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Role of some intralesional immune therapeutics in verruca vulgaris

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Abstract
Verrucae or warts are benign epidermal growths of the skin and mucosa induced by the human papillomavirus. A range of immunogenic protein antigens has been used intralesionally for treating warts. Each antigen has distinct immunogenic characteristics, and individual patients may exhibit differing reactions to the same antigen. Intralesional administration of vitamin D is an efficient and safe therapy for verruca vulgaris, resulting in elevated expression of cathelicidin LL37. The capacity of 5-Fluorouracil (5-FU) to block DNA and RNA production enables the use of intralesional 5-FU for the management of viral warts. Methotrexate provided a cure rate nearly similar to 5 -FU, but vitamin D provided the least cure rate. Multiple studies have shown the efficacy of intralesional bleomycin for wart therapy, with rates of cure ranging from 14% to 99%. Bleomycin applied to the skin induces keratinocyte apoptosis, endothelial cell sclerosis, and collagen production inhibition.

Keywords: Intralesional immune, therapeutics, verruca vulgaris

Introduction
Verrucae or warts are benign epidermal growths of the skin and mucosa induced by the human papillomavirus. Despite spontaneous remission occurring within two years in 65%–78% of cases, the majority of individuals seek therapy for warts due to their cosmetic disfigurement and potential discomfort, particularly on the soles [1].

A range of immunogenic protein antigens has been used intralesionally for treating warts. Each antigen has distinct immunogenic characteristics, and individual patients may exhibit differing sensitivities to the same antigen. In some instances, the host's response to an antigen may be minimal or absent. A method to assess sensitivity to a particular antigen before intralesional treatment involves intradermal injection followed by the evaluation of induration and erythema. This approach may also facilitate the pre-sensitization of the patient prior to therapy [2].

Intralesional immunotherapy is often linked to minor, negligible side effects like local Pain at time of injection, but it was rarely prolonged [3]. Edema, erythema, itching, Systemic vasovagal attack and flu-like symptoms within 12h of injection, that resolved rapidly within 24h by non-steroidal anti-inflammatory drugs [4].

Advantage of intralesional immunotherapy
- Intralesional immunotherapy appears to be a straightforward, cost-effective, efficacious, and safe treatment approach, especially for numerous and refractory warts [5].
- Effective in eliminating remote warts with few adverse effects [3].
- Warts have been seen to retreat without scarring, making them advantageous for plantar, face, and genital lesions. The recurrence rate is minimal in comparison to destructive therapy [6].

Disadvantage of intralesional immunotherapy
- It is inappropriate for anyone with hypersensitivity to any of these antigens, pregnant women, and immunocompromised persons [6].

Classification of immunomodulator therapeutic agents
- Vitamin (Vit) D
- Methotrexate (MTX)
- 5-Flurouracil
- Bleomycin

Role of vit D in cutaneous warts [7]
- Vitamin D3 promotes innate immunity by enhancing the synthesis of defensin B2 and cathelicidin antimicrobial peptide in monocytes, macrophages, and keratinocytes, therefore augmenting their antimicrobial characteristics.
- It enhances their autophagic, chemotactic, and phagocytic capabilities.
- Vitamin D, via the vitamin D receptor (VDR), enhances the activity of antigen-presenting cells (dendritic cells) to elevate the levels of the anti-inflammatory cytokine IL-10 as well as stimulates the development of T-regulatory cells for promoting apoptosis.
- Vitamin D3 regulates the proliferation and differentiation of epidermal cells and modulates cytokine production. In reaction, viral-infected keratinocytes are eradicated 8. Intralesional administration of vitamin D is an efficient and secure therapy for verruca vulgaris, resulting in a rise in cathelicidin LL37 expression.
- Vitamin D3 also diminishes the production of IL-1α and IL-6, leading to reduced inflammation.

Adverse effect
- Intralesional injection of vitamin D3 associated with tolerable pain, erythema, rarely nail dystrophy in patients with periungual warts, swelling and mild symptoms of vasovagal attacks [8].
- Topical vitamin D3 associated with erythema, pruritus, burning sensation and scaling [9].

Measuring blood vitamin D and calcium levels prior to and following intralesional vitamin D3 administration is beneficial. The research conducted by Aktaş *et al*. [10] assessed serum calcium and parathormone concentrations. The findings were within standard parameters. Despite the absence of any signs or symptoms of hypervitaminosis D in patients, it is advisable to assess blood vitamin D and calcium levels prior to and during intralesional vitamin D therapy to avoid potential hypervitaminosis D.

Limitations of use
- Intralesional vitamin D3 should not be used in pregnant and breastfeeding women, those exhibiting any signs of immunosuppression, which includes HIV, those with a previous hypersensitivity history to vitamin D3, patients predisposed to keloids, and in cases of systemic or localized infection or inflammation [1].
- Topical vitamin D3 is not used in pregnant and lactating females and those with hypersensitivity to topical vitamin D derivatives [9].

Methotrexate
MTX, an agent initially designed for antineoplastic purposes, has been effectively used in the management of many dermatologic disorders. It is a folic acid analogue suitable for fast proliferating malignancies since it suppresses DNA synthesis in actively dividing cells [11].

Given the antineoplastic and antiviral capabilities of MTX, it may have a therapeutic impact on viral warts. *In vitro*, MTX exhibited an antiviral impact on Zika virus-infected cells, resulting in a 10-fold reduction in virus titer [12].

Adverse effects [13]
- Minor side-effects have been stated in the studies related to intralesional MTX such as transient post-injection pain.
- Serious adverse effects, including mucositis, pancytopenia, and hepatitis, were seen in a patient undergoing treatment for squamous cell carcinoma.
- Pancytopenia was also reported after a single injection of intralesional MTX 25 mg for keratoacanthoma treatment, with an individual suffering from kidney failure.

Investigation before use
Liver function tests, baseline blood cell counts, and renal function should be assessed before to therapy, with follow-up laboratory testing conducted one week following the initial therapy [13].

Limitation of use
Intralesional MTX is contraindicated in pregnant and lactating women, individuals under 18 years of age, elderly patients over 60 years, those exhibiting any form of immunosuppression (which includes drug-induced), hepatic disease, impairment of the kidneys, bleeding diathesis, cardiovascular disorders, or any chronic systemic illness [14].

Role of Five Fluorouracil (5-FU) in cutaneous warts:
5-FU may be integrated into both DNA and RNA, disrupting their production by inhibiting thymidylate synthase. 5-FU influences warts by interfering with viral DNA production [15].
5-FU rapidly permeates cells upon administration. 5-FU is conveyed into cells via the human nucleoside transporter (hNT). Within the cell, 5-FU undergoes phosphorylation to provide three main active metabolites: fluorodeoxyuridine triphosphate (FdUTP), fluorouridine triphosphate (FUTP), and fluorodeoxyuridine monophosphate (FdUMP).
The capacity of 5-FU to block DNA and RNA production enables its intralesional use in the management of viral warts. 5-FU is a fluorinated pyrimidine antimetabolite that may further serve as an immunomodulatory agent. 5-FU inhibits cell division, induces cell cycle arrest, and reduces epidermal proliferation, hence aiding in the reduction of wart tissue growth. Intralesional administration of 5-FU facilitates elevated concentrations of drugs inside the lesion [16].

Adverse effects
The most severe adverse effects of systemic 5-FU include myelosuppression and mucositis. Nonetheless, the topical application of 5-FU for various dermatologic conditions often results in local irritation and discomfort as typical adverse effects. Ulceration, hyperpigmentation, and inflammatory responses have also been documented, but the majority are temporary. While analogous side effects have been documented with both intralesional and topical 5-FU, intralesional 5-FU is more often correlated with

hyperpigmentation, pain, and blister formation. Additionally, superficial necrosis, localized infections, and wound dehiscence. In most instances, injection discomfort may be mitigated by local anesthetic and cool air [15].
Erosions and secondary bacterial infection may also occur [17].

Limitation of use
5-FU is contraindicated in pregnant or breastfeeding women, those with cardiovascular, kidney, or hepatic illnesses, those with compromised wound healing, or immune-compromised on immunosuppressant medications. Topical 5-FU use is limited in periungual region to avoid onycholysis [18].

Role of bleomycin in cutaneous warts
Multiple studies have shown the efficacy of intralesional bleomycin in wart therapy, with rates of cure ranging from 14% to 99% [19]. Bleomycin applied to the skin induces keratinocyte death, endothelial cell sclerosis, and collagen production inhibition [20]. It results in localized cutaneous necrosis, dyskeratosis, and neutrophil-predominant inflammation. Alternative mechanisms contributing to the effectiveness of bleomycin include the production of tumor necrosis factor (TNF) and the emergence of apoptotic cells in warts [19]. It also stimulates an immune response. It is theoretically possible that induction of local tumor necrosis factor (TNF) production by bleomycin may partially account for the observed effect of bleomycin in warts. TNF is recognized for upregulating the intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1, and cell adhesion molecule-1 expression, hence inducing tissue factor-like procoagulant function in human endothelial cells and resulting in hemorrhagic necrosis of tumors [21].

Adverse effect
Significant adverse effects have been seen following intravenous treatment with bleomycin. Pulmonary fibrosis was identified as the most severe documented adverse event with a total dosage beyond 400 U. Significant cutaneous toxicity has been seen with cumulative doses of 200 to 300 units, which includes neutrophilic eccrine hidradenitis, scleroderma, and acute generalized exanthematous pustulosis. In dermatology, bleomycin is primarily employed as an intralesional therapy, with the dose often not exceeding 2 to 6 units each session. Sporadic adverse effects observed following intralesional injection include gangrene, Raynaud phenomenon, onychodystrophy, scleroderma, and flagellate erythema. Local cutaneous responses to bleomycin injections including temporary manifestations of erythema, edema, eschar development, blackening, discomfort, and alterations in pigmentation [20].

Limitation of use
Bleomycin is contraindicated in pregnancy, peripheral vascular disorders, Raynaud's phenomenon, and intolerance to bleomycin [20]. Bleomycin is not used also in patients with known hypersensitivity, renal disease, pulmonary disease, or cardiac comorbidities [22].

Conflict of Interest
Not available

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Not available

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