Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.177931.2691 Volume 30, Issue 1, January 2024

Manuscript ID ZUMJ-2211-2691
DOI 10.21608/ZUMJ.2023.177931.2691

ORIGINAL ARTICLE

Warts as a Therapeutic Dilemma; Different Therapies with focus on Intralesional Acyclovir and Intralesional Hepatitis-b Virus Vaccine

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Submit Date 22-12-2022
Accept Date 19-01-2023

ABSTRACT:

BACKGROUND: Warts are widespread epidermal growths caused by diverse strains of human papillomavirus (HPV) that affect all age groups. As in the case of palmoplantar warts, they are typically asymptomatic and unattractive, but occasionally painful. In spite of treatment, recalcitrant warts grow in size and number and are resistant to standard therapeutic approaches. Vaccine and antigen therapy are assumed to work by stimulating the host immune system into recognizing the virus, which leads to the removal of warts that is known as intralesional immunotherapy.Vaccination against Hepatitis B virus (HBV) is linked to the induction of humoral and cell-mediated immunity. Recent use of intralesional HBV vaccination as an immunotherapy for common warts has been relatively unsuccessful.The viral etiology of warts implies that acyclovir, an antiviral medication with demonstrated efficacy against DNA viruses, may be a viable treatment option.

AIM: This literature review aimed to discuss the comparative efficacy of intralesional HBV vaccination and acyclovir in treating plantar warts.

KEYWORDS:Warts; Immunotherapy; Intralesional, HBV Vaccine; Acyclovir

INTRODUCTION

Human papillomavirus (HPV) is the causative agent of warts (HPV). The DNA viruses are diverse, with about 100 different genotypes. Most routes of HPV infection are spread either directly contact with an infected person or indirectly contact with a contaminated surface or object. Primary targets of HPV infections, basal keratinocytes of epidermis, are susceptible to virus through minor abrasions, and infection is enhanced through epithelium maceration **[1]**.Most HBV strains cause distinct warts forms and have a preference for particular anatomical places. Extragenital cutaneous warts can manifest as common warts (verrucae vulgares), plane warts (often found on face and dorsum of hands (verruca plana [juvenilis]), or warts on the soles of feet (plantar warts). Common and plantar warts are typically induced by HPV types 1, 2, 4, and 7, however juvenile (plane) warts are typically induced by types 3, 10, 27, and 41 **[2].**

This literature review summarizes what is currently known about the link between plantar wart pathogenesis, HPV transmission, and epidemiologic features. Diagnostic and current therapy approaches are discussed besides the comparison between intralesional injection of hepatitis b virus vaccine and acyclovir as a prospective treatment modality.

Epidemiology:

Warts are a prevalent medical condition that affects roughly 10% of the population. As high as 10% to 20% of school-aged youngsters are affected. Immunocompromised patients and meat handlers are also at higher risk. Warts arise at any age. School-aged children had a higher prevalence, peaking at 12–16 years. Whites have twice as many warts as Blacks or Asians. Inuit and American Indians have a higher prevalence of focal epithelial hyperplasia (Heck disease). Approximately equal male to female ratio exist **[3]**.

Etiology:

Despite the existence of more than 100 different HPV subtypes, only a few of those can trigger skin warts in certain anatomical sites (**Table 1**). With skin contact, HPV can spread to any region of the body. HPV is commonly correlated with flat warts, genital warts and, palmoplantar warts. If epithelial barrier is disrupted, warts can spread through direct or indirect contact. Additionally to skin, warts can form on mucous membranes. HPV typically infects only the epithelial layers of the skin, and systemic spread is quite uncommon. It is known that virus replicates in the upper epithelium layer, however viral particles can also be discovered in basal layer **[3]**.

HPV different types and their clinical manifestations are showed in table (1) **[4].**

Incubation period:

The wart incubation period lasts between one and eight months. In a few months, spontaneous healing may occur, although it is typically accompanied by the emergence of other warts in the same region **[5].**

Mode of infection:

HPV enters epithelial cells via putative surface receptors and proliferates after a slight breach. Persistent viral infection leads to metaplasia of keratinocytes, which collect keratohyalin granules 6 and are sloughed off. HPV virions rarely reach the skin's Langerhans cells and avoid systemic immunity because these virally infected keratinocytes are not destroyed. This boosts wart's viral persistence and continued growth **[6]**.

Clinical picture:

Common warts:

Common warts can be single or multiple; in the latter instance, there may be dozens of lesions, occasionally confluent in sheets, with one bigger, older, or "mother" wart. It is typically found on the back of the hand, where it manifests as a tiny, keratinized, greyish tumor with an uneven surface traversed by projections. When the lesion is young, these projections are less noticeable, however older lesions have a creviced, blackish appearance. Frequently, it is painless, and the surrounding skin is healthy **[1**].The front of the hand wart is typically darker and more deeply embedded in the palm, with a keratotic rim surrounding lesion. Fingertip warts are same but sensitive to pressure**[7].**

Plantar warts:

Plantar warts develop on the bottom of the foot, also called the sole (the plantar foot surface), and a wart on the bottom of foot is a plantar wart because of its location. Because of the callus that forms over wart, walking can be very painful. Possible association between plantar warts and common warts. The macules are tiny, sometimes punctiform, buff in color, and seem finely granular under magnification, almost like a miniature of a common wart. They are frequently multiple, if not abundant. Mosaic warts are another type of verruca and are commonly found in clusters around the feet **[8].**

Periungual warts:

The periungual wart is distinct because it becomes lodged in the nail fold and grows outward to form a more or less continuous rim around the nail's edge. There may be longitudinal or transverse striae in the nail formation. Common symptoms include redness, swelling, and pain at the wart's implant site. Periungual warts are the type that arise below or at the sides of the nails and sometimes the intervention involves nail removal as well. Also; oral warts can appear on the lips and sometimes inside the cheeks of the mouth **[9].**

Plane warts:

Plane warts are the most prevalent on the face and the hand palms, and manifest clinically as flat, skin-colored or yellowish-red papules (a few millimeters in diameter) with a smooth surface and a susceptibility to coalesce **[2].**

Symptoms:

Typically, plane and common warts are asymptomatic or cosmetically unpleasant. Conversely, plantar warts are painful and impede walking. Occasionally, other warts may be itchy [8].

Pathogenesis:

HBV belongs to Papovaviridae family of non-enveloped, dsDNA viruses. Limiting viral replication to surface tissue basal cell layer. The virus will invade both cutaneous and mucosal epithelium in quest of a suitable host cell. It will then penetrate infecting epidermis' basal keratinocytes. Mucosa infections are possible everywhere throughout genital tract, as vulva, vagina, cervix, and perianal regions among females and the penile shaft, scrotum, periurethral, and perianal regions among males. Infected areas will be characterized by a multiplication of viral DNA and production of papules or plaques **[10].**

Six early-open reading frames (E1-E7) and two late-open reading frames (L1, L2) make up viral genome. Important for regulatory function, early-open E genes encode proteins for viral propagation and cell transformation. However, viral capsid proteins are encoded by late-open L genes. Variations in L1 genotype result in slightly varied viral DNA replication patterns, that are believed to cause different HPV subtypes **[11].**

Low-risk HBV subtypes replicate independently from host cell DNA. High-risk HPV subtypes immediately insert their DNA into host cell's DNA.

Dysregulation and unregulated activation of the E6 and E7 genes induces oncoprotein transcription after viral and host cell DNA integration. These bind and inactivate tumor suppressor genes p53 and Rb, increasing cell proliferation and malignant progression **[12].**

Host immune response:

It is unknown if these antibodies play a role in limiting reinfection with the same type from autoinoculation or from an infected sexual partner. Latent HPV infections are defined as persistence of HPV DNA in clinically and cytologically normal epithelium. However, it is difficult to distinguish true viral latency from persistent infection with a low level of DNA replication. The mechanisms by which HPV enters into and is activated out of latency are unknown **[13]**.

Diagnosis:

Clinical appearance is usually used to diagnose warts. Typically, common warts and solitary plantar warts exhibit capillary haemorrhage, which manifests clinically as blackish spots. Dermoscopy is ideally suited for visualizing them **[2].**

Dermatoscopy has been demonstrated to assist diagnosis of infectious skin disorders, and various morphological characteristics of HPV-induced lesions have been characterized. Clinically, lesions are slightly pigmented due to an acanthotic epidermis and intermittent bleeding. Dermatoscopy relies on blood vessels and other light-colored structures to assess "background" pigmentation. These characteristics may aid in distinguishing viral warts from other disorders, including melanomas, however histopathology is sometimes required to determine the accurate diagnosis **[14].**

Plane warts have vasculature as spots on yellow to light brown structureless pigment. Melanocytic nevi, pigmented Bowen's disease, and other skin diseases have dot vessels alone. The most distinctive aspect is the symmetry between the vessels and the yellow to light brown structureless background (representing acanthotic epidermis). Seborrheic keratoses, a clinical differential diagnosis of plane warts, rarely display dot vessels but instead white dots/clods, orange clods, and thick reticular line **[15].**

The typing of HPV is restricted to a limited number of laboratories, but it may be relevant in some cases of genital warts in minors suspected of sexual abuse. There is no correlation between knowing HPV genotype of benign warts and the treatment that is chosen **[5].**

EGW treatment begins with accurate diagnosis. EGWs must be diagnosed and differentiated from other lesions by understanding their morphology. Warts are not restricted to the external genitalia alone. Sexual exposure can cause urethral, meatus, cervix, vagina, anus, and oral cavity warts. Before treating cervical warts, doctors must rule out high-grade dysplasia utilizing Papanicolaou (Pap) tests **[16].**

Management of WARTs

Warts can be treated using a variety of approaches, either individually or in combination. Many different immunotherapeutic destructive approaches have been utilized for treating viral warts.

a. ***Destructive therapies*** include medical agents (e.g., podophyllotoxin, trichloroacetic acid in high concentrations, cantharidin, 5-flurouracil, and bleomycin) and surgical methods (e.g., electrocautery, aggressive cryosurgery, curettage, surgical excision, laser ablation, and photodynamic therapy). These interventions are typically painful, and are frequently linked with variable success, high recurrence, and serious side effects like scarring **[17].**

b. Antiviral drugs such as Acyclovir

Acyclovir is a drug utilized for the treatment of herpes simplex virus infections (HSV). FDA-approved for the treatment of genital herpes and HSV encephalitis. Some off-label uses include the treatment of cold sores, chickenpox, and herpes zoster. It belongs to the antiviral medication class. This activity describes indications, mechanism of action, pharmacology, and contraindications for acyclovir as an effective medication in treating HSV and varicella-zoster virus-related disorders **[40].**

Mechanism of action:

Antiviral acyclovir works by inserting itself into viral DNA, that inhibits virus replication. Acyclovir is transformed to acyclovir triphosphate by viral and cellular enzymes, at which point it suppresses DNA synthesis and viral replication. Acyclovir is a synthetic purine nucleotide analog that has been shown to reduce the growth of HSV types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus in vitro and in vivo **[41].** HSV Infections can be treated with acyclovir. It has been authorized by the FDA for treating genital herpes and HSV encephalitis. Mucocutaneous HSV, herpes zoster (zoster) and varicella-zoster are non-FDA-approved indications (chickenpox). HSV encephalitis is treated initially with acyclovir. There are currently no alternative drugs recommended for management of this disease **[42].** Despite long-term usage of acyclovir for treating HSV encephalitis, no comprehensive research has examined its efficacy. Oral acyclovir and topical

steroids have been demonstrated to be effective against HSV keratitis among pediatric patients **[43].** Juvenile-onset recurrent respiratory papillomatosis is another type of prophylactic acyclovir usage. Oral acyclovir was utilized as a postoperative adjuvant in prospective observational research including 21 patients. It was found to reduce papilloma recurrence, hence reducing need for subsequent operations and their related consequences **[44].**

The consequences associated with VZV infections include cerebellitis. It has been demonstrated that treating source infection reduces the burden of complications as well. Cross et al. **[45]** characterized a patient having truncal ataxia. The patient was free from neurologic impairment and cerebellitis after receiving intravenous acyclovir. Oral acyclovir has also been demonstrated to be effective in treating paresis caused by dermatomal herpes zoster infections, an unusual consequence of herpes zoster in which virus attacks motor nerve fibers rather than the dorsal root ganglion. Acyclovir, a DNA virus-specific antiviral medication, may treat warts due to their viral origin. Bauer **[46]** found that local acyclovir cream cleared recalcitrant plantar warts of HPV infection. After oral valacyclovir and acyclovir for herpes zoster were taken together, refractory plantar warts eradicated[47]. Elsayed et al. **[48]** evaluated efficacy and safety of intralesional acyclovir in treating cutaneous warts and found that intralesional acyclovir is a well-tolerated and effective treatment for cutaneous warts.

C-Immunological approaches including topical contact sensitizers with squaric acid dibutylester or diphenyl cyclopropenone, intralesional injections of interferons, mumps, candida, measles, or rubella, and higher oral dosages of cimetidine have been studied as alternatives to earlier treatments. Immune therapies are based on the concept that the host's immune system, especially at cellular level, affects wart growth and may demonstrate cross-reactivity. Delaying cellular immune response may alter wart proliferation **[18].**

Unfortunately, neither individually nor combined therapeutic approaches have shown superiorty. Thus, wart treatments have been explored. Positive results have been seen most frequently from the use of immunomodulatory drugs directed against the underlying HPV infections **[19].**

Immunotherapy:

Immunotherapy is a biological therapy used to treat cancer, infections, and other disorders by manipulating the body's immune system. Topical and systemic immunotherapy currently play a key role in treating warts due to their non-destructive effect, simplicity of application, and promising results **[20].**

Numerous immunotherapeutic techniques have been studied to overcome the difficulties posed by damaging therapy (**Figure1**). Immune boosters, immunosuppressives, and proinflammatory cytokines like interferons and interleukins are examples. Other immunotherapeutic alternatives include cell-mediated immunity (CMI) inducers including Candida and mumps antigens, topical contact sensitizers like diphencyprone, and a combination of the drugs **[21].**

1- Topical therapy:

*** Contact sensitizer:**

In conventional contact immunotherapy, contact sensitizers as dinitrochlorobenzene (DNCB), diphenylcyclopropenone (diphencyprone [DPC]), or squaric acid dibutyster (SADBE) are being utilized. It is hypothesized that these medicines function by stimulating the host's adaptive immune system, resulting in an antiviral state that induces wart clearance. In addition to the local immune response, the existence of an immune response at both treatment and untreated wart sites is suggestive of a systemic reaction **[22].**

*** Immune modifiers:**

Imiquimod is an FDA-approved synthetic imidazoquinoline derivative used for treating external genital and perianal warts, actinic keratosis, and superficial basal cell carcinomas. It is believed to have both antiviral and antitumor properties and has been used off-label to treat non-genital cutaneous warts. The proposed mechanism of action involves the stimulation, synthesis, and release of interferon-α, Il-1, Il-6, and tumor necrosis factor-α. in order to activate both innate and cell-mediated immune responses. This induces a cell-mediated immunological response through toll-like receptors 7 and/or 8. **[23].**

*** Antigens:**

Children who have plane or common warts have the option of receiving topical Bacillus Calmette-Guerin (BCG), which is an effective and safe therapeutic option. Complete remission was seen among 65% of patients with common warts and 45% of patients with plane warts. No recurrences or side effects were observed **[24].**

2- Intralesional therapy:

Recalcitrant multiple common warts (RMCW) can be treated with a variety of treatments, but no one approach is guaranteed to be successful. Intralesional immunotherapy enables immune system to recognize wart virus and eliminates all lesions on body, not just locally treated lesion. Intralesional immunotherapy's precise mechanism of action is still up for debate. A proliferation of

peripheral blood mononuclear cells that increase T-helper type 1 cell (Th1) cytokine responses; a delayed-type hypersensitivity reaction against HPV-infected cells; traumatic clearing of wart in previously sensitized individuals **[25].**

*** Interferons:**

Interferons-α, INF-β, and INF-γ seem to suppress viral replication in HPV infection due to their antiviral and antiproliferative therapeutic action **[26].**

*** Antigens:**

Tuberculin PPD antigen:

Immunotherapy intralesional Purified protein derivative (PPD) or tuberculin antigen increases IL-12 cytokine, indicating a cell-mediated immune response. This prevents infection and recurrence. For cutaneous warts management in previously immunized patients, it is a low-cost, effective, and safe approach with a high cure rate. The majority of reported side effects were local redness, soreness, and edema, which disappeared 4 days following injection without the use of medication **[25].**

Candida albicans antigen:

The Candida antigen mode of action is yet unknown, but it appears to be mediated by activation of Th1 cytokines such as IFN- γ and IL-2, which activate cytotoxic and natural killer cells to destroy HPV infection not just at the injection site but throughout the entire body [21].

Even for genital warts, the efficiency of candida immunotherapy has been documented. Candida immunotherapy has been associated with febrile reactivity, myalgia, pain, erythema, and edema at injection site, as well as painful purple digit syndrome. Nonetheless, this therapy is affordable **[27].**

***Vaccines:**

Measles, mumps, rubella (MMR) vaccine:

The mechanism of action of the Measles, mumps, and rubella (MMR) vaccination remains unclear. It has been hypothesized that an efficient intralesional antigen immunotherapy requires a functional host immune system, specifically CMI. This may be accomplished via the direct effect of the trauma, a strong nonspecific inflammatory response against HPV-infected cells, and the involvement of activated macrophages, T-helper cells, neutrophils, and natural killer cells **[28].**

Bacillus Calmette-Guérin (BCG) therapy:

The similar concept underlies the usage of Bacillus Calmette-Guérin (BCG) vaccination as the Mw vaccine. The delayed hypersensitivity reaction to an antigen is essential for clinical response to warts. It boosts IL-12 serum levels while decreasing IL4 levels. Between one and three monthly doses are administered **[20].**

Hepatitis B virus vaccine: The hepatitis B virus (HBV) envelope has three surface glycoproteins, namely the large (L), middle (M), and small (S) proteins, which are encoded by a single open reading frame consisting of preS1, preS2, and S sections. To investigate the immunological features necessary to elicit virus-neutralizing and protective antibodies, PreS1 epitope was selected as a model **[29].**

The HBV vaccination has been proven safe and effective; thus, it should be given to all newborns and children under the age of 18. Extremely stable and relatively simple to manufacture. Not only does HBV cause an increase in humoral immunity, but it also causes an increase in cell mediated immunity. Also, the HBV vaccine is advantageous since it is not a live vaccination, therefore it can be administered to immunocompromised patients without risk **[30].** The safe and universal vaccination of neonates and high-risk healthy adults has been made possible by the development of recombinant hepatitis B (rHB) vaccine. During primary immunization, B-lymphocytes in the germinal centers differentiate into plasma cells or memory B-cells. The proliferation of plasma cells results in the generation of antibodies **[31].**

Mechanism of action:

The effectiveness of vaccination is directly proportional to antibodies against HBsAg (anti-HBs). Injectable HBV vaccines containing HBsAg proteins are taken up and processed by APC. APCs then modify the antigen so that it may be shown on the cell surface. APC present antigen to T helper cells, clonal growth and memory T cell generation. B cells can directly recognize the antigen and produce a weak immune response by binding it to the Fab region on the B cell receptor and secondary signaling from cytokines released by T-helper cells. B cells begin somatic hypermutation at the Fab region, which increases the fit between the Fab region and the antigen. Plasma cells make neutralizing antibodies from B cells. They also generate memory cells and clone for defense **[19].** During the last decade, the protective cut-off level for anti-HBs was defined at ≥10 IU/L. Approximately 5–10% of healthy vaccine recipients fail to generate protective levels of antibodies following standard vaccination **[32].**

Types of hepatitis B vaccine:

Different strains with different characters are available for active immunization against HBV:

First generation vaccines:

First-generation vaccinations were inactivated and purified HBsAg particles taken from the plasma of

chronic carriers, because HBV cannot be produced efficiently in tissue culture. Second-generation vaccinations, made by expressing the HBsAg gene sequence in recombinant vectors using the yeast Saccharomyces cerevisiae, have since largely superseded the first-generation immunizations in all countries **[33].**

Second generation vaccines:

Yeast cells (Saccharomyces cerevisiae) transfected with HBV-DNA coding for the small S antigen have been utilized to generate a recombinant small envelope protein (S protein) that is noninfectious. Therefore, these vaccines use the S protein without the glycosylation, and they suspend it in aluminum hydroxide. The safety and immunogenicity of vaccines made from yeast have been well-documented, particularly after 3 intramuscular doses given at 0, 1, and 6 months in immunocompetent adults **[34].**

Third-generation vaccines:

Third-generation vaccinations are recombinant vaccines made by mammalian cells expressing HBV envelope protein components S, Pre-S2, or Pre-S2+Pre-S1 (Chinese hamster ovary). To boost T-cell recognition of HBV, Sci-B-Vac™/BioHep B vaccine includes 2 additional Pre-S antigens [**34]**.

Two-dose vaccine:

This vaccine is yeast-derived vaccine adjuvanted with a novel immunostimulatory phosphorothioate oligodeoxyribonucleotide (HBVISS). When compared to the standard 6-month course, only 0 and 4 weeks of dosage are needed **[35].**

Routes of administration:

Intramuscular administration:

HBV vaccine is administered IM, but skeletal muscle injection dose not always provide optimal immune responses **[36].**

Intradermal administration:

Muscle is regarded as a poorly immunogenic organ. The skin is a better immunogenic site for vaccination. Intradermal vaccination stimulates both humoral and cellular immune responses by directly activating dendritic cells, which then promote CD4+ and CD8+ T-cell activation and production of IL-6, IL-12, and TNF- α **[36].**

Oral administration:

Oral vaccination for hepatitis B would be appealing and likely improve compliance **[37].**

HBV vaccine in Wart treatment

The precise mechanism of action of the HBV vaccine in the warts management has not yet been investigated. We believed that HBV vaccination would function similarly to other antigens utilized in intralesional immunotherapy, which relies primarily on the induction of Th1 cytokine profile response including IFN-g, IL-2, and IL-12 [38]. This has been also identified with HBV vaccine usage as reported by Velu and colleagues**[39]**, and Sabry and colleagues **[30]** who have demonstrated that overall Th1 cytokine profile, particularly IFN-g, was elevated among high-responders to HBV vaccine in comparison with low-nonresponders.

Table (1): different types of HPV and their clinical manifestations

Clinical manifestation	HPV types
Plantar warts	1
Common Warts	2,4,29
Flat Warts	3,10,28,49
Epidermodysplasia verruciformis	5,8,9,12,14,15,17,19,20-25,36,47,50
Genital warts, laryngeal papillomas	6,11
Butcher's warts	7
Oral focal epithelial hypoplasia	13,32
Anogenital dysplasias and neoplasms (rarely laryngeal carcinoma)	16,18,26,27,30,31,33-35,39,40,42-45,51-59,61,62,64,66-69,71-74
Keratoacanthoma	37
Cutaneous squamous cell carcinoma	38,41,48
Oral papillomas, inverted nasal & papillomas	57

Bushke-Löwenstein tumors	6,11
Bowenoid papulosis	16,18,33,39
Epidermal cysts	60
Myrmecia wart	63
Pigmented wart	65
Vulvar papilloma	70
Oral papillomas (HIV patients)	72,73
Common wart in renal allograft recipient	75-77
Cutaneous wart	78

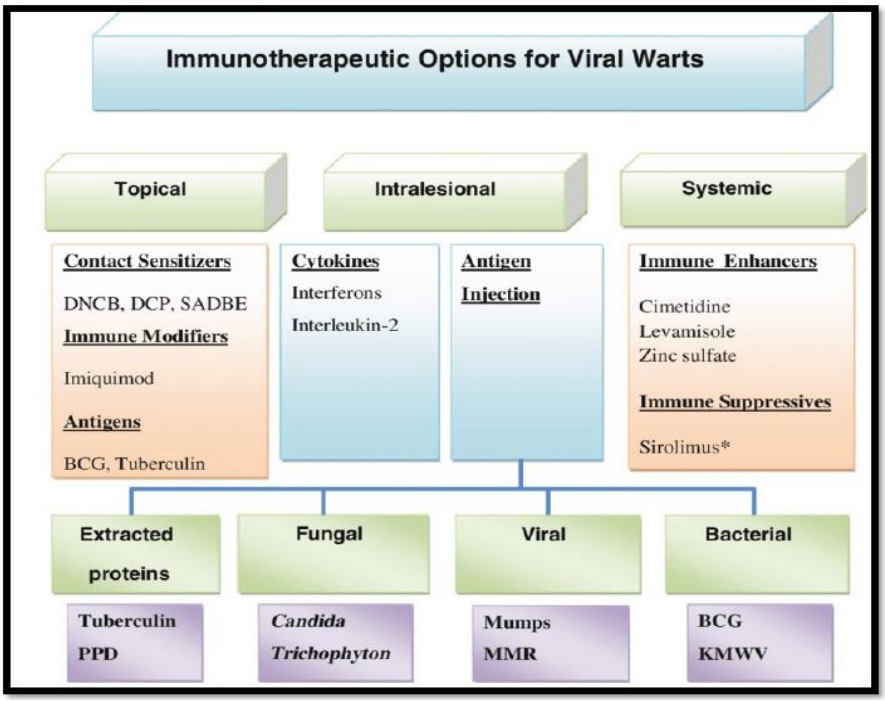

Figure (1): Immunotherapeutic options for viral warts. DNCP dinitrochlorobenzene, (DPC) diphencyprone, (SADBE) squaric acid dibutylester, (MMR) measles, mumps, rubella, (BCG) Bacillus Calmette Guerin, (KMWV) killed Mycobacterium w vaccine, (PPD) purified protein derivative

CONCLUSION

Intralesional HBV vaccine and Acyclovir injection are safe, affordable, and efficacious treatment for wart. Although randomized studies have established the efficacy of numerous modalities, more randomized comparative studies are needed to identify the optimal treatment and accurate standardized doses for the treatment of warts in individual patients.

Conflict of interest

The authors declare no conflicts of interest.

Funding

No funding was received to conduct this study.

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To Cite :

Ismail, A., Imam, M., Gharib, K. Warts as a Therapeutic Dilemma; Different Therapies with focus on Intralesional Acyclovir and Intralesional Hepatitis-b Virus Vaccine. *Zagazig University Medical Journal*, 2024; (262-270): -. doi: 10.21608/zumj.2023.177931.2691