Vaccine 33 (2015) 2141–2151

Contents lists available at ScienceDirect

Vaccine

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

Rationale and design of a long term follow-up study of women who did and did not receive HPV 16/18 vaccination in Guanacaste, Costa Rica

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ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 2 March 2015
Accepted 6 March 2015
Available online 18 March 2015

Keywords:
Human papillomavirus
Vaccines
Methods
Long term follow-up

ABSTRACT

The Costa Rica Vaccine Trial (CVT) was a randomized clinical trial conducted between 2004 and 2010, which randomized 7466 women aged 18 to 25 to receive the bivalent HPV-16/18 vaccine or control Hepatitis-A vaccine. Participants were followed for 4 years with cross-over vaccination at the study end. In 2010 the long term follow-up (LTFU) study was initiated to evaluate the 10-year impact of HPV-16/18 vaccination, determinants of the immune response, and HPV natural history in a vaccinated population. Herein, the rationale, design and methods of the LTFU study are described, which actively follows CVT participants in the HPV-arm 6 additional years at biennial intervals (3 additional study visits for 10 years of total follow-up), or more often if clinically indicated. According to the initial commitment, women in the Hepatitis-A arm were offered HPV vaccination at cross-over; they were followed 2 additional years and exited from the study. 92% of eligible CVT women accepted participation in LTFU. To provide underlying rates of HPV acquisition and cervical disease among unvaccinated women to compare with the HPV-arm during LTFU, a new unvaccinated control group (UCG) of women who are beyond the age generally recommended for routine vaccination was enrolled, and will be followed by cervical cancer screening over 6 years. To form the UCG, 5000 women were selected from a local census, of whom 2836 women (61% of eligible women) agreed to participate. Over 90% of participants complied with an interview, blood and cervical specimen collection. Evaluation of comparability between the original (Hepatitis-A arm of CVT) and new (UCG) control groups showed that women's characteristics, as well as their predicted future risk for cervical HPV acquisition, were similar, thus validating use of the UCG. LTFU is poised to comprehensively address many important questions related to long-term effects of prophylactic HPV vaccines.

Abbreviations: CVT, Costa Rica vaccine trial; LTFU, long term follow up study; UCG, new unvaccinated control group, followed by screening only; ISC, immunogenicity sub-cohort; LN, liquid nitrogen; PC, PreservCyt® solution; HC2, hybrid capture 2; ACD, anticoagulant citrate dextrose solution; DEIA, DNA enzyme immunoassay; LiPA, line probe assay; SOP, standard operating procedure; IQR, interquartile range; VE, vaccine efficacy.

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http://dx.doi.org/10.1016/j.vaccine.2015.03.015
0264-410X/

1. Introduction

Cervical cancer affects more than 500,000 women per year worldwide [1]. Persistent infection with carcinogenic HPV is the necessary cause of cervical cancer [2], and also causes a subset of cancers of the anus, vulva, vagina, penis, and oropharynx [2], comprising approximately 70,000 additional cases of HPV-associated cancers per year [3]. HPV 16 and 18 are responsible for 70% of cervical cancers [4] and for most cases of HPV-driven cancers at the other anatomical sites [5,6]. HPV prophylactic vaccines have the potential to dramatically reduce the burden of HPV-associated disease if incorporated into cervical cancer prevention programs, especially in developing countries.

Two HPV vaccines are approved in most countries: the bivalent (Cervarix®, GlaxoSmithKline Biologicals) and quadrivalent (Gardasil™, Merck and Co, Inc.) vaccines, which confer near complete protection against HPV-16/18 infection and disease in women naïve to these types prior to vaccination [7,8]. The quadrivalent vaccine additionally protects against HPV 6 and 11, which cause most genital warts [8]. Recently the US Food and Drug Administration (FDA) approved a new nonavalent vaccine produced with technology similar to the quadrivalent vaccine but directed against nine HPV types (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58).

Data from the Costa Rica Vaccine Trial (CVT) [9], our community-based vaccine efficacy study, confirmed that the bivalent vaccine is highly efficacious against HPV-16/18 persistent infections and resultant CIN2+ among women unexposed to HPV at the time of initial vaccination, and observed partial cross-protection against HPV 31, 33 and 45 comparable to published estimates [10–12]. CVT was initiated in 2004 and enrolled 7466 women aged 18 to 25 years. Women were randomized to receive the HPV or control (Hepatitis-A) vaccine, and were followed for 4 years with high participation rates [9,10,13]. Novel findings from our trial included that: (1) the vaccine does not treat existing infections [14]; (2) fewer than 3 doses of the vaccine protect as well as the full 3-dose series for 4 years [15]; (3) antibodies levels achieved following two doses (0 and 6 months) of the HPV-vaccine are high and only slightly lower than those observed after three doses (one dose antibodies levels were lower than those of two and three doses, but higher than natural infection levels, and remained stably elevated over four years) [16]; (4) the vaccine protects against HPV-16/18 infections at the anus and oral region [17,18]; (5) vaccine impact declines with increasing age at vaccination [10]; (6) vaccination induces cross-neutralizing potential in sera of vaccinated individuals [19]; (7) modest levels of antibodies generated by natural HPV infection provide partial protection against re-infection [20]; and, (8) vaccination of young adult women leads to a modest decrease in the number of women who require treatment for HPV-associated cervical disease in the initial years following vaccination [21]. As promised in the informed consent, at the end of CVT, participants were unblinded to their vaccine status and cross-over vaccination was offered.

At the completion of CVT in 2010, the long term follow-up study (LTFU) was implemented, to extend follow-up of CVT participants in the HPV-arm of CVT to 10 years and enroll a new, screening-only, control group in order to provide necessary data that will allow for continued investigation into the risks and benefits of the prophylactic HPV-vaccine.

The goals of this paper are to (1) report the rationale for the LTFU study to extend the follow-up of CVT participants and the inclusion of a new unvaccinated control group (UCG), (2) describe the design and methods of the LTFU study, (3) present data from the enrollment phase of the LTFU study and (4) evaluate the validity of the UCG.

1.1. Rationale for LTFU

The LTFU study was designed in order to evaluate (1) the 10-year impact of HPV-16/18 vaccination of young adult women; (2) determinants of the immune response to HPV and the vaccine and markers of long-term protection; and (3) the natural history of HPV and cervical disease in a vaccinated population, including behavior of other oncogenic HPV types in the absence of HPV-16/18 infections ("disease unmasking").

1.1.1. HPV arm

To evaluate the long-term efficacy of the HPV-vaccine, the follow-up period of CVT women originally vaccinated with the HPV-16/18 vaccine was extended by 6 years with screening at 6, 8, and 10 years after initial HPV vaccination.

1.1.2. Control-arm

Women in the original CVT control-arm, regardless of whether they accepted cross-over vaccination, were followed for 2 additional years, to monitor vaccine safety post-crossover and maximize detection of persistent infections and lesions resultant from HPV exposure that occurred before cross-over to the HPV vaccination. Of these women, roughly 600 accepting cross-over are being followed for the full 6 years as part of a special group providing additional samples for immunogenicity studies.

1.1.3. UCG

To account for the loss of the randomized original control-arm (due to cross-over), a new control group ($n = 2827$) was enrolled from the same geographic areas and birth cohorts as the original CVT women. Women in this group will be followed for 6 years in LTFU via screening only, to provide a contemporaneous referent group for rates of HPV acquisition, clearance, and disease progression in unvaccinated women.

1.1.4. Ethical justification for the UCG

Women asked to enroll in the UCG are over 20 years old, thus far older than the ideal age for vaccination (9 or 10 to 13 years according to WHO [22]). 50% were older than 26, the maximum age generally recommended for catch-up vaccination [23], and thus vaccination was not standard of care. Among sexually experienced women (97% of those recruited), HPV vaccination is not effective at treating established infection [14], whereas screening programs followed by treatment are highly effective. Participants received high quality cervical cytology screening, due to the extensive quality assurance measures in place in the study [9], HPV testing is used for deciding follow-up among screen-positive women and state-of-the-art treatment is provided when necessary.

Vaccination of adolescents has not yet been incorporated into the Costa Rican national health care system vaccination program, and implementation of catch-up vaccination of young adult women appears highly unlikely to be considered by national authorities. Women may obtain the vaccine outside of the study if they choose; such information will be documented and used in the analytic phase of the study.

2. Materials and methods

2.1. Brief review of CVT—The randomized, blinded phase

CVT was a community-based, double-blind, randomized controlled phase III trial of the bivalent vaccine, provided by GSK for the trial under a clinical trial agreement with NCI. Between 2004 and 2005, 7466 women were enrolled and randomized in a 1:1 ratio to receive either Cervarix or Hepatitis-A control vaccine in a three dose schedule at 0, 1 and 6 months.