Vaccine 26 (2008) 6844–6851

Contents lists available at ScienceDirect

Vaccine

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

HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine

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ARTICLE INFO

Article history:
Received 9 July 2008
Received in revised form 4 September 2008
Accepted 26 September 2008
Available online 16 October 2008

Keywords:
Human Papillomavirus
Humoral immunity
Immune memory

ABSTRACT

The efficacy of the quadrivalent Human Papillomavirus (HPV) vaccine is thought to be mediated by humoral immunity. We evaluated the correlation between quadrivalent HPV vaccine-induced serum anti-HPV responses and efficacy. 17,622 women were vaccinated at day 1, and months 2 and 6. At day 1 and at 6–12 months intervals for up to 48 months, subjects underwent Papanicolaou and genital HPV testing. No immune correlate of protection could be found due to low number of cases. Although 40% of vaccine subjects were anti-HPV 18 seronegative at end-of-study, efficacy against HPV 18-related disease remained high (98.4%; 95% CI: 90.5–100.0) despite high attack rates in the placebo group. These results suggest vaccine-induced protection via immune memory, or lower than detectable HPV 18 antibody titers.

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doi:10.1016/j.vaccine.2008.09.073

1. Introduction

The lifetime risk of infection with the Human Papillomavirus (HPV) exceeds 50% [1,2]. HPV infection can cause epithelial dysplasia and cancer of the cervix, a significant proportion of cancers of the genitalia (both genders), anal canal, and the oropharynx, as well as benign tumors of the genitalia (condylomata acuminata) and the larynx (recurrent respiratory papillomatosis [RRP]) [3–8].

HPV types are defined by sequence variation in the gene encoding the L1 protein, the major constituent of the viral capsid. Over 40 different HPV types are known to infect cervical, anogenital, and oropharyngeal epithelia. These types are divided into two groups: (a) high-risk HPV types that can cause cancer; and (b) low-risk HPV types that rarely cause cancer, but commonly cause dysplastic lesions. Among the high-risk HPV types, HPV 16 and HPV 18 cause approximately 70% of cervical and anal cancer cases [9], and over 80% of HPV-related external genital and oropharyngeal cancer cases. HPV 6 and HPV 11 are low-risk HPV types that cause approximately 90% of all genital wart cases [10] and virtually all RRP cases [11].

A prophylactic vaccine targeting HPV types 6, 11, 16, and 18 has been developed, and is currently available in many countries. This vaccine contains L1 proteins of the 4 vaccine HPV types arranged as 4 separate species of virus-like particles (VLPs) adsorbed onto amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant. In studies, prophylactic administration of this vaccine to 16–26-year-old women was 96–100% effective in preventing HPV 16- and HPV 18-related cervical squamous cell cancer, cervical adenocarcinoma, vulvar cancer, and vaginal cancer (based on a demonstration of efficacy against HPV 16- and HPV 18-related cervical intraepithelial neoplasia [CIN] grade 3, cervical adenocarcinoma in situ [AIS], vulvar intraepithelial neoplasia [VIN] grades 2/3, and vaginal intraepithelial neoplasia [VaIN] grades 2/3, respectively) [12–15]. The vaccine was 98–100% effective in preventing HPV 6- and HPV 11-related genital warts and CIN.

Because HPV infection is sexually transmitted, men and women remain at risk of infection as long as they are sexually active. Thus, to be maximally effective, prophylactic HPV vaccines should induce long-lived protective efficacy (i.e., at least 10 years, preferably lifelong). In clinical trials, sustained protective efficacy was observed through at least 5 years following vaccination onset [16]. Ongoing studies are evaluating the longer-term effectiveness of the vaccine.

To date, an immune marker that can identify vaccinated subjects who are protected from acquisition of infection with types targeted by the vaccine has not been identified. Such a marker would be useful in defining the duration of vaccine-induced protective efficacy (and the timing of administration of a booster dose of vaccine, if needed). An immune marker would also simplify the bridging of protective efficacy of the quadrivalent HPV vaccine to new populations and to new formulations. Additionally, an immune marker would aid in the evaluation of follow-on multivalent vaccines.

Preclinical studies have suggested that the protective efficacy of the quadrivalent HPV vaccine is mediated by anti-HPV L1 humoral responses [17–19]. Administration of L1 VLP vaccines targeting animal papillomaviruses prevents infection and disease and is accompanied by induction of anti-L1 neutralizing antibodies. Transfer of serum from vaccinated animals to unvaccinated animals protected the unvaccinated animals from acquisition of infection and disease following a virus challenge. On the basis of these findings, Phase II and Phase III clinical trials of the quadrivalent HPV vaccine in young–adult women have focused on measurement of serum anti-HPV L1 responses shortly after completion of the 3-dose vaccination regimen and for up to 4.5 years thereafter. To define a candidate immune correlate of vaccine efficacy, an evaluation of the correlation between vaccine-induced serum anti-HPV responses and the vaccine's protective efficacy was conducted. We evaluated this correlation among 17,622 young adult women enrolled in efficacy studies of the quadrivalent HPV vaccine.

2. Materials and methods

2.1. Design of the phase III clinical trials

Protocols 013 (NCT00092521) and 015 (NCT00092534) (termed FUTURE I and FUTURE II, respectively) were phase III, randomized, double-blind, placebo-controlled clinical trials designed to investigate the prophylactic efficacy of the quadrivalent (types 6, 11, 16, 18) HPV L1 VLP vaccine (GARDASIL™/SILGARD™, Merck and Co., Inc., Whitehouse Station, NJ) on HPV 6/11/16/18-related CIN, AIS, or cervical cancer (protocol 013 co-primary endpoint); HPV 6/11/16/18-related condylomata acuminata, VIN, VaIN, vulvar cancer, or vaginal cancer (protocol 013 co-primary endpoint), and HPV 16/18-related CIN 2/3, AIS, or cervical cancer (protocol 015 primary endpoint) [12,15].

Between December 2001 and May 2003, 17,622 15–26-year-old women were enrolled in the two trials (17,599 received at least 1 dose of vaccine or placebo). The trials enrolled women who reported 0–4 lifetime sexual partners at day 1. Enrolled subjects with clinical evidence of genital HPV disease at day 1 were discontinued from the study prior to randomization. Subjects received intramuscular injections of quadrivalent HPV vaccine or visually indistinguishable placebo at enrollment (day 1), month 2, and month 6. Each protocol was approved by the institutional review boards (ethical review committees) at participating centers and informed consent was received from all subjects enrolled. The designs of protocols 013 and 015 are described elsewhere [15,20].

2.2. Study vaccine

The quadrivalent vaccine consisted of a mixture of four recombinant HPV type-specific VLPs composed of full-length L1 major capsid proteins of HPV types 6, 11, 16 and 18 synthesized in *Saccharomyces cerevisiae* [21–23]. The vaccine is comprised of 20 μg of HPV 6 VLP, 40 μg of HPV 11 VLP, 40 μg of HPV 16 VLP and 20 μg of HPV 18 VLP, formulated with 225 μg of amorphous aluminum hydroxyphosphate sulfate adjuvant. The placebo contained the same adjuvant and was visually indistinguishable from vaccine.

2.3. Clinical follow-up and laboratory testing

Examination for the presence of genital warts and vulvar and vaginal lesions was performed at enrolment (day 1), month 3 (protocol 013 only), and months 7, 12, 24, 36, and 48 (also at months 18 and 30 for protocol 013). ThinPrep™ (Cytyc, Boxborough MA, USA) cytology specimens for Pap testing were collected at enrollment (day 1), month 7, and at 6–12-month intervals thereafter. Cytology specimens were classified using The Bethesda System-2001 [24]. Procedures for algorithm-based cytology, colposcopy and biopsy referral have been described previously [12,15]. Biopsy material was first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN), and then read for endpoint determination by a blinded panel of four pathologists as described previously.

Blood samples were obtained at enrollment (day 1) for anti-HPV serology testing for HPV types 6, 11, 16, and 18 using competitive Luminex-based immunoassays (cLIA; developed by Merck Research Laboratories, West Point, PA, using technology from the Luminex Corporation, Austin, TX) [25]. Dilution-corrected serostatus cutoffs were 20 mMU/mL for HPV 6, 16 mMU/mL for HPV 11, 20 mMU/mL