Original Article

IMMUNOTHERAPY AGENTS USE FOR TREATMENT OF WARTS

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Abstract

Background: HPVs infect stratified epithelium and establish infections that can persist for decades. For these infections to persist, papillomaviruses have evolved strategies to evade the effects of the innate immune system during the initial phases of infection as well as long-term surveillance by the adaptive immune system. Warts are the cutaneous manifestations of HPV infection. Warts may exist in different forms according to the epithelial surface and HPV type responsible for the infection. Common warts (Verruca vulgaris), plantar warts (Verruca plantaris), flat or plane warts (Verruca plana) and genital warts (Condyloma acuminata) are some of the clinical manifestations of HPV infection. There are numerous immunomodulators that have been used for treating warts. Although topical mmunotherapy agents have their own clinical advantages over other destructive treatment modalities, an updated assessment of these agents is required.

Keywords: warts, immunotherapy

Introduction

Warts are the cutaneous manifestations of HPV infection. Warts may exist in different forms according to the epithelial surface and HPV type responsible for the infection. Common warts (Verruca vulgaris), plantar warts (Verruca plantaris), flat or plane warts (Verruca plana) and genital warts (Condyloma acuminata) are some of the clinical manifestations of HPV infection **(1).**

Transmission of warts:

Subclinical and latent forms

By applying 3% acetic acid to the mucosal surfaces of healthy people, as is done during a colposcopic examination of the cervix or vaginal tract, chronic subclinical infections can be seen. During the first three years of life, high-risk HPV DNA can be found in the oral and genital mucosa of infants. It can also occasionally be found in immunocompetent and immunosuppressed people. HPV DNA can be found in clinically and histologically normal skin and mucosa as latent papillomavirus. It's possible for family members to horizontally spread HPV infections. In order to reduce the number of erroneous allegations of sexual abuse, it is crucial to keep this in mind. Detailed and proper history-taking, physical examination, and linkage with the socio-clinical setting continue to be the primary methods for identifying potential sexual abuse **(2)**.

Autoinoculation

Autoinoculation is a significant method of virus transmission. The face and extremities are the most common locations for HPV infection. Contact with other cutaneous locations, such as the lips, nose, and face, can spread hand warts **(3).**

Heteroinoculation and iatrogenic transmission

Saliva can spread HPV DNA during breast-feeding and plays a significant role in the transfer of HPV DNA within families. Mothers who continue to carry oral and genital HPV are more likely to get warts. Viral warts are spread by direct contact through fomites or indirectly by contaminated surfaces **(4).**

Iatrogenic transmission of the virus may occur indirectly through the use of inadequately sterilized instruments. Papillomaviruses can endure for a very long time. Maceration of the skin aids in viral transmission. Those with a history of viral warts are more susceptible to re-infection. The partner's sexual history, sexual conduct, and age are the most often mentioned risk factors for genital HPV infections. **(5).**

Vertical transmission

Normal skin can get infected with HPV as early as infancy. Laryngeal papillomas or anogenital warts that result from HPV transmission from mother to neonate can develop either in utero or during delivery; they may take months or years to manifest clinically. It has not been demonstrated that HPV causes viraemia. **(3).**

Sexual transmission

There are many different perspectives on the prevalence of HPV infection in children in the studies. Most children who have been sexually abused won't show viral carriage. External genital warts (EGWs) don't typically occur until at least three months after sexual HPV exposure in adults and teenagers; however, in young children, the timing is unclear **(6).**

Autoinoculation or heteroinoculation

Children's EGWs may develop from nongenital warts. Vaginal, oral, and cutaneous lesions have all been reported to include the phylogenetically related mucosal HPV strains 2, 27, and 57 **(3).**

Nongenital HPV27 and HPV3 are frequently found in paediatric genital lesions. The mucosal or cutaneous site specificity of children's HPV subtypes is not as high as that of adult subtypes **(3).**

Immunotherapy

Topical immunotherapy

There are numerous topical immunomodulators that have been used for treating warts. Although topical mmunotherapy agents have their own clinical advantages over other destructive treatment modalities, an updated assessment of these agents is required.

Diphencyprone

The compound diphencyprone (DCP) was originally created in 1959. Due to the ultraviolet (UV) light that causes its destruction, it is manufactured as dilutions in acetone and sold in brown UV-opaque bottles. It was first employed to treat alopecia areata before being successfully applied to the treatment of stubborn plantar warts**.** For the same concentration, dinitrochlorobenzene (DNCB) is a less effective contact sensitizer than DCP. Although DNCB is not mutagenic in the Ames assay and is not detectable in serum or urine after topical treatment, DCP might be a safer alternative. Sensitization to 2% DPC is used to cure viral warts on a 1 cm2 region of skin on the upper arm. DPC is given at a concentration of 0.1% (2% to the soles of the feet) when the warts have been reduced **(7).**

Diphenylcyclopropenone

Diphenylcyclopropenone (DPCP), a strong contact allergen in both humans and animals, was originally created in 1959. Heat and UV rays both cause DCP to deteriorate. DPCP dilutions are sold in brown UV-opaque bottles that should be kept at room temperature. After topical administration, DPCP does not appear to have considerable systemic absorption and is not mutagenic at concentrations of 50 and 100 mg/ml **(8).**

Dinitrochlorobenzene

DNCB has a well-established involvement in the production of experimental delayed-type hypersensitivity and was first identified as a powerful contact allergen in 1912. It has been regularly utilised to stimulate hair growth in alopecia areata over the past 30 years. Additionally, it was utilised to treat a variety of skin conditions, such as precancerous and malignant skin lesions **(9).**

Squaric acid dibutylester

Squaric acid dibutylester (SADBE) is a common topical sensitizer that has been used to treat AA since it was initially produced and demonstrated to be a powerful contact allergen in 1979. Although it costs a lot more than the other contact sensitizers, the Ames assay does not show it to be mutagenic. Multiple plantar and common warts can be effectively managed with topical immunotherapy with SADBE. The use of SADBE has some restrictions in the genital region because it may cause a substantial amount of irritation that causes the patient great discomfort **(10).**

5-Fluorouracil

A fluorinated pyrimidine antimetabolite called 5-fluorouracil (5-FU) acts as antineoplastic medication by preventing DNA synthesis. The medication is concentrated mostly on neoplastic tissue after administration. Most frequently, actinic keratosis and other skin neoplasms and precancerous lesions are treated with this antimetabolite medication. Since the early 1990s, doctors have utilised it to treat urethral condylomata **(11).**

Bacillus Calmette-Guérin

Only a few research have looked at how topical BCG affects genital warts and condylomata acuminata. Six out of ten individuals who received external BCG treatment saw the instantaneous elimination of genital warts within six weeks at a follow-up of 9.2 months. Topical BCG may also result in increased cellular reactivity and the subsequent eradication of HPV in people, although the exact mechanism of action needs to be clarified. It was determined that BCG immunotherapy is a recognised treatment for condylomata acuminata patients and that it appears to lessen recurrence (**12).**

Imiquimod

Imiquimod belongs to a brand-new class of artificial immune response modifiers with antiviral and anticancer properties. In 1997, the FDA gave its approval for the treatment of perianal and genital warts. It is more suited to moist, nonkeratinized warts that are between 0.5 and 1.0 cm in diameter. It has more recently been approved for the treatment of superficial basal cell carcinomas and nonhypertrophic actinic keratoses. Other people have stated that it works well for treating stubborn plantar, periungual, and subungual warts (**13).**

Activated vitamin D

The active vitamin D3 analogue maxacalcitol has been used to treat palmoplantar keratosis and psoriasis vulgaris. It is generally established that analogues of vitamin D3 have some biological effects on epidermal cells, including control over cell division and proliferation as well as cytokine generation. Recent research suggests that it has an impact on tumour invasion, angiogenesis, and cell death, making it a potential agent for controlling cancer **(14).**

Sinecatechins

The first herbal medication for the treatment of anogenital warts to receive FDA approval is topical sinecatechins ointment 15%. Sinecatechins is a standardised extract of green tea leaves from Camellia sinensis that is high in

catechins (>85%) and other polyphenols. Along with other green tea ingredients, it contains eight distinct catechins. Epigallocatechin gallate, which has the maximum biological activity, is the primary catechin in sinecatechins ointment. It is not fully understood how sinecatechins ointment 15% works to remove external genital warts (EGWs) **(15).**

Intralesional therapy

The immune system's capacity to create a delayed-type hypersensitivity response to numerous antigens as well as the wart tissue is used in intralesional immunotherapy. It has been discovered that this treatment is linked to the creation of Th1 cytokines, which activate natural killer cells and cytotoxic T cells to destroy HPV infection. In contrast to conventional wart remedies, this eliminates both nearby and distant warts. Numerous authors have injected immunotherapeutic substances intralesionally. These include the following: BCG vaccine, the measles, mumps, and rubella (MMR) vaccine, the mycobacterium w (Mw) vaccine, and the injection of IFN- and IFN-g. The widespread immunity to these antigens in the general population is the basis for the use of these agents. Because older people's immune systems are less developed than those of younger people, it has been discovered that older people (those over 40) are less likely to respond to this method **(16).**

There are two distinct strategies that diverse authors adopt. In the first method, an intradermal antigen is injected into the person's forearm on the volar side, and 48–72 hours later, erythema and induration are used to measure the delayed hypersensitivity reaction. The therapy can be used on responders who have erythema and induration that is 5 mm in diameter. The size of the test reaction determines the volume of antigen to inject into the wart, which is typically the largest one. Some writers, without first completing an intradermal test, have injected the antigen directly into the largest wart. An insulin syringe is used to administer wart injections intralesionally. The bevel of the syringe should be facing upward while it is held parallel to the skin's surface. This treatment is continued every three weeks until the warts are completely gone, or for a maximum of three treatments if there is no improvement **(17).**

Bleomycin

The capacity of the antibiotic bleomycin, which is generated from the bacterium Streptomyces verticillus to bond with DNA and cause bleomycin strand scission and the removal of pyrimidine and purine bases, may explain its anticancer, antibacterial, and antiviral properties. All bodily tissues generally contain the bleomycin hydrolase enzyme, which is known to inactivate bleomycin; however, skin only contains a very little amount of this enzyme. Bleomycin is therefore available at the location in substantial amounts after being injected intralesionally (**18).**

Interferon (α and g)

IFN- is a low-molecular-weight glycoprotein made by various cell types that prevents tumour growth and virus replication. IFN—2b is an intralesional IFN that the FDA has approved for the treatment of genital warts. For best results, it must be injected twice weekly for three weeks **(19).**

Measles, mumps, and rubella vaccine

The benefits of intralesional immunotherapy with the MMR vaccination include the potential for scar-free removal of both treated and untreated distant warts, a projected low recurrence rate, and a high safety profile. Although the mechanism underlying the effectiveness of intralesional injection of the MMR vaccination and antigens is unknown, it appears that the primary immunotherapy mechanism is a nonspecific inflammatory response to the antigens (**19).**

Lipid garlic extract

Garlic's antiviral properties and ability to stop virally infected cells from proliferating have both been demonstrated. Every night, apply a raw garlic clove to the wart and follow it with occlusion. Garlic extracts applied topically have been shown to completely eradicate cutaneous warts after 3–4 months with no recurrence (**20).**

Mycobacterium

The original Runyon class IV nonpathogenic, rapidly proliferating, atypical Mycobacterium used to create the Killed Mw vaccine was discovered in India. In India, it was authorised as a complementary immunotherapeutic treatment to multidrug therapy for multibacillary leprosy. It is highly antigenic and induces potent T-cell and cytokine (IL-2, IFN-g) responses. Later, it was given the name Mycobacterium indicus pranii

Bacillus Calmette-Guérin vaccine.

BCG was first used to treat recurring oral aphthosis, alopecia areata, and as a preventive against tuberculosis. The mechanism of action could be described by enhancing the function of NK cells, T and B lymphocytes, and macrophages, which could aid in the resolution of viral warts **(21).**

Systemic therapy

Different administrations may be used to activate the immune system during systemic therapy. The treatments that stimulate the immune system away from the site of the lesions are illustrated in this section. Levamisole, zinc sulphate, and cimetidine are examples of oral treatments. Acupuncture, intradermal injection, and auto-inoculation in remote locations are some additional administration methods (21).

Cimetidine

The well-known H2 receptor antagonist cimetidine was authorised in 1977 for the treatment of gastric acid hypersecretion and duodenal ulcer disease. Cimetidine was utilised as an adjuvant therapy in dermatological illnesses for several allergic conditions such urticaria, mastocytosis, and various eosinophilic dermatoses that are characterised by elevated histamine release. Cimetidine was also shown to promote lymphocyte proliferation, limit the function of suppressing T cells, and improve the reactivity of skin tests in addition to having an immunomodulator impact by inhibiting H2 receptors from suppression T cells **(22).**

Levamisole

A well-known antihelminthic medication called levamisole was first used to treat worm infestations in both people and animals. Despite being taken off the market in the USA and Canada, levamisole is still utilised in many other nations due to its immunomodulator properties. Levamisole has been used to treat bacterial, viral, and parasite illnesses including leprosy in dermatologic conditions. It has also been used in combination with other medications to treat a variety of dermatologic conditions, such as lichen planus, erythema multiforme, and oral aphthous ulcers when combined with prednisolone **(23).**

Zinc sulphate

One of the most essential minerals and micronutrients for humans is zinc. It is frequently used as a medicinal substance, both topically and orally. Zinc was used to treat a wide range of skin ailments in dermatology, including infections (such as leishmaniasis, leprosy, and dermatophytosis), inflammatory conditions (such as acne vulgaris, psoriasis, and eczema), and problems with the hair and nails (such as alopecia, seborrheic dermatitis, and erosive pustular dermatosis of the scalp) **(23).**

Acupuncture

The most widely used alternative therapy in the USA, Europe, and many Asian nations is undoubtedly acupuncture. A growing number of studies have shown that acupuncture treatment can regulate autonomic nervous system processes such blood pressure regulation, Sphincter Oddi relaxation, and immunological modulation in addition to the analgesic impact of acupuncture. Acupuncture treatment is beneficial for treating a variety of immunological conditions, including allergy disorders, infections, autoimmune diseases, and immunodeficiency syndromes, despite only a small number of control trials evaluating its effectiveness **(24).**

Purified protein derivative

Mycobacterium tuberculosis purified protein derivative (PPD) is an extract that is used to test for exposure to tuberculin protein in the environment or from past vaccinations. Mycobacterium bovis is present, however it is live and attenuated [105]. Eassa and others **(25).**

Reported on the use of PPD intradermally in treating anogenital warts in expectant mothers. 40 pregnant women who received PPD intradermal injections into their forearms on a weekly basis participated in the trial. The degree of tuberculin reactivity was correlated with the overall improvement, which was 85%. Three patients (7.5%) had a limited reaction, 15 (37.5%) had a partial response, and 19 (47.5%) had complete clearance. Only three patients (7.5%) did not improve after receiving treatment. The study's reported side effects were negligible and minor **(25).**

Autowart injection

Srivastava and Bajaj recommended the use of autowart injection as a treatment option for widespread and persistent warts because no single therapy has been discovered to be effective and cosmetically acceptable in the majority of individuals with warts. The procedure involved radiocauterizing 3–4 mm of wart tissue and depositing it on a sterile gauge. After that, distilled water was used to crush the tissue in a mortar and pestle. A sterile disposable syringe was filled with a prepared fine suspension before being injected into the gluteal area. They discovered an up to 89% response rate (66.03% with full resolution and 22.64% with partial improvement), whereas 11.32% showed no change **(26).**

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