Trials in Vaccinology 5 (2016) 92–96

Contents lists available at ScienceDirect

Trials in Vaccinology

journal homepage: www.elsevier.com/locate/trivac

Original Article

A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults)

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ARTICLE INFO

Article history:
Received 25 March 2016
Accepted 19 April 2016
Available online 4 May 2016

Keywords:
Community-acquired pneumonia
Invasive pneumococcal disease
PCV13
Pneumococcal conjugate vaccine
Persistence of vaccine efficacy

ABSTRACT

Background: The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was conducted to evaluate 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and vaccine-type invasive pneumococcal disease (VT-IPD) in adults aged ⩾65 years. Plotting the cumulative number of episodes against time from vaccination demonstrated that efficacy was evident soon after vaccination and persisted throughout the duration of the study. This post hoc analysis was performed to quantify the persistence of vaccine efficacy (VE) of PCV13.

Methods: This was a parallel-group, randomized, placebo-controlled, double-blind trial. Subjects were enrolled between September 15, 2008 and January 30, 2010 at 101 sites in the Netherlands and randomized 1:1 to receive a single dose of PCV13 or placebo. The observed accumulation of episodes for VT-CAP, nonbacteremic/noninvasive VT-CAP (NB/NI-VT-CAP), and VT-IPD over the course of the study after vaccination was assessed. Post hoc time-to-event analyses of primary and secondary endpoints were performed. VE behavior over time was derived and effects of treatment, time, and time by treatment interactions were estimated.

Results: A total of 84,496 individuals were enrolled (PCV13, $n = 42{,}240$; placebo, $n = 42{,}256$). Cases of VT-CAP, NB/NI-VT-CAP, and VT-IPD were greater among placebo recipients compared with PCV13 recipients throughout the postvaccination observation period with a periodic rise in cases in the placebo group that was consistent with varied exposure and ensuing disease over time. There was a significant difference in disease-free survival among PCV13 recipients compared with placebo recipients for VT-CAP (log-rank test $P = 0.0005$), NB/NI VT-CAP ($P = 0.0051$), and VT-IPD ($P = 0.0004$). VE ranged from 42.9% to 50.0% for VT-CAP, 36.2% to 48.5% for NB/NI-VT-CAP, and 66.7% to 75.0% for VT-IPD.

Conclusions: The results of this post hoc analysis of the persistence of PCV13 VE in adults ⩾65 years, indicate that PCV13 was protective over the 5-year duration of the study, with no waning of efficacy observed.

ClinicalTrials.gov identifier: NCT00744263

1. Introduction

The incidence of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* is higher in older adults [1–6], and the morbidity and mortality associated with pneumococcal disease increases with advanced age [3,5,7–9]. The natural diminution in the local/innate and adaptive immune systems or responses observed in

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http://dx.doi.org/10.1016/j.trivac.2016.04.004
1879-4378/

older adults may render them more susceptible to infection with *S. pneumoniae* [10]. In addition, CAP exerts a substantial economic burden on national healthcare systems that has been documented in Europe [11] and in the United States [12]. Thus, a vaccine that reduces the prevalence of CAP and IPD in this population could have public health benefits.

The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA; ClinicalTrials.gov identifier NCT00744263) was conducted to evaluate 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and vaccine-type invasive pneumococcal disease (VT-IPD) in adults ⩾65 years of age [13]. This was an event-driven study that targeted at least 130 first episodes of VT-CAP in subjects who were randomized 1:1 to receive 13-valent pneumococcal conjugate vaccine (PCV13) or placebo. The per-protocol analysis vaccine efficacy (VE) results (with 95.2% confidence intervals [CIs]) were 46% (22–62%) for VT-CAP, 45% (14–65%) for non-bacteremic/noninvasive VT-CAP (NB/NI-VT-CAP), and 75% (95% CI: 41–91%) for first episodes of vaccine-type IPD (VT-IPD).

Although efficacy was demonstrated for all endpoints in both the per-protocol and modified intent-to-treat (mITT) populations, the long-term persistence of PCV13 efficacy in older adults is not currently known. Plotting the cumulative number of episodes against time after vaccination demonstrated that efficacy was evident soon after vaccination and persisted throughout the duration of the study [13]. Determination of VE over a longer period of time in adults ⩾65 years is of importance for guiding recommendations for revaccination. This post hoc analysis of data from the Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was performed to more precisely quantify the persistence of VE of PCV13 in adults ⩾65 years of age.

2. Methods

2.1. Study design

The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was a parallel-group, randomized, placebo-controlled, double-blind trial. Subjects were enrolled between September 15, 2008 and January 30, 2010 at 101 sites in the Netherlands. Cases of suspected pneumonia and IPD were acquired between September 15, 2008 and August 28, 2013 at 59 sentinel centers. Study surveillance ended after identification of at least 130 per-protocol, first episodes of VT CAP. The complete study design and procedures were previously published [13,14].

2.2. Study participants

Eligible subjects were adults ⩾65 years of age with no previous pneumococcal vaccination and who were not immunocompromised. The study was conducted in compliance with Good Clinical Practice guidelines and was approved by the Central Committee on Research Involving Human Subjects and by the Ministry of Health, Welfare and Sport in the Netherlands. Written informed consent was obtained from all subjects before the performance of any study-related procedures. The per-protocol population included participants who had an episode of CAP or IPD with an onset of symptoms at least 14 days after vaccination, were eligible for the study, received a vaccination, were still immunocompetent at the time of the CAP or IPD episode, and had no other major protocol violations.

2.3. Study procedures

Subjects were randomized 1:1 to receive a single dose of PCV13 or placebo. Cases of pneumonia were diagnosed using standard procedures including X-rays and laboratory analysis (BinaxNOW® and serotype-specific urinary antigen detection [UAD]). Samples from sterile and non-sterile sites were assessed by laboratory culture and positive samples were serotyped. CAP was confirmed radiologically together with 2 predefined clinical criteria as described by Bonten and colleagues [13]; IPD was defined as the presence of *S. pneumoniae* in a normally sterile site using laboratory culture techniques.

2.4. Statistical methods

An interim analysis was planned at the time of at least 65 per-protocol first episodes of confirmed VT-CAP. The study was to be stopped at the time of the interim analysis if harm was demonstrated (i.e., an adjusted upper confidence bound of VE <0), or if clinically significant VE was demonstrated for first confirmed VT CAP (i.e., an adjusted lower confidence bound >20%) and for first confirmed NB/NI VT CAP (i.e., an adjusted lower confidence interval >0). The observed accumulation of episodes for VT-CAP, NB/NI-VT-CAP, and VT-IPD over the course of the study following vaccination was plotted. Post hoc Kaplan–Meier time-to-event analyses of the primary and secondary endpoints were performed. Behavior of VE over time was also derived, and Poisson regression was used to estimate the effects of treatment, time, and time by treatment interaction. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). Graphical representations of first episodes of vaccine-type pneumococcal disease over calendar time and cumulative episodes of vaccine-type pneumococcal disease over time since vaccination were produced using S-Plus 8.2 (Tibco Spotfire, Boston, MA).

3. Results

3.1. Study population

A total of 84,496 individuals were enrolled in the study (PCV13, $n = 42{,}240$; placebo, $n = 42{,}256$) [13]. Baseline characteristics were similar between the two vaccine groups and were described previously [13]. Subjects were followed for a mean of approximately 4 years.

3.2. Interim analysis

At the interim analysis, which was conducted for the 74 episodes for which data were available, the VE for the first episode of per-protocol confirmed VT-CAP was 49.0% (99.48% CI: −2.4%, 75.9%; $P = 0.007$), which did not meet the requirements for stopping the study (a lower confidence interval exceeding 20%) and CAP and IPD data acquisition continued until at least 130 per-protocol, first episodes of VT-CAP were observed.

3.3. First episodes of vaccine-type pneumococcal disease over time

The number of cases of VT-CAP, NB/NI-VT-CAP, and VT-IPD were higher among subjects who received placebo compared with the number of cases among subjects who received PCV13 throughout the postvaccination observation period (Fig. 1). There was a periodic rise in the number of cases in the placebo group that was consistent with exposure to pneumococcus and ensuing disease over time with most cases of pneumococcal disease occurring between September and April. However, these data do not take into consideration the time of vaccination (September 2008–January 2010).