CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

The prevention of pneumococcal infections

Clin Exp Vaccine Res 2016;5:3-5
http://dx.doi.org/10.7774/cevr.2016.5.1.3
pISSN 2287-3651 • eISSN 2287-366X

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Received: December 15, 2015
Revised: December 20, 2015
Accepted: December 25, 2015

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No potential conflict of interest relevant to this article was reported.

Streptococcus pneumoniae causes considerable number of diseases like pneumonia, bacteremia or sepsis, meningitis, otitis media, sinusitis, peritonitis, endocarditis, osteomyelitis, septic arthritis, and soft tissue infection [1-3]. According to the Korean statistics of death, 12,021 people died of pneumonia during the year 2014, mortality is 23.7 per 100,000 people, accounting for 4.5% of deaths, which meant the fifth frequent cause of mortality in Korea [4]. However, the morbidity and mortality of pneumonia caused by *S. pneumoniae* was not known because the national surveillance was not yet performed. Woo et al. [2] investigated the 588 patients with pneumonia admitted in University Hospitals and co-organized with the Korean Society of Infectious Diseases, which revealed the etiological agents in 225 patients (38.3%). *S. pneumoniae* was identified in 57 of 225 patients (21.7%). Average length of hospital stay was 13.4 days, 61 cases (10.4%) received intensive care, 42 died and mortality was 7.1%. Six patients died of pneumococcal pneumonia, mortality rate was 14% (6/42) [2-4].

For prophlaxis of pneumococcal infections and pneumonia, there are currently two types of pneumococcal vaccine available under license: pneumococcal polysaccharide vaccines (PPV23) and pneumococcal conjugate vaccines (PCV13) [5-9].

PPV23 is a capsular polysaccharide vaccine containing 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F), by which of 90% of invasive pneumococcal infections were caused. With neutralizing antibodies to induce an IgG anticapsular antibody and an opsonic effect associated with phagocytosis PPV23 represents the preventive effect. The unconjugated polysaccharide vaccine produced antibody by T cell–independent immune response [5-9]. Since the antibodies under two years of age who are still immature development of the immune system was not produced properly, PPV23 has very little effect for children under 2 years of age.

Antibodies produced in more than 80% of adults 2-3 weeks later, but the antibody production rate for the 23 serotypes is not constant. After vaccination antibody titer continued for at least 5 years, but in the patients with the underlying diseases it continued less than 5 years. The protective effect was reported in healthy adults less than 55 years of age compared to non-vaccinated adults. The effect in high-risk adults and adults over 65 years old was in controversy. It was not effective in preventing the pneumococcal infections of the serotypes not contained in the vaccine. The PPV23 is indicated for the older adults (>65 years of age) and adults or children who have increased risk for pneumococcal diseases such as splenic dysfunction, chronic renal failure, nephritic syndrome, chronic heart diseases, chronic lung diseases, diabetes mellitus, chronic alcoholics, chronic liver disease, sickle cell disease, malignancies, immune-

suppresive condition including human immunodeficiency virus disease, and cerebrospinal fluid leaks [5-10].

Yong and Shin [10] reported a geometric mean of the antibody after PPV23 vaccination was increased in 46%-84% in the adults over the age of 50. Chang et al. [11] reported that increase in immunogenicity was observed in 66% among the children (>2 years of age).

PCV13 is 13-valent pneumococcal vaccine (includes serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), to which a non-toxic variant of diphtheria toxin (cross-reactive material, CRM197) is conjugated. The vaccine induced T cell–dependent response, good antibody response, and immunological memory even in infancy and childhood [6,8,9,12,13]. Pneumococcal conjugate vaccine inhibits the acquisition of vaccine strain, affects the normal flora of the nasopharynx [14-17]. Conjugate vaccine reduced the pneumococcal otitis media, PCV13 suppressed the spread of *S. pneumoniae* in the community [12,13]. The reductions in disease burden reported among nonvaccinated adults are due to decreases in vaccine-serotype disease and reduced transmission of vaccine serotype from children. That is in other words the herd immunity

The efficacy of PCV13 is to reduce invasive pneumococcal disease caused by vaccine serotypes thant is to say invasive strains. The moderate reduction in pneumococcal carriage rates by PCV13, and a substantial decrease of vaccine-serotypes with increase of non-vaccine serotypes were reported [16,17].

Reducing the occurrence of pneumococcal pneumonia in developing countries, which showed the decreased incidence of radiological pneumonia, was one of the important effect of conjugate vaccines. The vaccine serotypes were usually antibiotic resistant. The conjugate vaccines reduced the carriage of antibiotic-resistant *S. pneumoniae* strains in children [12,13,18,19].

PCV-13 prevent the introduction of antibiotic resistant vaccine-serotypes, and vaccine-serotypes decreased compared to the non-vaccinated group on childhood vaccinations. The selective pressure in the vaccinated group is low compared to the non-vaccinated group due to the possibility of obtaining a resistant bacteria is decreased and less use of antibiotics [8,13,17].

The issue on children conjugate vaccination was the increase in resistant disease caused by serotype 19A, which is a common cause of respiratory tract infections [19,20]. The increase in resistance in serotype 19A or non-vaccine serotypes is an issue to be solved. This vaccine has limited serotype coverage, replacement phenomena.

In the non-invasive infection such as nasopharyngeal colonization reduction of vaccine serotypes and non-vaccine serotypes increase were observed after vaccination. The result of unwanted effects of the vaccine is the replacement phenomenon [5,6,9,12,13].

Chemoprophylaxis was used for patients with splenic dysfunction and sickle cell diseases. Oral penicillin V (twice daily 125 mg doses for children <5 years or 250 mg doses for those ≤5 years) was used for pneumococcal infection.

The chemoprophylaxis became not useful because penicillin-resistant strains increased. Isolation precautions are not currently recommended for patients with pneumococcal disease.

In brief, PPV23 contains T cell–independent antigens which stimulate mature B lymphocytes and produce an effective antibody response. However, T lymphocytes are not involved which leads to an absence of immunological memory and lack of an anamnestic response on challenge. The 23-valent vaccine is reported to be effective in older children and adults, and is currently recommended for high-risk patients such as hyposplenic patients and the general elderly population. PPV23 provides protection against ten additional serotypes, which is one of the advantage. PPV23 appears cost effective for elderly patients PCV13 has high efficacy against radiological pneumonia and invasive pneumococcal disease, acute otitis media, reduces the nasopharyngeal colonization rate of vaccine strain, and provides herd immunity.

PCV13 may also provide an effective new tool to reduce disease caused by drug-resistant strains of pneumococci. But, this vaccine has limited serotype coverage, replacement phenomena. In addition, the possibility of the spread and acquisition of virulent non-vaccine serotypes may be a real threat which must be monitored by continued surveillance.

The new vaccine candidates including more serotypes or protein-based pneumococcal will offer the potential advantage of protection in the near future.

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