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Short communication

Response to pneumococcal vaccine in interstitial lung disease patients: Influence of systemic immunosuppressive treatment

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ABSTRACT

Background: Interstitial lung diseases (ILD) are severe respiratory diseases, and ILD patients are treated with corticosteroid and immunosuppressive agents. However, it is unclear whether these medications influence the response of pneumococcal vaccine.
Objectives: We examined the immunogenicity of pneumococcal vaccines (PPSV23 and PCV13) in ILD patients undergoing immunosuppressive treatment.
Methods: ILD patients who were regularly followed at the outpatient clinic were enrolled. Sera were collected before and 4–8 weeks after vaccination. Serotype-specific immunoglobulin G (IgG) concentrations against pneumococcal serotype 19F were measured by ELISA.
Results: IgG concentrations to serotype 19F were increased in all groups in response to the vaccine. Both PCV13 and PPSV23 induced IgG concentrations in patients immunized for the first time. Response rates for the ILD group were comparable with those for the ILD group undergoing corticosteroid therapy. Only idiopathic pulmonary fibrosis patients undergoing immunosuppressive therapy had a significantly lower response.

1. Introduction

Interstitial lung disease (ILD) comprises a broad and heterogeneous spectrum of pulmonary parenchymal disorders of known and unknown causes [1]. Idiopathic ILDs include idiopathic interstitial pneumonias (IIPs) such as idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, acute interstitial pneumonia, idiopathic lymphoid interstitial pneumonia, and cryptogenic organizing pneumonia. ILD can also present as a manifestation of an underlying systemic illness, such as in connective tissue and vascular disease-related interstitial pneumonia (CVD-IP) or sarcoidosis, and can also result from occupational, environmental, or drug exposures [pneumoconiosis, chronic hypersensitive pneumonia (CHP) and drug-induced interstitial lung disease (DILD)]. ILD patients treated with corticosteroid and immunosuppressive agents sometimes contract severe respiratory infections. Furthermore, the phenomenon of "acute exacerbation" can worsen the clinical course of fibrotic ILD, which is in part associated with infections.

Streptococcus pneumoniae infection is responsible for substantial mortality and morbidity among adults aged >65 years or those with underlying chronic or immunosuppressive conditions. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommend the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugated vaccine (PCV13) for invasive pneumococcal disease prevention in at-risk populations [2]. PPSV23 was approved in 1988, however, vaccination rate was about 25% in Japan [3]. On the other hand, the extended use of PCV13 in adults aged 65 and older was approved in June 2014. Despite of these two vaccines being available for elderly, the national immunization program launched for the elderly aged 65 and older on October 1, 2014 only subsidized PPSV23 [4]. The elderly population eligible for the subsidized PPSV23 inoculation for the 1st year are those aged 65, 70, 75, 80, 85, 90, 95 and ≥100. While from the 2nd year to the 5th year, those who will age 65, 70, 75, 80, 85, 90, 95 and 100 will receive the same subsidized inoculation. The voluntary PCV13

Abbreviations: CHP, Chronic hypersensitive pneumonia; DILD, Drug-induced interstitial lung disease; IIP, Idiopathic interstitial pneumonia; ILD, Interstitial lung disease; IPF, Idiopathic pulmonary fibrosis; PCV13, 13-valent pneumococcal conjugated vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RA, Rheumatoid arthritis; WHO, World Health Organization.

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inoculation is recommended in ≥6 months before PPSV23 or ≥1 year after PPSV23. The elderly persons who have previously been inoculated with PPSV23 can re-inoculate PPSV23 voluntary after ≥5 years have passed.

Respiratory disease is a risk factor of pneumococcal diseases [5]. Immunization with pneumococcal vaccine has been recommended for several years for patients with chronic respiratory diseases including chronic obstructive pulmonary disease (COPD) [6]. In children with juvenile idiopathic arthritis, the immunogenicity of pneumococcal vaccine was lower in anti-TNF treatment patients [7]. In patients with nephrotic syndrome, steroids did not influence the vaccination response, as in patients with steroid-dependent asthma and COPD [6,8,9]. In rheumatoid arthritis patients, steroids did not influence the vaccination response, but MTX reduced the vaccination response [10]. However, little is known about vaccination response in ILD patients.

We describe the immunogenicity of pneumococcal vaccines (PPSV23 and PCV13) in ILD patients undergoing immunosuppressive therapy. We determined the serum concentrations of serotype-specific IgG using ELISA in control patients without respiratory diseases and ILD patients with or without corticosteroid and/or immunosuppressive agents.

2. Patients and methods

2.1. Ethical approval, study protocol, and sampling

Adult patients with ILD, including IPF, IIPs (except IPF), CVD-IP, DILD, and CHP, who were regularly followed at the outpatient clinic at Sapporo Medical University Hospital, were consecutively approached and invited to participate in this open-label study. Patients without pulmonary diseases who visited the SANWA clinic were included as controls. Exclusion criteria were (1) inability to give informed consent and (2) receipt of PPSV23 within one year. The participants were followed up for 12 months.

All participants met hospital ethics board approval (approval number 262-69) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to initiation of any protocol-specific study procedure. All respiratory physicians of ILD patients explained the eligibility of pneumococcal vaccination. In Japan, PCV13 is not acceptable in patients with ILD aged 6–64 years; however, PPSV23 is acceptable in those with ILD aged >2 years. Participants who aged 65, 70, 75, 80, 85, 90, 95 and ≥100 were recommended PPSV23 and ILD patients who aged ≤64 were recommended PPSV23. Participants who aged others were recommended PCV13 or PPSV23. Participants were enrolled from October 1st 2014 to September 31st 2015.

Overall, 126 of 218 ILD patients and 93 participants without pulmonary diseases were enrolled in the study. ILD patients were separated into two groups: those with and without immunosuppressive therapy including daily systemic corticosteroids.

2.2. Vaccines

We used commercially available PPSV23 (Pneumovax NP, Merck Sharp & Dohme Corp., Tokyo, Japan) containing 25 μg each of 23 capsular polysaccharide types and PCV13 (Prevnar 13, Pfizer, Tokyo, Japan) containing 2.2–4.4 μg each of 13 capsular polysaccharide types conjugated to a nontoxic variant of diphtheria toxin known as CRM197.

2.3. Elisas for serotype-specific IgG

Sera were collected prior to and 4–8 weeks after vaccination and stored at −80 °C until tested. To measure serotype-specific IgG concentrations against pneumococcal serotype 19F, we performed ELISA using the World Health Organization (WHO) protocol (007sp) [11]. The standard procedure was performed using the international reference serum, 007sp (kindly supplied by Dr. Mustafa Akkoyunlu, FDA, USA). Purified polysaccharide of serotype 19F and 22F was commercially purchased. To improve the specificity of the assay, a pneumococcal cell wall polysaccharide (C-PS) and 22F polysaccharide pre-absorption step was performed on the samples. Each sample was measured in triplicate and calculated as mean value.

2.4. Monitoring adverse effects

Adverse events that occurred over a 4- to 8-week follow-up period after vaccination were recorded. Systemic adverse effects included fever, headache, myalgia, asthenia, and fatigue. Local adverse events included pain/tenderness, swelling/induration, and erythema at the injection site.

2.5. Statistical analysis

To assess PPSV23 and PCV13 immunogenicity in each treatment group, IgG concentrations before and after vaccination were transformed into logarithmic values. All statistical analyses were performed using JMP 13.0 (SAS Institute, Inc, Cary, NC, USA).

3. Results

3.1. Clinical characteristics

Overall, 126 ILD patients and 93 participants without pulmonary diseases were enrolled (Fig. 1). First-time vaccination occurred in 100 ILD patients and 50 control subjects (Table 1A). All control subjects were vaccinated with PPSV23, and ILD patients were vaccinated with PPSV23 or PCV13, after physicians explained this study to the patients by written form and the patients agreed to participate. ILD with immunosuppressant (ILD IS) group was treated with corticosteroid alone or a combination of corticosteroid and immunosuppressant including cyclosporine A, tacrolimus, cyclophosphamide, methotrexate, azathioprine, and etanercept. Compared with the ILD group, the ILD IS group was significantly female-dominant (P = 0.0254) (Table 1B). Eight of 37 IPF patients (21.6%), 14 of 31 IIP (excluding IPF) patients (45.1%), and 23 of 28 CVD-IP patients (82.1%) received immunosuppressive therapy. The mean and median amount of PSL intake in the ILD IS group was 7.95 mg and 7.5 mg, respectively. Of 53 ILD patients, 40 received PPSV23, 13 received PCV13. Of 47 ILD IS patients, 29 received PPSV23, and 18 received PCV13.

The PPSV23/PCV13 ratio of ILD and ILD IS patients was 40/13 and 29/18, respectively. The PPSV23/PCV13 ratio was not statistically different (P = 0.1935, by Fisher's exact test).

3.2. Serotype-specific IgG concentrations

After vaccination, serotype-specific IgGs to pneumococcal serotype 19F were significantly increased in both the control and ILD groups (P < 0.001) (Table 2A). The median increases were ≥2-fold, and there was no statistically significant difference in either group (P = 0.2396), indicating that serotype-specific IgG concentration in vaccinated ILD patients and controls was elevated.

ILD patients were separated into two groups: those with and without immunosuppressive therapy (Table 2B). Serotype-specific IgGs to pneumococcal serotype 19F were significantly increased in both ILD without IS and ILD with IS groups (P < 0.001). Response rates for the ILD group were comparable with those for the ILD IS

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