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Topical and intralesional immunotherapy in cutaneous infections

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ABSTRACT

Immunotherapy has revolutionized the treatment of extensive and resistant warts. Promising results have extended the role of immunotherapy to other infections such as extensive molluscum contagiosum, recurrent herpes simplex infections, and cutaneous leishmaniasis, which are resistant to standard treatment. This review focuses on topical and intralesional immunotherapy in the management of cutaneous infections.

Keywords: Immunotherapy, Topical, Intralesional, Wart, Molluscum contagiosum

INTRODUCTION

Agents used for immunotherapy act by enhancing or suppressing the immune system.[1] Immune enhancing or immune-modulating agents are found to be effective in the management of recalcitrant warts.[1] Molluscum contagiosum, recurrent herpes labialis, and genitalis and cutaneous leishmaniasis are the other cutaneous infections where immunotherapy is found effective.[2-10]

This review focuses on the topical/intralesional agents used in cutaneous infections. The common topical agents used are imiquimod 5% cream, diphenylcyclopropenone (DPCP) (diphencyprone), squaric acid dibutyl ester (SADBE), 15% sinecatechins ointment, Bacillus Calmette–Guerin (BCG) vaccine in normal saline or salicylic acid, and 15% zinc ointment.[1,11-13] Intralesional agents found effective are *Mycobacterium indicus pranii* vaccine, BCG vaccine, tuberculin purified protein derivative (PPD), measles-mumps-rubella (MMR) vaccine, Candida extract, Trichophyton antigen, vitamin D3, zinc sulfate, and interferon alfa (IFN α)-2b.[1,14] Autoinoculation (autoimplantation) is another promising therapy that has achieved clearance of warts by stimulating the immune response.[1,14]

Mechanism of action: An overview

Imiquimod, an agonist of toll-like receptor 7, exerts antiviral effects by increasing the cellular levels of IFN-α, tumor necrosis factor-alpha, and interleukin-6.[1,15] The mechanism of action of SADBE and diphencyprone (DPCP) is not fully explained. The possible mechanisms include a type IV hypersensitivity reaction or a non-specific inflammatory reaction.[16] Cytokines released during the allergic reaction caused by the contact sensitizers tend to activate the natural killer cells which in turn lyse the virus-infected cells.[17]

The therapeutic effects of sinecatechins in cutaneous infections are attributed to their immunomodulatory, antioxidant, and antiviral properties.[2] The beneficial effect of zinc is believed to be due to its effects on macrophage and neutrophil functions, natural killer cell/phagocytic activity, and various cytokines.[13]

The various vaccines act by boosting cell-mediated immunity, while IFN α-2b shows antiviral activity through viral interference. In addition, it has immunomodulatory and antiproliferative properties.[1]

IMMUNOTHERAPY FOR WARTS

Recalcitrant, recurrent, or extensive warts as well as warts affecting periungual and palmoplantar sites (difficult to treat areas) are considered for immunotherapy.[1] The first contact allergen that was used in the treatment of resistant warts was dinitrochlorobenzene (DNCB) in 1973.[18] DNCB is no longer used widely due to its mutagenic potential.[11]

Autoimplantation (harvesting of wart tissue followed by autoimplantation) and Falknors needling method (index wart is punctured several times with a 26-gauge needle to produce a "beefy" red wound) are the other methods that act by modulating the immune system.[19]

The various topical and intralesional immunotherapy agents used in warts and the dose and frequency of administration are shown in Table 1.[1,12,13,16-18,20,21]

Among topical agents, an evidence-based review done by Ahn and Huang noted that clinical improvement was seen in 33–50% of patients who received 5% imiquimod cream, although none of the patients experienced complete clinical clearance.[22] A quantitative systematic review on genital warts reported that imiquimod achieved complete clearance in 51% of patients, but was not effective in human immunodeficiency virus (HIV) positive patients.[23]

Among immune sensitizers, SADBE is considered the safest – with complete clearance in 58% of patients.[24]

Sinecatechins are FDA approved for genital warts.[25] It is prepared from green tea leaves from the plant *Camellia sinensis*. A blend of eight different catechins and other green tea components constitute the ointment. Epigallocatechin-3-gallate is the main catechin in the preparation.[26] The clearance rate of genital warts documented following application of 15% sinecatechins ointment varied from 46% to 52% and recurrence rate was low at 6.5%.[27]

Topically applied BCG was effective in children with common warts and plane warts with 65% and 45% resolution, respectively.[28] In a placebo-controlled study, 80% of the patients had complete resolution of genital warts after a maximum of six BCG applications.[29]

Songsantiphap and Asawanonda, after assessing the efficacy of 15% zinc oxide ointment in 16 patients, found that the ointment applied three times a day for 4 weeks attained reduction in size of warts in comparison to placebo. The authors concluded that zinc oxide ointment can serve as adjunctive therapy to increase the efficacy of other modalities of treatment.[13]

A case series on recalcitrant cutaneous warts treated with intralesional MMR vaccine reported complete response in nine of the eleven treated (81.9%), which was comparable to the 82% complete clearance reported by Chauhan *et al.*[30,31] In an open, uncontrolled trial with intralesional vitamin D3 therapy in cutaneous warts, 78.5% of patients had complete resolution.[32] In a 2 year study of cutaneous warts treated with intralesional Candida antigen, 80% of patients showed complete clearance of lesions. Six out of the seven immunocompromised patients who were treated also demonstrated either a partial or complete response.[33] Hypersensitivity to Candida antigen is an absolute contraindication for this treatment modality.[1] In a randomized controlled study, 62% of the patients responded to Trichophyton when used as a single agent.[34] *Mycobacterium w vaccine* was found to have comparable efficacy to cryotherapy with 66.7% clearance in a study by Dhakar *et al.*[35] Sharquie *et al.* demonstrated 39.7% clearance of cutaneous warts in a single-blinded placebo-controlled trial using BCG vaccine.[36] Podder *et al.* in a double-blind, randomized controlled trial that assessed the effectiveness and safety of intradermal BCG vaccine in comparison to intradermal tuberculin PPD, observed both agents to be useful with better response in the BCG treated group (complete clearance in 48.5% of the BCG treated group and in 18.5% of the tuberculin PPD treated group).[37]

A randomized controlled trial reported the usefulness of Propionium bacterium parvum (0.1 ml injected intralesionally once a month for 3–5 months) in cutaneous warts.[21]

Another method attempted for warts is autoimplantation. In autoimplantation, a full-depth nick up to subcutis level (under local anesthesia and aseptic precautions) is made with an 18-gauge needle in a selected wart which serves as the donor wart. A chunk of wart tissue is removed and introduced in a subcutaneous pocket created with the same 18-gauge needle on the flexor aspect of the left forearm about 2 inches below the antecubital crease and secured in place by band-aid plaster. The dressings are removed after 5 days.[38] Autoimplantation achieved clearance of lesions in 91% of patients at 2 months.[38] ElGhareeb compared autoimplantation with MMR vaccine and noted that autoimplantation showed better efficacy in achieving clearance of distant warts (warts that were situated away from the treated wart).[39] Complete resolution was noted in 70.7% patients with palmoplantar warts treated with Falknors needling method.[19]

Table 1: Topical and intralesional immunotherapy agents used in warts.

Route of administration	Drug used	Dose, frequency of administration, and duration of treatment	Indication
Topical agents	Imiquimod	5% cream three times a week for 16 weeks	Cutaneous and genital warts
	Sinecatechins	15% ointment – three times a week for 16 weeks	Cutaneous warts
	Bacillus Calmette-Guerin	Application in normal saline or salicylic acid, wash off after 2 hours, weekly treatment for up to 6 to 12 weeks	Cutaneous and genital warts
	Topical zinc	15% ointment three times a day for 4 weeks	Cutaneous warts
	Topical interferon	Human leukocyte α-interferon (incorporated 2×10^6 IU/g) in hydrophilic cream, 6 gram thrice a day for 4 consecutive days a week up to 4 weeks	Vulvar and vaginal warts
	Squaric acid dibutyl ester (SADBE)	Paring of warts followed by application of SADBE. Occlude with dressings for four hours and then wash with soap and water. Repeat sessions every 2–4 weeks or till resolution	Cutaneous warts
	Diphencyprone	Sensitize with 2% and follow-up by weekly maintenance of 0.001–1% diphencyprone. Occlude with dressings for 48 hours and wash with soap and water. Repeat sessions at intervals of 2–4 weeks or till resolution	Cutaneous warts
Intralesional agents	Measles-mumps-rubella vaccine	0.3–0.5 ml into the largest wart, repeat every 2 weeks for 3 to 4 sessions	Cutaneous warts
	Vitamin D	0.2 ml of 7.5 mg/ml, 2 sittings 4 weeks apart	Cutaneous and genital warts
	Candida antigen	0.1–0.3ml into the largest wart, then 3 sessions at weekly intervals	Cutaneous warts
	Trichophyton antigen	0.3 ml into the largest wart every 3 weeks, maximum 5 sittings	Cutaneous and genital warts
	Mycobacterium Indicus Pranii vaccine	0.1 ml into 3–5 warts or all warts followed by up to 10 sessions 2–4 weekly	Cutaneous warts
	Bacillus Calmette-Guerin vaccine	0.1–0.5 ml into the largest wart, every 2 weeks for 5 sittings	Cutaneous and genital warts
	Tuberculin purified protein derivative	2.5 units into a few warts every 2 weeks	Cutaneous warts
	Interferon alfa-2b	1–2 million units 3 days/week for 3 weeks	Genital warts
	Propionium bacterium parvum	0.1 ml once a month for 3–5 months	Cutaneous warts

A network meta-analysis on intralesional immunotherapy for warts concluded that PPD and MMR showed superior efficacy in achieving complete primary and distant recovery and showed reduced recurrence rate at the same site in comparison to cryotherapy and other immunotherapeutic modalities.[14] Autoinoculation showed efficacy comparable to MMR and PPD in attaining distant recovery.[14]

Unlike PPD, intralesional MMR vaccine is not recommended in pregnancy.[40]

Molluscum contagiosum

Being a self-limiting condition, opinions differ on whether to treat molluscum contagiosum or not. According to general consensus, patients with extensive disease (mainly immunosuppressed individuals), secondary bacterial infection, conjunctivitis, molluscum dermatitis, or esthetic complications require treatment.[41]

The topical immunomodulatory methods that have been tried in molluscum contagiosum are 5% imiquimod cream, diphencyprone, and topical sinecatechins.[2-7] Al-Mutairi *et al.*, in a prospective, randomized, comparative, and observer-blinded study, found imiquimod 5% cream applied 5 days a week to be of comparable efficacy (complete cure rate 91.8%) to weekly cryotherapy (complete cure rate 100%) at the end of 16 weeks. Pain, bullae formation, pigmentary changes, and superficial scarring were significantly more in the cryotherapy group. The authors concluded that imiquimod could be the preferred option, especially in children with several small lesions.[3] However, van der Wouden *et al.* found imiquimod to be not more effective than placebo.[42]

Kang *et al.* studied the effect of diphencyprone solution applied weekly starting with 0.0001% and increased to a maximum of 0.1%, based on the response observed. The authors documented complete cure in 14/22 children (63.6%) within a mean treatment period of 5.1 weeks. Although most

Table 2: Intralesional immunotherapy agents used in molluscum contagiosum.

Intralesional immunotherapy agent	Dose and frequency	Percentage of patients who achieved complete resolution	Serious side effects
Measles-mumps-rubella vaccine	0.3 ml into the largest lesion at an interval of 2 weeks	Two patients treated - complete resolution in both (100%) after two and four injections, respectively	None
Candida antigen	0.3 ml into 1–3 lesions, at an interval of 2–6 weeks	50-56%	None
Purified protein derivative	10 IU (0.1 ml) into the largest lesion every 2 weeks up to six injections	85%	One case of anaphylaxis in 20 patients treated
Vitamin D	0.2ml into two relatively large lesions at 4 weeks interval	Complete resolution of all lesions in two immunosuppressed patients (100%) after 2 injections	None

of the treated children could tolerate the treatment (most common adverse effects being erythema and pruritus), four patients had to discontinue diphencyprone.[4]

Sinecatechins 10% ointment twice daily for 4 weeks applied to the top of the lesions was found effective in a 5-year-old child with extensive molluscum lesions.[2]

Intralesional immunotherapies [Table 2] used in molluscum contagiosum include measles-mumps-rubella vaccine, Candida, tuberculin PPD, vitamin D3, interferon α, and Streptococcal substrain OK-432.[5-7]

Nelson *et al.* reported 10 patients with HIV infection who received intralesional IFN α (one mega unit) at weekly intervals for 4 weeks. Three Mollusca of each patient were chosen for treatment. Complete resolution was seen in 36.7% of the treated lesions. A reduction in size (50-90%) was observed in 18 lesions (18/30, 60%), while one lesion remained unchanged (3.3%).[5] Inui *et al.* reported successful treatment of molluscum contagiosum with intralesional penicillin-treated and heat-treated lyophilized powder of a substrain *of Streptococcus pyogenes A* (OK 432) in a patient receiving chemotherapy.[6]

After reviewing 10 studies on intralesional immunotherapy for molluscum contagiosum, Wells *et al.* concluded that none of the patients who completely responded to Candida, MMR vaccine, OK-432, and vitamin D3 showed recurrence after immunotherapy, while intralesional PPD and interferon α showed less efficacy in preventing recurrences.[7]

RECURRENT HERPES SIMPLEX INFECTION

A double-blind, randomized placebo-controlled study in patients who had six or more self-reported episodes of herpes labialis in the preceding 12 months suggested that topical sensitization dose of SADBE (2%) on the arm may prevent herpes simplex virus (HSV) outbreaks and this was supported by another multicentre study.[8,9]

Bernstein *et al.* after evaluation of subunit vaccines and imiquimod in guinea pig model of recurrent HSV type-2 infection concluded that the strategy of prime (subunit HSV vaccine) and topical pull (intravaginal/topical imiquimod) decreased recurrent HSV more effectively than vaccine alone.[43]

CUTANEOUS LEISHMANIASIS

Nahidi *et al.* found a combination of topical diphencyprone and intralesional meglumine antimoniate to be more effective in acute urban cutaneous leishmaniasis than meglumine antimoniate administered alone.[44] Topical imiquimod (5–7.5%) in combination with meglumine antimoniate was able to cure cutaneous leishmaniasis in patients who did not respond to meglumine antimoniate alone.[10,15,45]

CONCLUSION

With the emergence of pathogens resistant to commonly used antimicrobials, immunotherapy alone or in combination with other modalities appears to be the need of the hour. Immunotherapy could be the key to treatment-resistant infections and focused research in this area may uncover lasting solutions.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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