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Immunomodulators in warts: Unexplored or ineffective?

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Abstract

Cutaneous warts are known to be recurrent and often resistant to therapy. Resistant warts may reflect a localized or systemic cell mediated immune (CMI) deficiency to HPV. Many modalities of treatment are in use; most of the provider-administered therapies are destructive and cause scarring, such as cryotherapy, chemical cauterisation, curettage, electrodessication and laser removal. Most patient-applied agents like podophyllotoxin have the risk of application-site reactions and recurrence. Thus immunotherapy is a promising modality which could lead to resolution of warts without any physical changes or scarring and in addition would augment the host response against the causative agent, thereby leading to complete resolution and decreased recurrences. Immunomodulators can be administered systemically, intralesionally or intradermally, and topically. A few agents have been tried and studied extensively such as cimetidine and interferons; others are new on the horizon, such as Echinacea, green tea catechins and quadrivalent HPV vaccine, and their efficacy is yet to be completely established. Though some like levamisole have shown no efficacy as monotherapy and are now used only in combination, other more recent agents require large and long term randomized placebo-controlled trials to clearly establish their efficacy or lack of it. In this review, we focus on the immunomodulators that have been used for the treatment of warts and the studies that have been conducted on them.

Keywords: *Cimetidine*, *imiquimod*, *immunomodulator*, *levamisole*, *resistant*, *warts*

What was known?

1. Immunotherapy is a promising modality for recurrent and/or resistant warts which could lead to resolution without any physical changes or scarring and in addition would augment the host response against the causative agent, thereby leading to complete resolution and decreased recurrences.
2. Immunomodulators can be administered systemically, intralesionally or intradermally, and topically.
3. Some agents like Cimetidine, Levamisole and Zinc have been studied in few randomized trials and their efficacy or lack of it has been established.
4. Newer immunomodulator agents have been arriving on the scene and studies are required to define their role more clearly.

Introduction

Cutaneous infections caused by human papillomavirus (HPV) are usually recurrent and are among the most troublesome conditions presenting to dermatologists.

HPV causes a myriad of infectious lesions, out of which common warts are the most prevalent. Warts are usually self-limiting but spontaneous resolution may take months to years. Spontaneous clearance rates are also painfully low (23% at 2 months, 30% at 3 months and 65-78% at 2 years), hence underlining the need for intervention.[1] The fact that they can recur even after complete physical removal makes them extremely frustrating both for the patient and the physician. Recalcitrant warts may reflect a localized or systemic cell-mediated immune (CMI) deficiency to HPV. Various reasons like lack of production of memory T cells to target HPV infection, failure of clonal expansion of lymphocytes to adequate stimulation, inability of T lymphocytes to traffic to sites of infection and weak effector response mechanism have been hypothesized.[2] Consequently, warts are particularly exuberant in patients with Hodgkin's disease, AIDS and those on immunosuppressants.

Genital warts pose an even bigger challenge to dermatologists. Firstly, because of the reluctance of patients to consult a physician, and secondly, because of their propensity to relapse. Individuals with frequent relapses suffer a substantial psychological morbidity. Thus, drugs with immune-stimulating properties are potentially useful agents in them.

Many modalities of treatment are in use; most of the provider-administered therapies are destructive and cause scarring, such as cryotherapy, chemical cauterisation, curettage, electrodessication and laser removal. Most patient-applied antimitotic agents like podophyllotoxin have the risk of application-site reactions such as erythema, edema and ulceration. Recurrence rates are also high due to the possibility of some microbial organisms remaining after physical destruction of the visible lesions. Recurrence rates of warts up to 30% have been reported with cryotherapy, probably due to a lack of immune response. Thus, immunotherapy is a potential logical modality which could lead to resolution without any physical changes or scarring and in addition would augment the host response against the causative agent, thereby leading to complete resolution and decreased recurrences. Though many immunomodulators have been tried, none of them has been found to be ideal, due to inadequate sample sizes in studies, impracticality of use, adverse effects or limited efficacy.[3] Hence, the search for the ideal drug still continues! Table 1 lists the various agents that have been tried as immunomodulators in the treatment of warts. However, the treating physician must remember that none of the treatments discussed in the review are FDA approved (except Polyphenon - E) for the treatment of warts.

Systemic agents

H2 antagonists (strength of evidence D, I) H2 receptor antagonists are believed to possess immunomodulatory properties, but only cimetidine and ranitidine have been documented to have clinically significant effects.[4,5,6] Both have been tried, but ranitidine has shown only limited efficacy in a single open-label trial by Karaman *et al*.[7] At high doses (25-40 mg/kg/d), cimetidine stimulates IL-12 and decreases IL-10, leading to an increase in Th1 response and suppression of Th2 cells.[4,8,9] It also increases IL-2 production thus stimulating lymphocyte proliferation which in turn increases the CMI. It prevents histamine-induced stimulation of T suppressor cells.[5,6]

Cimetidine has been used in various trials in warts. Four open label studies were done and reported a complete response (CR) rate ranging from 48.8% to a very impressive 81.8%.[10,11,12,13] However, the randomized placebo controlled trials conducted later [Table 2] did not support such high clearance rates and showed rather disappointing results.

It has also been used in HSV infections, herpes zoster virus (HZV) in immunocompromised individuals and in mucocutaneous candidiasis and common variable immunodeficiency disease (CVID).[21,22,23,24,25,26,27] Dohil *et al*. treated 13 children with Molluscum Contagiosum with cimetidine 40 mg/kg/d.[28] Nine of them cleared completely while one showed partial clearance. Facial MC lesions responded more promptly than body lesions.

Its side effects include headache, dizziness, diarrhea, rash, urticaria, alopecia, gynecomastia, breast soreness, arthralgias and myalgias. A higher dose up to 40 mg/kg/day (with a maximum of 3500 mg/day) has been seen to correlate with an increased response in an open label study in adults. The FDA-approved maximum dose is 2400 mg/day, so the risk-benefit ratio has to be clearly evaluated before using higher doses. It is not officially approved in children less than 16 years of age, but continues to be used.[29]

Levamisole Levamisole is an immunomodulator used in many patients with extensive viral infections such as warts and molluscum contagiosum. It alters polymorphonuclear leukocyte (PMN) chemotactic responsiveness.[30] It stimulates phosphodiesterase breakdown of cyclic AMP while inhibiting destruction of cyclic GMP-this appears to correlate with increased chemotactic responsiveness.[31] An increase in adenosine deaminase and a “scavenger” effect on free radicals are also believed to play a role in its action. It stimulates delayed type hypersensitivity (DTH) preferentially, involving upregulation of Th1 cells and IL-2, 12, IFN-gamma and downregulation of Th2 cells with a concomitant effect on IL-4,5,10.[32] It is prescribed in a dose of 2.5 mg/kg two to three times weekly.

Though in combination with cimetidine it has shown promise in treatment of warts, monotherapy has not. Only one double-blind placebo-controlled trial by Amer *et al*. in 40 patients with warts treated with 5 mg/kg on 3 consecutive days fortnightly for 5 months showed 60% cure rate (vs 5% for placebo) but other randomized trials have not shown much efficacy (Saul *et al*., Schou *et al*.).[33,34,35]

Most common side effects are nausea, taste alteration, rash, alopecia and a flu-like illness. Patients need to be monitored for the rare but potentially fatal agranulocytosis (<20% PMNs), which is reversible initially. The bone marrow is not damaged permanently and patients with HLA-B27 genotype are more susceptible. Cases of multifocal leukoencephalopathy have also been described.[36]

Zinc (strength of evidence - C, II) Zinc is perhaps the most important trace element for immune function. Kitamura *et al*. proposed that toll-like receptor (TLR)-mediated regulation of zinc homeostasis influences dendritic cell function.[37] Zinc deficiency has been shown to cause decreased immunity to cutaneous infections.[38,39] It also has specific anti-viral activity; firstly, by cross-linking the double helix of viral DNA so that it is unable to undergo the scission necessary for viral replication, and secondly, by inactivating the viral surface glycoproteins thus interfering with penetration into a susceptible host cell.

Zinc sulfate is the most well-tolerated compound with highest bioavailability. Each 100 mg capsule of zinc sulfate contains 22.5 mg elemental zinc. Side effects are nausea, vomiting and mild epigastric distress.

A placebo-controlled (PC) trial was attempted using oral zinc sulfate 10 mg/kg (2.5 mg/kg/d elemental zinc) once daily for treatment of recalcitrant warts.[40] Complete clearance was seen in 87% of the treatment group versus 0% of the placebo group. In another randomized double-blind placebo-controlled (DB PC) trial, oral zinc sulfate 10 mg/kg/d was given up to 2 months in patients with recalcitrant warts.[41] After 2 months, complete clearance rate was 76.9% (10/13) in the treatment group versus 7.8% (1/13) in the placebo group. The regression of the warts was not asymptomatic as occurs in the natural evolution of the disease. Instead, it was associated with itching, increase in size and number of lesion for the first 2 weeks followed by subsidence. However, Lopez-Garcia *et al*. conducted a DB PC trial in 50 patients with ≥ 5 resistant warts.[42] They found similar clearance rates with zinc sulfate and placebo (28% vs 24%) and pointed out that none of the patients in either group had low baseline zinc levels. Stefani *et al*. conducted a randomized double-blind trial in 18 patients where they compared zinc sulfate (10 mg/kg/d) and cimetidine (35 mg/kg/d) for 3 months for resistant warts. They found zinc to be more effective than cimetidine.[43]

Zinc has also been found useful in cutaneous leishmaniasis, recurrent ENL and common variable immunodeficiency.[40,44,45]

Interferon Interferons (IFNs) are a class of small (15-28 kD) protein and glycoprotein cytokines produced by T cells, fibroblasts, and other cells in response to viral infection and other biologic and synthetic stimuli.[46] As a curative drug, IFN are divided into three major classes (alpha, beta, and gamma) on the basis of physicochemical properties, cells of origin, mode of induction, and antibody reactions.[47] IFN has been shown to be active against HPV by three mechanisms: Antiviral, antiproliferative and immunostimulation.[48,49,50,51] It is reported that IFNs exert their activities mainly by binding to specific membrane receptors on the cell surface and initiating specific intracellular events, including the induction of enzymes, suppression of cell proliferation, enhancement of macrophage phagocytosis, augmentation of lymphocytic cytotoxicity for target cells, and inhibition of virus replication in virus-infected cells.

Yang *et al*. conducted a systematic review of 12 randomized control studies on IFN in treatment of genital warts, which involved a total of 1445 patients. Five studies compared systemic IFN and placebo.[46] They found that there was no significant difference in the clearance rates of the two groups. They concluded that locally used IFN was more efficacious for genital warts than systemic IFN. The most common reported adverse reaction of systemic IFN was a flu-like syndrome, (the simultaneous occurrence of two of the following: Fever/chills, headache, malaise/fatigue, and myalgias/muscle aches).

Echinacea Echinacea (purple coneflower) is a member of the compositae family.[52] Three main medically important species are *E. purpurea*, *E. augustifolia* and *E. pallida*. Earlier it was mostly used for prevention and treatment of common cold and upper respiratory tract infections. Coeugni and Kuhnast reported a chance finding of decreased recurrences of vaginal candidiasis during the 6-month monitoring period following treatment of URTIs.[53] It was then tried in cutaneous infections. It influences immune function through T-cell activation, increase in number and activity of macrophages, production of TNF and IFN-γ, and inhibition of hyaluronidase produced by bacteria and viruses.[52]

Zedan *et al*. compared Propolis (Bee Propolis®) (Pollen Assiut, Egypt) 500 mg, *Echinacea purpurea* 600 mg and placebo all single oral dose for 3 months or till complete cure for treatment of plane, plantar and common warts.[52] They observed significant difference between Propolis and Echinacea in common and plane warts ($P < 0.05$ for each) and significant difference between Propolis and placebo in common and plane warts ($P < 0.01$ and $P < 0.05$, respectively). However, there was no significant difference between Echinacea and placebo in the treatment of any type of wart.

Cassano *et al*. used Echinacea in an oral supplement (OS) formulation for resistant warts.[54] The nutraceutical OS (ImmunoSkin Plus® tablets, Morgan Pharma s.r.l., Vicenza, Italy) consisted of a cocktail of *Echinacea augustifolia*, *Echinacea purpurea*, methionine, inulin, probiotics, taurine, vitamins C, A, B3, coenzyme Q10 and zinc gluconate. They divided their patients into two groups: one receiving conventional standard therapy (CST) alone and the other receiving CST plus OS. CST consisted of liquid nitrogen cryotherapy or topical salicylic acid 15% + lactic acid 15% continued until complete remission. The OS was prescribed as 1 tablet once daily for 20 days every month initiated concomitantly with CST continued for four consecutive months. The authors observed complete remission of warts in 86% of the CST + OS group versus 54.5% in the CST group ($P < 0.001$). Development of new warts was significantly reduced in the CST + OS group (9%) versus the CST group (25%) ($P = 0.004$). The absence of the OS was also more likely to be associated with treatment failure (8% in the CST + OS group versus 37% in the CST group) ($P < 0.001$).

No significant adverse effects, except mild allergic reactions have been reported.

Quadrivalent human papillomavirus vaccine The quadrivalent HPV vaccine was first used by Venugopal and Murrell for the treatment of recalcitrant warts in an adult male.[55] Ault hypothesized that the vaccine had potential to show cross protection against strains other than HPV types 6, 11, 16 and 18.[56] Common capsid epitopes and significant homology of L1 between various HPV types are believed to result in the cross protection. Subsequently there have been a few more case reports of the successful use of the vaccine for treating recalcitrant common as well as plantar warts.[57,58] The vaccine is administered intramuscularly in the arm at 0 (or 1), 2 and 6 months. No significant adverse reactions have been reported by any author. Obviously, the vaccine cannot be recommended for more extensive use unless backed by larger controlled trials, but these results are surely encouraging.

Intralesional agents Intralesional immunotherapy utilizes the ability of the immune system to mount a delayed type hypersensitivity response to various antigens or wart tissue. It leads to production of Th1 cytokines which stimulate cytotoxic T cells and natural killer cells to eradicate HPV infection. What is interesting is that this immune attack has a potential to resolve the distant warts as well and not the wart alone that has been primarily injected.[59,60] Many authors have used different immunotherapeutic agents for intralesional injection. These include, *Candida* antigen, mumps antigen, MMR vaccine, trichophytin skin test antigen, tuberculin, BCG vaccine, *Mycobacterium* w vaccine autologous wart tissue and IFN-alpha and -gamma injection. This procedure utilizes the fact that there is a high prevalence of

immunity to these antigens in the general population.[57] However, this procedure is not suitable for those with hypersensitivity to any of these antigens, pregnant females and immunosuppressed individuals.[61] The antigens can be injected in normal skin or into the wart tissue itself. In case of multiple warts, it is usually the mother wart or the wart that appeared first that is injected. Tables 3 and 4 detail the studies that have been conducted with vaccines and skin test antigens in immunotherapy of warts.

Intralesional interferon The basis of IFN therapy in warts is the observation that a T-helper lymphocyte deficiency associated with an inversion of T4/T8 ratio is seen to exist in warts, and it improves after IFN therapy.[77] Intralesional IFN-alpha (IFN-α) has been tried in a randomized double-blind placebo-controlled multicenter trial for recalcitrant genital warts where the warts were injected twice weekly for up to 8 weeks. Complete clearance was seen in 62% of the IFN group versus 21% of the placebo group.[78]

Yang *et al*. conducted a review of 12 studies on IFN used in genital warts, out of which 7 used local IFN.[46] They found out that the rate of complete response with IFN was significantly better than with placebo (44.4% vs 16.1%, $P < 0.00001$). The results demonstrated that HPV-infected patients given local IFN were less likely to relapse. Because genital warts are widely regarded as a local illness, it is probable that warts are more sensitive to local administration, optimizing suppression of viral replication and cellular proliferation. Also, systemic administration of IFN may result in much lower intralesional effects of IFN. Intralesional IFN-α has also been successfully used in the treatment of recurrent oral warts in AIDS patients.[79]

Application-site reactions, such as itching, burning sensation and pain, may occur in parts of patients treated with intralesional IFN.

Propioniumbacterium parvum

Propionium bacterium parvum, also known as *Propionibacterium acnes* or *Coryneobacterium parvum* is a gram-positive, pleomorphic, strictly anaerobic bacterium.[80,81,82] It has a potent stimulant effect on the reticuloendothelial system and has been used in recent years as an antibacterial and adjuvant immune stimulant to chemotherapy in numerous tumors.[83,84,85] It can be administered parenterally or topically.[82,85] It stimulates the activity of natural killer (NK) cells by releasing IFN and TNF.[80]

Nasser conducted a randomized DB PC trial in 28 volunteers with common warts, out of which 20 completed the study.[86] Intradermal application of 0.1 ml of the drug or placebo was done in one wart each time at intervals of 30-40 days for a total of up to five times. A mild local reaction developed in some warts, indicating the antigen-antibody complex formation. They found that in the group receiving the drug, 8/10 volunteers showed complete clearance of all their warts, 1 had a reduction in size and number of warts and 1 showed no change. On the other hand, none of the placebo group except one showed any change in their warts ($P < 0.001$) which was highly significant.

Autoimplantation therapy Autoimplantation refers to injection of homologous wart tissue into untreated warts leading to resolution of the injected wart as well as distant lesions. Shivakumar *et al*., in 2009, used homologous autoimplantation in the treatment of multiple palmoplantar and common warts in 60 patients in an open trial.[87] They removed a chunk of wart tissue with an 18G needle and introduced it subcutaneously into a nick on the flexor aspect of the left forearm. A total of 73.3% patients showed total clearance, 91% within the first 2 months itself. They hypothesized that autoimplantation induced a

CMI response. In 2010, Srivastava and Bajaj also evaluated autowart therapy.[88] However, they removed 3-4 mm of wart tissue with radiocautery, crushed it in distilled water and then injected the fine suspension into the gluteal area intramuscularly. Out of 53 patients, 35 (66%) had complete clearance. Though impressive results have been seen, RCTs with autoimplantation therapy are yet to be conducted.

Topical agents Immunotherapy in warts can be administered by various methods. The simplest method is topical application of certain inorganic molecules that are capable of eliciting a contact hypersensitivity reaction with secondary activation of an immunological response, or even topical applications of immune modulators like Imiquimod and BCG vaccine. Table 5 lists the studies that have been conducted with topical application of BCG vaccine.

Imiquimod Imiquimod is an immunomodulator that stimulates cytokines including IFN-α, IL-1,6 TNF-α, GM-CSF and GCSF.[93] It is US FDA approved for the treatment of external genital warts. However, its absorption through intact skin is minimal hence has not been used in cutaneous warts very often.[94] In an open-label, uncontrolled study, 5% Imiquimod cream was applied on five successive days a week and washed off in the morning.[95] It was continued up to 16 weeks or until warts were not visible. Complete clearance occurred in 30%, 26% had > 50% reduction in wart size. Follow up at 32 weeks revealed no recurrence in treated areas. Mild transient local inflammation was the only side effect. It has also been used in recalcitrant plantar, periungual, subungual warts.[96,97,98,99,100,101]

Contact sensitizers (strength of evidence C, IV) Contact sensitizers are a mode of inducing a type IV hypersensitivity reaction thus making them a form of topical immunotherapy.[94] The three agents that have been used are dinitrochlorobenzene (DNCB), squaric acid dibutyl ester (SADBE) and diphencyprone (DCP). DNCB has been shown to be mutagenic and is no longer used. SADBE is costly and less stable in solution than DCP; hence, DCP is the preferred compound.

Buckley *et al*. reviewed resistant palmoplantar warts treated with DCP over 8 years.[102] Patients were sensitized with a 2% DCP solution on medial upper arm every 10-14 days until local erythema and vesiculation occurred. Treatment was repeated up to three times. Pared warts were then treated with stepwise concentrations of DCP: 0.01%, 0.05%, 0.10%, 0.25%, 0.50%, 1.0%, 1.5%, 2.0%, 3.0%, 4.0% and 6.0%. Treatments were applied every 1-4 weeks. They found that 42/48 patients completed treatment and exhibited 88% clearance rate. However, a large percentage of patients developed adverse effects (56%), including painful blistering at the site of sensitization and near warts, pompholyx like or generalized eczematous eruption, influenza like symptoms, vesiculation elsewhere due to passive transfer of DCP and inguinal lymphadenopathy. They concluded that patients with recalcitrant palmar, plantar, periungual and digital warts are good candidates for DCP therapy.[103]

In another trial, Rampen *et al*. applied DCP weekly for 8 weeks in 134 patients and obtained a response rate of 60% (complete clearance in 44% patients at 4 months).[104]

DCP is a potentially useful option as it is less destructive than most destructive modalities, less costly, less time consuming and can be used for multiple warts at a single time.

Green tea catechins (Polyphenon® E) Polyphenon® E (MediGene AG, Munich, Germany) is a defined extract of catechins of green tea leaves of Camellia sinensis, a species of the Theaceae family. It contains mainly tea polyphenols, including a group of related flavonoids, particularly catechins (>80%). The lead catechin, (−)-epigallocatechin gallate (EGCG), comprises 50-72% of the catechin fraction. Tea catechins are very powerful antioxidants, and Rösl *et al*. demonstrated the inhibition of transcrip-

tion of HPV viral proteins by antioxidants.[105,106,107,108] In addition, inhibition of viral binding to receptors, signal transduction and cell cycle modification, antiproliferative effects as well as induction of apoptosis by tea catechins may add to the pharmacological effect of Polyphenon E ointment.[109,110,111,112] These potential properties support its use in the treatment of warts, mainly anogenital warts.

It is a patient-applied modality to be applied three times daily. Mild local symptoms are the most common side effects. Rarely, herpes simplex infection, balanitis, phimosis and lymphadenitis have been reported.[113] Food and Drug Administration has recently approved Polyphenon E ointment for treatment of external genital warts in 2006.[114]

Gross *et al*. conducted a randomized, double-blind, placebo controlled study comparing a 15% ointment and a 10% cream formulation versus placebo in the treatment of external genital warts.[115] They concluded that the 15% ointment was more effective than the placebo while retaining a favorable safety profile too; however, the 10% cream formulation did not show any statistically significant benefit.

In another trial, Stockfleth *et al*. found that the use of Polyphenon E 15% and 10% ointment for external genital warts was associated with recurrence rates of 5.9% and 4.1%, respectively.[113] Other treatment modalities gave recurrence rates of 5%-65%. Cryotherapy, for instance, showed a convincing clearance rate but risk of recurrence is about 20-40%. Likewise, imiquimod 5% cream and podofilox demonstrated comparable efficacy rates but recurrence rates ranged from 13% to 19% and up to 91%, respectively.[116,117]

Thus, Polyphenon® E is a promising and relatively safe self-applied topical treatment with few advantages over the other self-applied modalities.

Glizigen (Glycyrrhizinic acid) Glizigen has been developed by Catalysis Laboratories and the main ingredient is glycyrrhizinic acid, a substance found in the *Glycyrrhiza glabra* root (sweet root).[118] It is known to possess anti-inflammatory, antiulcerative and antiviral effects. It interacts with viral proteins leading to inactivation of extracellular virus, prevention of intracellular decapsulation of infectious particles and the deterioration of the assembling capacity of the virus particles. Gomez *et al*. conducted a study to evaluate its use in external genital warts.[118] They combined it with viusid, a food supplement that was immunostimulatory. They compared glizigen-viusid with podophyllin in two groups of 50 patients each. Podophyllin was applied weekly for 6 weeks by the physician. Glizigen was to be sprayed on the lesions by the patients themselves according to the surface area involved - 1-3.9cm^2, three times a day; 4-6.9 cm^2, four times a day; 7-10 cm^2, five times a day, for 8 weeks. In addition, they were told to drink 30 ml Viusid syrup three times a day throughout the treatment period. They found that 84% of total patients had <5 cm^2 involved. Of them, in the Glizigen group, 38 were cured while 5 were not; while in the podophyllin group, 36 were cured while 10 were not. Hence, Glizigen was slightly better and was also tolerated better. However, further larger and better planned studies would be needed before glizigen can be used more extensively.

The peak incidence of warts is in children aged 12 to 16 years; hence, the role of immunotherapy for warts in children needs to be studied in greater detail. Systemic drugs like cimetidine have had disappointing results in randomized controlled trials, but continue to be used by some practitioners in children due to their convenience of administration, lack of pain and local adverse effects.[119] Topical sensitizers like SADBE and DPC have been tried on the face and neck and imiquimod on external genital warts in children, both being painless and extremely convenient.[120,121] Intralesional vaccines and

skin test antigens are the most popular kids on the block currently, and are being tried in different sites and patient populations, including children.[60,74] However, the attendant pain is less likely to find favor with children, unless their topical use (for example, topical BCG) is proven to have consistent documented success in large controlled trials.

Thus, a plethora of immunotherapeutic agents has been tried in recurrent warts. Some like intralesional or intradermal PPD may be an effective, well-accepted and very cost-effective treatment, especially in countries like India where vaccination against TB is performed routinely and mandatorily. That immunomodulators are effective and devoid of major adverse effects has been shown in open studies and small randomized trials. An added advantage is their potential to avoid recurrences. However, large-scale standardized studies with these agents are the need of the hour in this age of evidence-based dermatology for them to be used more widely and routinely.

What is new?

1. Many new agents have now become available such as Echinacea, green tea catechins and Propionium bacterium parvum, and few studies have been carried out on them. However, no definite role has yet been defined due to lack of larger randomized, placebo-controlled trials.
2. There is lack of standardization with regard to the dose, mode of administration, duration and interval of treatment with most of these agents; hence underlining the need for further evaluation.
3. Spontaneous resolution is a potential confounding factor in all trials on warts, and hence open uncontrolled trials are redundant as far as establishing the efficacy of an agent is concerned.

Footnotes

Source of support: Nil

Conflict of Interest: Nil.

Multiple Choice Questions

1. The maximum dose of cimetidine approved by FDA is:

   a. 1200 mg/day
   b. 2400 mg/day
   c. 3600 mg/day
   d. 4800 mg/day

2. The use of cimetidine is not approved for:

a. Children under 4 years of age
b. Children under 12 years of age
c. Children under 16 years of age
d. There is no such criterion

3. Mechanisms of action of levamisole include all except:

a. It alters PMN chemotactic responsiveness
b. It stimulates breakdown of cyclic AMP
c. It increases adenosine deaminase levels
d. It decreases delayed type hypersensitivity

4. Dose of levamisole used for immunostimulation is:

a. 2.5 mg/kg once a week
b. 2.5 mg/kg twice a week
c. 5 mg/kg once a week
d. 5 mg/kg twice a week

5. The most common reported side effect of systemic interferons is:

a. Flu-like syndrome
b. Chest pain
c. Wheezing
d. Diarrhea

6. Which is not one of the modes of action of Echinacea?

a. B-cell activation
b. Increase in number of macrophages
c. Stimulation of production of IFN and TNF
d. Inhibition of hyaluronidase produced by viruses

7. Intralesional agents are not recommended for all except:

a. Pregnant females
b. Immunosuppressed individuals
c. Known hypersensitivity to the antigen
d. Previous exposure to similar agent

8. Which of the following statements for imiquimod is incorrect:

a. Stimulates cytokines like IL-1
b. Approved for treatment of external genital warts
c. Absorption through intact skin is good
d. It is used for treatment of recalcitrant plantar warts

9. Contact sensitizers induce:

a. Type I hypersensitivity reaction
b. Type II hypersensitivity reaction
c. Type III hypersensitivity reaction
d. Type IV hypersensitivity reaction

10. One of the following statements regarding Polyphenon® E is incorrect:

a. It is extracted from tea leaves
b. It contains antioxidant substances
c. It is a physician applied modality
d. The FDA has approved it for external genital wart treatment

Answers:

1. B

2. C

3. D

4. B

5. A

6. A

7. D

8. C

9. D

10. C

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Figures and Tables

Table 1

The various immunomodulatory agents that have been used in the treatment of warts

Systemic	Intralesional	Topical
Cimetidine	Vaccines – MMR, Mycobacterium w	Bacillus Calmette-Guerin vaccine
Levamisole	Skin test antigens - PPD/ Candida/Mumps/ Trichophyton	Imiquimod
Zinc	Interferon	Contact sensitizers
Interferon	*Propionium bacterium parvum*	Green tea catechins (polyphenon-E)
Echinacea	Autoimplantation	Glizigen (Glycyrrhizinic acid)
Quadrivalent HPV vaccine		

MMR: Mumps measles rubella, HPV: Human papilloma virus

Table 2

Randomized controlled trials for Cimetidine in the treatment of verruca vulgaris

Reference	Design of study	Patient group	Drug used	Control group	Results	Remarks
Yilmaz *et al.*[14]	Randomized placebo-controlled double-blind	*n*=70, ≥5 warts	Cimetidine 25-40 mg/kg/d for 3 months	Placebo	32% CR (9/28) vs 30.7% (8/26)	*P*=0.85. No statistically significant difference
Karabulut *et al.* [15]	Placebo-controlled double-blind, randomized in 2:1 ratio	54 adults, multiple warts for ≥6 months	Cimetidine 400 mg TID (*n*=36) for 3 months	Placebo TID (*n*=18)	37% CR vs 25%	*P*>0.05. No significant difference
Rogers *et al.*[16]	Placebo-controlled double-blind	46 adults, ≥1 resistant wart for ≥2 years	Cimetidine 800 mg TID (22-46 mg/kg/d) for 3 months	Placebo TID	26.3% CR (5/19) vs 4.8% (1/21)	*P*=0.085. No significant difference
Sarnz- Santamaria *et al.*[17]	Randomized trial	40 children, ≥4 resistant warts	Cimetidine 20-40 mg/kg/d for 4 months	Cimetidine 20-40 mg/kg/d+topical therapy (caustic agents or cryotherapy)	10% CR vs 35%	*P*<0.001 Combination therapy significantly better
Bauman *et al.*[18]	Randomized trial	13 children, ≥4 warts on hands and feet	Cimetidine 30-40 mg/kg/d	Standard therapy with liquid N_2/salicylic acid	33.3% (2/6) CR vs 42.8% (3/7) CR	Standard therapy better (no significant difference)
Parsad *et al.*[19]	Randomized double-blind trial	44 Children	Cimetidine 30 mg/kg/d for 3 months	Levamisole 2.5 mg/kg on 2 d/wk+Cimetidine 30 mg/kg/d	39.8% vs 80% complete cure/ significant improvement	Combination significantly better (*P*=0.0150), Faster cure with combination
Parsad *et al.*[20]	Randomized double-blind trial	48 Adults	Cimetidine 30 mg/kg/d for 3 months	Levamisole 150 mg on 2 d/wk+Cimetidine 30 mg/kg/d	41.6% vs 75% complete cure/ significant improvement	Combination significantly better (*P*<0.01)

TID: Three times a day, CR: Complete cure

Table 3

Intralesional vaccines used in immunotherapy of warts

Vaccine	Patients*	Procedure	Results†	Follow up and recurrence	Side effects
MMR (Nofal *et al.*)[62]	2 groups of 85 and 50 pts with ≥1 common warts → I/L MMR vs saline (70 vs 40 completed)	I/L into single/largest wart. 2 wkly for max of 5/till CR	CR - 57 (81.4%) vs 11 (27.5%) NR - 6 (8.6%) vs 23 (57.5%) *P*<0.001	6 months, no recurrence	Pain (85.7%), flu-like syndrome (8.6%)
MMR (Gamil *et al.*)[63]‡	40 pts with plantar warts (23 completed)	0.1 ml of MMR I/L into largest wart. 3 wkly for max of 3/till CR	CR - 20 (87%)	9 months, 1 recurrence (4.3%)	Pain (82.6%), flu-like (4.3%)
Mw vaccine (Meena *et al.*)[64]	40 pts with ≥3 warts (37 completed)	0.1 ml of Mw vaccine I/L into 3-5 warts wkly till CR/max of 10	CR - 33 (83%)	4.48 months, 3 recurrences	Erythema, swelling, fever, ulcer, lymphadenopathy
Mw vaccine (Gupta *et al.*)[65]	10 pts with ext. CA (2 PLHA, 1 on immunosuppressants)	0.1 ml of Mw vaccine I/L into all warts wkly till CR/max of 10	CR - 8/9 (88.9%), 1/9 was giant wart, decreased to 5%	5.1 months, no recurrence	Edema, pain, HZV, balanitis in PLHA

*Only patients who tested reactive with intradermal injection of the respective vaccine (into ventral aspect of the forearm) were enrolled, †CR: Complete response (100%), NR: No response (0%), ‡This article was later retracted by the journal (*Journal of American Academy of Dermatology*) MMR: Mumps measles rubella, CR: Complete cure, HZV: Herpes Zoster virus, PLHA: Living with HIV/AIDS

Table 4

Intralesional/intradermal skin test antigens used in immunotherapy of warts

Antigen (Ag)	Patients*	Procedure	Results†	Follow up and recurrence	Side effects
PPD (Eassa *et al.*)[66]‡	40 pregnant females with anogenital warts into 2 groups of 20 each	Weekly Intradermal PPD injections in forearm×12 wks	CR-19 (47%) vs 0, NR–3 (7.5%) vs 100%	6 months, no recurrence	Pain, erythema, tenderness at site
Tuberculin (Kus *et al.*)[67]	18 pts with 22 resistant warts ≥2 years (13 pts with 17 warts completed)	3 Intralesional Tuberculin injections 3 weekly into each wart	CR-5 (29%), Partial response-10 (59%), NR-2 (12%)	NA	Pain, edema, erythema at site
Candida Ag (Summers *et al.*)[68]	1 PLHA with recalcitrant warts x 3 years	Intralesional (I/L) Candida Ag	CR of all warts in 1 month		
Candida Ag (Maronn M)[69]	55 pts with warts	I/L Candida Ag+concurrent Liquid N2/other treatments	CR– 48 (87%), NR - 4 (7%)		
Candida Ag (Phillips *et al.*)[70]	104 pts with longstanding warts, I/L 1:1 Mixture of Candida Ag and Lignocaine	0.1 ml injected into each wart 4 wkly x CR/3 doses	CR-75 (72%), 79 (76%)-v. Happy, 2 (2%)-v.unhappy	NA	Pain, blister peeling, numbness
Candida Ag (Kim *et al.*)[71]	18 pts with ≥2 non-facial cutaneous warts (11 completed)	I/L injection of 0.3 ml Candida Ag into largest wart 3 weekly	CR–9 (82%), NR–1 (9%)	NA	Pain, erythema at site
Candida Ag (Majid and Imran)[72]	40 pts with recurrent/ resistant warts (34 completed)	I/L injection of Candida Ag in single wart 3 wkly×3 doses	CR- 19 (56%), NR - 13 (38%)	No recurrence	
Candida Ag (Ritter *et al.*)[73]	13 yr old female with resistant flat warts on face, scalp, hand	I/L injection of Candida Ag 0.3 ml (face), 0.2 ml (hand), 0.1 ml (scalp) reptd at 3 wks		4 wks	Redness of treated warts, initial flare, hyperpigmentation
Candida and Mumps Ag (Johnson *et al.*)[74]	81 pts divided in 3 groups - 26 (32%) - cryotherapy, 45 (56%)- I/L Mumps antiserum, 10 (12%)-I/L Candida antiserum, 39/55 of antisera group completed	I/L 3 weekly till CR/3 doses	CR - 29/39 (74%), 14 of 18 with distant warts had resolution of distant warts too	NA	Flu-like syndrome (6), pain, pruritus.
Candida, Mumps, Trichophyton (C/M/T) Ag (Horn *et al.*)[75]§	201 pts div into 4 groups- a. 54– I/L M/C/T Ag b. 41- I/L M/C/T+IFN α2b c. 46- I/L IFN α2b only d. I/N Normal saline	Largest warts injected 3 weekly till CR/max of 5 doses	a. R-29 (54%), NR-25 (46%) b. R-28 (68%), NR-13 (32%) c. R-12 (26%), NR-34 (74%) d. R-13 (22%), NR-47 (78%)	NA	Fever, edema, erythema
Candida, Mumps, Trichophyton Ag (C/M/T) (King *et al.*)[76]	Adults and Children with genital warts	3 wkly I/L injection into 1 warts each of M/T/ M+C+T/C+T	CR-47% (vs 34%)	NA	NA

*Only patients who tested reactive with intradermal injection of the skin test antigen (into ventral aspect of the forearm) were enrolled, †CR: Complete response (100%), NR: No response (0%), ‡PPD: Purified protein derivative falls in pregnancy Category C, §>75%: Responder (R), <75%: Non-responder (NR), IFNs: Interferons, PLHA: People Living with HIV/AIDS, NA: Not Available

Table 5

Trials with topical BCG vaccine used in immunotherapy of warts

Vaccine	Patients*	Procedure	Results†	Follow up and recurrence	Side effects
Topical viable BCG (Salem *et al.*)[89]	2 groups each of 40 children with ≥3 common and plane warts → topical BCG paste vs saline (37 vs 34 completed)	BCG mixed with Salicylic acid and Glycerin made into a paste made → applied on all warts → washed after 2 hrs. Weekly ×12 wks	Common warts: CR - 13 (65%) vs 0 Plane warts: CR - 9 (45%) vs 0 *P*>0.001	6 months, no recurrence	Nil
Topical viable BCG (Metawea *et al.*)[90]	2 groups each of 25 pts with untreated condyloma acuminata (CA) → BCG in normal saline (NS) Vs NS	BCG in NS solution applied directly or with cotton gauze on all warts → washed after 2 hrs. Wkly×6 wks. (extendable to wkly ×3 wks after gap of 3 wks)	CR - 23 (92%) vs 0 (all control group pts shifted to BCG therapy)	6 months, no recurrence	Mild burning, erythema
Topical viable BCG (Bohle *et al.*)[91]	10 men with untreated CA<2 cmsq area (9 completed)	BCG in Salicylic acid solution applied → covered with condom → removed and washed after 2 hrs. Wkly ×6 wks (extendable wkly ×3 wks)	6/9 - CR, 3/9 - NR	29-50 months, no recurrence	Fever, erythema preputial swelling
Topical and intraurethral BCG (Bohle *et al.*)[92]	6 men with recurrent ext. and intraurethral CA	NdYAG laser done → 3 wks later, BCG in NS applied topically and instilled intraurethrally → washed off after 2 hrs. Wkly ×6 wks	5/6 - CR	NA, annual recurrence rate 0.75	Mild dysuria, penile edema, fever

*Only patients who tested reactive with intradermal injection of the vaccine (into ventral aspect of the forearm) were enrolled,
†CR: Complete response (100%), NR: No response (0%), BCG: Bacillus Calmette Guerin, NdYAG: Neodymium doped yttrium aluminium garnet