Prophylactic HPV vaccines: Reducing the burden of HPV-related diseases

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Abstract

HPV-associated diseases, such as cervical and other anogenital cancers, cervical and anal intraepithelial neoplasia, genital warts, and recurrent respiratory papillomatosis confer considerable morbidity and mortality, and are significant health care concerns. Successful vaccination strategies that protect against HPV infection are expected to substantially reduce HPV-related disease burden. Prophylactic HPV vaccines in late stages of clinical testing are composed of HPV L1 capsid protein that self-assemble into virus-like particles (VLPs) when expressed in recombinant systems. Proof-of-principle trials have suggested that intramuscular injections of VLPs results in strong adaptive immune responses, both B- and T-cell mediated, that are capable of neutralizing subsequent natural infections. Furthermore, phase 2 trials of a bivalent vaccine designed to protect against high-risk HPV types 16 and 18 and a quadrivalent vaccine designed to protect against HPV 16 and 18, and low-risk, genital wart-causing HPV 6 and 11 have demonstrated that VLP vaccines reduce the incidence of HPV-associated disease in vaccinated individuals. To derive the greatest public health benefit, HPV vaccines offering protection from cervical cancer and genital warts will, ideally, be administered prior to the initiation of sexual activity; therefore, educational initiatives will be essential to communicate the risks and adverse consequences of HPV infection and to foster widespread vaccine acceptance.

Keywords: HPV; Cervical cancer; Genital warts; VLP vaccines; Vaccination; Cervical dysplasia

1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted diseases worldwide. Clinical manifestations of HPV infection are exceedingly common, and subclinical infection is widespread. One in 100 sexually active Americans has clinically apparent genital warts [1], and 8% of college-aged women have PAP test abnormalities indicative of infection with HPV [2]. When polymerase chain reaction (PCR) analysis is used to detect evidence of HPV infection, the prevalence becomes substantially higher: 46% of women in one sample [1] and 33% of men in another [3] were diagnosed as HPV positive. The highest incidence of HPV infection is consistently found in sexually active women less than 25 years of age; this holds true even when adjustments are made for number of sexual partners [1]. Furthermore, while condoms may offer some protection against HPV [4], because the virus is transmitted through skin-to-skin contact, they may not fully prevent infection. In support of this hypothesis, HPV DNA has been reported in approximately 20% of women who have never had vaginal intercourse [5], suggesting that abstaining from penetrative intercourse is not completely protective against infection. Thus, a majority of the population is at risk for acquiring HPV; the lifetime risk of HPV infection for sexually active males and females is approximately 50% [1].

Papillomaviruses are epitheliotropic viruses present in the skin and mucosa of several animals. In humans, more than 100 types have been described. Mucosal and genital HPVs, consisting of about 30 types, are divided into low-risk (HPV 6, 11, 40, 42, 44, 54, 61, 70, 72, 81) and high-risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, 68, 73, and 82), according to their presence in malignant lesions of the cervix [6]. The
four HPV types implicated in the majority of HPV-related diseases have been the focus of vaccine development efforts. HPV 6 and 11 are low-risk types associated with the majority of cases of genital warts, and HPV 16 and 18 are high-risk types implicated in approximately 50% of cases of high-grade cervical intraepithelial neoplasia (CIN), invasive cancer at a variety of anogenital sites [1], and 60–72% of cervical cancers [7]. Cervical cancer is the leading female malignancy in many developing countries. Every year, persistent HPV infection results in nearly 500,000 cases of cervical cancer. Furthermore, screening programs and treatment for precancerous states are a major economic burden in developed countries [7]. While cervical cancer screening reduces mortality from cervical neoplasia, it does not prevent HPV infection or development of pre-cancerous lesions, such as high-grade CIN 2/3 or persistent low-grade lesions (CIN 1), all of which may require treatment. Although cervical cancer is the cancer most frequently associated with HPV, HPV is also implicated in many anal, perianal, vulvar, and penile cancers, as well as approximately 20% of oropharyngeal cancers [8]. Genital warts, although not malignant, are associated with significant psychosocial morbidity and typically require multiple physician visits for diagnosis and treatment [9,10]. Recurrent respiratory papillomatosis, a disease that can affect the children of women with HPV infection, is rare but, together with ongoing surgical interventions required to maintain an open airway, can cause chronic inflammation, permanent vocal cord damage, and significant childhood morbidity and mortality [11]. A vaccine that is formulated to protect against the most common disease-causing HPV types would be expected to reduce the morbidity, mortality, and cost burden of HPV associated diseases.

Vaccines in clinical development are based upon recombinant HPV capsids, termed virus-like particles (VLPs), formed by heterologous expression of the major capsid protein L1 in yeast or insect cells. Purified VLPs are morphologically identical to natural HPV virions and have been shown to produce type-specific antibody responses in both animal and human models [12–14]. Because VLPs do not contain viral genetic material, there is no risk of oncogenic progression or productive infection associated with vaccination [15,16].

2. Monovalent proof-of-principle vaccine trials

Randomized, placebo-controlled proof-of-principle trials of monovalent vaccines for HPV types 11, 16, and 18 have been performed to determine the safety of vaccine formulations, as well as the immunogenicity of VLPs in humans [17–21]. Each study measured anti-HPV antibody titers before, during, and after vaccination. Overall, HPV VLPs induced high levels of antibodies at concentrations much higher than those found during naturally occurring infections (Fig. 1). Nearly all vaccine recipients seroconverted to anti-HPV positive, and produced antibodies that were capable of neutralizing VLPs in vitro [18–21]. Furthermore, between 24 and 52% of women who received an HPV 11 vaccine, and 5–10% of women who received an HPV 16 vaccine showed measurable levels of the appropriate HPV antibody in cervicovaginal secretions [20]. This number is far smaller than the number of women who developed serum antibodies and was not strongly correlated with the level of serum antibodies. Research is ongoing to determine the factors that contribute to this desirable effect. In addition, the levels of activated HPV-specific T cells were far higher in vaccinated individuals than in individuals naturally infected with HPV [19]. This result suggests that vaccination with VLPs may induce adaptive immune responses that are superior to those induced by natural infection, and provided strong grounds to continue VLP vaccination studies. Moreover, in a placebo-controlled study, an HPV 16 L1 VLP vaccine was shown to be 100% efficacious in preventing HPV 16-related CIN through 17 months following vaccination in women who were HPV 16-naïve at the time of vaccination [22].

Across these trials, the most common side effects were pain at the injection-site and injection-site reactions. Pain was frequently associated with both placebo and active immunizations [19–22]. Pain was also more common with an MF59 adjuvant than with an aluminum adjuvant or no adjuvant [21]. Injection-site reactions occurred in both placebo and active agent inoculations [19–22], although the tendency was for such reactions to be more common in the vaccine group [17] and at higher doses of vaccine [20,21]. Serious adverse events were extremely rare and judged to be unrelated to vaccine [17,19–22].

Since many types of HPV cause disease in the mucosal epithelium, and the immune response to HPV is thought to be mainly type specific [16], the utility of vaccination can be greatly increased by combining VLPs into multivalent vaccines that provide protection against multiple HPV types.
3. Clinical trials of polivalent vaccines

3.1. Bivalent vaccine for prevention of cervical cancer

Phase 2 testing of a bivalent HPV 16/18 vaccine aimed at preventing cervical cancer took place in North America and Brazil [23]. Subjects were healthy women ages 15–25 years with a history of ≤6 male sexual partners, and were seronegative for HPV types 16 and 18 and HPV DNA negative for 14 high-risk types at study entry. Each dose of vaccine consisted of 20 μg of HPV 16 L1 VLP, 20 μg of HPV 18 L1 VLP both produced in insect cells, and 500 μg of aluminum hydroxide and 50 μg of 3-deacylated monophosphoryl lipid A as an adjuvant. The placebo contained only AS04. Placebo (n = 553) or vaccine (n = 560) was administered by intramuscular injection at 0, 1, and 6 months. To assess immunogenicity, serum was collected at 0, 1, 6, 7, 12, and 18 months. HPV DNA testing was conducted at 0, 6, 12, and 18 months, and self-obtained cervicovaginal samples were requested at months 0 and 6, and then every 3 months. Eighty-five percent of participants (n = 958) completed the trial through month 18. The few study dropouts were minimal and equally distributed between the vaccine and placebo groups.

The randomized, double-blind controlled study found the HPV 16/18 L1 VLP vaccine effective at preventing both incident (one positive PCR test) and persistent (at least two positive PCR tests for the same HPV type) of HPV 16 and 18 infections. The vaccine was 75.2% (95% CI, 55.3–86.2; P < .0001) and 59.5% (95% CI, 22.7–78.8; P = .005) effective at preventing incident HPV 16 and HPV 18 infection, respectively, in the intent-to-treat cohort. Efficacy was higher in the smaller according-to-protocol cohort: 81.2% (95% CI, 54.8–92.2; P < .0001) against HPV 16 and 65.1% (95% CI, 10.8–86.3; P = .021) against HPV 18. The vaccine was more effective in preventing persistent infection: 84.5% (95% CI, 55.2–94.6; P < .0001) for HPV 16 and 91.1% for HPV 18 (95% CI, 51.0–98.9; P = .003) in the modified intent-to-treat population, and 100% for both HPV 16 and HPV 18 in the according-to-protocol population (95% CI, 71.5–100; P = .0002; and 95% CI, 72.2–100; P = .040, respectively). In addition, HPV 16/18-associated cytological abnormalities were significantly less common in the vaccine than in the placebo group, with a calculated efficacy of 92.9% (95% CI, 70.0–98.3; P < .0001) (Fig. 2).

This bivalent vaccine was very safe, and the adverse events were both mild and transient. The vaccine group had significantly more injection-site reactions than did the placebo group, but these symptoms were observed to be transient and mild. General symptoms such as fatigue, gastrointestinal complaints, headache, itching, and rash, were equally distributed between the placebo and vaccine groups. Discontinuations were not attributed to adverse events related to the vaccine [23].

3.2. Quadrivalent vaccine for prevention of cervical cancer and genital warts

Results of a phase 2 randomized double-blind placebo-controlled trial have also been reported for a quadrivalent vaccine designed to protect against the most common HPV types associated with both genital warts (HPV types 6 and 11) and cervical cancer (HPV types 16 and 18) [24]. Subjects were healthy female residents of Brazil, Europe, and the United States between the ages of 16 and 23 years with a history of ≤4 sexual partners. Women with prior HPV infection were not excluded.

Study participants received either quadrivalent vaccine (20 μg of HPV type 6, 40 μg of HPV type 11, 40 μg of HPV type 16, and 20 μg of HPV type 18, with aluminum adjuvant; n = 277) or placebo (n = 275), at day 1, month 2, and month 6. Gynecologic exams were performed at day 1 and months 7, 12, 24, and 36; external genital, lateral vaginal, and cervical swabs for type specific PCR analysis were obtained at day 1 and months 7, 12, 18, 24, 30, and 36; and serum samples were taken at day 1 and months 2, 3, 6, 7, 12, 18, 24, 30, and 36. In addition, all subjects underwent colposcopy at the end of the study. Study dropout was low and similar between placebo (5.5%) and vaccination (7.6%) groups.

In addition to consistently producing high levels of antibodies – much higher than those found in individuals with a history of infection – the quadrivalent vaccine was overall 90% effective at preventing persistent infection with HPV types 6, 11, 16, or 18 and associated genital disease in the per-protocol cohort (P < .001; 95% CI, 71–97). Similar efficacy against infection or disease was reported in the modified intent-to-treat cohort (89%; 95% CI, 73–96). Specifically, in the modified intent-to-treat population, the vaccine was 88% effective at preventing persistent infection (P < .0001) and 100% effective at preventing histologically proven disease associated with HPV types 6, 11, 16, or 18 (P = .0009).
16/18-associated CIN 2/3, AIS, and cervical cancer over two valent HPV vaccine was 100% effective at preventing HPV disease (FUTURE II) trial were recently released: the quadrivalent vaccine was expected to become available by the end of 2005. Data from cacy studies of the quadrivalent vaccine, and results are expected to be published soon. Data from the placebo group.

Both of these vaccine studies were restricted to young women. From a public health perspective, young women who have yet to become sexually active would be the ideal target population for vaccination. In addition, men would also benefit from the quadrivalent vaccine because they are susceptible to genital warts, can serve as vectors for HPV types associated with cervical cancer, and can develop penile, scrotal, and anal cancer, which, similar to cervical cancer, are strongly associated with HPV. In addition, more information is needed to determine when, if ever, booster vaccines will be required so that immunity can be sustained throughout an individual’s sexual life. More than 25,000 men and women from across the globe were recruited to participate in phase 3 safety and efficacy studies of the quadrivalent vaccine [25], and results are expected to become available by the end of 2005. Data from the FUTURE II trial were recently released: the quadrivalent HPV vaccine was 100% effective at preventing HPV 16/18-associated CIN 2/3, AIS, and cervical cancer over two years of follow-up [26].

4. Cost-benefit analysis of HPV vaccination

Potential reductions in disease and the cost-benefit ratio of HPV vaccines can be assessed via mathematical models that combine known factors, such as disease prevalence and cost, with estimates of unknown variables, such as vaccine efficacy or length of vaccine-induced immunity. Multiple publications have used this approach and come to similar conclusions in modeling the cost-benefit ratio of an HPV vaccine to prevent cervical cancer [27–30]. However, these models do not include reductions in HPV-associated, non-cervical anogenital and oropharyngeal cancers that may occur with widespread administration of an HPV vaccine.

If an HPV vaccine has a high efficacy rate and immunity is maintained for several years, vaccinating women earlier in adolescence is predicted to be the best strategy for reducing HPV infections and HPV-associated disease. It is estimated that the lifetime incidence of cervical cancers would decrease by more than half if an early vaccination program is implemented [27]. Vaccinating men in addition to women may further reduce the incidence of cervical cancers. If booster shots are eliminated from the model, or if the vaccine is revealed to have a rapid decline in efficacy, it becomes even more advantageous to vaccinate young men [27]. Regardless of vaccine efficacy and the window of immunity, it is crucial to vaccinate individuals before they become sexually active.

Mathematical models have been designed to evaluate the cost-benefit of an HPV vaccine using vaccination cost estimates of $200–$300 plus an additional $100 for booster shot [27–29]. Using these hypothetical numbers as a starting point, cost/quality-adjusted life-year (QALY) of a vaccine administered to early adolescent girls and accompanied by a booster shot 10 years later would be considerably lower than the cost/life-year (LY) of the annual Pap test currently recommended to detect cervical cancer ($14,583/QALY versus $166,000/LY) [27]. However, an HPV vaccine would not completely eliminate the need for Pap tests because Pap tests would still be required to detect cervical cancers caused by non-vaccine HPV types. Cost-effectiveness of the vaccine will rely heavily on its ability to delay screening initiation and to extend the interval between screenings [30]. Mathematical modeling suggests that the most effective strategy with a cost-effectiveness ratio of less than $60,000 would be vaccination of females at age 12 with triennial cytologic screening starting at age 25. Such an approach is estimated to reduce the overall lifetime cervical cancer risk by 94% compared with no intervention. The estimate is based on 70% vaccine efficacy; if the vaccine efficacy were greater, the frequency of cytologic screening could decrease correspondingly [30].

Other models with slightly different parameters have suggested similar solutions at similar costs [29] (Fig. 4). These models do not address potential cost reductions for both the treatment of cervical cancer and genital warts. Genital warts, although not life threatening, are exceedingly common, and carry significant costs as well as psychosocial morbidity and stigma. Furthermore, a mother with genital
Fostering HPV vaccine acceptance

The best vaccine is of no use unless it is correctly administered to the individuals that would benefit most. HPV vaccines may offer several distinct challenges, many of which have to do with the ideal age for vaccination. Adolescents visit doctors infrequently and the HPV vaccination will most likely require three distinct visits. In addition, among those individuals who do have adequate access to health care resources, there will be the dual challenge of educating health care practitioners about the importance of recommending the vaccine and gaining parental acceptance and consent. In particular, pediatricians will play key roles in administering HPV vaccines and fostering vaccine acceptance. Educational efforts directed towards pediatricians should stress the importance of recommending the vaccine about the need to consider sexual health prior to initiation of activity. Physician attitudes are extremely influential to both parents and adolescents, and perception that the physician regards the HPV vaccine as important and recommended will be a critical step towards vaccine acceptance.

6. Summary

HPV VLP vaccines that protect against the most common disease-causing HPV types are in late stages of clinical development and will become available in the near future. Results from phase 2 and 3 clinical trials have suggested that HPV vaccines are safe, highly immunogenic, and protect against disease-causing HPV types are in late stages of clinical development will become available in the near future. Results from phase 2 and 3 clinical trials have suggested that HPV vaccines are safe, highly immunogenic, and protect against incident and persistent infection, as well as HPV-associated diseases. These vaccines are expected to offer a cost-effective means for dramatically reducing the morbidity and mortality of cervical/anogenital cancers and recurrent respiratory papillomatosis, as well as the emotional and economic burdens of abnormal Pap tests and genital warts. Widespread vaccine acceptance will require the combined efforts of policy makers, health care providers, and parents to fully realize the potential public health benefits of mass vaccination. Indeed, education of physicians, parents, and adolescents will be crucial for delivering HPV vaccines to target populations during the window of highest vaccine efficacy, prior to sexual debut.

References


