Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008365

Therapeutic Vaccines as a Secondary Prevention Line to Treat Cervical Cancer

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ARTICLE INFO

Received: September 15, 2023

Published: October 09, 2023

Citation: Gustavo Acosta Altamirano, Enoc Mariano Cortés Malagón, Mónica Sierra Martínez, Julia Dolores Toscano Garibay, Carmen Palacios Reyes, Miguel Ángel Ontiveros Torres, Catalina Flores Maldonado, Rubén Gerardo Contreras and José Bonilla Delgado . Therapeutic Vaccines as a Secondary Prevention Line to Treat Cervical Cancer. Biomed J Sci & Tech Res 53(2)-2023. BJSTR. MS.ID.008365.

ABSTRACT

Infection with high-risk Human Papillomavirus (HR-HPV) is the main factor to prime cervical cancer (CC). Currently, the primary prevention of CC through prophylactic vaccines allows protection against the main oncogenic genotypes of HR-HPVs and could supposed to be the most effective solution in underdeveloped countries. However, its effectiveness in protecting women over 35 years of age against a primary infection, or reinfections, is unclear, and no significant therapeutic effects have been observed on the available prophylactic vaccines to clear existing infections or cervical lesions. Therefore, the design of therapeutic vaccines, capable of eliminating infected cells, is imperative. The present review is focused on the current panorama of HPV therapeutic vaccination as a secondary prevention approach.

Keywords: HR-HPVs; E6/E7; Therapeutic Vaccines

Abbreviations: CC: Cervical Cancer; HPV: Human Papillomavirus; HR: High-Risk; APC: Antigen-Presenting Cells; SE: Salmonella; AD: Adenovirus; FV: Foam Viruses; FFV: Foam Virus Protein; DC: Dendritic Cells; SLP: Synthetic Long-Chain Peptides; HLA: Human Leukocyte Antigens; EDA: CRT: Calreticulin; TLR: Toll-Like Receptors; CLR: C-Type Lectin Receptors

Introduction

In 2020, cervical cancer (CC) was positioned as the third cause of cancer death in women worldwide [1]. Currently, it is possible to count on prophylactic vaccination as primary prevention of CC, and screening and treating cervical lesions as secondary prevention methods. To date, there are three prophylactic vaccines on the market to prevent infection with high-risk HPVs, all of them designed from a multiple combination of subtypes of the L1 recombinant protein, which spontaneously produces highly immunogenic VLPs which will produce high titers of neutralizing antibodies. Unfortunately, there is a large number of women on productive age for whom the protection of prophylactic vaccines is not clear, or whether they can clear previous infections.

Therapeutic Vaccines as Secondary Prevention of CC

Basically, the mechanism of preventive vaccines consists of the production of neutralizing antibodies. However, when patients become infected, preventive vaccines are not capable of eliminating infection, and when the virus genome is integrated into the host genome during infection, there is an infection that evolves towards a nonproductive phase (it does not produce viruses). Furthermore, HPV's early genes such as E1, E2, E4, E5; and late genes (L1 and L2) are missing in the nonproductive phase, so preventive vaccines are ineffective against many HPV-related cancer.

Therapeutic vaccines currently in development are based on four main strategies:

1. Vaccines based on live vectors,
2. Vaccines based on peptides and proteins,
3. Vaccines based on nucleic acids, and
4. Whole-cell vaccines.

The objective of each of the four strategies is to deliver target immunogens to the antigen-presenting cells (APCs), to activate CD8+ T lymphocytes responses subsequently, specific cytotoxic T lymphocytes (CTL), as well as CD4+ helper T lymphocytes (Th) [2].

The oncoprotein E6 and E7 are the most important transformation proteins for HPV. They are necessary for the formation, maintenance, and promotion of cervical tumors [3]. However, E6 and E7 expressions are not consistent throughout cervical cancer generation and are usually elevated only in high-grade lesion; therefore, other targets such as E2 protein (negative regulator of E6 and E7) may also be relevant, especially in pre-cancer lesions and condylomata acuminata [4].

Vaccines Based on Live Vectors

Vaccines based on live vectors are classified into two categories, bacterial and viral. Such vaccines utilize selective vectors that encode for E6 or E7 specific antigens, reproduce in host cells, and eventually induce immune responses to HPV [5]. Vaccines based on living mitigation vectors usually have a high degree of humor and cell immunity and may be risky in low-immune patients [6]. Another possible risk of a living vector is that the immune response to the vector is stronger than that of the coding antigen [7].

Vaccines Based on Bacterial Vectors: This strategy is based on bacterial vectors such as Listeria monocytogenes, Salmonella sp (SE), or Lactobacillus casei; however, the development of such vaccines was limited by safety and efnicacy problems. ADXS11-001 is a live vaccine which is based on Listeria monocytogenes. The antigen is integrated of HPV16E7 fused with LLO toxin fragments, and the nirst clinical study on patients was carried out in 2009 [8]. Listeria monocytogenes is an intracellular gram-positive bacterial that interacts with host cell receptor proteins and enters the cell via phagosomes, but distinguishes itself from other bacteria by using LLO toxins and PLC to escape from the cell. Phageosomes [9,10]. To manage Listeria monocytogenes, the MHC is activated trough two pathways in adaptive response; first, for bacteria that couldn't escape from phages, the MHC Class II pathway stimulates CD4+ T responses, and second, for bacteria that could escape from phages, the MHC Class I pathway extracts the polypeptides from bacterial antigens and presents them to host-cell surface to activate the CD8+ T activity [11].

In the Phase II clinical trial that evaluated the safety-efficacy of ADXS11-001 vaccine in patients with recurrence/refractory cervical cancer following chemotherapy and/or radiotherapy, indicating that monotherapy with ADXS11-001 had fewer adverse effects than combination therapy groups ADXS11-001 and Cisplatin. On the other hand, the median survival rate was comparable between the single therapy group and combination therapy (8.28 months for ADXS-11-001; 5.85–10.5 months for 95% CI; 8.78 months for ADXS-11-001 + Cisplatin; 5.85–10.5 months for 95%; 7.4-13.3 months for 75%). The overall survival rate of the two groups was 34.9% (38/109) in 12 months and 24.8% (27/109) in 18 months. This is such a promising result that requires further research [12].

The oral vaccine GLBL101c is produced in recombinant Lactobacillus casei, which expresses a mutated HPV16 E7 protein. In a Phase I/IIa clinical trial which showed that oral GLBL101c vaccines may cause a regressive CN3 associated with HPV-16, and after 9 weeks of treatment, the CN3 to CN2 regression rate was around 80% [13]. Recent studies investigating the effectiveness and adverse reactions of GLBL101c vaccines in patients with inflammatory disease 2 have shown no severe adverse reactions. The effective CR rate of GLBL101c was 22%, which means that the effectiveness of the medicine is not ideal and may require the development of new approaches [14].

Vaccines Based on Viral Vectors: Replication-deficient viral vectors are very useful vectors for vaccine design. Main viral vectors include lentivirus, adenovirus (Ad), adeno-associated virus, alphavirus, and vaccinia virus [15-18]. Adenovirus-based technology is the most advanced recombinant vaccine technology due to its ability to induce a strong systemic T cell response and a high serum antibody titer after intramuscular application [19]. As a vaccine vector, Ad5 is the most widely used human serotype; However, vector technology based on multiple serotypes has also achieved good results in the experimental design of vaccines for various diseases [20].

Preclinical studies of recombinant vaccines in Ad26 and Ad35 that lack replication due to E1/E3 deletion suggest that fusion proteins containing HPV16's E6/E7 oncoproteins can cause strong CD8+T cell response. Specific to E6/E7, and injected into the muscle and/or vagina, it also secretes multifunctional cytokines. However, although the vaccine generates strong CD8+T responses, the specif-

ic CD4+T response cannot be detected by this strategy [21]. In the Ad26 and Ad35, another preclinical design is to use fusion antigens for the E2/E6/E7 HPVs 16-18. The design is aimed at treating all stages of cervical cancer and to achieve this, the antigen consists of three E6 oncoprotein segments and two E7 segments fused with E2. HPV16/18's fusion antigens are as follows: HPV16E2SH: E2+E61-44+E735-98+E692-157+E71-59+E621-115 and HPV18E2SH: E2+E61-39+E724-104+E680-156+E71-45+E615-103) [22]. In this preclinical study, promising results have been obtained both in mice's immunogenicity and in TC-1 tumor models.

Vaccinia virus is a large, stable dsDNA virus that can be used to express many antigens and is also a good immunological carrier [23]. TA-HPV is a vaccine that is a recombinant vaccine produced by Vaccinia virus and expresses E6 and E7 oncoproteins of HPV16/18 genetics. In a first- to second-stage clinical study in 8 advanced cervical cancer patients, three patients found specific antibody responses to HPV, of which one patient had specific immune T-cell responses to HPV. In the latter, combined therapy with TA-HPV + cisplatin boosted the response of specific CD8+T cells to E7 [24].

The recombinant vaccine MVA-E2 from vaccinia expresses the E2 protein derived from bovine. As an inhibitor of E6/E7-expression, the E2 protein is introduced into hosts cells to inhibit the expression activity of E6 and E7, eventually leading to a reduction in cell immortalization/transformation. The MVA-E2 strategy has been shown to prevent human tumor growth in mice, and tumor regression in xenotransplanted rabbits. MVA-E2 was also tested in intraepithelial angiogenesis injuries caused by HPV. In a phase III clinical trial conducted in 2014, 1356 patients (males and females) were involved; MVA-E2 was 90% effective in treating CIN injuries (interestingly, all men showed complete lesion eradication) [25].

The TG4001 is also a vaccine that expresses an HPV16-E6/E7 fusion antigen, and in CIN-2/3 clinical trials, the HPV16 mRNA elimination was associated with lymphatic regression in 70% of CIN patients [26]. These promising data justify further trials of TG4001 for CIN-2/3 treatment. Vvax001, a novel beta virus-based cancer vaccine expressing HPV16-E6/E7 antigen also demonstrated that a single injection can induce CD4+ and CD8+ T cells against E6 and E7 native antigens [27]. Replicable viral vector vaccines are also promising for treating HPV-associated cancers such as foam viruses (FVs). Replication-resistant FVs can trigger immune signals and integrate them into the host genome, producing continued antigen expression and robust immune responses. An interesting study found that animal foam virus protein (FFV) is a scaffold for in vitro delivery of B and T cell epitopes, and mice that are immunized with T cell epitope peptide E749-57 from E7-HPV16 and attached to their expression vector protect mice from transformed HPV16 tumor cells [28].

Vaccines Based on Peptides or Proteins

These vaccines include antigens in the form of peptides or entire proteins acquired by the dendritic cells (DC), processed, and presented to activate the MHC I or II molecular pathways to stimulate CD8+T or CD4+T cells [6]. Peptide vaccines are divided into synthetic long-chain peptides (SLPs) and specific epitopes (short) peptides. Short peptides are MHCspecific and must be consistent with specific human leukocyte antigens (HLAs), whereas long peptide and entire proteins are rich in CD4+T and CD8+T cell epitopes, which can avoid MHC restriction limitations. Although protein and peptide vaccines are safe and stable, the lack of immunity of protein vaccines is a significant limitation in their development, with a focus on the MHC II presentation pathway resulting in a weaker CTL immunity. Improvements in protein vaccines can be achieved by adding immunostimulatory molecules to increase endogenous processing to improve the MHC I response [29].

ISA 101 is SLP HPV16-derived vaccine from nine SLP E6 overlapping sequences, and four SLP E7 overlapping sequences, [30]. In Phase II ISA 101 trails combined with nivolumab, an anti-PD-1 antibody, and evaluated in patients with untreated HPV16-positive cancer [31]. Compared to PD-1 antibody alone, the overall response rate was 33%, with an average survival of 17.5%, suggesting further research. Another clinical study with advanced, recurrent or metastatic cervical cancer receiving ISA101 vaccines and standard chemotherapy, including carboplatin and paclitaxel, found that in 43% percent of patients were able to respond to T cells of type 1 vaccines, suggesting that chemotherapy can be used to treat advanced cancer patients effectively [32].

In a mouse model, mHSP110 was used as an immune antagonist to enhance the immune response to CTL epitopes produced by HPV16 E7 [33,34]. HSP110 has a high affinity for protein binding and can improve the immuneness of protein antibodies. They used mHSP110-E7 as a fusion protein to prove that mHSP110 formed a complex with E7 oncoprotein [33-36]. Then, immunizing mice leads to a strong CTL reaction, protects mice from tumor attacks, significantly suppresses tumor growth in antitumor tests, and extends the life of animals carrying tumors [37].

Fibronectin Additional Domain A (EDA) is a protein agonist similar to the toll TLR-4 that targets antigens to DCs in vivo, induces maturation by binding to TLR4, and better delivers the short peptides treated to the naive T cells [38]. A combination of E7 proteins derived from HPV16/18 and the extra domain A of human fibronectin (hEDA) are combined into a bivalent recombinant protein, combined with the auxiliary poly-IC (polyinosinic-polycytidyl acid) and poly-ICLC (synthetic compounds of carboxymethylcellulose, polyinosinicpolycytidyl acid, and poly-L-lysine double-stranded RNA) to assess the effect, immune activity, and potential therapeutic activity of the HPV16 TC-1 tumors. The results show that vaccines induced specific immune T lymphocyte (CTL) responses to E7 and eliminated well established tumors and that when combined with adjuvants, some groups achieved 100% immune effects [39]. This is an exciting result and also promises to be a good clinical outcome.

Overall, the hEDA-HPVE7-16/18+Poly-ICLC is a promising regimen for cancer treatment, and improving its protocol to improve the benefits of clinical treatment. Some improvements are also analyzed, one of which is the future consideration of the effect of tumor-suppressing environment on vaccine effectiveness as proposed in the article itself, which means establishing a place closer to tumor growth in an in vivo context. The second is to improve experimental design, combining vaccine treatment data for large tumor experimental groups and incorporating vaccine treatment levels for advanced patients. In addition, vaccine dosage is an essential factor in immune effectiveness, and high doses of vaccine injections can cause adverse reactions, which should be documented as they occur.

Vaccines Based on Nucleic Acids

DNA Vaccines

DNA vaccines are a valuable cancer treatment method because of their simplicity, stability, and effective antigen-specific immunotherapy. DNA vaccines are based on bacterial plasmids, which express antigens triggered by high-efficiency eukaryotic promoters, and effective DNA vaccines must enter the nucleus after injection to induce the expression of antigens delivered by MHC class I molecules to activate the immune system [40,41]. Unlike living vector vaccines, DNA vaccines are relatively safe, produce no body-specific antibodies, and can be used for immunity increases by repeated vaccines [42]. The lack of independent amplitude of the exposed DNA leads to a poor body immune system, one of the main disadvantages of DNA vaccines. One of the main disadvantages of DNA vaccines is their low immunogenicity, to enhance immunogenicity, vaccine design uses several methods, such as electroporation of DC cells, immunomodulators and distinct immunostimulators (such as entire cells and/or metabolic molecules) [43,44].

A clinical study evaluated the safety, efficacy, and immunogenicity of DNA vaccines for pNGVL4a-CRT/E7 vector in HPV-related infection [45]. DNA vaccines are composed of expression vectors of pNGVL4a and contain the HPV16E7 encoded sequence associated with calreticulin (CRT) [46]. Patients were vaccinated by subcutaneous administration, intramuscular injection, or direct intrauterine injection. Of them, 69% had adverse reactions to vaccination, and 30% had vascular regression of CIN 1 or less. Similarly, the corresponding data show that immune solid reactions are also induced and more CD8+T lymphocyte responses occur [45].

Recent clinical trials have explored the therapeutic effects of the GX-188e therapeutic DNA vaccine on regressive CIN3 of the uterus [47]. GX-188e consists of tissue plasminogen activator signal sequences, tyrosine kinase 3 ligands, and recombinant HPV-16/18-E6/E7 genes [48]. As a result, 52% of patients with V7 and 67 percent of patients with V8 experienced a histopathological reduction, 73 percent (V7) and 77 percent (V8) of patients with a histological reduction showed a clearance of HPV [47]. This shows that the GX-188E vaccine induces strong cell immunity to eliminate the cytological lesions of HPV. In another AMV 002 vaccine study, the results showed that AMV 002 vaccines were well tolerated at all doses and enhanced the specific immunity of patients treated with tumor-related antigens [49].

RNA Vaccines

mRNA vaccines are currently the most popular forms of vaccines and have been widely proven to be a promising therapeutic strategy for immunotherapy. In 1989, Malone and colleagues demonstrated that by encapsulating cationic lipids (N-[1-(2,3dioleyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA)) in various eukaryotic cells, mRNAs can be successfully transfected and expressed [50]. In 1990, mRNA transposed in vitro was fully expressed in mouse skeletal muscle cells, and successful expression of mRNA in vitro was shown to be the first proof of the feasibility of mRNA vaccines [51]. The mRNA structure includes 5'cap structures, 5' and 3'UTR structures, code sequences and 3'poly A tails [52]. Many studies have shown that mRNA is not integrated (safe), and new generation self-amplify mRNA vaccines (saRNA vaccines) have high autonomy replication capacity. The self-replicating viral vectors of RNA also have high expression rates and a natural anti-inflammatory activity, TLR 7/8 ligand, which induces strong immune responses [53,54]. Compared to DNA vaccines, the main reasons for slow development of mRNA vaccines are poor stability and low efficiency of delivery. Consequently, mRNA is often packaged in the body by a delivery vector, including DC vectors, protamines, cationic lipid delivery systems, and polymer materials [55,56].

There are few reports of HPV mRNA vaccines. In a new study, mRNA expressing antigen HPV16E7 is encapsulated in liposome preparations and RNA-LPX-like molecules, resulting in immune responses in mice with strong antigen-specific effects and memory CD8+T cell responses [57]. With the outbreak of new coronavirus, research into mRNA vaccines has been pushed to a higher level and development prospects are also promising.

In conclusion, nuclear acid vaccines are hardly studied in the field of HPV, and animal experiments yield different results. Currently, because of its safety and effectiveness, mRNA vaccines are becoming increasingly popular in the case of epidemics.

Whole Cell Vaccines

Dendritic Cell Vaccines: Dendritic cells are the strongest and most effective APCs in the presence of antigens and play an important role in immune regulation. It has a strong ability to obtain and process antigens to be presented in vivo and in vitro to T lymphocytes, and many evidence has confirmed that DCs derived from monocytes can stimulate nervous CD4+ T lymphocytes and CD8+ T lymphocytes in vitro and in vitro [58,59]. Furthermore, DC is also a natural adjuvant to increase vaccine immunogenicity [60]. There are two methods of producing HPV vaccines with DC as the core. One of these is

to cultivate DCs in vitro and then stimulate DCs with HPV E6/E7 antigens. Another is DC's stability transposition in vitro with vectors expressing HPV antigens and then DC's adoption to patient transmission, presenting the antigen to nave T cells, resulting in CTL responses [61,62]. The application of receptor antagonists similar to TOLL to promote the maturation of DC is also widely used in the treatment of DC vaccines. Toll-like receptors (TLRs) are part of the DC cell pattern recognition receptor, while the DC cell pattern recognition receptors also have C-type lectin receptors (CLRs), NLRs, and RLRs that induce genes such as receptors (RLRs) associated with nucleic acid binding (NLRs), and TLR ligands induce DC cell phenotypes and functional maturation, regulate cell metabolism, and lifespan [63,64].

In patients with stage IB or IIA cervical cancer, the safety and immunogenicity of HPV16/18E7 antibodies and keyhole hemocyanin pulsed mature neurocytic cells (DCs) were assessed [65]. Three doses (low, medium, high) are injected every 21 days (total 5 times). Patients receiving DC vaccines showed good tolerance, without significant toxic or side effects, and significantly increased the expression of CD4+T specific to E7 and KLH after vaccination. Camelid-derived monodomain antibody fragments (nanobodies or VHHs) recognize the surface proteins of the cell on the antigen-presenting cells (APCs) and can act as a target delivery vehicle for antigens associated with them. A study aimed at VHH+CD11bE749-57 cells in DC2.4 cells, and mice vaccinations produced more CD8-tumor-infiltrating lymphocytes in HPV mice [66].

DC vaccines also have limitations. First, because the preparation technology is limited, the quantity and quality of the extracted DC cannot be guaranteed. On the other hand, large-scale production is difficult, and different processes can lead to inconsistent vaccine quality. As a result, there are still many obstacles to the development of DC vaccines.

Tumor Vaccines: Each cancer has a large number of potential tumor antigens, so the best strategy is to immunize entire tumor cells to include all potential antigens. Furthermore, the vaccine approach circumvents the limitations of the major inflammatory complex (MCH) and does not require epitope identification on a patient's request [67]. The effectiveness of this method has been evaluated over the years in clinical trials on different tumors such as lung cancer, colorectal cancer, renal cell cancer, and prostate cancer. Because HPV is a wellknown tumor-specific antigen, cellular-based tumor-based vaccines are not the most practical immune therapy for HPV-related cancer, and few studies have been conducted to evaluate the real effectiveness of this type of vaccine for HPV-related cancers.

Conclusion

The disease caused by HPV infections has always attracted the attention of the human eye and is the necessary factor for cervical cancer (100%). Vaccines currently play an essential and effective role in the prevention and treatment of cervical cancer. Over the past 20 years, vaccine research has developed rapidly, and the issuance of bivalent, quadrivalent, and nonvalent vaccines has effectively prevented 90% of HPV infections worldwide. However, new preventive vaccine research has never stopped, such as the study of new expression systems (e.g., E. coli) to reduce vaccine costs and the development of broad-spectrum L2 vaccines for simplicity and efficiency. In the treatment of cervical cancer, surgery is currently the main treatment and a therapeutic vaccine is not approved for marketing. The development of therapeutic vaccines is promising, with most vaccines based on E6/E7 tumor protein being developed to induce strong cell immunity and the hope of eradicating HPV-related diseases and malignant diseases. Vaccines are generally effective in preclinical studies, but not in clinical trials. In addition, the effectiveness of vaccines will be improved by exploring more in situ tumor models, combined therapy, and the design of new antigen targets (e.g. E1 and E5). We hope that a therapeutic vaccine will soon be available.

Acknowledgment

Not applicable.

Conflict of Interest

The authors have no conflicts of interest to declare.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008365

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