Journal of Pakistan Association of Dermatologists.2023;**33(3)**:1081-1089.

Review Article

A review of the literature on intra-lesional immunotherapeutic intervention for the treatment of recalcitrant warts

Ghada Farouk Mohammed[1], Mohammed Saleh Al-Dhubaibi[2], Saleh Salem Bahaj[3], Ahmed Ibrahim AbdElneam[4,5]

[1] Department of Dermatology, Venereology and Sexology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
[2] Dermatology, Department of Medicine, College of Medicine, Shaqra University, Dawadmi, Saudi Arabia.
[3] Department of Microbiology and Immunology, Faculty of medicine and health sciences, Sana'a University, Yemen.
[4] Department of Clinical Biochemistry, Department of Basic Medical Sciences, College of Medicine, Shaqra University, Dawadmi, Saudi Arabia.
[5] Molecular Genetics and Enzymology Department, Human Genetics and Genome Research Institute, National Research Center, 33 El Bohouth St. (former El Tahrir St.), Dokki 12622, Cairo, Egypt.

Abstract

Immunotherapeutic intervention has become a crucial treatment modality for the intervention of warts. Immunotherapeutic intervention for warts is typically limited to stubborn lesions. Conventional therapy is not working even though there are numerous immunotherapeutic agents available. Only a few treatment modalities seem to be particularly efficient. Furthermore, evidence-based research is scarce. Data on their efficiency 5-Fluorouracil is typically performed with systemic immunotherapeutic regimens, activated vitamin D, Bleomycin, Interferon (α and γ), Corynebacterium parvum, trichophyton antigen, measles, mumps, and rubella vaccine, Candida albicans antigen, Mycobacteria; all of these therapeutic approaches have been disclosed to be beneficial for numerous forms of warts.

The major part of the mentioned therapies' safety and efficacy have not been assessed in double-blind, controlled clinical studies, attempting to make the reliability and validity of a number of the enumerated therapeutic interventions challenging to assess. This report discusses various types of intra lesional Immunotherapeutic intervention for warts.

Key words
Intra-lesional; Recalcitrant warts.

Introduction

Human papillomavirus (HPV) types 1 and 2 cause most verruca vulgaris and plantar warts, while types 6 and 11 typically cause ninety percent of genital warts.[1] The beneficial effects of treatment for epidermal warts differs and eventually resulted in relapses. Multiple clinical immunotherapies have been employed to boost the host immune response. To fight warts, this modality of therapy makes depends on the usage of the person's immune response. Immunotherapeutic intervention can only target a specific cell immune system. Some have an overall impact on the immune system. It causes a T-cell-mediated reaction. Cytokines obtained

Address for correspondence
Dr. Ghada Farouk Mohammed
Department of Dermatology and Venereology,
Faculty of Medicine, Suez Canal University,
Ismailia, Egypt.
Ph: +2 01029808940
Email: Dr_ghada77@hotmail.com

by Th1 cells, which including IL-2 and IF-γ, are principally increased in response to an injection. Injecting intralesionally also assists in concentrating the regional immune reaction; however, some claim that the trauma of needling itself effectively elicits an adequate immune response in immunocompetent patients.[2]

Immunotherapeutic intervention is becoming increasingly popular, particularly for treating resistant cutaneous and genital warts. Topical, intralesional, or systemic agents are among them. Due to the lack of strict criteria for when Immunotherapeutic intervention must be repeatedly tried in a person with warts.[2]

Immunotherapeutic intervention, Regardless of the fact that the system of actions is not completely understood, is relatively inexpensive and has the ability to significantly boost wart therapies, as well as distanced uncontrolled warts by preliminary treatment.[3] The efficacy, safety profile, pain compliance, the feasibility of numerous different intravenous vaccines for treating warts are investigated within that review. Intralesional Immunotherapeutic intervention uses the immunological system's ability to direct a delayed-type hypersensitivity reactions to different epitopes and wart cells. Such therapy has produced Th1 cytokines, that also stimulate cytotoxic and NK cells in the fight against HPV infection. This, in addition to traditional wart therapies, removes both local and distant warts.[3]

Many researchers use different potential therapeutic elements for intralesional treatment. Candida antigen, Trichophyton, mumps antigen, MMR vaccine, skin test antigen, Mycobacterium w (Mw) vaccine, BCG vaccine, and IFN-α and γ injection are among them. The use of these agents is justified by the fact that the general population has a higher incidence of immunogenicity to such antigen's epitop. Because of the less rigorous immune activation with advancing age, elderly adults (>40 years) are much less inclined to respond to this method of treatment than young adults.[4]

The different authors take two approaches: The first strategy, the participant is inoculated with the antigen via an intradermal on the anterior facet of the forearm, and delayed hypersensitivity reaction is measured 48-72 hours later as erythema, oedema, and induration. Responders (with ≥5 mm diameter) are able for therapies. The mumps or candida antigen is then injected into the wart in an account maintained by the diameter of the test reaction.[5]

The second strategy, researchers injected the peptide with insulin syringe straightforwardly into the biggest wart without accomplishing intradermal testing first. The needle is carried parallel to the skin's surface, with the bevel up. This intervention is replicated every three weeks until the warts are entirely eliminated, or for a total of three therapies if no response is obtained.[6]

Intralesional therapy [Figure 1]

1- ***5-Fluorouracil (5-FU)***

5-FU is a fluorinated pyrimidine antimetabolite that works as an anticancer agent by inhibiting DNA and RNA synthesizing.[7] In concentrations ranging from 1 to 5%, 5-FU was used to handle genital warts as a cream or as an injected solution. According to the evidence out from experiments we evaluated, 5-FU had higher therapeutic efficacy than no treatment or placebo, meta-cresol sulfonic acid treatment, and podophyllin 2, 4, or 25% treatment.[8] Additionally, intralesional 5-FU injection was found to be both safe and treat a variety of multiple recalcitrant cutaneous warts.[9]

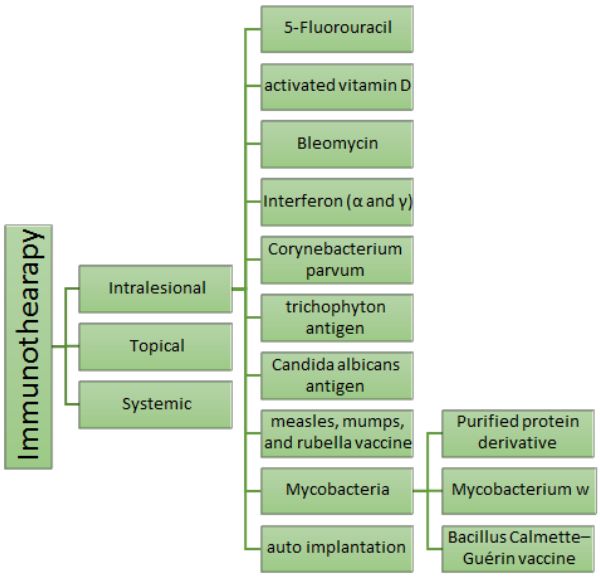

Figure 1 Immunotherapy involve systemic, intra-lesional or topical modalities of therapy for wart.

Thirty-nine children with at least two hand warts received topical 5% 5-fluorouracil cream once or twice daily for 6 weeks, with 6-month follow-ups. After 6 weeks of treatment, 88% of handled warts improved, and 41% of subjects had complete resolution of at least one wart. At the 6-month follow-up, 87% of complete responders had no recurrence of warts.[10]

5-FU may become an alternative topical therapy because it allows for self-application; additionally, a concentration of 1% 5-FU cream is advised due to milder side effects.[11]

A research of individuals diagnosed with warts utilised antigen of C. albicans, 5-FU injections, or bleomycin every 14 days till the lesions were completely cleared, or for a max of four intervention sessions, and was immediately abided on for an extra 2 months. Bleomycin had a proportionally valuable more incidence of full reacting (85%) than antigen of C. albicans (60%) and was greater than 5-FU (45%), with a substantially fewer therapy sessions required to obtain better effect with bleomycin and antigen of candida than 5-FU. Bleomycin emerged as the most appropriate cure, followed by antigen of C. albicans and 5-FU. A single interventional location, clearing of distanced warts, and a decreased risk of new lesion growth are all advantages of C. albicans Immunotherapeutic intervention. These therapies are cheap and have only small side reactions.[12,13]

The active vitamin D3 analog maxacalcitol inhibits apoptosis, tumor progression, and vascular endothelial growth, making it a potential cancer-regulating agent.[14] For four months, a 74-year-old man was treated with a topical vitamin D3 derivative twice a day for condylomata acuminata upon that corona as well as glans.[15] Intralesional vitamin D3 is efficacious and useful in the treatment of multiple cutaneous warts, as well as,[16] recalcitrant warts.[17]

The ability to control stratum corneum cellular proliferation, as well as regulate cytokine secretion, contribute to its efficacy. The activation of Toll-like receptors (TLR) in macrophages upregulated of vitamin D receptor as well as vitamin D-1-hydroxylase genes, actually resulting in the initiation of the antimicrobial peptide. This points to a connection among TLRs as well as vitamin D mediated innate immune function.[18] A case of an infant treated effectively with calcipotriene topical application, a vitamin D3 synthetic form, for an anogenital lesion on the anus.[19]

2- *Bleomycin*

Bleomycin, a Streptomyces verticillus-derived antibiotic, has anticancer properties, antimicrobial, and virucidal owing to its capacity to entangle with DNA, allowing bleomycin strand scission and eradication of pyrimidine and purine bases. The bleomycin hydrolase enzyme, which is recognized to eliminate bleomycin, is discovered in all body tissues

except skin in trace amounts. As a result, after injecting bleomycin intravenously, a considerable percentage of the active drug is present in the area.[20]

Numerous studies on intralesional bleomycin for recalcitrant warts have been published, with healing rates from 14 to 99 percent. Intralesional bleomycin was remarkably effective in the treatment of warts, particularly in the periungual as well as palmoplantar areas.[21] The amount injected is determined by the size of the warts. Upon two weeks, a black, ecchymosed eschar types, that is trimmed, and any remnant warts are inoculated again.[22] Bleomycin can be implemented using syringes, dermojet, prick, or dermatographic methods. Some studies have reported using a pulsed dye laser prior to bleomycin injection. Routine complete blood picture, liver and renal function tests, as well as a chest radiograph should be performed before and after 3 months of therapy.[23] There have been no reports of systemic side effects. Necrosis, pigment change, scarring, pain, Raynaud's phenomenon, as well as nail dystrophy occur in some cases. Bleomycin should be managed to avoid in pregnant women, children, and individuals with peripheral vascular disease.[24]

3- *Interferon (α and γ)*

IFN-α-2b is an intralesional IFN that has been approved for the Treatment for the treatment of genital lesions, requiring twice-weekly injections for three weeks to achieve the best results.[25] IFN-γ, produced by activated T cells, has greater antiproliferative activity than IFN-α and -γ. IFN-γ appears to be a more IFN for eliciting cellular immune responses against resistant warts.[26] IFN-γ was shown to stimulate the formation of TNF receptors in some cells, rising their responsiveness to TNF's direct cytotoxic or cytolytic activity. Exogenous IFN-γ may therefore increase TNF receptors on virus-infected keratinocytes, making them more responsive to TNF produced by activated T cells and macrophages.[27] IFN intralesional injection eliminates 40–60% of warts. Temperature elevation, chills, fatigue, diarrhea, headache, nausea, and vomiting are possible side effects (flu-like symptoms). The intensity of these symptoms appears to be dose dependent.[28]

4- *Corynebacterium parvum*

The immune stimulant and modulator Propionium bacterium parvum generated antibodies in the skin, destroying warts without leaving scars. Warts vanished without leaving scars in 9 of the 10 patients who received the Propionium bacterium parvum solution, and they shrank in 1 patient.[29]

5- *Trichophyton antigen*

Intralesional Immunotherapeutic intervention with antigens from Candida, mumps, or Trichophyton skin tests is a successful therapy for warts, as evidenced by significantly greater effectiveness and distanced clinical outcomes in antigen-treated subjects. The virion category or major histocompatibility complex antigens had no effect on remission. The expansion of peripheral blood mononuclear cells in reply to human papillomavirus epitopes suggests that a cell-mediated immune reaction oriented by the virus plays a significant role in wart resolution.[5]

6- *Candida albicans antigen*

Several studies have looked into intralesional Candida albicans antigen for wart treatments. Intralesional Candida albicans antigen inoculation is a simple as well as efficient process tool for recalcitrant plantar lesions, without a post-procedural idle time but only temporary infrequent adverse effects.[30] Majid and Imran utilised 0.1 mL of Candida antigen

intralesionally once a 3 weeks for three sessions on study participants with recalcitrant wart in their study. Overall, 56 percent of people had their warts eliminated, while 6 percent had only a limited response. In only 6 months, neither of the patients had a recurrence.[31] Large doses were used to elicit a stronger immunostimulatory reaction. After two doses of 0.3 mL Candida antigen inoculated three weeks away, a patient with recalcitrant flat warts had a complete response.[32]

Every 2-3 weeks, seven HIV-positive patients with recalcitrant common warts were provided 0.3 mL of Candida antigen. Only three warts (43 percent) cleared up after such an average of 3.7 therapies; nevertheless, the immunodeficient state of this clinical setting may have played an important role in the poor therapeutic outcomes.[33]

Intralesional Candida Immunotherapeutic intervention also was tried in kids with recalcitrant warts, with such a 47 percent of respondents for the handled wart and a 34 percent response rate for all body warts.[34] Candida Immunotherapeutic intervention works well for genital warts. Candida Immunotherapeutic intervention has been linked to feverish responses, pain, myalgia, erythema, oedema at the puncture site, as well as painful purple digit syndrome. This treatment, on the other hand, is inexpensive.[35]

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

Intra-lesional Immunotherapeutic intervention of MMR vaccine seems to have the ability to clear both untreated as well as treated distanced and anogenitallesions without scarring, has a low risk of recurrence, and has an excellent safety record.[36] The nonspecific inflammatory response to antigens appears to be the primary pathway of Immunotherapeutic intervention .[37] The MMR vaccine was reported to completely resolve cutaneous warts in 81.4 percent of patients, compared to 27.5 percent who received a placebo, with fewer complications such like flu-like symptoms in the remaining patients.[38]

46 subjects were assigned at random to receive either the MMR vaccine or saline solution within a double-blind, randomized controlled experiment. Standard MMR vaccine injection of 0.5 mL at 2-week distances. In the MMR vaccine injection group, eighteen (75%) had a full response, while four (17%) had a limited response. Flu-like symptoms were revealed by 29% of patients.[39]

The inverse relationship between wart length and response to MMR vaccine therapy is attributed to the increase infectivity forecasted to rise with wart length and the increase in such factors that inhibit the local interpretation of cellular immunity against HPV in long-lasting warts.[40]

8- ***Mycobacteria***

Mycobacterial virulence factors are also used to treat warts intravenously. Mycobacterium w vaccine (MWV), Purified protein derivatives (PPD), and Bacillus Calmette-Guerin inoculations have all been investigated for this aim (BCG).[41]

I- ***Purified protein derivative (PPD)*** PPD is a Mycobacterium tuberculosis extract, and it has live, attenuated Mycobacterium Bovis in it.[41] Eassa *et al.*[42] described PPD intradermal injection to treat anogenital warts in pregnant women. The study found that tuberculin reactivity was related to the extent of overall improvement, which was 85%. In this study, the reported side effects

were minor and insignificant.[42] Abd-Elazeim *et al*.[43] used PPD as an intralesional method in a controlled study that revealed a 75% complete response after 5.8±0.7 sessions. PPD was used to treat 20 persons with recalcitrant veruca vulgaris; 60 percent of patients had a complete clinical response after such an average of 5.8 therapies at 1-week distances. There were no full resolutions in the control group. They also discovered a statistically significant rise in IL-12. Erythema and transient hypopigmentation were also minor side effects.[43]

PPD was used at 0.05 mL per lesion to treat 55 participant with relapsed or recalcitrant warts. Sixty-seven percent of individuals accomplished full response after four treatment programs spaced two weeks apart. After six months, only one person had a re - occurrence of the lesion. Although a patient developed a fever, another established temporary lid edema after a brow injection, and a third developed an eczematous reaction, side effects were generally mild.[44]

II- ***Mycobacterium w (Mw)*** The Killed Mw vaccine was created using a nonpathogenic, growing rapidly, atypical Mycobacterium from Runyon class IV. It is extremely antigenic and elicits powerful cytokine (IL-2, IFN-γ) and T-cell reactions. Its name was later altered to Mycobacterium indicus pranii.[45]

After the patient has been sensitized, 0.1 ml of vaccine is injected intraepidermally and into the superficial dermis in lesions, with bigger ones favored. The treatments were replicated every two weeks until appropriate adjustments, a total of ten treatments, with a 55% full clearance rate and a 39% incomplete clearance rate with least side effects.[46] Mw vaccine reported (82.5%) full clinical response, with four patients showing partial response (10%). Possible side effects include fever, pain, sterile pustules at the injection site, and paraesthesias in arms and legs caudally to the injected lesions.[47]

III- ***Bacillus Calmette–Guérin vaccine (BCG)*** The mechanism of action may be explained by stimulating T and B lymphocytes, macrophages, and NK cell function, which may aid in the resolution of viral warts.[48] After intradermal BCG vaccine injection, 65% of patients with verruca vulgaris and 45% of plane warts had a complete response.[48]

Salem *et al*.[48] attempted to treat verruca vulgaris and plane warts in kids, focusing on small and recent-onset verruca. This type of Immunotherapeutic intervention works by activating CD4 and increasing levels of cytokines like IL-1, -2, and TNF-α. TNF-α and IL-1 were shown to inhibit gene transcription and thus have antiviral activity on HPV. [48] In 81 patients, viable BCG has been used as Immunotherapeutic intervention in warts as an intradermal therapies, with a 39.7 percent full response.[49]

In two scenarios of condyloma acuminata of the male genitals that had resisted previous medical treatments, BCG was administered intravenously in 0.4-0.5 mL to each patient. At 6 follow-up visits, both patients' lesions were completely cleared, with no relapse.[50] After 3 or 5 therapies with 0.1 mL BCG, recalcitrant non-genital warts were removed completely. As a result of their treatment, both patients described temporary flu-like symptoms.[51] According to these reports, warts can be treated in a few sessions with few adverse reactions; nevertheless, the accuracy of such findings has yet to be defined. These findings will need to be supported by greater

clinical studies. In impoverished and developing countries, it will be a very valuable strategy for treating warts.[52]

9- *Autoimplantation injection*

The outcomes of the autoimplantation injection humoral and cell-mediated immune reactions research showed that the autoimplantation technique substantially increased both humoral and CMI responses.[53]

Srivastava and Bajaj proposed autowart injection as a therapeutic approach for comprehensive and resistant warts.[54] Advancement of more than 75% in comprehensive and recalcitrant warts with the injection of crushed wart suspension in the gluteal area or autoimplantation of wart tissue in subcutaneous tissue.[54–56]

In patients treated with autoimplantation, full wart clearing was noted in 60% of patients.[57] Autoimplantation is an appropriate treatment option for patients suffering from multiple warts affiliated with distanced lesions.[57] The quadrivalent HPV vaccine provides long-term protection against HPV6, 11, 16, and 18-related anogenital diseases. The findings support quadrivalent HPV vaccination, including catch-up vaccination, in men.

Conclusion

Immunotherapeutic intervention has become a major wart therapeutic approach. Not only are such treatments demanded for recalcitrant or multiple lesions, but they are also obliged in the vast majority of treated cases. Based on our findings, we believe that Immunotherapeutic intervention is ineffective as a stand-alone treatment for warts and should be used in conjunction with traditional methods.

References

1. Cardoso, J. C. & Calonje, E. Cutaneous manifestations of human papillomaviruses: a review. Acta Dermatovenerol Alp Pannonica Adriat. 2011;20(3):145–54.
2. Nofal, A., Salah, E., Nofal, E. & Yosef, A. Intralesional antigen immunotherapy for the treatment of warts: current concepts and future prospects. Am J Clin Dermatol. 2013;14(4):253–60.
3. Nofal, A., Nofal, E., Yosef, A. & Nofal, H. Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: a promising approach. Int J Dermatol. 2015;54:667–71.
4. Johnson, S. M., Roberson, P. K. & Horn, T. D. Intralesional injection of mumps or Candida skin test antigens: a novel immunotherapy for warts. Arch Dermatol. 2001;137:451–5.
5. Horn, T. D., Johnson, S. M., Helm, R. M. & Roberson, P. K. Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: a single-blinded, randomized, and controlled trial. Arch Dermatol. 2005;141: 589–94.
6. Chandrashekar, L. Intralesional immunotherapy for the management of warts. Indian J Dermatol Venereol Leprol. 2011;77:261–263.
7. Pride, G. L. Treatment of large lower genital tract condylomata acuminata with topical 5-fluorouracil. J Reprod Med. 1990;35:384–7.
8. Reid, R. et al. Superficial laser vulvectomy. IV. Extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus-associated vulvar disease. Obstet Gynecol. 1990;76:439–48
9. Department of Dermatology Venereology and Leprosy, Rajah Muthiah Medical College & Hospital, Annamalai University, Chidambaram, India – 608002 & K, K. Efficacy of Intralesional 5- Fluorouracil in Recalcitrant Warts a study at Tertiary Care Centre. JMSCR 7, (2019).
10. Gladsjo, J. A., Alió Sáenz, A. B., Bergman, J., Kricorian, G. & Cunningham, B. B. 5% 5-Fluorouracil cream for treatment of verruca vulgaris in children. Pediatr Dermatol 26, 279–285 (2009).
11. Anggraini, I., Hoemardani, A. S., Nilasari, H. & Indriatmi, W. Randomised controlled trial of 1% and 5% 5-fluorouracil creams

compared with 90% trichloroacetic acid solution for anogenital wart treatment. Int J STD AIDS 31, 849–858 (2020).
12. Hodeib, A. A. E., Al-Sharkawy, B. G., Hegab, D. S. & Talaat, R. A. Z. A comparative study of intralesional injection of Candida albicans antigen, bleomycin and 5-fluorouracil for treatment of plane warts. J Dermatolog Treat 32, 663–668 (2021).
13. Sepaskhah, M., Sarani, M. B. & Bagheri, Z. Comparison of the efficacy of intralesional 5-fluorouracil/lidocaine/epinephrine injection with cryotherapy to treat common and palmoplantar warts: A randomized, controlled trial. Dermatol Ther 35, e15726 (2022).
14. Imagawa, I. & Suzuki, H. Successful treatment of refractory warts with topical vitamin D3 derivative (maxacalcitol, 1alpha, 25-dihydroxy-22-oxacalcitriol) in 17 patients. J Dermatol 34, 264–266 (2007).
15. Egawa, K. & Ono, T. Topical vitamin D3 derivatives for recalcitrant warts in three immunocompromised patients. Br J Dermatol 150, 374–376 (2004).
16. Kavya, M., Shashikumar, B. M., Harish, M. R. & Shweta, B. P. Safety and Efficacy of Intralesional Vitamin D3 in Cutaneous Warts: An Open Uncontrolled Trial. J Cutan Aesthet Surg 10, 90–94 (2017).
17. Raghukumar, S. et al. Intralesional Vitamin D3 Injection in the Treatment of Recalcitrant Warts: A Novel Proposition. J Cutan Med Surg 21, 320–324 (2017).
18. Labandeira, J., Vázquez-Blanco, M., Paredes, C., Suárez-Penaranda, J. M. & Toribio, J. Efficacy of topical calcipotriol in the treatment of a giant viral wart. Pediatr Dermatol 22, 375–376 (2005).
19. Rind, T., Oiso, N. & Kawada, A. Successful Treatment of Anogenital Wart with a Topical Vitamin D(3) Derivative in an Infant. Case Rep Dermatol 2, 46–49 (2010).
20. Lewis, T. G. & Nydorf, E. D. Intralesional bleomycin for warts: a review. J Drugs Dermatol 5, 499–504 (2006).
21. Lipke, M. M. An armamentarium of wart treatments. Clin Med Res 4, 273–293 (2006).
22. Munn, S. E., Higgins, E., Marshall, M. & Clement, M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. Br J Dermatol 135, 969–971 (1996).
23. Soni, P. et al. Efficacy of Intralesional Bleomycin in Palmo-plantar and Periungual Warts. J Cutan Aesthet Surg 4, 188–191 (2011).
24. Yamamoto, T. Bleomycin and the skin. Br J Dermatol 155, 869–875 (2006).
25. Blalock, J. E., Georgiades, J. A., Langford, M. P. & Johnson, H. M. Purified human immune interferon has more potent anticellular activity than fibroblast or leukocyte interferon. Cell Immunol 49, 390–394 (1980).
26. Tsujimoto, M., Yip, Y. K. & Vilcek, J. Interferon-gamma enhances expression of cellular receptors for tumor necrosis factor. J Immunol 136, 2441–2444 (1986).
27. Bacelieri, R. & Johnson, S. M. Cutaneous warts: an evidence-based approach to therapy. Am Fam Physician 72, 647–652 (2005).
28. Al-Zahrani, D. et al. Successful interferon-alpha 2b therapy for unremitting warts in a patient with DOCK8 deficiency. Clin Immunol 153, 104–108 (2014).
29. Nasser, N. Treatment of common warts with the immune stimulant Propionium bacterium parvum. An Bras Dermatol 87, 585–589 (2012).
30. Rageh, R. M., Hewedy, E.-S. S. & Hegab, D. S. Intralesional injection of Candida albicans antigen versus measles, mumps, and rubella vaccine for treatment of plantar warts. Acta Dermatovenerol Alp Pannonica Adriat 30, 1–5 (2021).
31. Majid, I. & Imran, S. Immunotherapy with intralesional Candida albicans antigen in resistant or recurrent warts: a study. Indian J Dermatol 58, 360–365 (2013).
32. Ritter, S. E. & Meffert, J. Successful treatment of flat warts using intralesional Candida antigen. Arch Dermatol 139, 541–542 (2003).
33. Wong, A. & Crawford, R. I. Intralesional Candida antigen for common warts in people with HIV. J Cutan Med Surg 17, 313–315 (2013).
34. Maronn, M., Salm, C., Lyon, V. & Galbraith, S. One-year experience with candida antigen immunotherapy for warts and molluscum. Pediatr Dermatol 25, 189–192 (2008).
35. Perman, M., Sterling, J. B. & Gaspari, A. The painful purple digit: an alarming complication of Candida albicans antigen treatment of recalcitrant warts. Dermatitis 16, 38–40 (2005).

36. Kansal, N. K. Immunotherapy of anogenital warts with measles, mumps, and rubella vaccine. Dermatol Ther 33, e13987 (2020).
37. Na, C. H., Choi, H., Song, S. H., Kim, M. S. & Shin, B. S. Two-year experience of using the measles, mumps and rubella vaccine as intralesional immunotherapy for warts. Clin Exp Dermatol 39, 583–589 (2014).
38. Nofal, A. & Nofal, E. Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. J Eur Acad Dermatol Venereol 24, 1166–1170 (2010).
39. Zamanian, A., Mobasher, P. & Jazi, G. A. Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with wart. Adv Biomed Res 3, 107 (2014).
40. Freed, D. L. & Eyres, K. E. Persistent warts protected from immune attack by a blocking factor. Br J Dermatol 100, 731–733 (1979).
41. Fine, P. E. M., Carneiro, I. A. M., Milstien, J. B., Clements, C. J. & Organization, W. H. Issues relating to the use of BCG in immunization programmes: a discussion document. https://apps.who.int/iris/handle/10665/66120 (1999).
42. Eassa, B. I., Abou-Bakr, A. A. & El-Khalawany, M. A. Intradermal injection of PPD as a novel approach of immunotherapy in anogenital warts in pregnant women. Dermatol Ther 24, 137–143 (2011).
43. Abd-Elazeim, F. M. A., Mohammed, G. F. A., Fathy, A. & Mohamed, R. W. Evaluation of IL-12 serum level in patients with recalcitrant multiple common warts, treated by intralesional tuberculin antigen. J Dermatolog Treat 25, 264–267 (2014).
44. Saoji, V., Lade, N. R., Gadegone, R. & Bhat, A. Immunotherapy using purified protein derivative in the treatment of warts: An open uncontrolled trial. Indian J Dermatol Venereol Leprol 82, 42–46 (2016).
45. Sharma, P. et al. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8-10 years. Lepr Rev 76, 127–143 (2005).
46. Singh, S., Chouhan, K. & Gupta, S. Intralesional immunotherapy with killed Mycobacterium indicus pranii vaccine for the treatment of extensive cutaneous warts. Indian J Dermatol Venereol Leprol 80, 509–514 (2014).
47. Meena, J. K., Malhotra, A. K., Mathur, D. K. & Mathur, D. C. Intralesional immunotherapy with Mycobacterium w vaccine in patients with multiple cutaneous warts: uncontrolled open study. JAMA Dermatol 149, 237–239 (2013).
48. Salem, A., Nofal, A. & Hosny, D. Treatment of common and plane warts in children with topical viable Bacillus Calmette-Guerin. Pediatr Dermatol 30, 60–63 (2013).
49. Metawea, B., El-Nashar, A.-R., Kamel, I., Kassem, W. & Shamloul, R. Application of viable bacille Calmette-Guérin topically as a potential therapeutic modality in condylomata acuminata: a placebo-controlled study. Urology 65, 247–250 (2005).
50. Gupta, S. K. Single dose intralesional immunotherapy with BCG of medically resistant condylomata acuminata of the penis: report of two cases. Int J Dermatol 55, 583–586 (2016).
51. Nofal, A., Yosef, A. & Salah, E. Treatment of recalcitrant warts with Bacillus Calmette-Guérin: a promising new approach. Dermatol Ther 26, 481–485 (2013).
52. Sharquie, K. E., Al-Rawi, J. R., Al-Nuaimy, A. A. & Radhy, S. H. Bacille Calmette-Guerin immunotherapy of viral warts. Saudi Med J 29, 589–593 (2008).
53. Usman, N., Udayashankar, K., Subramanian, S. & Thyagarajan, S. P. Autoimplantation technique in the treatment of anogenital warts: a clinico-immunological study. Int J STD AIDS 7, 55–57 (1996).
54. Srivastava, P. K. & Bajaj, A. K. Autowart injection therapy for recalcitrant warts. Indian J Dermatol 55, 367–369 (2010).
55. Nischal, K. C. et al. A novel modification of the autoimplantation therapy for the treatment of multiple, recurrent and palmoplantar warts. J Cutan Aesthet Surg 5, 26–29 (2012).
56. Shivakumar, V., Okade, R. & Rajkumar, V. Autoimplantation therapy for multiple warts. Indian J Dermatol Venereol Leprol 75, 593–595 (2009).
57. ElGhareeb, M. I. Comparative study of autoimplantation therapy and intralesional injection of MMR vaccine in warts treatment. Dermatol Ther 32, e13135 (2019).