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ORIGINAL ARTICLE

Intralesional Immunotherapy for the Treatment of Warts: a mini-review.

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ABSTRACT

Background: Warts are a common dermatological disease. They occur due to infection by the human papillomavirus. They can occur at any site and at any age. Sometimes they persist for many years and their treatment becomes difficult and challenging for dermatologists and patients.

Methods: Various modalities have been utilized for warts treatment including destructive methods and immunotherapy. None of them proved to be a completely effective treatment. Immunotherapy has the advantage of stimulating the immune system to recognize the virus so that both treated and distant warts are cleared. It also avoids the undesired side effects of destructive methods such as severe pain, scarring, and hypo or hyperpigmentation.

Results: Intralesional immunotherapy stimulates a delayed-type hypersensitivity response through the infiltration of CD4 T-lymphocytes and macrophages in wart lesions, activation of CD4 lymphocytes with the release of IL2, TNF α and (IFN-α, β, and γ) which have antiviral effects on HPV.

Conclusions: Various antigens have been tried like BCG, PPD, MMR, candida antigen, and the recently utilized Hepatitis B virus vaccine.

Keywords: Warts; Treatment; Immunotherapy; Vaccines; Intralesional

INTRODUCTION

Warts are hyperkeratotic lesions. They present over hands in most patients but can occur anywhere on the surface of the skin or the mucosa [1].

Two methods of treatment are widely utilized. The first one includes the destruction of the lesions by the means of chemical or electrocautery and cryotherapy. The second method relies on immune system enhancement by immunotherapy [2].

MATERIAL AND METHOD

The search was done via PubMed and Google Scholar by the use of the following keywords: warts, treatment, immunotherapy, intralesional. Suitable studies were included. The study was approved by the research ethics committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

INTRALESIONAL ANTIGEN IMMUNOTHERAPY

Immunotherapy is a form of biological treatment. It depends on substances that enhance or inhibit immunity to get rid of the infection. It is either directed against particular types of cells or stimulates the general defense mechanisms [3].

Its role is not fully known, however, it is supposed to work by stimulating T cell-dependent mechanisms by increasing the level of Th1 immune response over Th2 to fight the infection [4].

Different types of antigens are utilized for the treatment of warts.

- **Candida antigen**

Candida antigen is recommended for use in patients with warts especially if warts are large and multiple. It gives good results without scarring or severe side effects [5].

Amer et al. [6] assessed the efficacy of candida antigen in warts and the study showed a complete clearance in 69.6% of patients.

- **Measles, mumps, rubella (MMR) vaccine**

MMR vaccine is one of the immunotherapeutic agents that appear to be efficient and safe in children and adults with a low rate of recurrence [7].

Shaheen et al. [8] assessed the effectiveness of the MMR vaccine for warts and found a complete response in 80% of the patients.

- **Bacillus Calmette Guerin (BCG) Vaccine**

BCG vaccine stimulates T and B lymphocytes and enhances IL1 production with subsequent inhibition of viral transcription [9].

Jaisinghani et al. [10] assessed the efficacy of the BCG vaccine for multiple warts treatment and a complete response was achieved in 73, 53% of the patients.

- **Purified protein derivative (PPD)**

Injection of PPD leads to enhanced delayed hypersensitivity response. The previously sensitized T lymphocytes are attracted to the injection site with the production of lymphokines and the mobilization of more cells [11].

Jaiswal et al. [12] conducted a study to assess the efficacy of PPD in warts and a complete response was reported in 68.6%.

- **Killed Mycobacterium (Mw) Vaccine**

Injection of the Mw vaccine leads to a great immune response. The APC is attracted by the increased release of IL1. Then the viral particles are processed leading to an adaptive response [13]. **Chandra et al**. [14] assessed the response to the Mw vaccine in patients with warts and found a complete response in (68.8%).

- **Human papilloma virus (HPV) vaccines**

Types of HPV vaccine include a bivalent one (bHPV) against HPV 16 and 18 and a quadrivalent one (qHPV) against HPV18, 16, 11, 6. non-valent HPV vaccine was produced from the quadrivalent with the addition of 5 other types 31, 33, 45, 52, 58 [15].

Nofal et al. [16] used bivalent HPV vaccines in recalcitrant warts and a complete response of 81.8% was reported in the patients who received the vaccine intralesionally.

- **Varicella zoster virus (VZV) vaccine**

VZV is one of the live attenuated vaccines that significantly stimulate cell-mediated immunity, so it was tried for the treatment of warts [6].

- **Interferon**

IFN-α is a glycoprotein of low molecular weight produced by cells that inhibit viral replication. IFN-α-2b is FDA approved for the intralesional treatment of genital warts. IFN-g is more potent than IFN-α and IFN-b. It is produced by activated T cells thus stimulating more cellular immune responses to eradicate warts [17].

- **Hepatitis B vaccine**

The Hepatitis B virus vaccine is a DNA vaccine that is generally considered to be safe, low cost, and can be produced easily without requiring particular storage [18].

Nofal et al. [19] supposed that the vaccine could act like other immunotherapeutic agents utilized in warts mainly the vaccine antigens such as MMR and BCG.

Types of Hepatitis B virus vaccine

- **First generation vaccines**

HBV growth on tissue culture is difficult to occur, so hepatitis B surface antigens were obtained from the carriers' plasma [20].

- **Second generation vaccines**

They are recombinant, yeast-derived containing only the S protein of the viral envelope [21].

- **Third-generation vaccines**

They contain two additional components (pres1 and pres2) with the S protein [21].

- **Two-dose vaccine**

This vaccine is yeast-derived and used in adults aged 18 years or more [21].

Children and young adults respond strongly to the vaccine, but old persons and immunosuppressed patients usually respond poorly [20].

Intradermal injection is better than intramuscular injection as the muscles are poor sites for immunogenicity [21].

Nofal et al. [19] studied the response to the Hepatitis B vaccine in patients with warts and a complete response was achieved in 20.7 %

Table 1: Clinical trials of intralesional immunotherapy utilized in the treatment of warts.

Authors	Agent utilized	Complete response (%)	Partial response (%)	No response (%)	Treatment interval (week)	Sessions (no.)
Amer et al [6]	Candida antigen	69.6	30.4	0	2	4
Amer et al [6]	VZV vaccine	65.2	34.8	0	2	4
Chuhan et al [7]	MMR vaccine	82.4	17.6	0	2	5
Shaheen et al [8]	MMR vaccine	80	10	10	3	3
Shaheen et al [8]	PPD	60	30	10	3	3
Jaisinghan et al [10]	BCG vaccine	73.53	23.53	2.94	3	3
Jaiswal et al [12]	PPD	68.6	11.7	19.6	1	6
Meena et al [13]	MW vaccine	83	4.25	12.75	1	10
Nofal et al[16]	Bivalent HPV	81.8	9.1	9.1	2	6
Nofal et al[19]	HBV vaccine	20.7	17.2	62.1	2	5
Marei et al [22]	Candida antigen	40	25	35	2	5

Table 2: Common side effects of Intralesional immunotherapy.

Agent utilized	Side effects
Candida antigen	Pain[6], non-significant side effects[22]
MMR vaccine	Pain[7,8], erythema, swelling, and vasovagal attack in a few cases[8]
BCG vaccine	Pain, erythema, swelling, Itching, ulceration, scarring, BCGitis[10]
PPD	Pain [8,12], swelling, erythema, and postinflammatory hyperpigmentation[14]
MW vaccine	Erythema, swelling [13,14], ulceration[14]
Bivalent HPV	Pain, fatigue, and itching [16]
VZV vaccine	Pain, numbness, and erthema[6]
HBV vaccine	Pain, edema, and erythema[19]

DISCUSSION

Intralesional antigen immunotherapy has been utilized in the treatment of warts in many studies either as monotheraputic, comparative, or combination studies. Many agents have been tried with variable results and side effects as shown in Table**s** 1 and 2.

Amer et al. [6] compare the effectiveness of candida antigen and varicella-zoster vaccine in the treatment of warts. Complete clearance was found in 69.6% treated with candida antigen versus 65.2% treated with varicella zoster vaccine. The results were nearly equal which encourages further studies to evaluate the efficacy of VZV.

Shaheen et al. [8] compared the efficacy of intralesional PPD and MMR vaccines for the treatment of multiple warts. In the PPD group, 60% showed a complete response, 30% showed a minimal response and 10% showed no response. In the MMR group, 80% showed a complete response, 10% showed a minimal response and 10% showed no response.

Some studies showed different responses of the different types of warts to the same antigen utilized as shown by **Jaiswal et al.** [12] who studied the efficacy of PPD in the treatment of warts. Clearance was 100% in Periungual and palmar types, 60% in-plane warts, 47% in common warts, and 78.5% in plantar warts.

Some authors compared different routes of administration of the same antigen as conducted by **Nofal et al.** [16] who compared intralesional versus intramuscular bivalent HPV in the treatment of warts. Complete response was achieved in 81.8% of the intralesional group and in 63.3% of the intramuscular group which was not statistically significant.

The efficacy of combined intralesional antigens for warts was studied by **Marei et al.** [22] who compared the efficacy of candida antigen versus combined candida antigen and bivalent HPV vaccine.40% complete response was achieved in the candida antigen group and 70% complete clearance was achieved in the combined group.

Nofal et al. [23] studied the efficacy of the alternating injection of two different agents in the same patient. The study compared the results of the alternating injection of PPD and candida antigen versus either agent alone. Complete response was 61.1% in the PPD group, 36.8% in the candida antigen group, and 70.6% in the alternating injection group which was explained by the synergetic effect between agents.

Nofal et al. [19] assessed the efficacy of the HBV vaccine for warts with a complete response of 20.7%. The low success rate was explained by different dosing and route of administration, so they recommended further studies to compare intralesional by intramuscular injection of the vaccine. Most of the non-responders were above the age of 40 years, so they recommended the use of the vaccine in children and patients younger than 40 years.

CONCLUSION

Intralesional antigen immunotherapy is a wart treatment that combines safety, efficacy, and easy procedure. Side effects are generally accepted such as edema, erythema, and mild pain.

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