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Review Article

Issues related to topical immunotherapy for the treatment of warts: A review of the literature

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Abstract

Immunotherapy has emerged as a critical therapeutic tool for the treatment of warts. Immunotherapy for warts is currently restricted to recalcitrant lesions. Conventional therapy is not working despite the fact that there are numerous immunotherapeutic agents available. A small number of regimens appear to be extremely effective. Furthermore, there is a scarcity of evidence-based research. Data on their efficiency topical immunotherapeutic modalities commonly used in the treatment have all been reported as effective treatment modalities for different types of warts. Furthermore, in the majority of cases, their safety and effectiveness have not been evaluated in double-blind, controlled clinical trials, making the reproducibility of many of the listed treatments difficult to analyze and a possible placebo effect difficult to rule out. The different types of immunotherapy for warts are mentioned in this report.

Key words
Topical immunotherapy, warts.

Introduction

Human papillomavirus induces prevalent lesions such as cutaneous and ano-genital warts (HPV).[1,2] HPV is by far the most prevalent disease in the world, representing nearly one in every ten women.[3] The virus first targets epidermal basal cells and then enters a dormant phase of slow multiplication. Because of physical pain and awkwardness, warts have a considerable effect on quality of life.[4] They frequently relapse autonomously after months or years in healthy patients, but they also have a greater risk of relapse.[5] HPV types 1 and 2 are primarily responsible for common and plantar warts, while types 6 and 11 are responsible for approximately 90% of genital warts.[6] Therapies for cutaneous warts varies in efficacy and frequently results in recurrence.

To enhance the host immune response, various systemic immunotherapies have been tried. To combat the warts, this treatment employs the patient's own immune system. Specific types of

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immunotherapy only target specific immune system cells. Some have an overall impact on

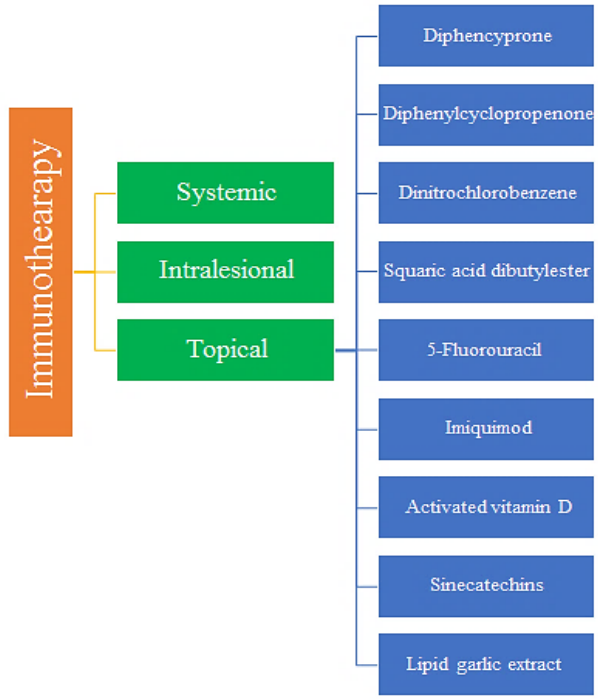

Figure 1 Immunotherapy involve systemic, intra-lesional or topical modalities of therapy for wart.

the immune system. It works by inducing a T-cell-mediated response throughout the body. In responding to injection, cytokines produced by Th1 cells, such as interleukin-2 and interferon-gamma, are primarily risen. Injecting intralesionally may also help to concentrate the local immune response; however, some argue that the trauma of injection alone may be effective in eliciting an adequate immune reaction in immunocompetent patients.[7,8]

Immunotherapy is gaining popularity, particularly in the treatment of refractory cutaneous and genital warts. Of this are topical, intralesional, and systemic agents. There are no clear guidelines or consensus on when immunotherapy should be attempted in a patient with warts.[7,8]

Immunotherapy is comparatively cheap, despite the fact that the mechanism is not fully comprehended, has the potential to dramatically increase the treatment of warts, including distant uncontrolled warts by previous treatment.[9,10] This review investigates the efficacy, tolerability, and feasibility of various vaccines used intravenously to treat cutaneous warts.

Topical therapy (Figure 1)

1 ***Diphencyprone*** 2 percent sensitization Diphencyprone (DPC) is performed on a 1 cm^2 patch of skin on the upper arm. Following the removal of the warts, DPC at a concentration of 0.1 percent is implemented (2 percent to the soles of the feet).[11] The most known side effect of DCP treatment is blistering at the location of sensitization. Distanced or more pervasive eczematous eruptions may also occur as a result of DCP passive transfer or autoeczematization. Regional lymphadenopathy, contact urticaria, erythema multiforme-like reactions, and vitiligo are some of the less known side effects.[12] Because it is still an unauthorized therapeutic strategy, it is probably better avoided during pregnancy. DCP should not be used to treat genital or facial warts because the risk of passive transfer is high in the genital area, and bullous or eczematous side effects on the face would be less acceptable. DCP immunotherapy is ideal for plantar, palmar, periungual, and digital warts.[13] Changes in cytokine levels, nonspecific inflammation causing wart regression, and DPC binding to wart protein inducing a specific immune response are all theories. It was proposed that topical DCP therapy could induce long-term immunity to HPV, potentially lowering the incidence of wart recurrence.[14]

2 ***Diphenylcyclopropenone*** (DPCP) is implemented to warts at an initial concentration of 0.1 percent on fingers, periungual regions, palms, toes, and heel, and 2 percent on the sole (the density of DPCP is adjusted to induce local erythema, pruritus, and/ or vesiculation). The

warts are then carefully covered with adhesive dressings for 48 hours to prevent passive DPCP transfer.[15] The prospective negative consequences are not insignificant. Numerous patients develop unsightly pigmentation at the sensitization site, so sensitization is best performed on the inner upper arm. Local blistering at the treatment site and/ or sensitization site is common during therapies.[16] Changes in cytokine levels, nonspecific inflammation resulting wart regression, and binding of DPCP to wart protein trying to induce a specific immune response are all theories. The latter is supported by the fact that untreated warts may sometimes enhance or disappear during therapies. DPCP causes a CD4:CD8 ratio reversal, with CD8 cells predominating in a heavy epidermal and dermal inflammatory infiltrate. Immunotherapy with DPCP should not be used as a primary therapy for warts, but it is an option in certain patients with recalcitrant multiple warts.[17]

3 ***Dinitrochlorobenzene*** DNCB plays a role in the development of delayed-type hypersensitivity.[18] In human skin fibroblasts, DNCB causes mutagenesis and is genotoxic via sister chromatid exchange.

DNCB raises the prevalence of complement-binding wart virus antibodies from 15% before treatment to 48% afterward, implying a role for humoral factors in the evolution of viral warts.[18]

4 ***Squaric acid dibutylester*** Squaric acid dibutylester (SADBE) topical immunotherapy is an effective therapy for the treatment of multiple plantar and common warts. SADBE has some limitations in the genital area because it can cause massive irritation, which causes massive discomfort to the patient.[20] SADBE's immunomodulatory action in warts works by inducing a type IV hypersensitivity response in an HPV-infected tissue, which results in wart destruction. It is unknown whether the contact sensitizer, as a hapten, attaches to wart protein and induces a specific immune response to wart antigen. Other theories contend that SADBE-induced inflammation determines wart resolution via a nonspecific inflammatory response.[21] There are no significant side effects associated with SADBE topical immunotherapy.[22]

5 ***5-Fluorouracil*** (5-FU) is a fluorinated pyrimidine antimetabolite that acts as an antineoplastic agent by inhibiting the synthesis of DNA and RNA.[23] 5-FU has been used to treat genital warts as a cream or an injected solution in concentrations ranging from 1 to 5%. The evidence from the studies we reviewed showed that 5-FU had better cure rates than placebo or no treatment, meta-cresol sulfonic acid treatment, and podophyllin 2, 4, or 25% treatment.[24] In addition, intralesional 5-FU injection was found to be both safe and treat a variety of multiple recalcitrant cutaneous warts.[25]

6 ***Imiquimod*** is a synthetic immunostimulant with antiviral and antitumor activity. It is better suited for warts with a diameter of 0.5-1.0 cm and moist nonkeratinized warts. It is effective in treating recalcitrant plantar, periungual, and subungual warts.[26] Imiquimod is a TLR (Toll-like receptor) agonist. It binds to TLR7, which activates dendritic cells, macrophages, and monocytes, triggering a complex chain of reactions in the cytoplasm that eventually leads to the activation of nuclear factor-β (NF-β) and the production of cytokines and chemokines outside of the cell. Interferon-(IFN-α), IFN-γ, ILs 1, 6, 8, 10, and 12, and TNF-α are the most important of these cytokines and chemokines.[27] It is used to treat ano-genital warts three times a week at bedtime, followed by four days of rest or every other day (three times a week). 6-10 hours after application, it should be washed with

soap and water. The treatment can last up to 16 weeks. It works better on women than on men. Local reactions such as erythema are common (33-80%). Flu-like symptoms, fatigue, diarrhea, fever, skin blistering, erosion, excoriation, flaking, edema, paresthesia, pruritus, burning, tenderness, stinging, crusting, and superficial ulceration are all possible.[28]

7 ***Activated vitamin D*** Maxacalcitol, an active vitamin D3 analog, inhibits cell death, tumor invasion, and angiogenesis, making it a potential cancer-regulating agent.[29] A 74-year-old man was treated for condylomata acuminata on the corona and glans with a topical vitamin D3 derivative twice a day for four months.[30] Intralesional Vitamin D3 is both effective and safe in treating multiple cutaneous warts,[31] and recalcitrant warts.[32]

The effectivity stemmed from its ability to control epidermal cell proliferation and differentiation, as well as modulate cytokine secretion. An important finding suggested that TLR activation of human macrophages increased the expression of vitamin D receptor and vitamin D-1-hydroxylase genes, resulting in the induction of the antimicrobial peptide. This suggests a link between TLRs and vitamin D-mediated innate immunity. Thus, imiquimod and vitamin D3 derivatives may share some antiviral effectiveness.[33] A case of an infant with an anogenital wart on the anus that was successfully treated with calcipotriene ointment, a vitamin D3 derivative.[34] Also oral vitamin D could be use in conjugation to other therapies for managing warts.[35]

8 ***Sinecatechins*** Topical sinecatechins ointment 15% is a standardized extract of Camellia sinensis green tea leaves rich in polyphenols, particularly catechins (>85%). The most biologically active catechin is epigallocatechin gallate.[36] Sinecatechins are used in the treatment of external genital and perianal warts in adults.[37] Catechins' direct action is to scavenge reactive oxygen-free radicals. Catechins may exert indirect antioxidant activity by inhibiting transcription factors (e.g., NF-β, activator protein-1) and inhibiting the activity of enzymes that increase oxidative stress (e.g. lipoxygenases, cyclooxygenases, and inducible nitric oxide). Endogenous antioxidant systems are also activated by epigallocatechin gallate. Catechins also inhibit cell proliferation by inhibiting kinases and promoting apoptosis.

Furthermore, catechins stimulate the immune system by increasing the activation of macrophages, lymphocytes, Langerhans cells, and the induction of cytokines (IL-1, TNF-α, IFN-γ), as a result, cell-mediated immunity against HPV.[38] The one most frequently reported reactions are local skin reactions [redness, burning, pain, itching, swelling on and around the treatment site].[39] The safety and effectiveness of sinecatechins ointment 15% in pediatric patients has not been identified, and it is unknown whether it is excreted in breast milk.[40] Furthermore, sinecatechins ointment 15% is not recommended for people who have HIV, are immunocompromised, or have genital herpes because the safety and effectiveness in these groups has not been ascertained. Not only do sinecatechins have a broad spectrum of action, but they are also related to lower recurrence rate (6.5 %). As a result, in the future, it may be a better option for treating anogenital warts. Sinecatechins has a lower treatment cost than imiquimod.[41]

9 ***Lipid garlic extract (LGE)*** The use of garlic chloroform extracts was noted to result in the total abolition of cutaneous warts with no recurrence after 6 months.[42] Alternatively, raw garlic cloves can be massaged onto the wart on a nightly basis, followed by blockage.[43]

Garlic and its active organosulfur compounds (OSCs) have been shown in pre-clinical and clinical studies to alleviate a variety of viral infections.[44]

LGE could indirectly modulate the immune system. Garlic extracts have cytotoxic and anticancer properties.[45-47] It has a number of growth arrest mechanisms, including the inhibition of initial events caused by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) type tumor promoters.[48] S-allylcysteine already has anti-proliferative and anti-metastatic properties.[49] LGE's primary antitumor effect may trigger a secondary immunomodulatory response. TNF- is not solely responsible for the immune response to LGE application.[42]

Conclusion

Immunotherapy has emerged as one of the most important therapeutic modalities for warts. Such treatment is required not only for recalcitrant or multiple lesions, but also in the majority of treated cases. Although not all immune-therapeutic agents have been thoroughly studied, the various methods of application, ease of application, suitability for children, and role in reducing relapse have encouraged their use either alone or in combination with other conventional methods. Based on our findings, we believe that immunotherapy as a single therapy is ineffective for the treatment of warts and that it is best used in conjunction with conventional methods.

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