Review Article

Prophylactic and Therapeutic Human Papillomavirus Vaccine: A breakthrough for women health

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Abstract

Human Papilloma Virus (HPV) associated cervical cancer is amongst the ten most common cancers in women in the developing world. New vaccines markedly reduce the economic burden of diseases on a country's health system. Two types of HPV vaccines are available; prophylactic and therapeutic. Prophylactic vaccines target (Late protein) L1 and to a lesser extent L2, which stimulate neutralizing antibody response and are recommended to individuals prior to infection. Therapeutic vaccines are recommended to individuals who are already exposed to HPV infection and these induce a specific T-cell mediated immune response targeted to (Early protein) E6 and E7 oncogenes for the eradication of existing lesion. Several studies have been done which show that these vaccines are highly effective. This review highlights the pathogenesis of HPV infection, importance of HPV vaccines, recent advances and few clinical trials on prophylactic and therapeutic HPV vaccine, their economic impact and the need to implement the vaccination programmes in the developing world.

Introduction

The modern era of vaccination initiated over 200 years ago, with the urge to eradicate smallpox using prior immunization with the cowpox. This continued during the nineteenth century with the introduction of several more vaccines to counter several infections. But major progress occurred in the 20th century.[1] Vaccines, especially for childhood use, are one of the most successful public health measures used in the last two centuries and have a good safety record. With the evident new technology- especially biotechnology - the ability to manipulate an immune response and increasing evidence of efficacy of many new vaccines, more interest is being shown in the use of vaccines to reduce the economic burden of diseases on a country's health system. Under the limelight are cancer preventing and therapeutic vaccines, because of the high economical impact of cancer on the health system.

Cervical cancer is one of the common cancers in women of the developing world. The risk factors of cervical cancer are early marriage, multiparty, prolong use of contraceptives, low socio-economic status and HPV (Human Papilloma Virus), particularly HPV- 16 which is associated with most cervical cancers.[2,3] The prevalence of cervical cancer in the developing world is 59.4 per 100,000,[4] which contributes a major cause in gynaecological cancer-related deaths. Globally, 493,000 new cases and 274,000 deaths are annually reported from cervical cancer.[5] It is estimated by the American Cancer Society that in 2008, approximately 11,070 new cases and 3870 deaths will be due to cervical cancer.[6] It reveals that even in a high coverage screening programme like that in the United States, all women are not able to receive the pap smear test.[7]

The clinical spectrum of diseases associated with HPV infection ranges from asymptomatic infection through benign warts (primarily caused by low risk HPV type 6 and 11) to invasive malignancy with over 70% of all cervical cancers associated with the high risk genotype 16 and 18.[8] Papanicolaou (Pap) smear test was introduced in 1943 to identify the precursor malignant lesions (dysplasia) and has proven to decrease the incidence of cervical cancer related mortality. But there is limitation of the screening method. This test is prone to errors at different levels,[9] resulting in a high number of false negative results (20-40%).[10] The major factor is the failure of detection of abnormal precursor's cells.[11] Due to the limitations of Pap smear test to miss a number of patients, frequently it leads to fatal consequences. Early detection of precursor lesions by screening programmes encompasses the cervical cancer and allows early initiation of ablative therapy to neoplasia.[12] Due to availability of prophylactic vaccines, morbidity and mortality due to cervical cancers can be reduced.

This review summarizes the pathogenesis of HPV infection, importance of HPV vaccines, recent advances and a few clinical trials on prophylactic and therapeutic HPV vaccines, their economic impact and issues that need to be considered prior to licensing and implementation of the vaccine in the developing world. It may be that an HPV vaccine that protects against the complications of HPV infection, such as cervical cancer will be one of the most significant health initiatives of this decade.

Pathogenesis of HPV infection:

Human Papilloma Viruses are small, enveloped viruses with a capsid, enclosing a double-stranded circular DNA genome and about 8 kb in length. Molecular techniques, especially PCR has detected more than 100 subtypes of HPV.[13] HPV subtypes are classified on the basis of their oncogenic potential into high risk subtypes (16, 18, 31, 33, 35. 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) and low risk subtypes (6, 11, 40, 42, 44, 54, 61, 70, 72, 81).[14] Low risk HPV 6 and 11 are responsible for anogenital warts, which is a common clinical presentation. High risk HPV16 and 18 are commonly found in cervical cancers and require about 10-15 years to transform from the initial infection to pre-invasive and invasive lesions. Sequence analysis of the genome shows that HPV16 and 18 are made up of early (E) and late (L) gene proteins. Six genes encode for transcription of the non-structural early proteins (E1, E2, E4, E5, E6, and E7) and two genes (L1, L2) encode for transcription of the major capsid proteins.[15] HPV oncogenic proteins, E6 and E7 are responsible for the malignant transformation of cervical cells. The function of E6 is to bind, inactivate and degrade p53 gene, while E7 binds to and inactivates retinoblastoma (rb) gene and causes uncontrolled cell proliferation. The E2 protein integrates with the host DNA and results in loss of E2 protein, which causes over expression of E6 and E7 proteins and results in malignant transformation of cells.[16,17]

Infections and malignancies associated with HPV are controlled by cytotoxic-T cell mediated immunity and to a lesser extent humoral immunity. Antibodies to capsid proteins and cytotoxic T-cell immunity are responsible for clearance of HPV infection.[12]

HPV is not transmitted from one cell to another but is released upon degradation of the cell. Hence, DNA of HPV evades the local immune system which results in prolonged exposure of the cell to the virus, favouring malignant transformation of the cell.

HPV vaccines:

Vaccines appear to be a very important tool in countering HPV infection at an early stage and thus, eventually decreasing the incidence of cervical cancer in women. The use of an attenuated virus would not be possible because an effective culturing system for HPV is not available and it would be ethically unacceptable to expose healthy individuals to the oncogenic properties of HPV. Both prophylactic and therapeutic HPV vaccines are available. Prophylactic vaccines are given to individuals prior to infection and it stimulates the neutralizing antibody response against L1 and to a lesser extent L2. L1 and L2 are viral capsid proteins. Antibodies against these two proteins can neutralize extracellular viruses. L1 and L2 capsid antigens are not expressed in precancerous and cancerous tissue and therefore, may not be beneficial for therapeutic purposes.[18] It has been observed that L1 proteins have the intrinsic ability to self-assemble into virus like proteins (VLPs) when they are administered as an immunogenic. The VLP mimics the natural structure of virion and is able to induce an antibody response.[12] VLPs do not contain genomic DNA and are non-infectious. So it is difficult to distinguish VLPs from the native virion. Theoretically, no autoimmune response will be elicited as these epitopes have no morphological resemblance with human cellular proteins.

Therapeutic vaccines are recommended to individuals who are already exposed to HPV infection and this type of vaccine induces a specific T-cell mediated immune response targeted to E6 and E7 for the regression of the existing lesion.

A number of clinical trials have been done on prophylactic vaccines, but therapeutic vaccines still need to be studied further. Particularly in the developing countries, there is a need for the development of therapeutic strategies for existing HPV infections to reduce the incidence and recurrence of existing disease.

Prophylactic HPV vaccine and clinical trials:

Different studies have been done on phase I of HPV LP1 VPL vaccine in healthy adults which show that these vaccines are safe, immunogenic and highly tolerated. They produce a higher titer than natural infection, with or without adjuvants and without any major side effects.[19]

Another double blind vaccination trial study by Harro et al[20] on HPV 16 VLP vaccine was done in young women. It was conducted on HPV 16 seronegative women who did not have HPV 16 in their genital tract either at enrolment or on last vaccination. Three doses of vaccination were given to one group and placebo was given to another group at different time intervals. A follow-up of about median 17.4 months was done and results revealed that in the vaccinated group, no persistent HPV 16 or associated CIN were found, while a small number of patients had developed HPV 16 infection. This shows that the prophylactic vaccine was highly efficacious.

GlaxoSmithKline Biologicals (Rixensart, Belgium) and MedImmune (Gaithersburg, MD)[21] and Merck Research Laborites, (West Point, PA) have developed vaccines for prevention against HPV 16 and 18 associated cervical infections and neoplasia. In June 2006, The Food and Drug Administration (FDA) has approved Merck vaccine (Gardasil), on the bases of a clinical trial which reported excellent results. These vaccines contains VLPs with an adjuvant containing aluminum hydroxide and 3-decylated monophosphoryl lipid A. Studies show that this combination with the adjuvant elicited a superior immune response as compared to the antigen alone or

adjuvant with aluminum salt only.

Another double blind placebo-controlled clinical trial of a prophylactic vaccine (types 6, 11, 16 and 18) was done in women. This trial reported a 90% reduction in the incidence of HPV infections as compared to those in placebo group and also that even low doses elicited a good immune response.[22]

The safety and efficacy of prophylactic HPV 16/18 L1 VLP vaccine formulated with 3- decylated monophosphoryl lipid A and aluminum salt was evaluated in a multicenter trail.[23] In this trial, women were asked to record their symptoms after receiving the vaccine or placebo. The results showed that 87.6% women who received placebo and 94% of women who received the vaccine developed local reaction along with pain. Fatigue and headache were the most frequent complaints of both groups. This study shows a higher efficacy of the vaccine and that it provided protection against incidental HPV 16, HPV16/or 18 and persistent HPV 16 and/18 infections. It was concluded that a bivalent vaccine against incidental and its persistent HPV 16 and/or 18 associated cervical infections was safe and well tolerated.

These results are encouraging for prevention of infection with HPV and its associated diseases.

Therapeutic vaccine and clinical trial:

The main purpose of therapeutic vaccine is to stimulate a strong, long-lasting, and specific cell-mediated immune response for the reduction and eradication of HPV-induced infections. It must range from eradication of cervical warts to eradication of HPV induced malignancy. The important therapeutic targets are high risk HPV E6 and E7 proteins, which are often referred to as the hallmark of cervical cancer.[24] E6 and E7 protein based vaccines are available and are relatively non-toxic. Several strategies have been evaluated in a preclinical and clinical setting for the treatment and eradication of existing HPV-induced infection.

Different studies have been done and show a promising clinical response of therapeutic vaccines.[25,26] A study shows that HPV 6b HLP L1 protein vaccine is responsible for complete regression of anogenital warts in 76% of subjects over a period of 20 weeks.[27]

Another study was done in HPV associated intraepithelial neoplasia (CIN1, 2, 3 lesions)[28] in which they used a modified Ankara (MVA) — E2 reconstitution vaccinia virus. The results of this study show that 94% of patients had complete elimination of the disease and the remaining had a lower viral load after treatment with the vaccine.

Another study done by Xu et al, shows that cytotoxic T- lymphocyte and T-helper epitope response can be induced with lipopeptide molecule. This can improve immunogenicity and thus, can be considered a more effective therapeutic vaccine against cervical cancer.[29]

A Phase I trial was done to assess the safety and immunogenicity of a mixture of HPV16 E6E7 fusion protein and ISCOMATRIX™ adjuvant in patients with CIN (Cervical Intraepithelial Neoplasia) and the results show that the use of ISCOMATRIX™ adjuvant in combination with the HPV16 immunotherapeutic vaccine is safe and immunogenic, and has promising effects in the reduction of the HPV viral load.[30] But further studies are needed to determine efficacy.

Therapeutic vaccines appear to be safe and immunogenic, and well tolerated but limited data is available in this regard. There is a need to understand therapeutic vaccination strategies deeply and so a larger number of trials are needed to be done prior to its implementation in the population.

Targeted population for HPV vaccination:

HPV is the most common sexually transmitted disease so early teen and young women will be the ideal target population for immunization. In United Kingdom, HPV vaccination has been recommended to be included in the NHS immunization programme, in 2007. The schedule of HPV immunization recommends targeting girls of the age of 12-13 years for routine vaccination and girls up to the age 18 years for catch-up programme.[31] A study done in a university in the United States, which included HPV negative women, revealed that 55% of these women developed HPV within 3 years.[32] It indicates that the infection rate increases as the girls becomes sexually active. Thus it would be favorable to immunize them at an early stage of life.

Economic Impact:

Cost effectiveness is always an important issue before licensing a vaccine. There is a need to assess the incidence and prevalence of a disease, the cost of a vaccine, the economical burden due to the disease and its treatment and the outcome of the vaccine prior to the implementation of a vaccination programme.

In the developing countries, HPV associated morbidity and mortality is still high and it accounts for a significant burden on their economy. The combined cost of screening, disease and its treatment gives us an even greater incentive to promote the use of the vaccine as it reduces the economic health burden on the country's health system

A study done in UK shows that during the long run, a vaccination strategy can reduce the incidence of HPV related disease including cervical cancer, CIN and genital warts. It recommended that it would be cost effective at cost per QALY ratio if the target population would be between 12-24 years of age.[33] According to the Centre of Disease Control and Prevention, the prophylactic vaccine consists of three doses at an interval of 1, 2 and 6 months.

Logistical uncertainties:

A number of clinical trials are needed prior to be the inclusion of the HPV vaccine in the national immunization programme, as currently very limited data is available. Another issue is that the side effects of the vaccine have not been completely determined. Studies show that the vaccine appears to be effective for only five years, so that it is also a query as to if a booster dose of immunization would be required and how often and at what age should it be administered.

Importance of HPV vaccine:

Even though there might be some logistical uncertainties regarding the use of HPV vaccines in a country's immunization schedule, it is still a very important medical achievement for the prevention of four strains of HPV (6, 11, 16 and 18), which are responsible for the symptomatic diseases caused by HPV including cervical cancer, and it has proven to be 100% effective and safe. Hopefully HPV vaccine would be able to reduce the pschycological and economic burden due to cervical cancer.

Community attitude and awareness regarding HPV vaccine:

It is understood that women and adolescents would be the most likely recipients of the vaccine after knowing the hazards of HPV associated diseases. A study done in Australia regarding the community attitude towards vaccination shows that 83% of the population considered that both men and women should receive HPV vaccination and 77% of parents agreed that they would immunize their children if available.[34]

It is important to educate the community regarding the complications of HPV infection, its preventive measures and the importance of immunization because the knowledge of people regarding the role of HPV infection is lacking, especially in developing countries where the economical burden due to cervical cancer is significant.

Conclusion

A comprehensive frame work including epidemiological, demographical, behavioural screening, treatment and economical parameters need to be obtained and this frame would help the policy makers to improve the health of women. Screening of HPV is not commonly practiced in Pakistan and its modes of transmission have not been evaluated due to social taboos. A primary preventive strategy aims to reduce the incidence of disease with or without symptoms by proper education of risk reduction, early detection by implementation of mass screening programmes and vaccination against the most prevalent high risk strains of HPV. The prophylactic vaccines are in the last stages of clinical trials and studies have shown that they are well tolerated and also are able to produce high titers of neutralizing antibodies thus prone to be well established for the prevention of HPV associated cervical cancers.

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