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Is 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Combined With 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) Superior to PPSV23 Alone for Reducing Incidence or Severity of Pneumonia in Older Adults? A Clin-IQ

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Abstract

Pneumonia infection is a significant cause of morbidity and mortality worldwide. In addition to the public health concerns, pneumonia also accounts for a significant cost to the health care system. Currently there are two leading vaccines targeted against S. pneumoniae: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Until recently the recommendation for adult pneumonia vaccination has been a single dose of PPSV23 for all adults 65 years and older. However, concerns were raised regarding the vaccine's efficacy due to the persistent burden of pneumococcal disease in the elderly population. This paper focuses on two trials which evaluate the safety and efficacy of PCV13 in the adult population. The first study reveals improved immune response with the addition of PCV13 to PPSV23, while the second shows PCV13 was effective in the prevention of vaccine-type community-acquired pneumonia. The two studies observed adequate safety profiles for PCV13 in series with PPSV23 and with PCV13 compared to placebo.

Keywords

pneumococcal conjugate vaccine; pneumococcal polysaccharide vaccine; adults; PPSV23; PCV13

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Clinical Question: In patients 65 years of age or older, is 13-valent pneumococcal conjugate vaccine (PCV13) combined with 23-valent pneumococcal polysaccharide vaccine (PPSV23) superior to PPSV23 alone for reducing the incidence and/or severity of pneumonia?

Answer: The answer is possibly, although the clinical relevance is still unclear. The current research shows an improved immune response with the combination of PCV13 and PPSV23 compared to PPSV23 alone. However, there is no proven correlation between improved immune titer response and reduction of clinical disease incidence or severity.

Conflict of Interest: None

Search Terms

Adults ages 65 and older; pneumococcal conjugate vaccine; pneumococcal polysaccharide vaccine; PPSV23; PCV13

Summary of the Issues

Pneumonia infection is a significant cause of morbidity and mortality worldwide, and Streptococcus pneumoniae is currently the most commonly identified pathogen in community-acquired pneumonia. In the United States, S. pneumoniae is responsible for 500,000 cases of pneumonia and 50,000 cases of bacteremia each year with an annual mortality rate of 5–7% and 20%, respectively. Pneumococcal disease in all of its forms is estimated to cause 1.6 million deaths globally per year. In addition to the public health concerns, pneumonia also accounts for a significant cost to the health care system.

Currently there are two leading vaccines targeted against S. pneumoniae: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Pneumococci bacteria are contained within a polysaccharide capsule. The capsules contain antigenic variation, and over 90 distinct capsular serotypes have been identified. PPSV23 contains antigens from 23 common serotypes, while PCV13 contains antigens from 13 serotypes. Although both vaccines aim to induce immunity against the most common serotypes to cause clinical disease, there is substantial overlap in the antigens contained within each vaccine. Twelve of the thirteen serotypes included in PCV13 are common to PPSV23.

The other major difference between PPSV23 and PCV13 is the design of the vaccine itself. PPSV23 contains capsular polysaccharide antigens. These antigens elicit a T-cell independent antibody response. The antibodies produced boost activity of phagocytic cells and thereby induce killing of pneumococcus. PCV13 is a conjugate vaccine that combines these capsular polysaccharides with a protein carrier. With the addition of the protein, PCV13 produces a T-cell dependent immune response with antibody production and the potential for immune memory.

Until recently the recommendation for adult pneumonia vaccinations has been a single dose of PPSV23 for all adults 65 years and older. However, concerns were raised regarding the vaccines efficacy due to the persistent burden of pneumococcal disease in the elderly population. PCV13 was introduced in the pediatric population in 2010 as a replacement for 7-valent pneumococcal conjugate vaccine (PCV7). The conjugated vaccines have proven to be successful at reducing the burden of pneumococcal disease in the pediatric population. New research has focused on PCV13 in the adult population to evaluate both safety and efficacy, as well as determine the most appropriate vaccination strategy for prevention of pneumococcal disease.

Summary of the Evidence

A 2013 study examined the safety and effectiveness of PCV13 in elderly adults who had previously received vaccination with PPSV23. In this study, anti-pneumococcal opsonophagocytic activity (OPA) titers were measured to evaluate vaccine efficacy. The study was a randomized, modified double-blinded trial including 936 adults aged 70 years and older who had been previously vaccinated with PPSV23 at least 5 years prior to the trial. Study participants were divided into two groups. One group received a second dose of PPSV23, while the other received PCV13. Both groups received a dose of PCV13 1 year later. OPA titers were measured prior to and at 1 month following each vaccine administration. Safety assessments were also performed at 2 weeks, 1 month and 6 months post-vaccination status.

Study results revealed a significantly greater OPA response for 10 of the 12 common serotypes following vaccination with PCV13 compared to PPSV23. The study then evaluated immune response following PCV13 administration in both groups 1 year following the initial PCV13 or PPSV23 vaccine. This was performed to assess the impact of initial vaccine choice on response of subsequent vaccinations. Using a 95% confidence interval, OPA titer responses were statistically significantly higher for 11 common serotypes in the group that received PCV13 at enrollment and at 1 year compared to the group receiving PPSV23 initially. The results propose a booster dose of PPSV23 given prior to PCV13 may not improve coverage, and it may be more beneficial to administer PCV13 following initial vaccination with PPSV23. PCV13 also had a satisfactory safety profile compared to PPSV23.

This study highlights the limitations of PPSV23 alone in prevention of pneumococcal disease in the elderly population. However, it is limited by the fact that Wyeth Vaccines Research funded the study. Wyeth Pharmaceuticals, Inc. is the manufacturer of Prevnar 13®. Additionally, while OPA titers are considered a measurement of functional immune response, it is difficult to extrapolate this data into prevention of clinical illness. The primary concern for health care providers is a vaccination strategy that will reduce morbidity and mortality in their patient population.

The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) was developed to determine the clinical efficacy and safety of PCV13 in the adult population. The study included 84,496 pneumococcal vaccine naïve adults 65 years or older in a randomized, double-blinded, placebo-controlled trial. The trial was conducted in the Netherlands, where there were no recommendations for routine pneumococcal vaccination in older adults. Participants were randomly divided into two groups in a 1:1 ratio, either receiving PCV13 or placebo injection. Study participants were then followed for an average of approximately 4 years.

The primary objective of the study was to demonstrate prevention of a first-episode of vaccine-type community-acquired pneumonia (CAP). Secondary objectives included prevention of first-episode nonbacteremic and noninvasive vaccine-type CAP (negative cultures of sterile sites) and vaccine-type invasive pneumococcal disease (S. pneumonia

present in sterile site). Fifty-nine sentinel centers participated in the study. For patients presenting with symptoms of lower respiratory tract infection routine diagnostic evaluation was performed. A database was searched for study participation if pneumonia was the suspected diagnosis. For study participants, a urine sample was obtained for testing of serotype-specific urinary antigen. Culture results were monitored for determination of invasive pneumococcal disease. Chest x-rays performed were read at a central location, and radiologists were not informed of the patients' vaccination status.

The CAPiTA study concluded PCV13 was effective in preventing vaccine-type CAP and vaccine-type invasive pneumococcal disease in immunocompetent adults 65 years or older for a duration of at least 4 years. Vaccine efficacy was statistically significant in these groups and was found to be 46% in prevention of first episode vaccine-type CAP, 45% in first-episode nonbacteremic and noninvasive vaccine-type CAP, and 75% in vaccine-type invasive pneumococcal disease (see Table 1). PCV13 was also found to be safe in the adult population. While there were more local reactions and systemic events in the PCV13 group compared to placebo, there were no documented serious adverse events. Additional endpoints observed during the study included first episode of nonbacteremic and noninvasive pneumococcal CAP including non-vaccine serotypes and first-episode of all-cause CAP. PCV13 efficacy was not found to be statistically significant in either of these groups.

The trial was successful in establishing efficacy and safety for PCV13 in adults for prevention of vaccine-type pneumococcal disease, but this study does have several limitations. Funding and support was namely provided by Pfizer. Pfizer Inc. purchased Wyeth, the manufacturer of Prevnar 13™ in October 2009. The study was also conducted within one country in a population with little variation in race (98.5% white). Vaccine efficacy may be altered in a more diverse patient population. Additionally, this population was pneumococcal vaccine naïve. Unlike the Netherlands, the United States has a developed vaccination strategy for pneumonia. Many adults aged 65 years or older have received PPSV23 according to current guidelines. Therefore, while this study shows effectiveness of PCV13, it does not address the question of superiority of PPSV23 in combination with PCV13 compared to PPSV23 alone.

Conclusion

Each vaccine has its own set of benefits and limitations. PPSV23 covers a greater number of pneumococcal serotypes but may not induce effective or lasting immunity. PCV13 seems to produce greater potential for immune memory. However, there are questions of necessity since introduction of PCV13 in the pediatric population has decreased the incidence of these pneumococcal strains in the population as a whole. Regardless, the current vaccination strategy has not been as successful as desired in prevention of pneumococcal disease in the adult population. This has prompted the Advisory Committee on Immunization Practices (ACIP) to update their recommendations for pneumococcal vaccination. Guidelines were released August of 2014, but have not yet been widely adopted. Current updated guidelines recommend routine administration of PCV13 in series with PPSV23 in all adults 65 years of age or older (see Table 2). Based on current studies available, the combination of PPSV23

with PCV13 should produce a superior immune response than with PPSV23 alone. Improving immune response should result in an overall reduction in clinical incidence and severity of pneumococcal disease.

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Table 1

PCV13 Efficacy in First Episode Vaccine-Type Pneumococcal Disease

	PCV13 (N=42,240)	Placebo (N=42,256)	% Vaccine Efficacy	P Value
1st episode Vaccine-type CAP*	49	90	45.6%	<0.001
1st episode Vaccine-type Nonbacteremic, Noninvasive CAP	33	60	45.0%	0.007
1st episode Vaccine-type Invasive Pneumococcal Disease	7	28	75.0%	<0.001

Adapted from Bonten et al.

*Community-acquired pneumonia

Table 2

Current Updated Recommendations Regarding Pneumococcal Vaccination

Pneumococcal vaccine-naïve persons aged ≥ 65 years:		
Give PCV13 at age ≥ 65 years	≥ 1 year →	Give PPSV23
Previously received PPSV23 at age ≥ 65 years:		
PPSV23 received at age ≥ 65 years	≥ 1 year →	Give PCV13

Previously received PPSV23 before age 65 years and are now aged ≥ 65 years:				
PPSV23 received age <65 years	≥ 1 year →	PCV13 at age ≥65 years	→ ≥ 1 year	PPSV23 Booster*

Adapted from Kobayashi et al, Advisory Committee on Immunization Practices, *MMWR.*

Recommend ≥ 5 years between initial PPSV23 vaccine and PPSV23 booster.