

Immunotherapy Growing Role in Warts Management: Review Article

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ABSTRACT

Background: Common dermatological disorders induced by the human papillomavirus (HPV) include warts (both cutaneous and genital). It's not dangerous, but it's unpleasant to look at, can spread to others, and sometimes koebnerizes. So, it's crucial to get the right care at the right time. Several conventional therapies are available, although their efficacy varies. Noninvasive, user-friendly, and showing great promise, topical and systemic immunotherapy has quickly become a mainstay in the treatment of warts.

Objective: Assessment of Growing role of immunotherapy in treatment of warts.

Methods: We searched PubMed, Google Scholar, and Science Direct for information on Immunotherapy with Warts and human papillomavirus. However, only the most current or comprehensive study from April 2005 to July 2022 was considered. The authors also assessed references from pertinent literature. Documents in languages other than English have been disregarded since there aren't enough resources for translation. Unpublished manuscripts, oral presentations, conference abstracts, and dissertations were examples of papers that weren't considered to be serious scientific research.

Conclusion: Intralesional immunotherapy using Candida antigen has the benefits of being inexpensive, showing promise, being simple and easy to inject into a single wart. A promising immunotherapeutic strategy is intralesional injection of the Candida antigen. In both injected and non-injected lesions, this modality is related to Th1 cytokines production.

Keywords: Immunotherapy, Warts, Human papillomavirus.

INTRODUCTION

An extensive group of non-enveloped, epitheliotropic, double-stranded DNA viruses called human papillomavirus (HPV) is responsible for a variety of human malignancies. Infection causes enhanced epithelial proliferation in particular areas, which might lead to cancer in some cases ⁽¹⁾. Double-stranded DNA viruses, human papillomaviruses (HPV) are about 8 kilobases in length and 50-55 nm in diameter. The viral DNA is enveloped in an icosahedral spherical capsid that has a preference for epithelial cells and infects the skin and mucous membrane ⁽²⁾.

Abrasion to the skin or mucous membranes frequently results in HPV infection. Through contact with contaminated surfaces like gym floors or the area around swimming pools, cutaneous forms can also spread inadvertently ⁽³⁾.

The ability of HPV to elude the immune system is unique. Three fundamental viral characteristics allow for this ability. Since there is no viremic phase, immune cells in circulation have difficulty accessing the virus. Despite the abundance of Langerhans cells on the mucosal surface, infections typically begin at the basement membrane. Second, HPV is able to replicate "silently" because it does not cause significant harm to the host cells, such as lysis of the infected cell, hence reducing inflammation and the accompanying signaling ⁽⁴⁾.

The inflammation associated with warts is not always present, and they might persist for years. The wart may first shrink in size a few months to years

following infection, at which point it may vanish on its own. In children, clearing often begins within a few months, with around 50% clearing by one year and 2/3 clearing by two years. While childhood warts often disappear after a year or two, adult ones can linger for five to 10 years ⁽⁵⁾.

Two main therapeutic approaches are used to treat warts: immunotherapy, which is based on immune system activation, and the traditional aggressive and destructive strategy, laser ablation, chemical cauterization, cryotherapy, electrocautery, surgical excision, and surgical excision all fall under this category ⁽⁶⁾.

Immunotherapy in Warts Management (Figure 1):

Immunotherapy is a biological therapy that employs medicines that stimulate or suppress the immune system to combat cancer, infections, and other diseases. Topical and systemic immunotherapy has now assumed a pivotal position in the treatment of warts because of its non-invasive nature, ease of use, and promising results ⁽⁷⁾.

Growing evidence of the importance of cell mediated immunity (CMI) in wart elimination, particularly in patients with many and persistent warts, has justified the use of a variety of immunomodulatory alternatives to eliminate warts on the skin. These include topical sensitizers like diphenylcyprone, pro-inflammatory cytokines like interferons, intralesional antigen therapies like Candida antigen therapy, and others ⁽⁸⁾.

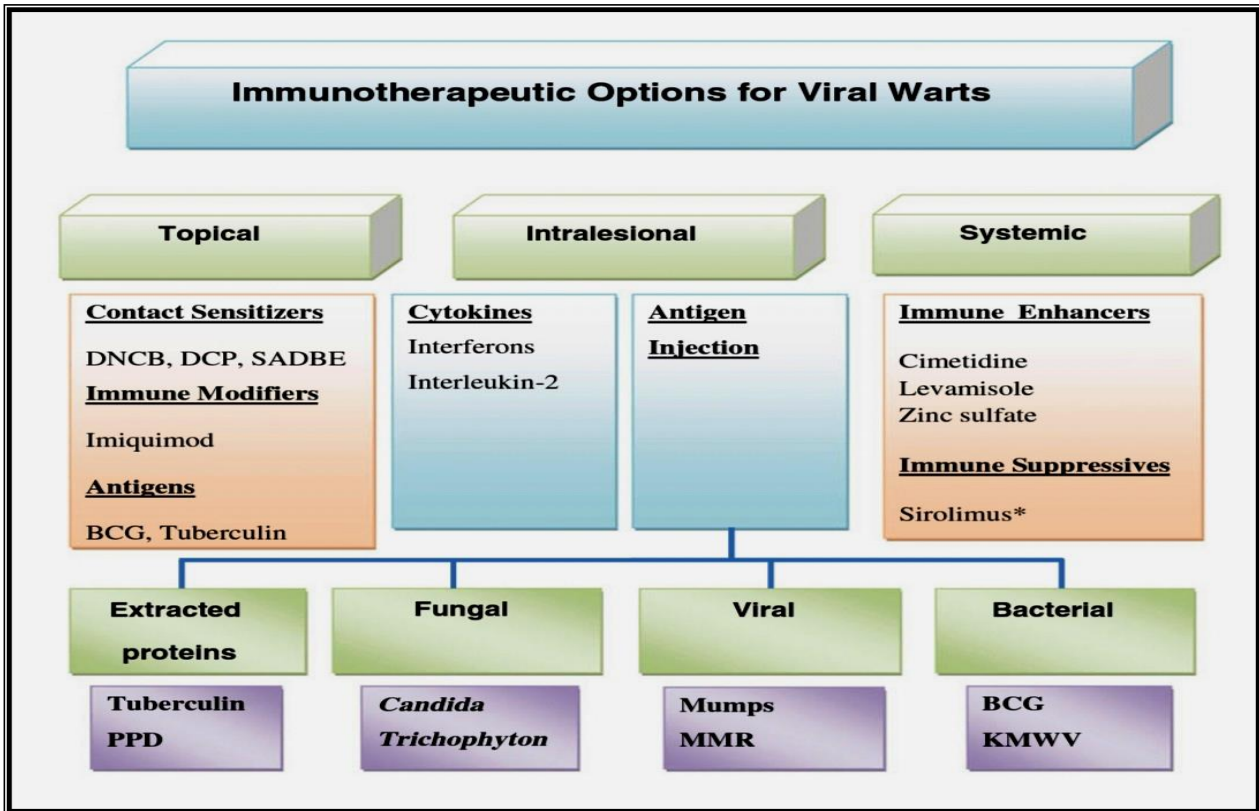


Figure (1): Immunotherapeutic options for viral warts ⁽⁹⁾.

(A) Topical immunotherapy:

1-Dinitrochlorobenzene:

After topical administration, dinitrochlorobenzene is quickly absorbed, and the kidneys are principally responsible for its excretion. It is no longer used in therapeutic settings because it includes pollutants that are carcinogenic and mutagenic to animals ⁽¹⁰⁾.

2-Diphenylcyclopropenone (DPCP):

Warts can also be effectively treated with topical immunotherapy using diphenylcyclopropenone. Recalcitrant warts can be treated with it safely and successfully. Weekly applications with increasing concentration are made. Warts are removed using DPCD, which causes contact dermatitis ⁽¹¹⁾.

3-Dibutyl ester of squaric acid (SADBE):

Warts that are resistant to therapy have been treated with squaric acid dibutyl ester. It is more costly than DPCP and less stable in acetone dilutions. SADBE may function by triggering a type IV hypersensitivity response in an HPV-infected tissue, resulting in the removal of warts. Also, it needs to be used in 2 phases: sensitization and treatment ⁽¹²⁾.

4-Imiquimod:

A non-nucleoside heterocyclic amine called imiquimod has the ability to alter the immune response. Powerful antiviral and anticancer effects are achieved by increasing cellular levels of interferon alpha (IFN- α), tumour necrosis factor alpha (TNF- α), and interleukin-6 (IL-6). Home use of imiquimod for the treatment of genital warts has been approved by the Food and Drug Administration ⁽¹³⁾.

5- Topically applied Bacillus Calmette-Guerin (BCG): Children with common and plane warts can be

treated successfully and safely with topical immunotherapeutic BCG. A rise in cytokines like IL-1, IL-2, and TNF- α as well as CD4 cell activation are key components of the mechanism of action. The antiviral actions of IL-1 and TNF- have been demonstrated through their ability to inhibit the transcription of HPV genes ⁽¹⁴⁾.

(B) Intralesional immunotherapy (Figure 2):

Intralesional immunotherapy currently lacks a clear mechanism of action. A non-specific immune response to the wart antigens can result from trauma of any kind, including the trauma caused by an intralesional injection, as is well documented. It is likely that intralesional antigen injection causes a potent, non-specific inflammatory response against the HPV-infected cells ⁽⁸⁾.

Mechanism of action:

Intralesional immunotherapy works by stimulating a strong cell-mediated immune response that tips the scales in favour of Th1 responses and away from Th2 responses, thus eliminating HPV ⁽⁹⁾.

Advantages ⁽¹⁵⁾:

1. Particularly in underdeveloped nations, its low cost is one of the major benefits. It is a treatment that is effective, simple, and safe
2. The ease of use, the effectiveness that seems promising, the low risk to patients, and the lack of any permanent impairments to mobility, scarring, or coloration,
3. Intralesional immunotherapy has been proven to be effective in reducing or even preventing recurrences following successful therapy in numerous studies.

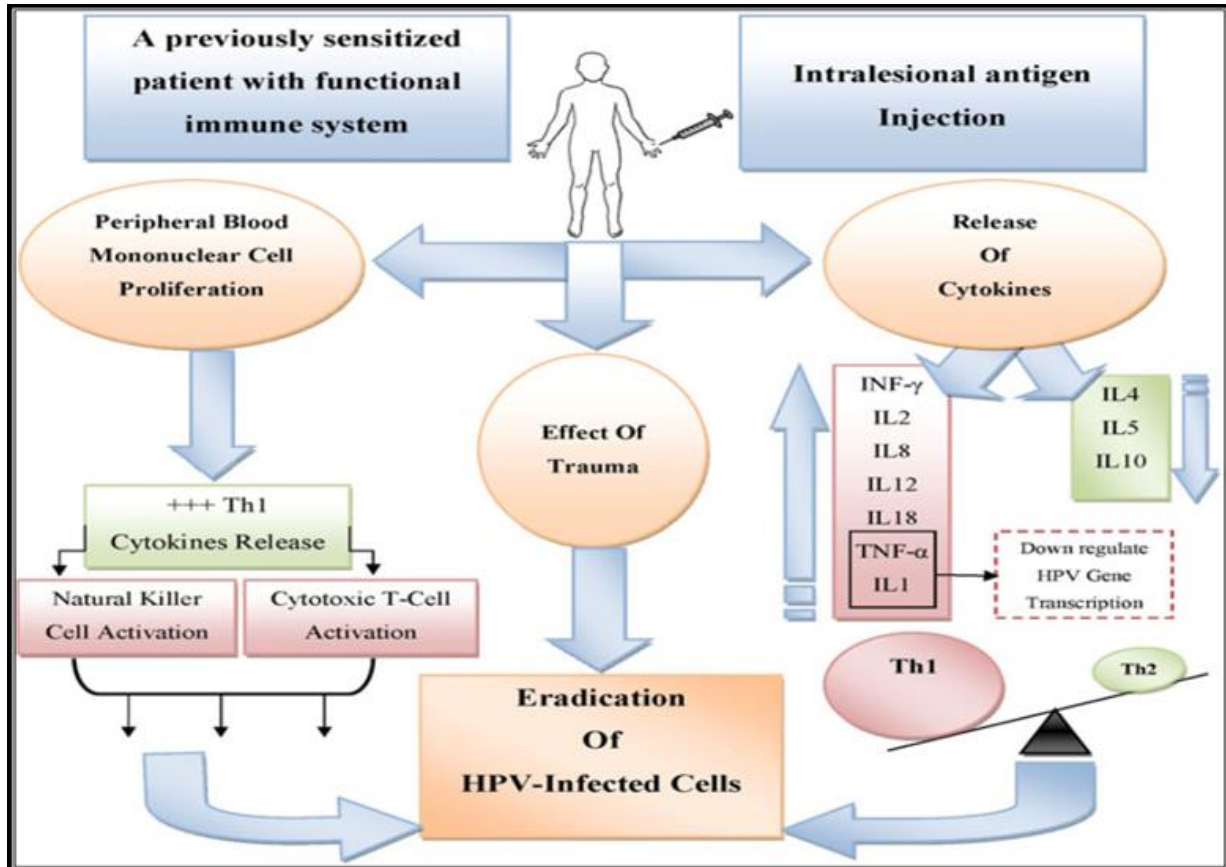


Figure (2): Mode of action of intralesional antigen immunotherapy ⁽⁹⁾.

Disadvantages:

The majority of patients can withstand the injection's associated pain, however certain patients, such as those with periungual warts, who favor painless topical administration, as well as youngsters who prefer painless topical application, still find it to be an inconvenience ⁽⁹⁾.

Types of Antigens:

1. Measles, mumps, and rubella (MMR) vaccine:

The intralesional immunotherapy based on the MMR vaccine may have the advantages of eradicating scarring, reducing the chance of recurrence, and ensuring a high safety profile in the case of both treated and untreated remote warts. The effectiveness of the immunization in treating cutaneous warts was evaluated. Aches at the injection sites and flu-like symptoms were the only reported negative effects ⁽¹⁶⁾.

2- Bacillus Calmette Guerin (BCG) Vaccine:

Similar mechanisms underpin both the Mw vaccination and the BCG vaccine. A delayed hypersensitivity reaction to the antigen is essential for a clinical response against warts. Serum IL4 levels are reduced while IL12 levels are increased. One to three doses are given over the course of a month ⁽⁷⁾.

3- Killed Mycobacterium (M W) vaccine:

Injecting the quickly growing non-tuberculous mycobacterium. Mycobacterium w or Mycobacterium indicus pranii intralesionally elicits a significant pro-inflammatory response. Increased production of IL-2, IL-4, IL-6, and IFN-gamma from T helper 1 cells, together with natural killer cell and cytotoxic T cell

activation, characterize a delayed hypersensitive reaction. Due to the exchange of fire between the HPV-infected cells, warts are eliminated both locally and systemically ⁽⁷⁾.

There are a number of negative side effects as fever, discomfort, sterile pustules at the injection site, and paresthesia in limbs far from the warts that were injected ⁽⁷⁾.

4-Purified protein derivative (PPD):

A cell-mediated immune response activated by intralesional immunotherapy PPD tuberculin antigen. As a result, infection is under control and recurrence is prevented. The treatment of cutaneous warts in individuals who have received vaccinations is a low-cost, safe, and successful technique with a high rate of cure. Localized redness, soreness, and edema were the most often reported side effects, and they disappeared four days after injection without the need of any drugs ⁽¹⁷⁾.

5-Candida albicans antigen:

According to Nofal *et al.* ⁽¹⁸⁾, intralesional immunotherapy using Candida antigen has the benefits of being inexpensive, showing promise, being simple and easy to inject into a single wart, having a high safety profile, being associated with distant responses, not causing scarring and pigmentary changes like destructive therapies do, and having low or no recurrence rates. A good indicator of the efficacy of treatment is the measurement of IFN-c production in a culture treated with Candida antigen before treatment begins.

A promising immunotherapeutic strategy is intralesional injection of the Candida antigen. In both injected and non-injected lesions. To eliminate HPV infection, this strategy is linked to the generation of Th1 cytokines including TNF- α which in turn activate cytotoxic and NK cells⁽¹⁸⁾.

Wart remission following intralesional Candida treatment was linked to the discovery of an immune response to the HPV-57 LI-peptide, indicating that LI-specific T cells may play a role in wart regression⁽¹⁹⁾.

Adverse effects of Candida antigen injection

Intralesional Candida antigen injection side effects can include a fever reaction, a typically moderate flu-like sickness, reactive pain, and edoema at the injection site. There have also been reports of painful purple digit syndrome and post-injection cicatrization. However, reports of discomfort during injection are the most common, and other adverse effects are relatively uncommon⁽²⁰⁾.

(C) Systemic immunotherapy:

1- Cimetidine:

High dosages of the H₂-receptor antagonist cimetidine are thought to have immunomodulatory effects by suppressing suppressor T-cell activity while promoting lymphocyte proliferation and improving cell-mediated immunological responses. Headache, nausea, and vomiting are side effects⁽²¹⁾.

2- Zinc Sulphate:

It is unclear how zinc works to treat warts. Leucocytes and NK cells play a key role in immunological regulation, which is mediated by zinc^(22, 23).

3- Levamisole:

First created as an antihelminthic, levamisole's immunomodulatory effects were quickly recognized. It has been used to treat cutaneous warts at a dosage of 2.5-5 mg/kg/day for 3 consecutive days every 2 weeks for 4-5 months. Levamisole was effective for 60% of patients^(7, 23).

CONCLUSION

Intralesional immunotherapy using Candida antigen has the benefits of being inexpensive, showing promise, being simple and easy to inject into a single wart. A promising immunotherapeutic strategy is intralesional injection of the Candida antigen. In both injected and non-injected lesions, this modality is related to Th1 cytokines production.

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