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Evaluation on the persistence of anti-HPV immune responses to the quadrivalent HPV vaccine in Chinese females and males: Up to 3.5 years of follow-up

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ABSTRACT

Background: This was an extension study of a randomized, double-blind, placebo-controlled immunogenicity and safety study of the quadrivalent human papillomavirus (qHPV) (HPV 6, 11, 16, and 18) vaccine conducted in Chinese female subjects aged 9–45 years and male subjects aged 9–15 years. To investigate the persistence of anti-HPV 6, -11, -16, and -18 responses among Chinese subjects, subjects enrolled in the base study were followed up at around month 42 (approximately 3.5 years after vaccination).

Methods: Among 600 subjects enrolled in the base study, a total of 468 subjects consented for participation in the extension study. Anti-HPV 6, -11, -16, and -18 antibodies were detected by the competitive Luminex immunoassay (cLIA) and total IgG Luminex immunoassay (IgG LIA).

Results: Among the female subjects who received the qHPV vaccine, the proportions of subjects remained seropositive were high with both the cLIA and IgG LIA for HPV type 6, 11, and 16 through approximately 42 months following the first dose vaccination. For HPV 18, the seropositivity rate remained high as 82.0% with the IgG LIA, while it decreased to 53.6% with the cLIA, which was similar to the findings observed in other studies. The seropositivity rates remained high at month 42 for all qHPV types with both the cLIA and IgG LIA among the male subjects.

Conclusions: Administration of a 3-dose regimen of qHPV vaccine induces durable anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses among Chinese subjects for at least 3.5 years after vaccination.

ClinicalTrials.gov registry: NCT01427777

1. Introduction

In China, the incidence of cervical cancer is more than 60,000 new cases per year ranking 2nd among all cancers in women aged 15–44 years, and the annual mortality due to cervical cancer is approximately 30,000 which is the 3rd leading cause of cancer deaths in women aged 15–44 years [1]. Approximately 70% of cervical cancers in China are attributed to HPV 16 and 18 [1]. The incidence of HPV-related vulvar, vaginal, anal, penile and oropharyngeal cancers is estimated to be 13,000 new cases per year in China, affecting both men and women [2]. Furthermore, the prevalence of genital warts was 28.8/100,000 in Chinese women [3], and a meta-analysis showed that HPV types 6 and/or 11 can be detected in up to 83% of genital wart cases in China [4].

Prophylactic HPV vaccination is a promising strategy to prevent the occurrence of cervical cancer and other HPV-related diseases. Since the risk of acquiring HPV infection begins at sexual debut and the risk persists throughout individual's sexually active life, the duration of protection conferred by HPV vaccination is critical.

Although the immune correlate of protection has not been established, it is important to evaluate the immune responses induced by HPV vaccine over time since vaccination. Using the competitive Luminex immunoassay (cLIA), the quadrivalent HPV (qHPV) (HPV 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine

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studies showed that vaccination induced strong immune response to all qHPV types with peak titers achieved 1 month after the 3rd dose [5,6]. Antibody titers then declined until reaching a plateau that was sustained with minimal change through 48 months post-vaccination [6]. A more pronounced decline in HPV 18 titers was observed, as measured by cLIA with a month 48 seropositivity rate of 65%. However, when the same serum samples were tested by the total IgG Luminex immunoassay (IgG LIA) which measures all IgG antibodies to VLPs, the total HPV18 seropositivity was approximately 97% [7]. Another long-term follow-up (LTFU) study using cLIA and IgG LIA showed that anti-HPV GMTs and the seropositivity remained high up to 9 years after vaccination [8].

A clinical trial (V501-030) to assess the immunogenicity of the qHPV vaccine in China was conducted during 2008–2009 and the results at month 7 (i.e., 1 month after completion of the full vaccination series) measured by cLIA demonstrated the robust immune responses induced by the vaccine in Chinese subjects [9]. In this report, we further evaluated the immune responses to the qHPV vaccine in sera collected approximately 3.5 years postvaccination among the subjects included in the V501-030 study. The antibody responses at month 42 were assessed by the cLIA and IgG LIA.

2. Materials and methods

2.1. Study design and population

This study is an extension of protocol V501-030 in China. The base study was completed on 30 Jun 2009. Protocol V501-030 was a single site, randomized, double-blind, placebo-controlled study to investigate the immunogenicity and safety of the qHPV vaccine in Chinese subjects as described previously [9]. In the base study, a total of 600 subjects (500 female subjects aged 9–45 years and 100 male subjects aged 9–15 years) were randomized in a 1:1 ratio to receive either qHPV vaccine or placebo at day 1, month 2, and month 6, and blood samples were collected at day 1 prior to vaccination (baseline) and month 7 to assess the immunogenicity using cLIA. To evaluate the persistence of anti-HPV 6, -11, - 16, and -18 responses at month 42 with both the cLIA and IgG LIA, subjects who completed the base study were contacted for participation into the extension study.

This extension study was approved by the investigator's institutional review board. Written informed consent was obtained from each participant or legal guardian before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines.

2.2. Clinical follow-up and laboratory testing

Subjects who consented to participate in the extension study were invited to provide blood samples at around month 42. 3–5 mL blood sample was collected from each subject. The serum samples were stored at −20 °C until shipment on dry ice to the centralized laboratory (PPD® Vaccines and Biological Laboratory in the US) where all the analyses were done. The serum antibodies were measured using cLIA and IgG LIA as described [8]. The seropositivity cutoff values of HPV cLIA for type 6, 11, 16, and 18 are 20 mMU/mL, 16 mMU/mL, 20 mMU/mL, 24 mMU/mL, respectively. And the cutoff values of IgG LIA for the four types are 15 mMU/mL, 15 mMU/mL, 7 mMU/mL, and 10 mMU/mL, respectively.

2.3. Statistical analysis

The primary objective of this extension study was to evaluate the antibody titers of vaccine-induced serum anti-HPV 6, -11, -16, and -18 antibodies at month 42 following vaccination. The analyses were performed among the per-protocol immunogenicity (PPI) population as defined in the base study, who received all 3 doses vaccination within acceptable day ranges, have valid serology results with cLIA at both baseline and month 7 within acceptable day ranges, did not deviate from the protocol in ways that could have interfered with the effects of immunogenicity endpoints, and were seronegative to the relevant HPV type at baseline. Geometric mean titers (GMTs) and seropositivity rates of anti-HPV cLIA at month 42 were summarized by female and male subjects incorporating the results of the base study (day 1 and month 7). GMTs and seropositivity rates based on IgG LIA at month 42 by female and male subjects were computed. Because the IgG LIA was not used in the base study, immunogenicity data with IgG LIA at day 1 and month 7 were not available. The same PPI population was applied for the analysis with cLIA and IgG LIA.

3. Results

Among 600 subjects enrolled in the base study, 468 consented to participate in the extension study. Of these, 241 received qHPV vaccine and 227 received placebo (Fig. 1). The number of female and male subjects contributing to the PPI analyses is presented in Table 1.

The anti-HPV cLIA GMTs and seropositivity by study time point among the female subjects aged 9–45 years and male subjects aged 9–15 years who received the qHPV vaccine are summarized in Table 1 and Fig. 2, respectively. At month 42, GMTs in the female subjects declined to 6–15% of the levels at month 7, depending on HPV type. The lower bounds of the 95% confidence intervals (CIs) of GMTs at month 42 were still higher than the cutoff values of seropositivity for most qHPV types. GMTs in the placebo group remained below the lowest limit of quantification (LLOQ) for all qHPV types (data not shown). The seropositivity rates for HPV 6, 11, and 16 remained high with a range of 88.8–97.3% at month 42. For HPV 18, 53.6% (95% CI: 46.3, 60.8) of female subjects were still seropositive.

Anti-HPV cLIA responses by different age groups in the female subjects who received the qHPV vaccine were also analyzed. Among different age groups, cLIA GMTs at month 42 declined to 5–15% of the month 7 levels depending on HPV type (data not shown), which was similar to the finding in the whole female subjects. And month 42 cLIA GMTs of all qHPV types were generally higher in younger age groups compared to older age groups as the same as the data of month 7 [9]. High cLIA seropositivity rates at month 42 was seen for HPV 6, 11, and 16 across different age groups (ranging from 83.3% to 98.1%), while an obvious trend of

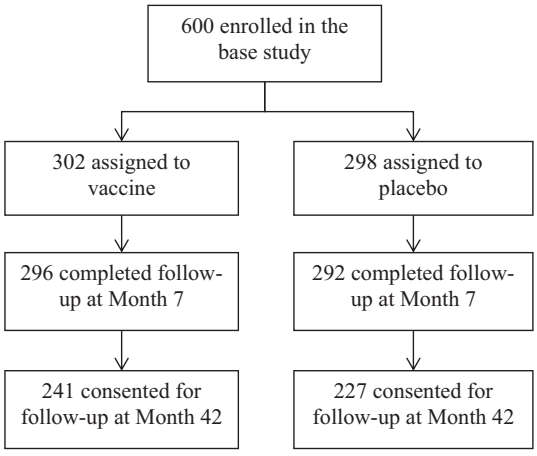

Fig. 1. Subject disposition of the base and extension study.