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Role of Different Immunotherapy Agents in Anogenital Warts Management: Review Article

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ABSTRACT

Background: Human Papillomavirus (HPV) types 6 and 11 are the causative agents of genital warts. HPV viruses come in over a hundred different varieties. The most common time for such skin-to-skin contact to occur is during sexual activity, where the risk of contracting HPV is highest. Cervical and anal cancer are caused by different kinds of HPV than genital warts. It's possible to be infected with multiple forms of HPV at once. For the treatment of warts immunotherapy could be used, which relies on the body's natural defenses to combat the infection and dampen down its activity. Immunotherapy can be administered orally, topically, intralesionally, or systemically.

Objective: Assessment of role of different immunotherapy agents in anogenital warts management.

Methods: Immunotherapy Agents, Anogenital Warts, and Management were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete studies from 2006 to 2020 were included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: This review article aimed to throw the light on the effectiveness of immunotherapy, which varies greatly from patient to patient, but the procedure is very promising because it works outside the injected wart.

Keywords: Immunotherapy Agents, Anogenital Warts.

INTRODUCTION

Warts are a well-known sign of HPV infections in the anogenital area. Ninety percent of those who are HPV-positive will never get warts on their genitalia. Only about 10% of infected people actually spread the virus. Types 6 and 11 of the human papillomavirus produce genital warts. More than a hundred distinct strains of HPV have been identified. The most common time for such intimate skin-to-skin contact to occur and hence spread HPV is during sexual activity. The types of HPV that cause genital warts are distinct from the kind that cause cervical and anal cancer. Multiple human papillomavirus (HPV) infections are conceivable [(1)].

Numerous research has documented the psychological burden of genital warts morbidity, which includes anxieties, emotional and sexual consequences, self-image issues, and control/life impact. But compared to males, women felt more burden. The psychological impacts of genital warts also have an impact on men [(2)].

The human papillomavirus (HPV) causes anogenital warts, which are benign epithelial skin lesions. HPV types 6 and 11 infection account for greater than 90% of all cases of anogenital warts. They are benign lesions that form in the anogenital region and manifest as lumps or raised plaques on the skin. In most cases, there will be no pain, but there is always the chance of discomfort or even bleeding. They can be distressing to deal with on an emotional level, and the treatment they often require is drawn-out, tiresome, and unpleasant. Treatment progress is often followed by a relapse [(3)].

Genital warts could only be treated until a few years ago with a combination of cryotherapy, podophyllotoxin, and laser ablation. Since then, the range of therapeutic choices has been widened by new pharmacological substances and techniques. The current study aimed to provide an overview of all currently available condylomata treatments and to explain the importance and utility of various treatment alternatives [(4)].

Provider-administered treatments and self-administered treatments can be broadly classified into two types. Ablative therapy (including microwave ablation, cryoablation, laser ablation, electrosurgery) and non-ablative therapy make up the majority of the provider's therapeutic options (e.g., trichloroacetic acid). Podophyllotoxin, imiquimod, and polyphenon E are the most common of the self-administered therapies [(5)].

Treatment methods for warts include chemical cautery, cryotherapy, electrocautery, surgical excision, and laser ablation, all of which are considered damaging and aggressive. Immunotherapy is the second line of defense, and it works by boosting the body's immune system to combat the virus and reduce its activity. Oral, topical, intralesional, and systemic administration are all viable options for immunotherapy [(6)].

The effectiveness of immunotherapy varies greatly from patient to patient, but the procedure is very promising because it works outside the injected wart, curing a large proportion of patients with remote warts. Adverse effects are mostly mild; nonsteroidal anti-inflammatory drug-responsive flu-like symptoms [(7)].

Due to the wide variety of immunotherapy options and the individuality of each patient's immune system, selecting the most effective treatment can be difficult. Several factors, such as the patient's age, sex,

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medical history, and the appearance of the warts themselves, must be considered before providing treatment. Patients with many warts or treatment-resistant warts are more likely to have a weakened cell-mediated immune response [7].

To reduce the risk of cervical cancer, immunization with any of the currently available HPV vaccinations is highly recommended, especially for young people. Cross-reactivity across HPV strains suggests that these vaccines also protect against the kinds of HPV that can cause skin warts to emerge beyond the vaginal region [8].

Candida Antigen

The substance known as candida antigen is made from 100% pure extracts of the yeast Candida albicans. It is injected intralesionally either undiluted or diluted with lidocaine to a concentration of 50%. There should be a three-week gap between each application and the total volume used is between 0.2 and 0.3 mL [9].

An immunotherapeutic strategy known as intralesional immunotherapy using Candida antigen has recently attracted more interest and has demonstrated potential efficacy in the treatment of warts [9].

It was discovered that candida antigen immunotherapy significantly stimulated the Th1 response, leading to the generation of IFN-, suggesting that it may be employed as the single immunotherapeutic agent for lesions associated with HPV as well as other viral infections or even malignancies [10].

HPV Vaccines

History of vaccine development:

The human papillomavirus (HPV) is responsible for several devastating diseases, such as cervical cancer in women, head and neck squamous cell carcinoma in adults, and recurrent respiratory papillomatosis (RRP) in infants. Developing a preventative HPV vaccine has been prioritised in an effort to lower the rate of cervical cancer in women [11].

In 1991, **Zhou *et al.*** [12] at the University of Queensland in Australia produced a non-infectious recombinant virus like particle (VLP) of L1, the major HPV virion protein. Indeed, a cellular immunological response was triggered by this VLP [12].

Two years later, at the National Cancer Institute, a structural equivalent of HPV type 16 was developed. This VLP served as the basis for the parallel development of an HPV vaccination at the aforementioned institutions and at the Universities of Rochester and Georgetown. As time went on, Merck approved a patent for their HPV vaccine. The Food and Drug Administration approved Gardasil, a quadrivalent immunization that protects against types 6, 11, 16, and 18 of the human papillomavirus, in June 2006. In 2007, the ACIP recommended that this vaccination can be administered to all females between the ages of 9 and 26 inclusive [13].

In 2009, Cervarix, a bivalent vaccine effective against HPV strains 16 and 18, was licensed by the Food and Drug Administration and the Advisory Committee on Immunization Practices [14]. The FDA granted approval of the quadrivalent HPV vaccine for boys and men ages 9 to 26 in October 2009. Even though the ACIP recommended vaccination for females in 2010, they also suggested it for males [15].

Mechanism:

Based on L1 VLPs, HPV vaccinations have proven to be highly effective at preventing HPV infection. The papillomavirus's L1 protein is a key capsid protein that can self-assemble virus like particles (VLPs). VLPs cause potent immune responses and make it safe and simple to produce vaccines. An effective first-serum HPV-type-neutralizing antibody response can be elicited by recombinant L1 VLPs due to their high immunogenicity [16].

Adaptive immune reactions are induced by commercial HPV VLP vaccinations that are administered intramuscularly. The antibodies stop the HPV virion from being ingested by the epithelial basal cells, neutralising it. Antibodies can enter the basement membrane via the dermal capillary network or by an exudate caused by tissue injury to the epithelium. Upon arrival, neutralising antibodies block L1 from attaching to its target, preventing infection [17].

Cells of bacteria, yeast, or insects can all create VLPs. HPV16 and 18 VLPs, monophosphoryl lipid A (MPL), and aluminium hydroxide are all components of the adjuvant system 04 (AS04) found in Cervix [18].

Both sexes can benefit from the HPV vaccine's effectiveness in avoiding genital warts and associated malignancies. Recently, the concept of vaccination's medicinal application was included. Therapeutic vaccination has not been formally approved in any jurisdiction due to the absence of an official evaluation in a randomised prospective study [19].

Benefits of the HPV Vaccine:

Cervarix causes elevated levels of antibodies against HPV16 and 18 that can protect against infection for up to a decade [20]. Cervarix also produces substantial and long-lasting HPV31 and 45 immunogenicity. More than 85% of people in a 10-years follow-up trial who had received Cervarix after three doses remained seropositive for anti-HPV31 and 45 antibodies [20]. Cervarix is effective (> 60%) in preventing all types of cervical precancerous lesions, regardless of whether or not they were caused by human papillomavirus (HPV) [15, 17].

The quadrivalent Gardasil vaccine is highly effective against genital warts (caused by the HPV strains covered by Gardasi) as well as cervical HPV infection, cervical cancer precursor lesions, and genital warts [21]. According to studies comparing several HPV vaccinations, Gardasil also significantly decreases anogenital, vulvar, and genital HPV infections [22, 23, 24].

When given before exposure to HPV, Gardasil has a high success rate (> 90%) in preventing cervical intraepithelial neoplasia grades 2 or worse (CIN 2+), CIN 3+, and VIN/VaIN 2+, all of which are caused by HPV 16 and 18. However, regardless of HPV type, suppression of CIN 2+ and CIN 3+ was modest (20-50%) [(25)].

Age of vaccination:

Before sexual activity begins, or prior to the first exposure to HPV infection, is the best age for HPV vaccination. Currently, it is advised that females receive the HPV vaccine between the ages of 11 and 12, with catch-up vaccinations offered to those who have not started or finished the series between the ages of 13 and 26 [(26)].

Adverse effects:

Injection-site reactions like pain and swelling were the most common adverse events (AEs) reported with Cervarix and Gardasil, probably as a result of the VLP-related inflammatory process [(27)].

The HPV vaccine is well-tolerated and safe. The most frequent adverse event (AE) was discomfort at the injection site. Additionally common were injection-site erythema and edema. Headache and weariness were the most frequently reported systemic AEs associated with vaccination, occurring in around 50–60% of vaccinations. It is advised to monitor vaccines for 15 minutes after injection because there has been an increase in the occurrence of syncope and tonic-clonic movements [(28)].

Contraindications and precautions:

For people who have a history of acute hypersensitivity to any vaccine component, vaccinations are contraindicated. People who have anaphylactic latex allergies shouldn't take Cervarix. Pregnant women should not receive HPV vaccinations. Pregnancy testing is not necessary before immunization, though, if a woman becomes pregnant after starting the vaccine series, the remaining two doses of the three-dose series should be postponed until after the pregnancy is over [(29)].

CONCLUSION

The effectiveness of immunotherapy varies greatly from patient to patient, but the procedure is very promising because it works outside the injected wart.

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