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Review Article

Advances in human papilloma virus vaccines: a review

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ABSTRACT

Cervical cancer is the second most common cancer among women and third leading cause of cancer death. Approximately 500,000 women worldwide develop new cases of cervical cancer annually, with 80% of these new cases occurring in developing countries. Human papilloma virus (HPV) infection is the main factor associated with the development of cervical cancer. The currently available HPV vaccines, gardasil and cervarix, can prevent infection by certain HPV types, but not all. At present, research efforts are being devoted to developing broader spectrum preventative vaccines, as well as therapeutic vaccines. To confer additional therapeutic activities, chimeric vaccines have been developed. Multivalent vaccine technologies employ strategies for addressing a broader spectrum of HPV types or for combining HPV with other pathogens. Edible vaccines are also disclosed. For needleless immunization, jet gun, gene gun and microneedles have been developed. Biodegradable and mucoadhesive polymer-based vaccine formulations have been developed to deliver vaccines through the mucosa and enhance immunogenicity. Various viral vectors of recombinant HPV DNA vaccine are disclosed.

Keywords: Cervical Cancer, HPV, Vaccines

INTRODUCTION

Cervical cancer is the fifth most common cancer in humans, the second most common cancer in women, third leading cause of cancer death worldwide and primary cause of cancer death in low and middle income countries. The worldwide incidence of cervical cancer is approximately 510,000 new cases annually with approximately 288,000 deaths worldwide.[1] According to World Health Organization (WHO), in India approximately 1,34,420 women are diagnosed with the disease every year, and of them 72,825 die.[2]

Persistent infection with high-risk human papillomavirus (hrHPV) has been recognized as the cause of cervical cancer and its precursor lesions (i.e. cervical intraepithelial neoplasia [CIN] or squamous intraepithelial lesion for squamous cell carcinoma and adenocarcinoma in situ [AIS] for adenocarcinoma).[3-5] More than 100 HPV types are known to occur that are categorized into three broad categories depending upon their oncogenic potential: high-risk types including HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73 and -82; intermediate types including HPV-26, -53, -66 and low-risk types including HPV-6, -11, -40, -42, -43, -44, -54, -61, -70, -72, -81 and -CP6108.[6] HPV infections with high-risk genotypes including types 16, 18, 31 and 45 can be found in more than 90% of invasive cervical cancer, while HPV types 16 and 18 have been detected in more than 70% of cervical cancers and are considered to be the leading causes of this disease.[7] It is also suggested that women co-infected with multiple HPV-type infections are prone to persistent HPV infection and hence advancement of the disease. Although biological significance of multiple HPV-type infection is not known, it seems that they act synergistically accelerating the process of disease progression.[8]

Most HPV infections of the cervix are asymptomatic and more than 90% of detected infections are cleared within 2 years. The degree of protection and duration of immunity after natural infection are not known. Only 50–60% of women develop serum antibodies to HPV after natural infection.

Genital HPV infection is primarily transmitted by genital skin-to-skin contact, usually but not necessarily during sexual intercourse.[10-12] HPV infection can occur at any age and has been reported in healthy young children.[13] In a cross-sectional study of nearly 20,000 women aged 15–74 years without cervical lesions,[14] age-standardized HPV prevalence varied more than 10-fold between populations. There is an inverse relationship between age and human papillomavirus (HPV) prevalence in many countries, but in some of the poorest areas studied HPV prevalence was high across all age groups.[14] In some countries, cross sectional and cohort studies have shown a U-shaped curve with a first peak in women under 30 years of age and a second peak in women aged 55–64 years.[14] Among women infected with HIV, a recent meta-analysis found that almost 40% of those with no cervical cytological abnormalities had HPV infection.[15] Simultaneous infection with multiple HPV genotypes is more common in HIV-infected women than in women without HIV. HIV-infected men and women are at increased risk of HPV associated anal cancer.[16]

HPV infection risk is associated with the number of sex partners that the woman or her partner has had over a lifetime and recently.[17-19] Some cross-sectional studies found no evidence of a reduction in HPV prevalence through condom use.[19-21] Lower HPV prevalence has been reported among women using condoms with their regular partners.[22] A protective effect against HPV infection and cervical cancer incidence has also been reported for women with circumcised partners.[23]

Compared with the available current strategy to control the cervical cancer like regular screening of women for precancerous lesions and treating them as necessary, condom use, circumcision and alteration in life style, immunization definitely offer a cheaper, logistically simpler, and more effective intervention to control cervical cancer and places fewer demands on the health care system as well as on women. Thus, the development of newer, safe and more effective vaccines and strengthening the immunogenicity of currently available vaccines are a primary need for reduction of cervical cancer incidences and deaths as well.

HPV VACCINE TYPES AND TARGETS

Since few types of HPV can be propagated in tissue culture, it is not possible to develop inactivated or attenuated live virus vaccines as with some other viral diseases.[24,25] Therefore, HPV vaccines currently under development are part of a new generation of vaccines that employ genetic engineering. Recombinant genetic engineering also allows the production of subunit vaccines that include only a portion of a disease causing organism; since they do not contain the cancer-inducing viral genes, these may be safer and create fewer side effects than vaccines made of whole organisms.[26] Three categories of HPV proteins are potential targets for vaccines; each is expressed during different stages of infection and disease.

The capsid proteins L1 and L2 make up the outside coat or shell of HPV particles. While neutralizing antibodies to both capsid proteins have been found, there is thirty times as much L1 as L2 on the shell of HPV particles, and the predominant immune response is to epitopes on L1.[25] Therefore, most candidate vaccines have targeted L1 rather than L2. Once HPV is integrated into tumor cells, however, the capsid proteins are not always present. This means L1 and L2 are not reliable targets for a therapeutic vaccine.[27]

The oncoproteins E6 and E7 continue to be expressed during later stages of disease. They bind p53 and pRB, which are human tumor suppressor genes.[27] The oncoproteins are involved in the malignant transformation of HPV-infected cells and are thought to be required for continued tumor growth.[28] They are the primary targets of therapeutic vaccines, most of which have been designed to treat later stages of disease. The replication proteins E1 and E2 are necessary for HPV to replicate within cells before the virus is integrated into the host DNA.[27,28] Because E1 and E2 are expressed in higher levels than E6 and E7 early in the progress of an HPV infection, several researchers have suggested that they may be the best targets for a therapeutic vaccine designed to treat early stages of disease, such as low-grade dysplasias.[29,30]

Researchers are investigating the following approaches to produce HPV vaccines.

Virus-Like Particles (VLPs)

A major breakthrough in HPV vaccine research came with the discovery that the capsid proteins L1 and L2 (or L1 alone) self-assemble into virus-like particles (VLPs) when expressed in cells. VLPs closely resemble native HPV particles and include the conformational epitopes that induce virus-neutralizing antibodies. Therefore, the immune system perceives VLPs as infectious viruses and responds accordingly.[24,30] Because VLPs are empty and do not include viral DNA, they are not infectious. VLPs have been produced for at least ten HPV types so far (6, 11, 16, 18, 31, 33, 35, 39, 45, and 58), proving the applicability of this approach for a multivalent vaccine.[31]

Two prophylactic HPV-VLP vaccines are available globally and in India. A bivalent HPV16/18 L1 VLP vaccine (Cervarix; Glaxo Smith Kline Biologicals, Rixensart, Belgium),[32-34] and a quadrivalent HPV6/11/16/18 L1 VLP vaccine (GARDASIL; Merck,

Whitehouse Station, NJ, USA).[35-39] The vaccines are administered by intramuscular injection (0.5ml) either in deltoid muscle or in the anterolateral thigh at a dose of 20–40 micrograms of each VLP at three time points over a 6-month period (0, 1 or 2, and 6 months).[40] For storage and administration of vaccine manufacturer's instructions should be followed.

The recommended age for initiation of vaccination is 9-12 years. Catch up vaccination is permitted up to the age of 26 years. At present there is no data available to recommend the use of boosters.[41,42] HPV vaccine can be given simultaneously, with Hepatitis B and TdaP. If the HPV vaccine schedule is interrupted, the vaccination needs not to be restarted. If vaccination is interrupted after the first dose, the second dose should be administered as soon as possible, with an interval of 12 weeks between the second and third doses. If only third dose is delayed, it should be administered as soon as possible.[42]

The most common adverse reactions are local reactions like pain and swelling with erythema. No serious vaccine- related side effects have been reported till date.[42] The vaccine is not recommended for use in pregnant women. Lactating and immunocompromised females can receive the vaccine, but the efficacy and the immune response may be poor in these females.[42,43]

Evidence to date suggests safety and immunogenicity of HPV vaccines in men (10–15 years of age) as well.[44] Theoretically, benefit of male vaccination includes a decrease in HPV infections and HPV16/18-associated (pre)malignant lesions and HPV6/11-associated anogenital warts (for the quadrivalent vaccine) in men. Models have shown that once vaccine coverage in both women and men exceeds 50%, the benefit of vaccination of men in addition to women is marginal and decreases further with increase in coverage.[45] Australia is the first country to approve quadrivalent HPV vaccine in males between 9 and 15 years old, and the vaccine was approved for administration to males between the ages of 9 and 26 years in other developed nations.[41]

Efficacy data of currently available HPV vaccines demonstrate protection against persistent HPV16 and/or HPV18 infections (lasting 6 months or more) of more than 90% up to at least 5 years after vaccination.[32-35,38-40,46,47] In addition, cross-protection was demonstrated for the bivalent vaccine reflected by a reduction of 6-month persistent infections with HPV31 (HPV16 related) by 36% (95% CI 0.5–60), HPV45 (HPV18 related) by 60% (95% CI 3–85), and HPV52 (HPV16 related) by 32%(95%CI 4–52).[33] In a combining analysis cross-protection against persistent infection with HPV31/33/35/39/45/51/ 52/56/58/59, mainly owing to HPV 31/45 [i.e. 45% protection (95% CI 18–63)], was observed for the quadrivalent vaccine.[48] The effect was most pronounced for HPV 31/45, i.e. 45% protection (95% CI 18–63).[48]

The current price of the quadrivalent vaccine is over $100 per dose (with three doses recommended to achieve full protection). Manufacturers have declared their willingness to tier prices for countries with different economic settings. Vaccine price is likely to be a major determinant of the cost and affordability of any vaccine programme. Administration costs are expected to be higher than for traditional vaccines, since very few countries have universal programmes for delivering health care to pre-adolescents.

Recombinant live vector vaccines

This vaccine strategy is used for the development of therapeutic vaccine against human papilloma virus. Since HPV cannot be raised in culture, researchers have added HPV genes to other bacteria and viruses to create recombinant live vector vaccines. Recombinant live vector vaccines combine the advantages of subunit and live, attenuated vaccines.[26] Because they express only selected HPV genes, they would be relatively safe. Like other live, attenuated vaccines, they could produce long-term protection with a single inoculation, and they could stimulate strong cell-mediated immunity as well as antibody-mediated immunity.

Recombinant live vector vaccines have some significant disadvantages, however.[26] Live vectors, even attenuated ones, are not safe for use in immunocompromised individuals (particularly vector vaccines using viruses). This poses a special problem in developing countries, where it may not be feasible to determine an individual's HIV status before immunization, and where other factors such as malnutrition may depress the immune system. Another problem is that the vector usually expresses low levels of foreign (HPV) antigens, so that the immune response to the vector may overshadow the immune response to HPV.

Either a virus or a bacterium can be used as the vector in a recombinant live vector vaccine so long as it is harmless. The key is selecting a vector that is capable of infecting humans without causing clinical illness.[50,51] Viral vectors that are being used are Adenovirus serotype 5 (Ad5), Semliki Forest Virus (SFV), Modified Vaccinia Virus Ankara (MVA), Measles virus based vectors and baculovirus, while Listeria monocytogenes is being as vector among bacteria for the development of vaccines against HPV. These therapeutic vaccines are in phase II clinical trials.

Naked DNA vaccines

"Naked" DNA is among the newest approaches to vaccine development. The simplicity and attractiveness of DNA vaccines are obvious, as they are represented by plasmid DNA which is easy to produce in laboratory bacterial strains at comparative low cost, as well as easy to store and transport since plasmid DNA is chemically

and biologically stable. Prophylactic naked DNA vaccines against HPV are under investigation.

It is found that DNA vaccines against HPV are potent vaccines with multiple advantages over other kinds of vaccines. They induce cell-mediated as well as antibody-mediated immunity, they raise antibodies against native forms of proteins, and they can induce long-lasting immunity since host cells may continue producing antigens for years.[52] They also simplify the production of multivalent vaccines since purification and characterization of only a single chemical entity, DNA, is needed. DNA vaccines also make it possible to define the immune response, producing exactly the types of T-cells desired, for example.[51,53]

DNA vaccines also have the potential to be less expensive than conventional vaccines, and easier to produce, distribute, and administer.[51, 53] Adjuvants are not needed. DNA vaccines are stable at both high and low temperatures, eliminating the need for a cold chain, which can account for 80 percent of the cost of vaccination programs in developing countries. They also have a long shelf life and can be stored dry or in an aqueous solution.

Although there is no risk of infection associated with DNA vaccines, they raise other potential safety issues that need further investigation. Injecting plasmid DNA into the genome of host cells might induce mutations, disrupt cellular genes, or cause other harm. It is possible that DNA vaccines might induce anti-DNA antibodies and produce autoimmune phenomena.[28]

Without an intranasal, oral, or other mucosal delivery system, DNA vaccines might not elicit mucosal immune responses as well as other types of vaccine.[53] In addition, introducing HPV genes that code for viral oncoproteins poses a risk and it is important that these be fully inactivated. To increase the potency of DNA vaccines, researchers are investigating the use of adjuvants, including genetic adjuvants that deliver immunostimulatory sequences along with the antigen sequences. Using DNA vaccines in combination with peptide or recombinant live vector vaccines also is under investigation.

Protein and peptide vaccines

Selected HPV genes are inserted into yeast or another organism, which produces large quantities of the chosen protein or peptide (short peptides also can be made synthetically). Once the peptides are purified, however, they lack the microbial components that trigger the human immune system and therefore prompt weaker immune responses than whole pathogens.[26] To overcome this problem, the peptides are combined with an adjuvant. Peptide vaccines are safe, easy to make at low cost, and involve minimal regulatory issues. However, it can be difficult to isolate the specific epitopes that elicit the desired immune response, and the peptides themselves may be misshapen and unable to elicit a potent immune response.[27,28]

Other disadvantages are that peptide vaccines do not generate a strong cytotoxic T-cell response, they may induce tolerance rather than protection, and multiple immunizations may be needed to produce long-lasting protective immunity.[26] Also, small peptides may be unstable *in vivo* and may not elicit the same immune response from different individuals.[30] These therapeutic vaccines are in phase I/II clinical trials.

Edible vaccines

Creating edible vaccines involves introduction of selected desired genes into plants and then inducing these altered plants to manufacture the encoded proteins. This process is known as transformation and the altered plants are called 'transgenic plants.' Like conventional subunit vaccines, edible vaccines are composed of antigenic proteins and are devoid of pathogenic genes. Thus they are safe especially in immunocompromised patients. These vaccines are inexpensive, heat stable, noninjectable, need not required purification and refrigeration and produce good mucosal response. These vaccines activate both mucosal and systemic immunity, as they come in contact with the digestive tract lining.[54] edible prophylactic vaccines are under investigation.

CONCLUSION

In developing countries, cervical cancer is the leading cause of cancer death in women, and 91% of global estimated HPV-related cancer deaths are due to cervical cancer. HPV vaccines are very effective at preventing infection and disease related to the vaccine-specific genotypes in women with no evidence of past or current HPV infection. Protection lasts for at least 5 years.

HPV vaccines will reduce but not eliminate the risk of cervical cancer, and screening programmes will be important interventions for cervical cancer even after HPV vaccines are introduced, although the procedures used for screening may need to be adapted.[55]

The primary target age group for HPV vaccines is likely to be pre-adolescent girls, but the cost-effectiveness of vaccinating other groups needs to be evaluated. With some HPV vaccine candidates about to enter Phase III clinical trials, a viable prophylactic vaccine against one or two types of HPV could be available in as little as five years. Most of the therapeutic vaccines under investigation are designed to complement conventional therapy for advanced disease, and it is not yet clear how much benefit they will offer and at what cost for these women. Therapeutic vaccines designed to clear HPV infections in their earliest stages are less well developed, but they hold greater promise for reducing the suffering and treatment costs associated with cervical disease. It is

important to continue developing appropriate screening and treatment programs for precancerous lesions at the same time as vaccine development efforts move forward.

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