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Treatment of warts by intralesional immunotherapy

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Abstract
Intralesional immunotherapy is considered a promising treatment options in various types of warts. It elicits a robust cellular immune response to modulate the equilibrium between Th1 and Th2 immune reactions, resulting in the elimination of HPV.
The antigen is injected intralesionally into the largest wart with or without pre-sensitization. The injected quantity typically exhibits variation within the range of 0.1 to 0.3 ml, whereas the average number of sessions required to get an adequate response often falls within the range of 2 to 6 sessions. Multiple antigens can be used as Candida albicans antigen, PPD, MWV, Vitamin D and vaccines like MMR, BCG, HBV and VZV.
The reduction of recurrences after successful therapy, and comprehensive eradication of each of the managed and untreated warts can occur either in close proximity to the injected wart or at anatomically distant locations, are promising advantages over traditional therapies.
It is linked to mild, inconsequential negative reactions that primarily manifest locally and systemically. These consequences include pain, oedema, erythema, and symptoms resembling those of flu. It is contraindicated in individuals having allergic response to antigens, immunosuppression and chronic diseases.

Keywords: Warts, immunotherapy, intralesional

1. Introduction
The utilization of immunotherapy intralesionally has emerged as a favored therapeutic approach for a diverse range of wart conditions. A delayed type hypersensitivity reactions is elicited in response to the administered antigens and the wart viruses. This phenomenon has the potential to enhance the immune system's capacity to identify and remove HPV in different bodily regions, hence avoiding the need for specific therapy for each wart [1].
According to current recommendations, the use of this treatment is advised as a first approach for managing multiple, persistent, and sizable warts [2]. Nonetheless, the clinical issue of choosing between various immuno-therapeutic drugs persists due to the lack of definitive evidence supporting the superiority of one drug over another. Hence, it is essential to conduct extensive trials in order to assess the relative safety and effectiveness of various intra-lesional immunotherapeutic drugs for the purpose of treating warts [3].

1.1 Mechanism of action
The proposition has been put up that the presence of a functioning host immune response is required for the effective implementation of intralesional antigen immunotherapy [4]. Previous studies have proposed that the administration of antigen immunotherapy intralesionally elicits a robust non-specific response of inflammation against cells contaminated with the HPV, including both treated and untreated lesions [5, 6]. Additionally, there has been a proposition suggesting that the elimination of warts in persons who were previously hypersensitive may be caused by the trauma itself, a phenomenon known as the Reverse Koebsuggener Phenomenon [7].
The efficacy of antigen immunotherapy intralesionally is linked to the induction of a predominant Th1 cytokine profile reaction, characterized by the production of IFN-Ɣ, IL-2, IL-12, and IFN-α. This immune response subsequently triggers the activation of natural killer cells and cytotoxic T cells, leading to the elimination of cells contaminated with the HPV. The lack of success of the subject under consideration is correlated with the existence of an elevated concentration of Th2 cytokines, specifically IL-10 and IL-4 [3, 8].

IL-10 and IL-4 [3, 8]. The proposal has been made to utilize antigen immunotherapy as a means to decrease the gene transcription of HPV by stimulating the production of TNF-α and IL-1 [9].

In brief, the mechanism by which intralesional immunotherapy operates is primarily associated with its capacity to elicit a robust cellular immune response, thereby modulating the equilibrium between Th1 and Th2 immune reactions in favour of the former. Ultimately, this culminates in the elimination of HPV (Fig. 1) [10].

1.2 Technique of intralesional immunotherapy

- **Patients selection:** Individuals with a healthy immune system, regardless of their gender or age, who have any form of warts, whether they are multiple or single, difficult to treat or not, and of varying sizes and durations, are eligible for this therapeutic approach [6].

The modality of therapy provided presents a favorable option for addressing warts in youngsters, given the challenges associated with treating this condition in this particular age group. Conventional methods of therapy may prove to be inadequate and potentially exacerbate the discomfort experienced by children, particularly when many warts are present. This therapy has also been shown effective in clearing distant warts [11].

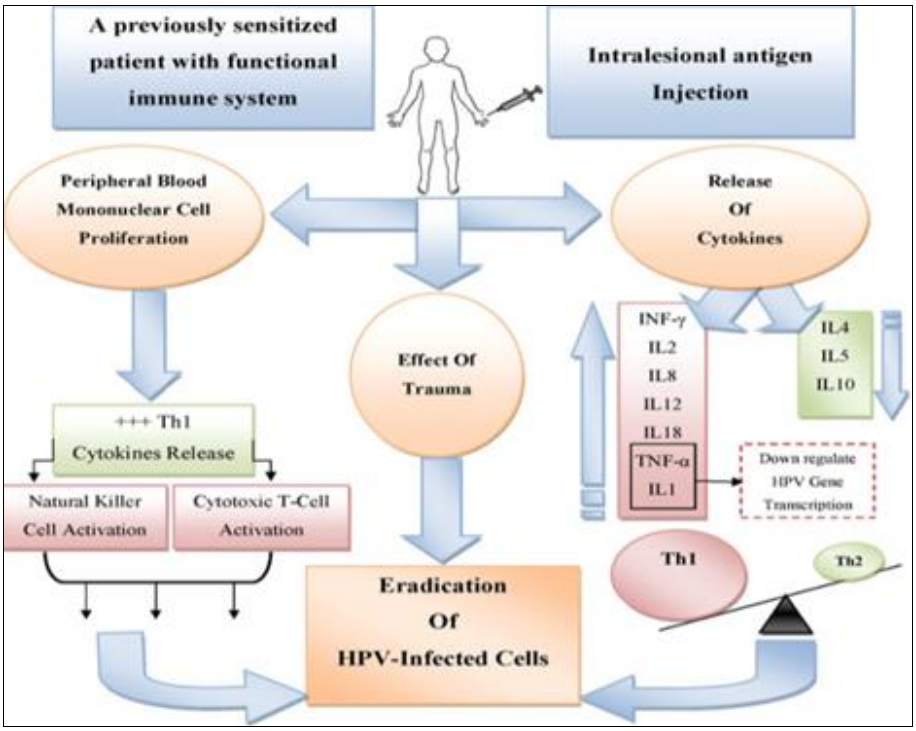

Fig 1: Mode of action of intralesional antigen immunotherapy [10]

HPV Human papillomavirus IFN Interferon IL Interleukin Th1 T helper 1
Th2 T helper 2 TNF tumor necrosis factor.

The criteria for exclusion ought to encompass individuals who have exhibited a previous allergic reaction to the administered antigen, those now experiencing an acute febrile illness, individuals with previous history of asthma or allergic skin conditions, pregnant or lactating women, and those who have undergone iatrogenic or primary immuno-suppression [6].

1.3 Methods of injection

Two distinct methodologies have been employed. The initial approach involves the implementation of a pre-sensitization test prior to the commencement of the experiment. In this test, an intradermal injection of 0.1 ml of the designated antigen is administered on the volar aspect of the forearm. A positive response is deemed necessary, characterized by the presence of erythema and induration measuring no less than 5 mm in diameter within a time frame of 48 to 72 hours. The individuals who participate in the study are considered responders, whereas those who do not participate are classified as non-responders [8].

In an alternative methodology, the antigen is administered directly towards the wart without prior sensitization. This strategy is suggested to be more feasible regards to duration, price, and compliance among patients [12]. This assertion is corroborated by other research [6, 13, 14], which have demonstrated the lack of a substantial correlation among the clinical response and the magnitude of the sensitization response.

The volume administered through intralesional injection typically ranges from 0.1 to 0.3 ml and is adjusted based on the dose-response relationship with the size of the test reactions in pre-sensitized participants. In order to harness the extensive immune response linked to antigen injections, it is common practice to administer the injection to a single wart, particularly if numerous lesions are present [12]. Intralesional injection of warts is performed by utilizing an insulin syringe, which is positioned parallel to the skin's surface, with the bevel oriented in an upward direction. The sessions number ranged from one to ten, whereas the period between sessions ranged from one to four weeks [11].

The number of therapies required to achieve complete response shown variability among various investigations, ranging from 2 [15] to 6 [16] sessions. The observed diversity can be attributed to various factors, including the specific

characteristics of the study, the type of antigen employed, the particular features of the warts being studied, or an integration of these factors.

2. Types of antigens

2.1 Candida albicans antigen

Candida albicans is categorized as a dimorphic fungus. As an integral component of the human microbiota, it is commonly found inhabiting many anatomical sites such as the oral cavity, pharynx, gastrointestinal tract, and genitourinary system. The Candida albicans cell walls serves as a substantial reservoir of candidal antigens. The primary constituents of the cell wall that trigger an immune reaction from the host are proteins and glycoproteins, with the latter being primarily composed of mannoproteins. Either carbohydrate or protein components, the two have the capability to elicit immunological responses [17].

The utilization of this substance in the management of warts is attributed to its ability to activate and regulate the immune system's reaction. In the instance of *C. albicans*, the immune system's reaction seems to depend on an intricate interaction between innate and acquired immunity, presenting intriguing difficulties for the host. Candidiasis is primarily combated by the immune response, specifically through cell-mediated immunity involving T cells, as well as innate immunity involving neutrophils, macrophages, and natural killer (NK) cells. These immune mechanisms are widely recognized as crucial defenses against candidiasis [17].

A recent study about intralesional *C. albicans* antigens for the management of planter warts, revealed 80% complete cure in patients treated with injection with a dosage of 0. 3 ml was intralesionally injected into the biggest wart at 3-week intervals. Regarding side effects, there was a statistically significant higher incidence of pain, redness, swelling, and flu-like symptoms [18].

2.2 Mumps, measles and rubella vaccine

Mumps, measles and rubella vaccines contain attenuated strains of these three viruses indicated for prevention of measles, mumps, and rubella. The utilization of intralesional MMR vaccine immunotherapy involves utilizing the immune system's capacity to identify viral antigens, resulting in the induction of a delayed-type hypersensitivity response. This response not only targets the specific antigen but also enhances the immune system's capability to identify and eliminate HPV infections. As a result of this, the immune system's reaction that is activated can effectively eliminate all lesions present on both the locally treated area and additional sites throughout the body [19].

According to a recent study, a significant proportion of individuals, notably 80%, achieved complete response when treated with 0.3 mL of MMR administered into their biggest wart at 3-week intervals. The therapy was continued until total elimination of the warts was achieved or for a maximum of 6 sessions of therapy, with minimal pain and erythema was recorded [20].

2.3 Mycobacteria

Intralesional therapy of warts has seen a significant utilization of mycobacterial antigens. The specific inoculations that have been examined for this objective encompass MWV, PPD, and BCG.

- **Purified protein derivative**

The technique described is utilized on a global scale for the purpose of diagnosing tuberculosis infections [21]. The tuberculin antigens are administered through intradermal injections, following which the individual's injection site is observed for the presence of induration [22]. The substance in question is a protein derivative that lacks live organisms, hence making it suitable for safe administration in youngsters and pregnant women. The administration of PPD induces a non-specific activation of cell-mediated immunity, primarily through the stimulation of natural killer cells, Th1 cytokines, and cytotoxic T cells. This therapeutic approach has been observed to effectively target various types of warts, including verruca vulgaris, verruca plana, and plantar warts, regardless of the specific serotype of the HPV involved [22].

According to a study, a significant proportion of individuals (76%) with common warts had complete clearance following four treatment sessions. Every patient was administered 2.5 tuberculin units (TU) of PPD through intralesional injection into each individual lesion. In cases where numerous lesions were present, a maximum of 25 TU of PPD was injected throughout each treatment session. The observed negative consequences included the presence of erythema, oedema, and pain specifically localized at the injection site [22].

- **Mycobacterium w vaccine**

The substance comprises particles of an aggressively proliferating non-typical mycobacterium with the ability to induce an immune response. This substance has been suggested and examined for its efficacy in treating warts [23]. The main application of this treatment is in the immunotherapy of multibacillary leprosy. However, its immuno-modulatory properties have also been observed in other mycobacterial diseases, including pulmonary tuberculosis, human immuno-deficiency infections, and malignant neoplasms affecting the head, neck, lung, bladder and [24].

The robust proinflammatory signals directed towards MWV elicit the recruitment of antigen-presenting cells, which subsequently produce helper T-cell type 1 cytokines and activate cytotoxic and natural killer T cells. These immune cells likely possess the ability to detect and handle low-profile HPV particles within the tissue that is infected. The robust adaptive immune response effectively eliminates not only localized lesions that have been treated, but additionally lesions that are located at a distance from the initial site [24].

In an open pilot study conducted by Gupta *et al.* [16], the efficacy of microwave ablation (MWV) in treating anogenital warts was investigated. The study included a total of nine participants. A total of eight individuals, accounting for 89% of the sample, experienced complete clearance of their condition following an average of 6.3 therapy sessions. The prevailing adverse reaction frequently documented was edema occurring at the site of injection. However, it is worth noting that one individual stated having granulomatous balanitis, while another patient claimed an occurrence of herpes zoster.

- **Bacillus Calmette-Guerin vaccine**

Bacillus Calmette-Guerin (BCG) is a type of vaccine that is derived from Mycobacterium bovis, a bacterium that causes

tuberculosis. It is a live attenuated vaccine, meaning that it has been weakened to reduce its virulence. BCG is included in the immunization schedule of many countries that have a high prevalence of tuberculosis. The safety of the vaccine is widely acknowledged, and it provides protection against the various disseminated manifestations of tuberculosis. The precise mechanism of action of this substance remains unknown; however, it is hypothesized that it may enhance the Th1 type of cytokine reaction, specifically IFN-γ, IL-2,12,18, IFN-α, and TNF-α, while also inducing a non-specific inflammatory reaction against the virus [25].

According to a study, a total of 30.8% of the participants experienced complete remission following four sessions of intralesional BCG treatment. A volume of 0.1 ml of the antigen was administered through injection into the biggest wart. In 61.5% of cases, individuals experienced the development of painful nodules at the site of the injection, while 7.7% of cases resulted in the formation of blisters in the same area [26].

2.4 Hepatitis B virus vaccine

Hepatitis B virus vaccinations incorporate a specific protein derived from the hepatitis B virus surface, known as HepB surface antigen (HBsAg). The production of this protein involves the introduction of the genetic code into a yeast cell. The vaccination under discussion is an inactivated form, meaning it contains no live viruses and so can't trigger hepatitis B infection [27].

The Hepatitis B virus vaccine is widely regarded as a secure and efficacious immunisation, with a recommendation for administration to newborns at the time of birth and to children up to the age of 18. The product is characterised by its affordability, simplicity of manufacturing, and exceptional durability. Moreover, the administration of HBV vaccine is linked to the activation of both humoral and cell-mediated immune responses, specifically Th1 cytokines. In addition, the HBV vaccine possesses the benefit of being a non-live vaccination, rendering it suitable for administration in immunocompromised individuals [28].

The precise mechanism through which the HBV vaccine operates in the management of warts remains unexplored. It is hypothesised that the effectiveness of the HBV vaccination is based on the same mechanism as other antigens used in immunotherapy intralesionally for warts. This mechanism involves the promotion of a Th1 cytokine profile reaction, specifically the production of IFN-γ, IL-2, and IL-12 [28]. The study reported that the negative reactions seen were of a minor and temporary nature, specifically manifesting as discomfort, redness, and swelling at the site of injection [29].

The safety profile of hepatitis B virus vaccinations is generally favourable. Nevertheless, individuals who exhibit hypersensitivity to yeast or any component of the vaccine are considered to have an unequivocal contraindication to HBV vaccination. Furthermore, there have been recorded cases of allergy, derangement of liver enzymes, erythema multiforme, multiple sclerosis, arthritis, Guillain-Barré syndrome, neuritis, optic neuritis, thrombocytopenia, transverse myelitis, and alopecia. According to the Global Advisory Committee on Vaccine Safety, it has been verified that the HBV immunisation is deemed to be highly safe [27].

The utilisation of intralesional HBV vaccination as an immunotherapeutic approach for the treatment of common warts has been observed to yield a rather modest rate of success in recent studies. A clinical experiment was conducted to investigate the efficacy of intralesional administration in patients diagnosed with multiple common warts. The individuals received an injection of 0.2 ml of HBV vaccines into the biggest wart at 2-week intervals, either until complete clearance was achieved or for a maximum of 5 sessions. A total of six patients (20.7%) obtained complete responses [29].

2.5 Vitamin D

An attempt was made to utilize intralesional vitamin D as an immune modulator in instances of verrucae, yielding favourable outcomes. The purported role of vitamin D in verrucae involves the regulation of epidermal cell differentiation and proliferation, as well as the modulation of the production of cytokines through its interaction with vitamin D receptors (VDR). Furthermore, the activation of Toll-like receptors in human macrophages results in the upregulation of the expression of VDR and vitamin D-hydroxylase genes, which subsequently leads to the synthesis and release of antimicrobial peptides [30].

A recent study showed 66. 7% of patients showed complete response, with intralesional 0. 4 mL of vitamin D3 (5 mg/2 mL equivalent to 20 000 IU cholecalciferol) solution every 3 weeks until full clearance or for a maximum 6 sessions of therapy [20].

2.6 Homologous autoinoculation

Auto-wart implantation is a technique that facilitates the stimulation of an effective cell-mediated immune system reaction, hence promoting the eradication of warts. There exist various methodologies that are contingent upon three distinct factors: a) The surface part of wart tissue, also known as pared tissues, or the fleshy warty tissues. b) Whether the tissues is crushed or not. c) The specific recipient area, which can be either the gluteal region or the volar aspect of the forearm, and whether the tissues is dermal or subcutaneous in nature [31]. The mechanism of action involves the initiation of a delayed hypersensitivity reaction against antigens present in wart tissue. This reaction facilitates the elimination of both local and distant warts, while also promoting the development of durable immunity, so avoiding future recurrences [32].

A single-arm clinical trial was conducted, involving a cohort of two hundred patients of both genders who presented with many resistant warts (≥ 5). The study revealed that 66% of the patients had complete clearance, while 26% experienced intermediate clearance, after 12 weeks of procedure [31].

2.7 Varicella zoster vaccine

The Varicella zoster vaccine (VZV) is classified as a live attenuated vaccination. The development of this intervention aimed to mitigate the occurrence of varicella. The administration of the VZV vaccine, that contains a substantial concentration of live attenuated virus, is necessary in order to achieve a notable enhancement in cell-mediated immunity. A research investigation was conducted to assess the effectiveness and safety of the VZV vaccination as a novel immunotherapeutic intervention for the management of warts. The experiment used a sample size of 23 individuals who received a direct injection of 0.1 ml of VZV. The time intervals between sessions were set at two weeks, either until complete resolution was accomplished or for a maximum of 4 sessions. It showed

complete clearance (65. 2%), partial response in (34. 8%) [31].

2.8 Advantages

One of the significant benefits of this therapy technique, especially in developing nations, lies in its affordability. Intralesional antigen immunotherapy offers several advantages over conventional treatments, including its straightforward application limited to the 'mother' wart, its promising efficiency, its high safety profile, and its lack of limitations on movement, scarring, and pigmentary alterations [8].

Several studies [8, 13, 14] have also documented the complete resolution of both treated and untreated warts among individuals with multiple lesions. This resolution has been observed either in the vicinity of the injected wart or at anatomical regions far from it. The aforementioned observation demonstrates a potentially advantageous aspect of intralesional immunotherapy, which could be attributed to the generation of a comprehensive cell-mediated immune response against HPV following antigen injection.

One of the most difficult challenges in the management of warts is the notable frequency of their reappearance, with rates as high as 30% or even greater, which is observed in the majority of therapeutic interventions that fail to eliminate the viral reservoir found in surrounding tissue [11]. In the present setting, a number of studies [6, 16, 33] have demonstrated the significant impact of intralesional immunotherapy in diminishing or perhaps averting recurrences subsequent to effective treatment. This discovery presents a promising benefit over conventional therapeutic approaches. The observed phenomenon could perhaps be elucidated by its capacity to elicit CMI, which facilitates the recognition of HPV by the host organism, triggers the generation of memory T cells targeting the virus, and enhances the effectiveness of the effector response mechanism [34]. Nevertheless, it is vital to use care when considering this advantage due to the limited sample sizes of individuals examined and the predominantly brief duration of follow-up reported in the majority of these investigations [10].

2.9 Disadvantages

A significant limitation of intralesional immunotherapy is the shortage of available research, with the majority of them being open-labeled. This renders any advice or conclusion relating to its effectiveness, harmful effects, prevention of recurrence, and other facets inconclusive [10].

Furthermore, it should be noted that the trials discussed in this context are subject to certain limitations. One such limitation is the lack of standardisation across various aspects of intralesional immunotherapy. These aspects include the quantity and concentration of the antigen that is injected, the number of sessions of the therapy administered, the intervals among these sessions, and the duration of the follow-up period required for a comprehensive assessment of recurrence rates [35].

Additionally, the exclusion of candidates who are otherwise healthy immunological individuals disregards a significant subset of individuals who have reduced immunity, such as recipients of organ transplants, who typically experience numerous warts [16].

2.10 Adverse Effects

Intralesional immunotherapy typically exhibits minor, inconsequential local and systemic negative consequences [10].

2.11 Local adverse effects

1. The most common complaint reported by nearly every individual was immediate pain experienced throughout the injection, which did not persist beyond the duration of the injection. The majority of research did not identify it as a contributing factor to withdrawal. [14], as it is well tolerated and less than that experienced with cryotherapy [35].
2. The presence of transient erythema, edoema, induration at the injection site, as well as a burning feeling and pruritus, were seen to varying degrees [8].

3. Systemic adverse effect

The most prevalent systemic negative impact is a flu-like sickness. The onset of this condition often occurs within a 12-hour timeframe following injections, and it is promptly alleviated within 24 to 48 hours by the administration of non-steroidal anti-inflammatory drugs [13]. The observed reaction could potentially be facilitated by the release of certain antigens into the bloodstream, leading to an immune system reaction and the production of inflammatory cytokines [6].

3.1 Rare adverse reactions

1. A painful purplish digit was detected subsequent to *C. albicans* immunotherapy, and post-immunotherapy examination confirmed the presence of fibrosis. This fibrotic response was noted among individuals who had already undergone destructive therapeutic interventions prior to receiving immunotherapy [11].
2. The occurrence of herpes zoster and reactivation of genital herpes in two individuals with HIV [16], suggests that caution should be exercised when considering the application of antigen immunotherapy in immunosuppressed individuals. It is advisable to wait until larger trials that can provide substantial evidence regarding the safety of this approach [36].

4. Contraindications

Individuals who exhibit an allergic reaction to the antigen employed, possess a medical history of asthma or allergic skin problems, are pregnant or lactating, have either relative or absolute immunosuppression, or suffer from chronic conditions that include hepatic insufficiency, chronic renal failure, hepatitis, or cardiovascular problems [20].

Conflict of Interest
Not available

Financial Support
Not available

5. References

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