 7-valent pneumococcal conjugate (PnCj) vaccine followed by PPS in patients with SLE and stable diseaase.

Methods: Multicenter randomized placebo-controlled double-blind trial: PPS vaccine alone (placebo-PPS group) or PnCj vaccine followed by PPS vaccine (PnCj-PPS group) 24 weeks later. The primary endpoint was the rate of responders at week 28 to at least 5 of the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) shared by both PPS and PnCj. Pneumococcal IgG antibodies' opsonophagocytic activity (OPA) were also assessed.

Results: Twenty-five patients in the placebo-PPS group and 17 in the PnCj-PPS group were included in a modified intention-to-treat analysis. The primary endpoint was reached in 72% (18/25) in the placebo-PPS and 76% (13/17) in the PnCj-PPS group ($p = 0.75$). There was no difference in the rates of responders with OPA. At week 52, 13/18 (72%) patients in the placebo-PPS group and 10/13 (77%) patients in the PnCj-PPS group ($p = 0.77$) that met the primary endpoint at week 28 were still responders to $\geq$5/7 serotypes shared by both PPS and PnCj vaccines. Nine SLE flares were reported in 6 patients (4 in the placebo-PPS and 2 in the PnCj-PPS groups respectively, $p = 0.70$).

Conclusion: Sequential administration of PnCj vaccine followed by PPS vaccine is safe and shows short-term immunological efficacy in patients with SLE but was not superior to the PPS vaccine alone.

Conclusion: Trial registration: www.clinicaltrials.gov, NCT NCT00611663

1. Introduction

Despite improvement of survival over the last decades, patients with systemic lupus erythematosus (SLE) have an increased mortality rate as compared with the general population [1,2]. Infections are one of the leading causes of death in this context [2–4].

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The excess risk of infections reported during the course of SLE is likely to be multifactorial, with factors (*e.g.* lymphopenia, functional asplenia) inherent to SLE [5] and others (*e.g.* the use of glucocorticoid and/or immunosuppressants) [6,7] acquired during the course of the disease. Both retrospective [8–11] and prospective studies [7] underline that invasive pneumococcal disease and respiratory tract infections are both frequent and severe in the context of SLE. Moreover, pneumonia is the leading cause of avoidable hospitalizations in this setting [12]. Preventing infections is necessary in order to improve both short and long-term prognoses.

Pneumococcal immunization is recommended in immunocompromised hosts [13,14] and in patients with autoimmune inflammatory rheumatic diseases (including SLE), regardless of their level of immunosuppression [15,16]. Previous studies have shown that the 23-valent pneumococcal polysaccharide (PPS) vaccine alone is safe in SLE patients [17–24] but data regarding the short-term immunogenicity of such vaccination are conflicting, and some studies report on a decreased rate of responders among SLE patients as compared to the general population. Moreover, since polysaccharide antigens induce specific antibody production in a T-lymphocyte-independent manner, the 23-valent PPS vaccine is associated with poor long-term immunogenicity and is unable to prime a booster response in case of subsequent re-exposure [25]. The pneumococcal conjugate (PnCj) vaccine, initially developed for children aged <2 years (who fail to mount an adequate immune response to the 23-valent vaccine alone), has led to a significant decrease of pneumococcal infections in young infants [26]. In the latter vaccine, polysaccharide antigens are linked to a protein-carrier that stimulates T-helper cells and thus enhances the vaccine's immunogenicity. Previous studies in immunocompromised hosts (*e.g.* HIV infection, Hodgkin's lymphoma, solid organ transplantation) [27–31] have shown that the PnCj vaccine was associated with increased immunogenicity as compared to vaccination with the PPS vaccine alone.

Neither immunization with the PnCj vaccine nor the sequential administrations of both PnCj and PPS vaccines (combined strategy) have been assessed in patients with SLE. The primary objective of this study was, in adult patients with SLE and stable disease, to compare the immunological efficacy and safety of pneumococcal vaccination with the PPS vaccine alone to a vaccination schedule combining PnCJ and PPS vaccines.

2. Patients and methods

2.1. Study population

Patients aged between 18 and 75 years with SLE (defined by the 1997 American College of Rheumatology classification criteria) [32] and stable disease (*i.e.* no modification of the treatment within 2 months before inclusion) were enrolled. Eligible patients had to be treated with at least one of the following drugs: (1) hydroxychloroquine, (2) ≥5 mg of daily prednisone or equivalent, (3) systemic glucocorticoids at any dose in combination with at least one immunosuppressant (mycophenolate mofetil, azathioprine or methotrexate). Patients were excluded if they met one of the following criteria: HIV, HBV or HVC infection; medical history of allergy to any vaccine component; pneumococcal vaccination in the 5 past years; vaccination (any vaccine) in the previous month; intravenous immunoglobulin infusion within three months; splenectomy; bleeding disorders with contraindication to intramuscular injections; active malignancy; cirrhosis; acute infection in the previous month; treatment with rituximab in the previous year. Women of childbearing age without contraception, with a positive urine β-hCG test before vaccination or with a desire of pregnancy within 7 months after inclusion were excluded.

2.2. Study design

The Vaccination in Lupus (VACCILUP, ClinicalTrials.gov NCT00611663) study was a Phase IIb multicenter randomized double-blind placebo-controlled trial comparing two pneumococcal vaccination strategies in patients with SLE. Patients were centrally randomized (1:1) to receive either (1) sequential administration of both the 7-valent PnCj vaccine at baseline followed by the 23-valent PPS vaccine at week 24 (PnCj-PPS group) or (2) vaccination with placebo at baseline and the 23-valent PPS vaccine at week 24 (placebo-PPS group). Randomization was stratified by centers, by the use of immunosuppressants (other than glucocorticoids) and by chronic kidney disease (defined by an estimated GFR <80 ml/mn). The "Unité de Recherche Clinique" centrally managed the randomization that was established using a computerized generator that used block size of 4. The study was conducted in 8 rheumatology and internal medicine departments in France. The protocol complied with the Declaration of Helsinki and French law for biomedical research and was approved on the 16th October 2007 by the national Ethic Committee "Comité de Protection des Personnes Ile-de France III" (approval n° 2477). Written informed consent was obtained from each patient.

Patients underwent physical examination at inclusion, weeks 4, 24, 28 and 52. Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [33] and physician's global disease assessment. Blood samples were collected from all patients at each study visit and tested for routine biochemical, hematological tests (including CD4/CD8 cell counts) and analysis of the immune response induced by the pneumococcal vaccination.

2.3. Vaccines

Either Pneumo 23® or Pneumovax 23® (Sanofi Pasteur MSD) were used as 23-valent PPS vaccines targeting serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F of *Streptococcus pneumoniae*. The PnCj vaccine, Prevenar® (Pfizer), is a pneumococcal 7-valent vaccine targeting serotypes 4, 6B, 9V, 14, 18C, 19F, 23F of *Streptococcus pneumoniae* in which antigens are conjugated to mutant diphtheria protein CRM_{197}. Vaccines and placebo (serum glucose 5%, 0.5 mL) were administered by intramuscular injections in the deltoid muscle.

2.4. Immunogenicity assessments

Immunogenicity measurements were performed in a central laboratory (Cochin hospital) blinded to the trial arm. IgG antibody concentrations for the 7-pneumococcal serotypes shared by both PPS and PnCj vaccines (4, 6B, 9V, 14, 18C, 19F and 23F) were measured at each study visit using a modified enzyme linked immunosorbent [www.vaccine.uab.edu] [34]. Briefly, 96-well plates (Corning, Inc., Corning, NY) were coated with a serotype-specific pneumococcal polysaccharide antigen (American Type Culture Collection, Manassas, VA) and incubated 5 h at 37 °C. Reference sera (007sp), quality control sera, or patient specimens were pre-absorbed with 5 μg/ml pneumococcal C-polysaccharide (Statens Serum Institut, Copenhagen, Denmark) and 10 μg/ml serotype 22F capsular polysaccharide (American Type Culture Collection) for 30 min at room temperature before being serially diluted. After washing plates, serially diluted serum was added and plates were incubated at room temperature for 2 h. Plates were then washed, and alkaline phosphatase-conjugated goat anti-human immunoglobulin G (IgG; Southern Biotech, Birmingham, AL) was

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