

Current HPV therapeutic vaccine development and impact on cervical cancer prevalence and mortality

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Abstract. Cervical cancer is considered to be the fourth most common cancer in the women's population globally, as reported by WHO in 2024. We have achieved great success in the research and development of HPV prophylactic vaccines, and HPV prophylactic vaccines have effectively reduced the prevalence of HPV. While 90% of HPV infections can be stopped by having injections of HPV prophylactic vaccine, there is currently no effective method that can prevent the spread of HPV induced malignancies and cervical cancer after infection takes place in unvaccinated individuals. This forces people who are diagnosed with cervical cancer to choose more painful treatment options; this high mortality rate and painful treatment increase awareness of the development of HPV therapeutic vaccines. Current HPV therapeutic vaccines are designed to target E6 and E7 oncoproteins, activate CD8⁺ T cells, clear the infection and prevent further development of infected cells. 9 HPV therapeutic vaccines are under development, with 8 in phase 2 clinical trials and one in phase 1. The development of the HPV therapeutic vaccine has the potential to reduce the mortality of cervical cancer, thereby improving the quality and lifespan of affected individuals. This article will summarise the development, advantages and disadvantages of HPV therapeutic vaccines to determine whether they can substantially help reduce the incidence of cervical cancer.

Keywords: Therapeutic Vaccine, Cervical cancer, Human Papilloma virus.

1. Introduction

In the United States, cervical cancer kills approximately 4,000 women for every 11,500 new cases in 2022. According to WHO, about 604,000 new cases are diagnosed, and 342,000 women die from cervical cancer each year. This affects middle and low-income countries even more as the limited access to HPV prophylactic vaccine, so it is so much easier for the pathogen to spread and cause infection, which will further into cervical cancer. The lowest survival rate of cervical cancer in Africa is only about 36%; the effects of cervical cancer lead to a reduced quality of life for patients with cervical cancer [1]. Meanwhile, cervical cancer also has a significant impact on the socioeconomic situation. The cost of cervical cancer treatment will place pressure on the medical insurance system and the patient's family in poverty areas. From a socioeconomic perspective, cervical cancer reduces the workforce availability and employment rate in the country. Many patients in poverty areas also die because they cannot find jobs and have no money to treat cervical cancer [2]. Cervical cancer also causes much psychological pressure on the patients themselves. Studies have shown that women with HPV-positive test results often feel ashamed of themselves, which makes them have difficulties communicating with their

partners and have gaps in sexual relationships. Very few women can accept and talk to their family and partners about their cervical cancer [3]. Out of shame, many poorly educated women choose to ignore the disease, which then develops to the point where it is incurable [1]. HPV therapeutic vaccines can reduce the psychological pressure of female patients and stop the spread of HPV to a certain extent. It solves socioeconomic problems and provides patients with a less painful and affordable treatment plan.

The uses of therapeutic vaccines are entirely different from those of prophylactic vaccines. Prophylactic vaccines aim to immunise individuals to avoid infection or diseases. In contrast, therapeutic vaccines aim to induce a cellular immune response by using biological products to fight against disease or infections in affected individuals. Therapeutic vaccines will also need to have the ability to target and cure the tumour and some chronic conditions [4].

Current therapeutic vaccine types are live vector-based, peptide-based, DNA/RNA based and dendritic/tumour cell-based [4]. The first approved therapeutic cancer vaccine was Sipuleucel-T (PROVENGE) by the FDA (Food and Drug Administration). In 2010, Dendreon developed and commercialised the vaccine. PROVENGE a dendritic cell-based therapeutic vaccine, the dendritic cell is first exposed to the fusion protein, which consists of an antigen (PAP) found in prostate cancer cells. The exposure of the dendritic cell can target PAP; then it will be injected into the patient's body to activate the immune response of CD8⁺ T-cell; this type of T-cell would release cytotoxic protein to destroy infected body cells, therefore stopping the cancer tissue further develop into a tumour [5]. This precedence contributed excellent research value to the development of therapeutic vaccines.

To date, the FDA has approved three therapeutic vaccines: Bacillus Calmette-Guerin, PROVENGE and tarlimogene loherparepvec [5]. Therapeutic vaccines for virus-induced infections are currently being developed to reduce the public health impact of HBV, HPV, and HIV, which are susceptible to infection and very hard to cure; therapeutic vaccines could provide an alternative path for controlling the spread of the diseases [6]. Although the development of therapeutic vaccines for virus-induced infection remains to be seen, some great results have been achieved in the research and development of cancer therapeutic vaccines, such as the provenge and tarlimogene loherparepvec for the treatment of melanoma that been mentioned above [4]. This review summarises the HPV therapeutic vaccine to give readers a more intuitive understanding. The summary of advantages and disadvantages will objectively help the future development of the HPV therapeutic vaccine.

2. Current development of HPV therapeutic vaccine

The urgent need for the HPV therapeutic vaccine nowadays is due to the DNA sequence of HPV will integrate before the HPV genome starts to replicate in the host cell; this action would lead to the deletion of some of the HPV genes (E1, E2, E3, E4, E5, L1, L2). Deletion of the L1 and L2 capsule protein is the main reason why the HPV prophylactic vaccine does not cure an HPV-induced disease, as all the HPV prophylactic vaccines function by using the capsule protein as a target antigen to stimulate the active immune response. Therefore, the therapeutic vaccine needs to target the remaining antigens (E6 & E7) to cure-induced cancer [4]. Table 1 shows all the HPV therapeutic vaccines currently under development, from the earliest TA-HPV to the recently developed BNT113. It highlights the evolution from traditional live vector-based vaccines to new biotechnology, such as mRNA vaccines [7]. The first mRNA vaccine known to the world is the COVID-19 prophylactic vaccine during the COVID-19 pandemic; Comirnaty was developed and commercialized by Pfizer to fight against the SARS-CoV-2 virus [8]. Among those HPV therapeutic vaccines under development, only two are live vector-based vaccines. Live vector-based vaccines have potential safety concerns and lack efficacy like other therapeutic vaccines [7]. Most HPV therapeutic vaccines are stuck in phase 2 clinical trials. Even though these vaccines activate efficient immune response in mice and clear cancerous cells, they all face a challenge in activating effective CD8⁺ T cells immune response in humans in phase 2 clinical trials, thus failing to completely clear the infected tissue and cancerous cells. The vaccine failed to achieve the expected immune effect [4]. This could be due to a few factors. The infection caused by HPV can be continuous and occurs in epithelial tissue less accessible to the immune system. HPV also evolved a mechanism to evacuate from the immune system, and it has many specific strains that the vaccine needs

to target. The micro-environment of the tumour also affects the vaccine's efficacy by reducing the ability of CD8⁺ T cells to recognise and attack cancerous cells. Phase 2 clinical trials aim to test vaccines' side effects and efficacy. Current HPV therapeutic vaccines have all failed in vaccine efficacy, so the current goal for all HPV therapeutic vaccines is to stimulate a more effective cellular immune response in humans to reach the predefined endpoint and advance beyond Phase 2 clinical trials [9].

Table 1. Current developing HPV therapeutic vaccine

Vaccine name	Targeting antigen	Vaccine type	Clinical stage	Clinical study ID	Development start time
TA-HPV	HPV16/18 E6, E7	Viral vector	Phase 2	NCT05799144	1990
SGN-00101	HPV16 E7	Recombinant protein	Phase 2	NCT00054041	1990-2000
ADXS11-001	HPV16 E7	Bacterial vector	Phase 2	NCT02291055	2000
ISA101b	HPV16 E6,E7	Recombinant protein	Phase 2	NCT02128126	2000
ProCervix	HPV16/18 E7	Recombinant protein	Phase 2	NCT01957878	2000-2010
pNGVL4a-Sig	HPV16 E7	DNA vaccine	Phase 1	NCT00788164	2010
INO-3112	HPV16/18 E6, E7	DNA vaccine	Phase 2	NCT03162224	2010
GX-188E	HPV16/18 E6, E7	DNA vaccine	Phase 2	NCT03444376	2010
BNT113	HPV16 E6, E7	mRNA vaccine	Phase 2	NCT04534205	2010

3. Design and mechanism of HPV therapeutic vaccine

All of the HPV therapeutic vaccines aim to target the E6 and E7 oncoproteins on the HPV genome; this is because these proteins contribute an important role in the development and progression of HPV-associated cancer. E6 prevents apoptosis of infected body cells and allows the viral gene to replicate and develop for longer, so this cell could develop further into cancerous cells. E7 protein disrupts the cell cycle's regulation, leading to the uncontrollable infected cell division. E6 and E7 proteins can also be recognised as tumour-associated antigens. Even though the tumour undergoes malignant E6 & E7 are still expressed in the cell, targeting E6 & E7 can minimise the damage to the non-infected body cell [7].

3.1. Live-vector based vaccine

TA-HPV is designed to treat pre-cancerous lesions and cervical cancer; it targets high-risk HPV types 16 and 18, as these are two common types of HPV that cause major HPV-associated diseases. TA-HPV uses an MVA (Modified Vaccinia Ankara) as the delivery platform, which uses genetic engineering to make the highly attenuated strain of the vaccinia virus express E6 and E7 antigens to the immune system. MVA cannot replicate, so it will infect the cell where it was injected. Then, it will express the E6 & E7 protein inside the cell to stimulate cellular immune response by activating MHC class I molecules, which will be recognised by CD8 T cells [7]. Activation of CD8⁺ T cells would attack cells expressing E6 & E7 protein, which means the infection will be cleared, and the virus will stop spreading as they cannot replicate.

ADXS11-001 is a vaccine designed for cervical cancer by using a genetically engineered version of *Listeria monocytogenes* to deliver the E7 antigen; this modification of LM is done by using a fusion protein to combine fragments of attenuated Listeriolysin O and the HPV E7 oncoprotein [10]. For safety concerns, the Lm bacteria used in ADXS11-001 is highly attenuated; this minimises the risk of using a live-vector-based vaccine to deliver the antigen [7]. ADXS11-001 stimulate the immune response by expressing E7 antigen to the antigen-presenting cells (APC), and then the same immune response as TA-HPV is processed. So, both adaptive and innate immune responses are stimulated. It is worth mentioning that Lm will stimulate an inflammatory response to help the vaccine overcome the local immune suppression around the cancerous cell; this might promote the higher efficacy of the vaccine [10].

3.2. Recombinant protein-based vaccine

SGN-00101 is designed for treating cervical dysplasia and cervical cancer by targeting HPV 16 E7 oncoprotein; the antigen is delivered through a combination of Hsp65 (heat shock protein) from *Mycobacterium bovis* and HPV 16 E7 protein by genetic fusion. Hsp65 can boost immune recognition and stimulate a higher level of cellular immune response. SGN-00101 stimulates the same immune response as ADXS11-001, but it also activates the CD4⁺ T cell to enhance a broader immune response. Therefore, both innate and adaptive immune responses are stimulated by SGN-00101, which could enhance the vaccine efficacy [11].

ISA101b is designed to focus on HPV 16 E6 & E7 protein by using long peptides that are synthesised from 4 E7 overlapping peptide chains and nine overlapping E6 peptide chains. It further improved the performance of the vaccine based on ISA101 by adjustments of the synthetic long peptides to ensure more safety and tolerability for clinical use [4]. ISA101b stimulates the same immune response as SGN-00101, but the combination of checkpoint inhibitors blocks PD-1, which is often used by tumour cells to avoid detection by T lymphocytes. This combination of synthetic long peptides and checkpoint inhibitors has a great advantage when dealing with immunosuppressive tumour microenvironments [10].

ProCervix targets HPV type 16 & 18 E7 oncoprotein; this is aimed to treat cervical intraepithelial neoplasia caused by these two types of HPV. Using synthetic peptides of E7 oncoprotein from HPV 16 and 18 as the delivery platform gives the vaccine the ability to target multiple strains of HPV. This peptide can stimulate the immune response by expressing E7 protein to the APC, then the activation of CD4⁺ and CD8⁺ T cells. The vaccine was formulated with an oil-based adjuvant Montanide ISA 51 that helps to stimulate a higher level of immune response by increasing the presentation of synthetic peptides to immune cells[9].

3.3. DNA&mRNA based vaccine

pNGVL4a-Sig is a DNA plasmid vector in which the gene code for HPV type 16 E7 antigen can be inserted into the multiple cloning site; the addition of polyadenylation sequence could help the mRNA to process more stable during translation. Therefore, a larger amount of CD8⁺ cells will be activated once the plasmid is injected[4]. The plasmid is injected and aims to enter the nucleus of the cell through methods like lipid nanoparticles and electroporation; it then enters the transcription and translation process in terms of expressing the antigen to the immune cells. After the HPV 16 E7 antigen is synthesised, it will pass through the endoplasmic reticulum and Golgi apparatus for the preparation for either being presented on the cell or secret into the extracellular space. This display and secretion of antigens can activate the MHC class I molecules. Therefore, T cell response can be stimulated like other vaccines do[12].

INO-3112 targets the E6 and E7 oncoprotein of HPV types 16 and 18. Therefore, this vaccine is aimed to treat a boarder range of HPV-induced cancers. This is achieved by combining two components: DNA-based immune activator IL-12(interleukin-12) and DNA plasmid vaccine(VGX-3100). The presence of IL-12 can enhance the immune response as it is a pro-inflammatory cytokine that enhances both adaptive and innate immune responses [4]. Different to pNGVL4a-Sig, INO-3112 is introduced into the body cell via electroporation; short electrical impulses create a short-lasting pore on the cell and deliver the DNA sequence into the nucleus for protein synthesis. Then, protein synthesis leads to the production of E6 and E7 antigens that are ready to be secreted and expressed by the immune cells[7].

GX-188E contain a DNA plasmid encoding E6 & E7 oncoprotein of HPV type 16 & 18; like INO-3112, they both target a wider range of HPV induced cancer. However, the DNA code for E6 and E7 oncoproteins has been modified to reduce their oncogenic potential, which makes the safety of GX-188E stand out among the HPV therapeutic vaccines. Similar to INO-3112, GX-188E also use electroporation as a delivery method. Then, a similar immune response is stimulated by E6 and E7 produced during protein synthesis[7].

BNT113 is the only mRNA vaccine that is developing; it mainly focuses on treatment for HPV-positive head and neck squamous cell carcinoma. Which is a cancer that is found in the head and neck region due to the infection of HPV; it is fast growing and could cause difficulties in daily life like

difficulty swallowing and ear pain[9]. Different to the DNA vaccine, BNT113 uses mRNA that codes for HPV type 16 E6 & E7 oncoprotein. The vaccine is delivered through a lipid nanoparticle(LNP), where an LNP encloses the mRNA strand and delivers it into the cell without getting degraded[8]. mRNA would carry out translation inside the cytoplasm, express the viral antigen to other cells, and activate both MHC class I and MHC class II molecules[7]

It is worth mentioning that the uses of new mRNA technology can be an outstanding technology to use in HPV therapeutic vaccine. mRNA vaccine can improve the time taken for the synthesis of E6 & E7 protein inside the cell, therefore immune response can be triggered in a shorter period of time. From a safety perspective, as mRNA does not enter the nucleus this reduces the risk of viral genome integration into patient's genome. 11 point Times or Times New Roman.

4. Challenges for HPV therapeutic vaccines

In general, the therapeutic vaccines that are all currently developing face the problem of reaching the minimum vaccine efficacy in humans as they cannot stimulate enough immune response in humans during the phase 2 clinical trial [10]. Only a very small amount of infected tissue is effectively cleared due to the immune evasion of HPV. HPV can create an immunosuppressive microenvironment around the tumour and limit the immune response, especially these vaccines that function by activating CD8+ T-cells. In terms of overcoming this problem, combined therapy can be used to boost the level of immune response and find more effective vaccine delivery platforms. From a safety perspective, live-vector-based vaccines still have the potential to cause infection even if they are highly attenuated. The vaccine needs more careful design with optimised doses to maintain the vaccine efficacy while considering from a safety perspective[13].

5. Conclusion

The development of HPV therapeutic vaccines represents a promising step forward in the development of targeted therapies for cervical cancer, which will reduce the negative impact of HPV on society. Although significant progress has been made in the design of therapeutic vaccines targeting E6 and E7 oncoproteins, many challenges remain, especially in stimulating effective immune responses in humans during clinical trials. Current approaches, including vaccines based on live vectors, recombinant proteins, DNA, and mRNA, have all achieved some success in preclinical models, but their efficacy in humans remains very limited due to immune escape mechanisms and immunosuppressive tumour microenvironments. Further research on enhancing immune responses, optimising delivery methods, and exploring combination therapies could significantly improve the effectiveness of these vaccines. If these challenges are overcome, HPV therapeutic vaccines not only have great potential to reduce the global burden of cervical cancer but also provide less invasive and more accessible treatments for individuals already infected with HPV, especially in low- and middle-income countries. Special groups of women no longer have to suffer from psychological torture and self-blame for having HPV, which will reduce their stress and allow them to enjoy life without burden.

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