New Drug Review

Recent Developments and Future Directions of Pneumococcal Vaccine Recommendations

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ABSTRACT

Purpose: The goal of this article was to review the key clinical trials that resulted in the recent recommendation from the Advisory Committee on Immunization Practices (ACIP) to vaccinate all adults aged ≥65 years with the 13-valent pneumococcal polysaccharide conjugate vaccine (PCV13) in addition to the previously recommended 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Methods: Pertinent articles were identified through searches of EMBASE and MEDLINE by using the terms *pneumococcal polysaccharide conjugate vaccine*, *pneumococcal vaccine*, and *PCV13*. Searches were limited to articles published between January 1, 2013, and January 31, 2015, and were limited to clinical trials. Resources from the Centers for Disease Control and Prevention's ACIP recommendations and cited references were also reviewed.

Findings: Recent clinical trials have focused on the order of administration of PPSV23 and PCV13, comparisons in immunogenicity of PPSV23 and PCV13, and efficacy of PCV13 in adults aged ≥65 years. Immunogenicity trials have shown that PCV13 elicits an equal or greater immune response than PPSV23 for most of the serotypes that both vaccines share. The evidence suggests that PCV13 should be administered before PPSV23 when possible. Most recently, clinical data demonstrated the efficacy of PCV13 in adults aged ≥65 years.

Implications: Recent randomized clinical trials and disease trends have prompted the ACIP to recommend that all adults aged ≥65 years receive a single dose of PCV13. This is in addition to the previous recommended single dose of PPSV23 in the same population. The ACIP and the Centers for Disease Control and Prevention plan to monitor disease trends and clinical data to determine if this recommendation will need to be changed in the future. (*Clin Ther*. 2015;37:928–934)

Key words: pneumococcal, vaccine, immunization, pneumonia.

INTRODUCTION

Community-acquired pneumonia (CAP) causes significant morbidity and mortality in the United States. It results in as many as 400,000 hospitalizations annually and is associated with a case fatality rate of 5% to 7%.[1,2] *Streptococcus pneumoniae* causes 25% to 40% of CAP cases in adults, making it the leading cause of this disease. In addition, *S pneumoniae* bacteria cause invasive pneumococcal disease (IPD) when the bacteria infect the spinal cord fluid and blood, resulting in meningitis and bacteremia.[3] The incidence and mortality associated with pneumonia increase as a person ages.[4,5]

Many serotypes of *S pneumoniae* exist, and a number of these serotypes can be found in 2 existing pneumococcal vaccines. The 2 currently available are the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal polysaccharide conjugate vaccine (PCV13). The first polysaccharide pneumococcal vaccine was licensed in 1977, and the first polysaccharide conjugate vaccine was licensed in 2000 (Figure 1). PPSV23 contains polysaccharide antigen from 23 serotypes of pneumococcal bacteria. In addition, the vaccine results in cross-sensitivity and protection to other types of bacteria. PCV13 contains capsular polysaccharide of 13 serotypes of *S pneumoniae* and is conjugated with a nontoxic form of diphtheria toxin.[1] Twelve of the

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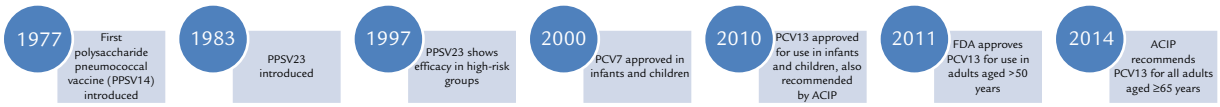

Figure 1. Timeline of developments in pneumococcal immunization, displaying some of the important dates in the development, approval, and recommendations of pneumococcal vaccines. PPSV14 = 14-valent polysaccharide vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; PCV7 = 7-valent pneumococcal polysaccharide conjugate vaccine; PCV13 = 13-valent pneumococcal polysaccharide conjugate vaccine; ACIP = Advisory Committee on Immunization Practices; FDA = US Food and Drug Administration.

13 serotypes in PCV13 are also found in PPSV23. Although PCV13 only contains 1 additional serotype compared with PPSV23, it elicits an immune response via T-cell activation. T-cell activation may result in longer lasting immunity with subsequent doses and/or natural exposure to the serotypes found in the vaccine.[4] It is believed that this contributes to increased immunogenicity.[6,7] Conversely, PPSV23 elicits an immune response that is T-cell independent. It works by directly stimulating B cells. This type of vaccine results in less immunogenicity and less of a booster effect than conjugated vaccines.[1]

The polysaccharide conjugate vaccine initially was indicated for infants and toddlers at ages 2, 4, 6, and 12 to 15 months.[8] The first polysaccharide conjugate vaccine contained 7 serotypes. In 2010, a 13-serotype version was approved. Between 2010 and 2013, the incidence of IPD caused by serotypes in the vaccine declined by 50% in persons aged ≥65 years. Despite the decline, there were still >13,000 cases of IPD in 2013. Due to the morbidity and mortality associated with IPD, it was necessary to determine if PCV13 could be safely and effectively used in adults aged ≥65 years.

The aim of the present article was to review the key clinical trials that resulted in the recent recommendation from the Advisory Committee on Immunization Practices (ACIP) to vaccinate all adults aged ≥65 years by using both PCV13 and PPSV23. These clinical trials are summarized in the Table. Before August 2014, the ACIP only routinely recommended the use of PPSV23 in adults aged ≥65 years.

RESULTS

Immunogenicity of PCV13 and PPSV23

Two studies have researched the immunogenicity of PCV13 compared with PPSV23, 1 in vaccine-naive patients and 1 in previously vaccinated patients.[6,7] The goal of these studies was to test the ability of the conjugated 13-valent vaccine to produce an immunogenicity equal to or greater than that of the polysaccharide vaccines, not only in the period directly after immunization but also over time. Because PPSV23 has been scrutinized for its lack of evidence regarding protection over time, the results of both studies would prove to be integral in this type of protection.

One of these studies focused specifically on vaccine-naive adults.[7] Two adult populations were studied. The main arm of the study examined the response of adults aged 60 to 64 years. The enrollees were randomly divided into 2 even groups, 1 of which received PCV13 vaccination, while the other received PPSV23 vaccination. The other arm included adults aged 50 to 59 years and compared the immunogenicity of PCV13 between the older and younger groups. Subjects were not excluded for having chronic conditions that could increase the risk of developing pneumonia. The exclusion criteria included unstable chronic disease, as well as malignancies, advanced chronic obstructive pulmonary disease, renal disease, cardiac disease, and impaired immune function. Follow-up visits occurred at 1 month and 1 year postvaccination.

In the main arm of the study, 818 patients were evaluated for the immunogenicity of their respective vaccines (411 in the PCV13 arm and 407 in the PPSV23 arm).[7] The study found that PCV13 was noninferior to PPSV23 in all common serotypes and that the younger group (aged 50–59 years) had a statistically significantly higher immunogenicity response for 9 of the serotypes included in PCV13. It also found a more profound response in the younger group, compared with the older group, in terms of persistence of immune response 1 year after vaccination.

The second immunogenicity study examined the response to revaccination in subjects previously vaccinated with PPSV23 as well as the effect of PCV13 administration 1 year after the study was initiated.[6] The