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REVIEW ARTICLE

Intraregional Antigen Immunotherapy for Warts

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ABSTRACT

Common epidermal growths called warts are brought on by the human papillomavirus and can be extremely uncomfortable and embarrassing. Topical medications, cryotherapy, laser vaporization, and surgical excision are among the available treatment options today. While less severe techniques may result in lesion recurrence, many of these options are damaging and may cause scarring. Additionally, patients with a high number of warts cannot benefit from these local methods. Systemic treatments, including immunotherapy, have shown promise in treating multiple lesions by combining an immune system upregulatory response with a targeted strategy. Different antigens used in intralesional immunotherapy have demonstrated encouraging safety and efficacy in the treatment of warts. These therapies are believed to boost cell-mediated immunity (CMI), which in turn increases HPV recognition. In this review, we assess the effectiveness and side effects of intralesional immunotherapy in managing warts. With a comparatively higher efficacy of Candida antigen, intralesional antigen immunotherapy appears to be a viable, well-tolerated, and effective therapeutic approach for treating multiple warts.

Keywords: Warts; Antigen immunotherapy; Candida.

INTRODUCTION

The use of immunotherapy is growing in popularity. It has been demonstrated that intralesional immunotherapy is a safe and effective treatment for many forms of warts **[1]**.

It makes use of the immune system's recognition of specific viral, bacterial, and fungal antigens that cause a delayed-type hypersensitivity reaction to both the antigen and the wart virus, so enhancing the immune system's capacity to identify and eradicate HPV**[2].**

Rather than just the locally treated lesion, this heightened immune response has the potential to eradicate all lesions on the body. Thus, the benefits of intralesional immunotherapy include a high safety profile, a decreased recurrence rate, and the ability to remove distant warts that have been treated or not without leaving scars [**3].**

Mode of Action

Intralesional antigen immunotherapy's precise mode of action is still unknown. Intralesional antigen immunotherapy cannot be successful without a healthy host immune system **[4].**Both treated and untreated lesions are

affected by the potent, non-specific inflammatory response that intralesional antigen immunotherapy elicits against the HPV-infected cells. Additionally, it has been suggested that among previously sensitized individuals, the stress itself may result in the resolution of warts **[5].**

Intralesional antigen immunotherapy that is successful is linked to a predominant T helper (Th1) cytokine profile response, including IFN-γ, IL-2, IL-12, and IFN-α, but the presence of a high level of (Th2) cytokines, such as IL-10 and IL-4, is linked to its failure. Therefore, intralesional immunotherapeutic antigens may work by stimulating Th1 responses while suppressing Th2 responses **[2] (Figure 1).**

Evidence for the proposed role of cell-mediated immunity in controlling warts [2]:

Marked wart multiplication and persistence in immunocompromised people. Rapid and widespread development of warts in recipients of solid organ transplants. Patients with epidermodysplasia verruciformis may have a large number of flat warts. A notable rise in CD4 T cells in the warts that are spontaneously receding. The application of intralesional immunotherapy to the clearance of untreated distant warts.

Success Rates:

Success rates that vary have been shown. There is no clear explanation for the wide variation in response rates; nevertheless, research features, antigens used, wart treatments, and patient immune response are all relevant considerations **[6].**

Factors affecting success rates of intralesional antigen immunotherapy [2]:

Study characteristics

The population chosen for the study, the number of patients studied, the number of therapy sessions and the time between sessions.

Factors related to the antigen

Antigenic power (vaccines may be more antigenic than skin test antigens). Single or mixed. Viable or nonviable antigen. Extent of reactivity. Dose (amount injected).

Wart characteristics;

Duration, number, size, site and type.

METHODS

There are two methods that have been applied. Before the trial begins, 0.1 ml of the antigen to be utilized is injected intradermally on the volar aspect of the forearm in the majority of the trials. A positive reaction is defined as erythema and induration measuring at least 5 mm in diameter within 48–72 hours. The study enrolls those who react, and it excludes those who do not **[7].**

Regarding time, cost, and patient compliance, the other approach which injects 0.1- 0.3 ml of the antigen straight into the wart without first sensitizing the area is suggested to be more feasible. The lack of a substantial correlation between the degree of sensitization reaction and the clinical response has provided evidence in favor of this. Pregnant women, people with compromised immune systems, and people who are hypersensitive to any of these antigens should not undergo this operation **[**4].

Advantagesof intralesional immuno-therapy:

This therapy approach has several benefits, including low cost, easy application into just the "mother" wart, high safety profile, and lack of scarring and pigmentary alterations in addition to freedom of mobility **[2].**

It also has a significant impact on the prevention or decrease of recurrences following effective therapy. When patients present with multiple lesions, complete elimination of both treated and untreated warts, either at the distant anatomic sites or close to the injected wart **[8].**

Disadvantages of intralesional immune-otherapy:

The lack of standardization in various aspects of intralesional immunotherapy, such as the concentration and quantity of injected antigen, the number of treatment sessions, the intervals between sessions, and the follow-up period required for an adequate evaluation of recurrence rates, is one of the main disadvantages of intralesional immunotherapy **[5]**.

Additionally, limiting the pool of candidates to individuals with healthy immune systems eliminates a huge portion of patients who have compromised immunity and typically have a large number of warts on their body, such as organ transplant recipients **[7]**.

The most frequent side effects are localized erythema, burning, blistering, and peeling, as well as pain at the injection site. An 18-year-old woman in good health experienced the first documented case of lymphangitis following an intralesional injection of Candida antigen for verruca vulgaris. With the use of cold compresses and ibuprofen, the lymphangitis quickly disappeared **[9]**.

Although most patients can withstand the pain associated with the injection, it is nevertheless a drawback for youngsters who would rather use topicals that don't hurt and for people who have warts in extremely painful places, including periungual warts **[7].**

Adverse effects of intralesional antigen immunotherapy [7]:

Local

Pain: The most common grievance

Erythema: Variable and transitory

Transient and varied edema and induration at the injection location

Burning and itching sensation: sporadic and unpredictable

Scarring and infection: Not documented

Injuries or ulcers: Not documented

Segmentary alterations: Not documented

Painful purple finger: Occasionally linked to Candida antigen

Post-immunotherapy revealed cicatrix: This can happen to people who had harmful therapies in the past.

Systemic

Flu-like symptoms: Generally prevalent and quickly disappearing

Anaphylaxis: Not documented, but possible

Controversial: Autism and vaccinations

Granulomatous hepatitis: One BCG report was made.

Antigens

According to a number of studies, intralesional antigen immunotherapy is a potentially effective treatment for a variety of wart types, especially the resistant and numerous varieties. They have used many antigen types, either in combination with one another or as a single antigen. These comprise viral antigens like the MMR vaccination, bacterial antigens like the BCG vaccine, fungal antigens like the yeast Candida and dermatophytes, and isolated proteins like tuberculin **[10].**

Candida antigen

The majority of patients treated with this test antigen showed improvement when the first antigen for wart immunotherapy was attempted, according to the researchers**[11].**

The most common pathogenic yeast in the skin is Candida albicans. Immune system defense against Candida albicans is mostly based on delayed hypersensitivity. Between 60 to 78% of healthy persons have delayed-type hypersensitivity to C.albicans. Consequently, injecting its extract intr-alesionally into a wart may cause the host to respond with CMI, which could lead to wart regression **[12]. Table 1**

Various antigens used as intralesional immunotherapy, as well as other immunotherapeutic agents, are illustrated in (**Table 2**)

Table (1): Clinical trials of intralesional Candida antigen immunotherapy for the treatment of wart:[2].

Reference	Type of wart	Candida antigen	Study design	Complete Response		Recurrence
				N	%	
Brunk [14]	Extragenital	Single	Placebo-controlled trial	35/41	85	None
Phillips et al. [15]	Common	Single	Retrospective	54/75	72	None
Johnson et al. [16]	Extragenital	Combined	Open-label pilot	29/39	74	One patient
Signore [17]	Common and plantar	Single	Open label	44/87	51	NA
Clifford et al. [18]	Recalcitrant extragenital	Combined	Open label	22/47	47	NA
Ritter and Meffert, [19]	Recalcitrant flat	single	Case report	1		NA
Johnson and Horn [20]	Extragenital	Combined	Open label	146/206	71	NA
King et al. [21]	Genital	Combined	Retrospective	5/10	50	NA
Horn et al. [22]	Common	Combined	Randomized controlled trial	29/54	54	NA
Maronn et al. [23] 2008	Extragenital	Combined	Retrospective	48/55	87	None
Khurshid and pal [24]	Extragenital	Single	Placebo Controlled	16/24	67	NA
Summer et al. [25]	Recalcitrant common	single	Case report	1		NA
Kim et al. [26]	Extragenital	Single	Open label	9/11	82	One patient
Majid and Imran[27]	Common	Single	Open label	19/34	56	None
Wong and Crawford[28]	Common	Single	Retrospective	3/7	43	NA

Reference	Type of wart	Candida antigen	Study design	Complete Response		Recurrence
				N	%	
Alikhan et al. [29]	Common	Combined	Retrospective	39/100	39	NA
Munoz-Garza et al. [30]	Recalcitrant extragenital	Single	Retrospective	156/220	70.9	NA
Vlahovic et al. [31] 2015	Plantar	Single	Retrospective	52/80	65	NA
Khozeimeh et al. [32]	Common Plantar	single	Randomized Clinical trial	23/30	76.7	NA
Nofal et al. [2]	Common	Single	Open label	33/54	61.1	None
Nofal et al. [33]	Recalcitrant extragenital	Single and Combined	Comparative	12/36 24/36	33.3 66.7	None None
Nofal et al. [34]	Recalcitrant extragenital	Single and Combined	Comparative	9/20 15/20	45 75	None none

NA: Not available

Table (2): Various agents used as immunotherapy for warts **[13]**

Agents	Indication, dosage & administration
Topical agents	
Imiquimod	For genital and cutaneous warts, 5% cream, 3 times a week, for 16 week
Sinecatechins	For cutaneous warts, 10% ointment 3 times a day for maximum 16 weeks
BCG	For cutaneous and genital warts, applied topically on the warts in normal saline or salicylic acid, washed after 2 hours, weekly treatment for 6 to 12 weeks
Intralesional agents	
Mw vaccine	For cutaneous warts, 0.1 ml intradermal into 3-5 warts or all warts, followed by 0.1 ml intralesional, 2- 4 weekly, maximum 10 sessions
BCG vaccine	For cutaneous and genital warts, 0.1-- 0.5 ml intralesional injection in the largest wart, in 2 weeks interval in 5 sessions.
PPD	For genital warts, 0.1 ml weekly intradermal injection in the forearm for 12 weeks
MMR vaccine	For cutaneous warts, 0.3- 0.5 ml into the largest wart fortnightly for up to 5 sessions
Candidal extract	For cutaneous warts, 0.1- 0.3 ml injected into the largest wart at first session, then 3 weekly intralesional injections
Trichophyton antigen	For cutaneous and genital warts, 0.3 ml injected into the largest wart every 3 weeks, maximum of 5 sessions
Tuberculin	For cutaneous warts, 2.5 units into few warts every 2 weeks
Vitamin D3	For cutaneous warts, 0.2 ml of 7.5 mg/ml, Vitamin D intralesional, 2 sessions 4 weeks apart
Interferon alpha 2B	For genital warts, 1-2 million units 3 days/week for 3 weeks
Systemic	
Zinc	For cutaneous warts, 10mg/kg/day (2.5 mg/kg/day elemental zinc) for 2 months
Cimetidine	For cutaneous warts, 20- 40 mg/kg/day for 3- 4 months
Levamisole	For cutaneous warts, 2.5-5 mg/kg/day, 2-3 consecutive days every 2 weeks for 4-5 months.
Echinacea	For cutaneous warts, 600 mg single oral dose (single study)
Propolis	For cutaneous warts, 500 mg single oral dose (single study)
HPV vaccines	For cutaneous warts, 0.5 ml intramuscularly, at 0, 2 and 6 months (2 dose or 3 dose regimen) may be followed

BCG, Babcilus Calmette-Guerin vaccine; MMR; Measles Mumps Rubella vaccine; Mw, Mycobacterium w; PPD;

Purified Protein Derivative

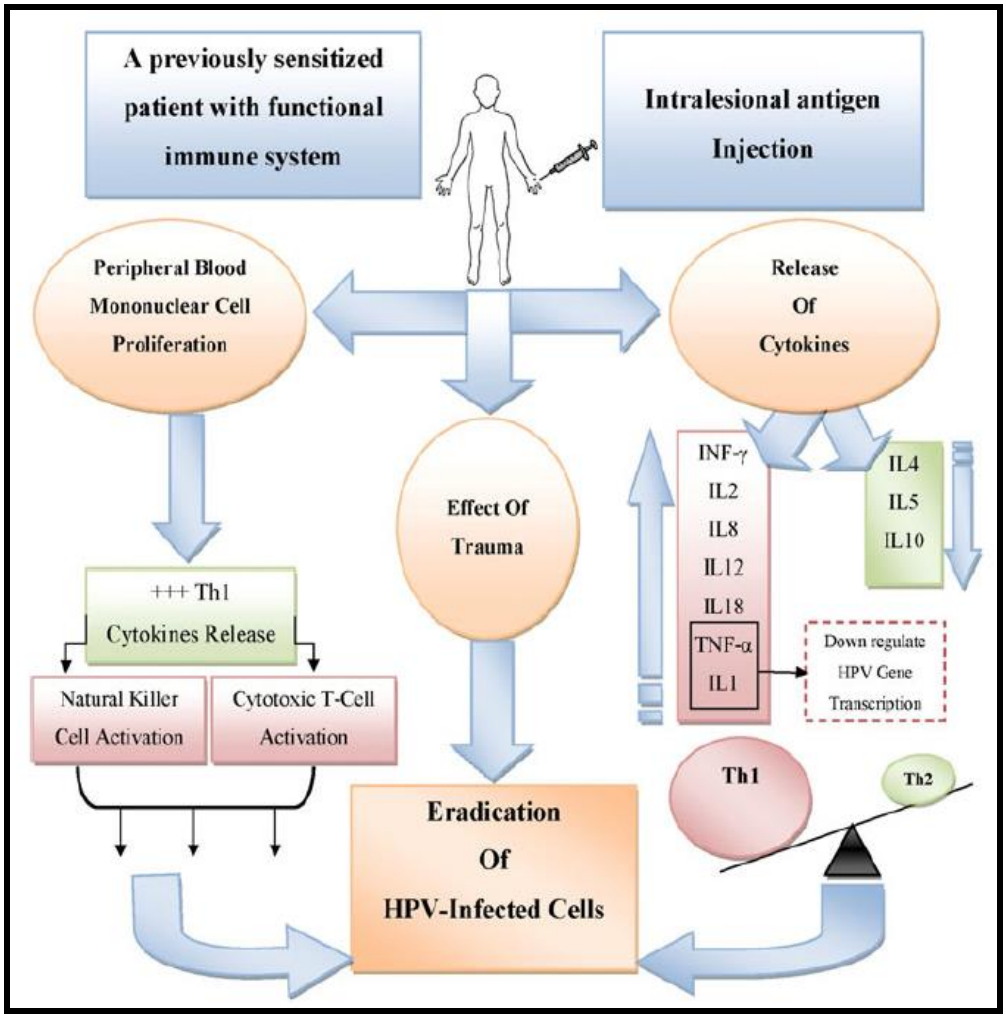

Fig. (1): Mode of action of intralesional antigen immunotherapy **[2].**

HPV: human papillomavirus, **IFN:** interferon, **IL:** interleukin, **Th1:** T helper 1, **Th2**: T helper 2, **TNF:** tumor necrosis factor

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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REFERENCES

1. **Nofal A, Alakad R.** Intralesional immunotherapy for the treatment of anogenital warts in the pediatric population. *J Dermatolog Treat. 2022; 33*(2), 1042-6.
2. **Nofal A, Marei A, Amer A, Amen H.** Significance of interferon gamma in the prediction of successful therapy of common warts by intralesional injection of Candida antigen. *Inter J Dermatol*, 2017; 56:1505-6.
3. **Xu J, Abudurusuli G, Rui J, Li Z, Zhao Z, Xia Y et al.** Epidemiological characteristics and transmissibility of HPV infection: A long-term

retrospective study in Hokkien Golden Triangle, China, 2013–2021. *Epidemics*, *2023;44*, 100707.

4. **Wang YB, Sun B, Han B.** Retinoic acid increases the anticancer effect of paclitaxel by inducing differentiation of cancer stem cells in melanoma. Die Pharmazie-An Int J Pharm Sci. 2018 Dec 1;73(12):729-32.
5. **El-Sharqawi H, Hassan R, Elgarhy H, El-Far NN.** Treatment of warts by intralesional immunotherapy, 2023.
6. **Nofal A, Khattab F, Nofal E, Elgohary A.** Combined acitretin and Candida antigen versus either agent alone in the treatment of recalcitrant warts. *J Am Acad Dermatol*, *2018a*; *79* (2): 377-8.
7. **Nofal A, Alakad R, Fouda I, Fawzy MM.** Intralesional antigen immunotherapy in the treatment of periungual warts. *J Cutan Med Surg. 2021; 25*(3), 286-92.
8. **Rageh RM, Hewedy ES, Hegab DS.** Intralesional injection of Candida albicans antigen versus measles, mumps, and rubella vaccine for treatment of plantar warts. Acta Dermatovenerol Alp Pannonica Adriat. 2021;30(1):1-5.
9. **Zubritsky L, Alikhan A.** Lymphangitis occurring after intralesional Candida antigen injection for verruca vulgaris. *Dermatol. Online J. 2016; 22*(6).
10. **Aldahan AS, Mlacker S, Shah VV, Kamath P, Alsaidan M, Samarkandy S et al.** Efficacy of intralesional immunotherapy for the treatment of warts: A review of the literature. Dermatol Ther. 2016; 29(3), 197-207.
11. **Elmaadawy EH, Shams SS, Hegab DS, Zaki RA.** Pulsed-dye laser versus intralesional Candida albicans antigen injection in treatment of genital warts. *Acta Dermatovenerol Alp Pannonica Adriat. 2019; 28*(1), 21-6.
12. **Tawfik NZ, Eyada MM, Abdel El Hamid RE, Halim HM.** Intralesional injection of purified protein derivative versus Candida antigen in treatment of genital warts. *Dermatol Ther. 2022;35*(10), e15762.
13. **Thappa DM, Chiramel MJ.** Evolving role of immunotherapy in the treatment of refractory warts. *Indian Dermatol Online J*. **2016;** 7(5):364-370.
14. **Brunk D**. Injection of Candida antigen works on warts. *Skin Allergy News***.** 1999*;* 30: 5.
15. **Phillips RC, Ruhl TS, Pfenniger JL, Garber MR.** Treatment of warts with Candida antigen injection. *Arch Dermatol***. 2000***;* 136 (10): 1274–5.
16. **Johnson SM, Roberson PK, Horn TD.**Intralesional injection of mumps or Candida skin test antigens: A novel immunotherapy for warts. *Arch Dermatol*. 2001*;* 137(4): 451-5.
17. **Signore RJ.** Candida albicans intralesional injection immunotherapy of warts. *Cutis*. 2002*;* 70 (3): 185-92.
18. **Clifford G, Smith J, Plummer M, Munoz N, Franceschi S.**Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer*. 2003*;* 88: 63–73.
19. **Ritter SE, Meffert J.**Successful treatment of flat warts using intralesional Candida antigen. *Arch Dermatol*. 2003; 139: 541–2.
20. **Johnson SM, Horn TD.**Intralesional immunotherapy for warts using a combination of skin test antigens: A safe and effective therapy. *J Drugs Dermatol*. 2004*;* 3(3): 263-5.
21. **King M, Johnson SM, Horn TD.**Intralesional immunotherapy for genital warts.*Arch Dermatol*. 2005*;* 141 (12): 1606–7.
22. **Horn TD, Johnson SM, Helm RM, Roberson PK.**Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: A single-blinded, randomized, and controlled trial. *Arch Dermatol***. 2005***;* 141(5): 589-94.
23. **Maronn M, Salm C, Lyon V, Galbraith S.**One-year experience with Candida antigen immunotherapy for warts and molluscum.

Pediatr Dermatol. **2008***;* 25: 189-92.

24. **Khurshid K, PalSS**. Role of Candida antigen in treatment of viral warts. *J Pak Assoc Dermatol*. **2009***;* 19 (3): 146-50.
25. **Summers P, Richards-Altmon P, Halder R.** Treatment of recalcitrant verruca vulgaris with Candida antigen in patient with human immunodeficiency virus. *J Drugs Dermatol*. **2009**; 8:268-9.
26. **Kim KH, Horn TD, Pharis J, Kincannon J, Jones R, O'Bryan K, et al.** Phase 1 clinical trial of intralesional injection of Candida antigen for the treatment of warts. *Arch Dermatol*. 2010*;* 146 (12): 1431–3.
27. **Majid I, Imran S.**Immunotherapy with intralesional Candida albicans antigen in resistant or recurrent warts.*Indian J Dermatol*. 2013*;* 58(5): 360-5.
28. **Wong A, Crawford RI.** Intralesional Candida antigen for common warts in people with HIV. *J Cutaneous Med Surg*. **2013**; 17:313–5.
29. **Alikhan A, Griffin J, Newman C.** Use of Candida antigen injections for the treatment of verruca vulgaris: A two-year mayo clinic experience.*J Dermatolog Treat*. 2015*;* 27: 355-358.
30. **Muñoz Garza FZ, Roé Crespo E, Torres Pradilla M, Aguilera Peirò P, Baltà Cruz S, Hernandez Ruiz ME et al.** Intralesional candida antigen immunotherapy for the treatment of recalcitrant and multiple warts in children. *Pediatr Dermatol*. 2015; 32: 797-801.
31. **Vlahovic TC, Spadone S, Dunn SP, Fussell T, Hersh I, Green T et al.** Candida albicans immunotherapy for verrucae plantaris. J Am Podiatr Med Assoc. 2015 Sep 1;105(5):395-400.
32. **Khozeimeh F, Jabbari AF, Mahboubi OY, Jafari M, Tehranian S, Alizadehsani R et al.** Intralesional immunotherapy compared to cryotherapy in the treatment of warts. *Int J Dermatol*. 2017*;* 56:474-8.
33. **Nofal A, Khattab F, Nofal E, Elgohary A.** Combined acitretin and Candida antigen versus either agent alone in the treatment of recalcitrant warts. *J Am Acad Dermato*l.2018A; 79 (2): 377-8.
34. **Nofal A, Elkot R, Nofal E, Mazen M.** Combination therapy versus monotherapy in the treatment of recalcitrant warts: A clinical and immunological study. *J cosmet dermatol*.2019 ; 18(5):1448-55.

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