# A review of intralesional wart therapy

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## Abstract

**Background**: New treatment options for warts include intralesional wart injection with agents such as vitamin D, measles, mumps, and rubella (MMR) vaccine antigen, Bacillus Calmette-Guerin (BCG) antigen, and candida antigen but there have been limited studies to compare their efficacies.
**Background**: New treatment options for warts include intralesional wart injection with agents such as vitamin D, measles, mumps, and rubella (MMR) vaccine antigen, Bacillus Calmette-Guerin (BCG) antigen, and candida antigen but there have been limited studies to compare their efficacies.
**Objective**: The purpose of this systematic review is to compare the efficacy and safety of injectable agents used for the treatment of warts.
**Methods**: A PubMed search included terms "intralesional wart therapy," "wart injection" and "verruca injection." Articles reviewed were published over 10 years.
**Results**: A total of 43 articles were reviewed; 30 covered studies with more than 10 participants and 13 were case reports, case series, and reviews. In comparison studies intralesional agents have equal or superior efficacy (66%-94.9%) compared to first-line salicylic acid or cryotherapy (65.5-76.5%). One advantage of intralesional injections is the rate of complete resolution of distant warts.
**Limitations**: Each study varied in their agents, treatment interval, and treatment dose, making comparisons difficult.
**Conclusions**: Intralesional wart injections are safe, affordable, and efficacious treatments for warts. Physicians should consider intralesional injections for patients with refractory warts, multiple warts, or warts in sensitive areas.

*Keywords: intralesional wart therapy, verruca injection*

## Introduction

Cutaneous warts are benign epithelial projections caused by the human papillomavirus (HPV) and are spread through direct contact. There are more than 150 different HPV strains, with HPV-1 and -2 usually found on the plantar surfaces and HPV-6 and -11 usually found in the anogenital region [1]. HPV infects the basal layer of the epithelial cells leading to verruca formation [2]. Although cutaneous warts may spontaneously resolve, patients often seek treatment because of pain, limited function, impaired cosmesis, or social stigma.

Treatment of verruca includes physical or chemical destruction of the tissue. First-line options include cryotherapy or salicylic acid. Salicylic acid is one of the most efficacious treatments, but must be applied daily for up to 12 weeks and complete resolution (CR) occurs in only 75% of cases [3]. Cryotherapy offers a similar efficacy for common and plantar warts, but also requires multiple treatments and is painful. Second-line treatments include cantharidin, trichloroacetic acid, topical therapies, surgery, laser therapy, and intralesional injection of warts with a variety of antigens and immune response enhancers [3, 4].

Certain patient populations are more prone to warts. Warts cause significant morbidity in the immunosuppressed and those unable to mount an adequate T-helper-1 cell mediated response to fight off viral infection [5]. Patients with HIV have a 7.7% prevalence of cutaneous warts, compared to a 0.84% prevalence in the general U.S. population [6, 7]. Owing to immunosuppression therapy, organ transplant patients are also at an increased risk, with over 90% of transplant patients diagnosed with

warts within 5 years of transplant and 65% of those having more than five warts [8]. Immunosuppressive medications such as cyclosporine and azathioprine may alter Langerhans cell development, reducing cutaneous immunosurveillance and increasing HPV activity [9]. Cutaneous warts in immunocompromised patients are less likely to resolve and more likely to recur [10].

Intralesional verruca injections may be a useful treatment option for patients with multiple or refractory warts. Although intralesional wart injections have equal efficacy to the other first-line treatments, they can also cause regression of distant warts along with the original wart injected. This review aims to evaluate the efficacy and safety of newer agents and the types of patients in whom these treatments have been tested.

## Methods

A PubMed included search terms for "wart injection," "intralesional wart therapy," and "verruca injection" (**Figure 1**). Search results mostly included case reports, studies, and reviews regarding wart injection treatment options. Titles were searched for relevance. Studies were limited to those published in English, performed in humans, and posted within the past 10 years, from January 2009-January 2019. Studies involving intramuscular vaccines or cervical HPV were excluded. Additional articles were found by reviewing the references of articles searched on PubMed.

## Results

The literature search yielded 43 articles, studies, and case reports covering intralesional verruca therapy. These intralesional agents can be broadly grouped by mechanism including immunotherapy [including measles mumps rubella (MMR) vaccine, mycobacterial agents, and candida antigen], virucidal drugs (cidofovir and interferon-α), antimitotic drugs (bleomycin, pinyangmycin, and vincristine), and other agents (5-aminolevulinic acid and vitamin D**)**, [2].

### Intralesional Agents with Immune Modulating Activity

*Measles, mumps, and rubella vaccine*

The MMR vaccine is used as an intralesional injection to stimulate the immune system to fight HPV. It is available almost universally and is relatively cheap, with a cost to the Centers for Disease Control and Prevention of $21.05 per vaccine dose [11].

In an open label study, 100 patients had 0.3ml of the MMR vaccine administered into the largest wart via an insulin syringe. This was repeated every 3 weeks for a maximum of 3 treatments and patients were followed for 6 months to detect recurrence. Of these, 86 patients completed the study and 40 (46.5%) achieved complete clearance. The mean number of injections required was 2.4 and the mean duration to achieve clearance was 7.2 weeks. Of the 50 patients who had multiple warts, 41 (82%) had clearance of

Figure 1: Flowchart of Article Selection Process

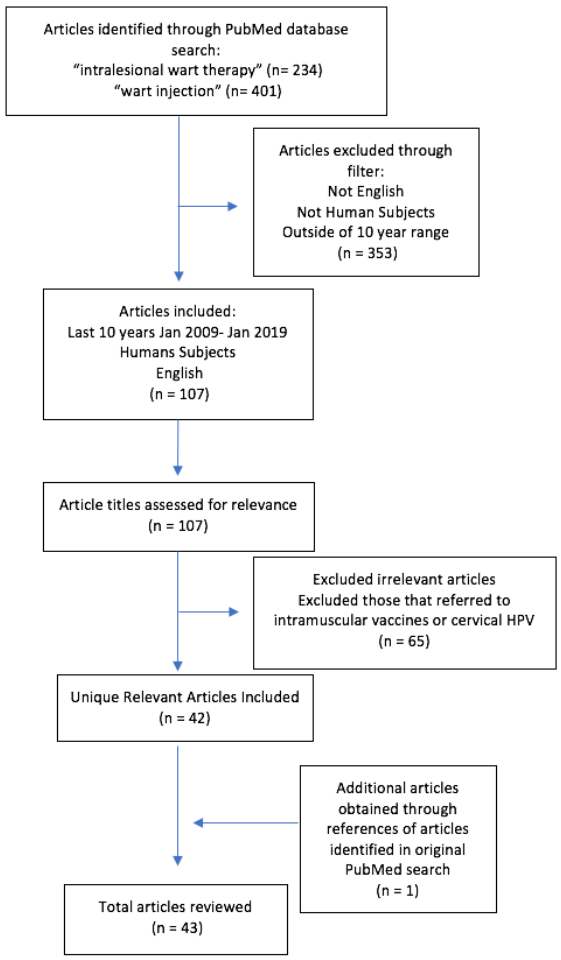


**Figure 1**. *Flowchart of the article selection process.*

distant warts even though the vaccine was only injected into the largest wart. Injection site pain was reported in 53.5% of patients, erythema in 8.1%, and post-inflammatory hyperpigmentation in 5.8% [12].

In an open label, nonrandomized, uncontrolled trial, 70 patients with multiple extragenital warts present for greater than two years received a 0.3ml of MMR vaccine injection into their largest wart. The injections were completed at 2-week intervals until either complete clearance or a maximum of 5 sessions. A total of 65 patients completed the study and 41 (63%) had complete resolution. In addition, 15 patients (23%) achieved a partial resolution defined as 50-99% clearance. The average number of treatments to complete response was 3.3. Complete clearance was seen in 38 patients (75%) with distant warts. Side effects included injection site pain (100%), local reactions such as itching (6.1%), erythema (4.6%), edema (1.5%), and mild flu like symptoms that resolved within 24 hours with use of nonsteroidal anti-inflammatory drugs (12.3%). Recurrence occurred in two patients after the 6-month follow up [13].

A retrospective study investigated the use of MMR in 136 patients with warts. Patients received injections at 2-week intervals until complete response with a maximum of 6 treatments. Patients had a lower response rate in this study, with 36 patients (26.5%) achieving complete response over an average of 5.38 treatments. Recurrence at the 6-month follow up occurred in two (5.6%) of the 36 patients who initially had complete resolution [14].

*MMR versus Control Studies*

A controlled study in 110 adult patients investigated intralesional MMR versus saline. Patients were injected at 2-week intervals and followed for 6 months to detect recurrence. MMR-treated patients had a complete response in 81% compared to 27.5% of the saline-treated patients (P<0.001). Complete clearance was achieved in 85% patients (17/20) with distant warts in the MMR group. Injection site pain was noted in 85.7% patients, and 8.6% experienced flu-like symptoms. Recurrence did not occur in the MMR group after the 6-month follow-up period [15].

A randomized, placebo-controlled, single-blinded trial evaluated MMR versus placebo in 150 patients. Patients were injected with 0.5ml of MMR or 0.5ml of normal saline every two weeks until clearance or a maximum of 5 treatments. Follow up was done at 6 and 16 weeks after the last injection. A complete response was achieved in 68% of the MMR-treated patients compared to 10% of placebo-treated patients (P<0.00001). Recurrence occurred in 2.7% of the MMR and 6% of the normal saline patients 16 weeks after the last injection. Patients in both groups experienced pain during injection (90% in MMR 88% in control). Flu-like symptoms occurred in 6% of patients in the MMR group versus 2% in the control group, and 3% in the MMR group experienced a local injection site reaction versus 0% in the control group [16].

Another double-blind, randomized, placebo controlled clinical trial compared MMR to normal saline in 60 patients. Eighteen of thirty (60%) treated with MMR injections had a complete response compared to 7 (23.3%) in the control group (P<0.01). Pain and mild erythema were reported in both groups [17].

*Mycobacteria*

Mycobacterial agents, including the mycobacterium W vaccine (MWV), Bacillus Calmette-Guerin (BCG), and purified protein derivate (PPD) have been used as intralesional therapies for warts.

Mycobacterium W vaccine (MWV)

The MWV is strongly antigenic, generating cytokine and T cell responses. The MWV contains killed nonpathogenic, saprophytic, cultivable, atypical mycobacterium. It is primarily used as immunotherapy for multibacillary leprosy [18]. Using the MWV as intralesional therapy for warts was first studied in 2008 [19].

A retrospective review evaluated 44 patients with more than 5 extragenital warts who received 0.1ml MCW injections into 2-4 warts after a 0.1ml sensitizing dose of MWV. The injections were repeated every 2 weeks until resolution or a maximum of 10 injections. Complete clearance was noted in 24 patients (54.5%) after a mean of 3.4 injections. All the patients developed a nodule at the

intradermal injection site on the shoulder, but 94% of the nodules resolved spontaneously in 2-3 weeks. The second most common side effect was fever (27.3% of patients). There were no recurrences among the 18 patients with complete clinical response during the follow up period ranging from three to 9 months [20].

In a similar study, there was no sensitizing dose of MWV. The MWV was injected into a single wart and repeated every four weeks until complete clearance or up to 10 injections. Treatment was discontinued if there was no response after three injections. Complete resolution of both the main and distant warts were obtained in 28 (93.3%) of the patients. The mean time to clearance was 43.7 days and the mean number of injection sessions required was 1.8. Of the 28 cleared patients, four had recurrence of warts at a site different from those previously involved. Side effects included fever (66.7%), local injection site reaction (33.3%), myalgias (23.3%), headache (10%), and vomiting (6.7%), [21].

An uncontrolled open label study of 37 patients showed 83% of patients had complete clearance of warts, and 22 of 33 patients had a resolution of distant warts. Recurrence was seen in three patients during the follow up period of 4.48 months. Adverse effects included tender papules that formed at the sites of sensitization and healed with a small BCG vaccine-like scar. In addition, erythema, swelling, low grade fever on the day vaccine was given, and swollen lymph nodes; one patient experienced superficial ulceration at the site of the treated wart [18].

Purified Protein Derivative (PPD)

The PPD test is most commonly used to diagnose tuberculosis infections. PPD is injected intradermally into the forearm and the response is assessed via diameter of induration at the injection site [22]. The erythema and induration are related to a T cell mediated delayed hypersensitivity reaction. Recently, investigators have used this mechanism in an attempt to fight off HPV infection in warts [23].

A randomized, placebo-controlled, parallel group study evaluated the use of PPD in 40 patients with warts. The patients were randomly assigned to receive intralesional PPD antigen (N=20) or intralesional saline (N=20). Subjects assigned to receive PPD were tested for existing immunity by injection of 0.1ml of PPD antigen in the left forearm. Patients not reactive were excluded. Intralesional PPD was given in a volume determined by the size of the test reaction and intralesional saline was given at 0.3ml into the largest wart every week for a maximum of 6 treatments. Serum levels of IL12 were measured by ELISA at the baseline, and sixth session in both groups. Of those receiving PPD, 12 patients (60%) had complete response of target lesions compared with none in the control group ($P<0.001$). Partial response occurred in three patients (15%) in the PPD group versus two patients (10%) in the control group. Only two patients in the PPD group experienced recurrence three months after stopping the injection versus three patients in the control group. In the PPD group, wart regression was associated with a relative increase in mean IL12 at week 6 compared to baseline ($2.6\pm1.4$pg/ml versus $1.9\pm1.2$pg/ml, $P<0.05$), [23].

In another study, 55 patients with warts received 2.5 TU of PPD into each lesion with a maximum of 10 lesions treated every two weeks for a total of four sessions. At the end of the sessions, 42 (76%) had complete clearance. One patient developed recurrence in the 6-month follow up. Side effects included mild erythema and edema at the injection site (23.6%), low grade fever and body aches (1.8%), and eczematous lesion at injection site (1.8%), [24].

Bacillus Calmette-Guerin (BCG)

Bacillus Calmette-Guerin stimulates macrophages, B and T cells, and natural killer cells to increase cytokine production, potentially boosting the immune response against HPV. In two cases of resistant genital condyloma acuminata, 0.4-0.5 ml injection of BCG demonstrated completely clearance [25]. Two other case reports noted complete clearance of recalcitrant warts after three or five treatments of 0.1ml BCG without recurrence at 6 months. Adverse effects were erythema and tenderness at injection site [26, 27].

*Candida*

Injection of *Candida* antigen is a safe and effective treatment option for verruca vulgaris [28]. The

therapeutic effect of the candida antigen is believed to be related to its stimulation of the cell-mediated immune response [29]. Langerhans cells may serve to mediate the therapeutic effect, although additional studies are needed [30, 31].

Patients with multiple warts, 44 adults and 10 children, underwent intralesional *Candida* injections. Prior to therapy, a blood sample was collected, cultured, and incubated with candida antigen to assess levels of IFNγ. The largest wart was then injected with 0.3 ml of a *Candida* antigen solution at 1/1000 dilution. Injections were given every two weeks for up to 5 treatments or until complete resolution. Follow-up occurred monthly for 6 months. Complete clearance of the injected wart occurred in 37 patients (68%). Complete resolution of the non-injected lesions occurred in 33 patients. Partial responses occurred in the injected warts of 12 patients (22%) and 5 patients (9%) had no response. Patients responsive to therapy had higher levels of IFNγ compared to those who showed no response to treatment (P=0.04), signifying that levels of IFNγ may mediate the response to treatment [32].

A retrospective review of 220 pediatric patients who received intralesional candida antigen injections showed a total response rate in 156 patients (71%) and no improvement in only 27 patients (12.2%), [28]. An additional retrospective review of 80 patients given serial candida injections showed a complete resolution in 52 patients (65%), [33]. Another study included 54 patients who received *Candida* antigen injections at 2-week intervals for a maximum of 5 treatments. After follow-up 6 months later, 33 patients (61.1%) had total clearance of the injected lesion [32]. A smaller study of 11 patients injected with 0.3ml of *Candida* antigen every three weeks for four sessions showed a complete response in 9 patients (82%) and a distant wart response in 6/8 patients (75%), [31].

Intralesional injections of *Candida* antigen are safe options for immunosuppressed patients. In a retrospective study of 100 immunosuppressed adult and pediatric patients with cutaneous warts, 39% had complete response and a 41% partial response to treatment [29]. A case series following HIV-positive patients treated with *Candida* antigen showed clearance of the injected warts in three of the 7 patients [34]. A case report demonstrated the efficacy of *Candida* antigen in the clearance of verruca vulgaris in an HIV-positive patient who had failed multiple other therapies including urea cream, imiquimod cream, cryotherapy, paring, salicylic acid gel, intralesional bleomycin, electrodesiccation, and curettage [35].

Few adverse effects are seen with *Candida* antigen injections. The most common side effects are insignificant and include pain and/or irritation at the injection site [34]. More noticeable adverse effects may include halo nevi and vitiligo [36, 37]. A case of lymphangitis, which resolved with conservative treatment, was observed in an 18-year-old woman following intralesional injection and should be regarded as a potential adverse effect [38].

*Propium bacterium parvum/ Propionibacterium acnes*

One randomized double-blind study tested intralesional antigen made from dead *Propionium bacterium parvum* (PBP), a gram-positive anaerobic bacterium. This antigen stimulates the immune system and natural killer cells by releasing interferon and tumor necrosis factor. A total of 20 patients with cutaneous warts were included; 10 patients received 0.1ml injections of PBP and 10 received placebo. Treatment intervals were one month and 3-5 treatments were given. Results showed 9 patients (90%) with PBP had a complete response and one (10%) had a partial response (P<0.001), compared with no response in 9 (90%) of the placebo group and reduction in size in one (10%) of the placebo group [39].

**Intralesional agents with anti-viral activity**

*Cidofovir*

Cidofovir is an injectable antiviral medication primarily used for CMV retinitis in patients with HIV/AIDS. Cidofovir's strong activity against DNA viruses allows it to be used for HPV and intralesional injections of cidofovir are an additional treatment option for patients with verruca vulgaris who have failed other therapies. A study of 280 patients with refractory warts who had failed to achieve resolution with two previous other treatments were included. They were treated intralesionally with 15mg/ml of cidofovir each month and 276 (98.5%) saw complete

resolution of their warts. An average of 2-3 treatments were required to achieve the desired effect. Documented adverse effects of cidofovir injections included local irritation and pain at the injection site [40]. Intralesional cidofovir has been demonstrated to be a safe and effective option for immunocompromised patients based on its use in a renal transplant patient with multiple cutaneous warts, and a patient with lymphoma, without notable adverse effects [41, 42].

**Intralesional agents with antimitotic activity**

*Bleomycin*

Bleomycin is an antibiotic produced by *Streptomyces verticillus* that creates free radicals, causing single-strand breaks and cell apoptosis [2]. In a prospective pilot study, 15 patients with periungual warts were injected with 0.1U/ml of bleomycin at 4-week intervals. Of these, 7 patients (46%) had complete resolution one month after injection and 13 patients (86%) had complete resolution at 6-month follow up after one injection. One patient had hyperpigmentation following injection that resolved after one month. Another adverse effect noted was pain for 2-3 days at injection site following treatment. Of 23 patients who received 0.1U/ml bleomycin injections at 4-week intervals, 17 (74%) had complete response and one patient (4.3%) had partial response. At the 3-month follow up, two warts had recurred and one of those recurrences was treated with an additional injection. The recurrence was not present at 6-month follow-up [43].

In one comparative study including 60 patients, the efficacy of direct injection of bleomycin was compared to microneedling plus topically applied bleomycin (**Table 1**). Efficacy was similar between both treatments with 70% of the intralesional bleomycin patients and 80% of the microneedling group having complete response. Side effects in both groups was limited to pain, erythema, and transient induration [44].

Small, diluted amounts of bleomycin used intralesionally are generally well-tolerated by patients. A retrospective chart review followed by telephone interviews revealed 74% patients (34/46) had complete resolution of warts after an average of 1.7 treatments with intralesional bleomycin. In addition, 78% (36/46) reported they would recommend it to others [45]. In a study of 50 patients, 80% of patients showed complete response and reported they were "very satisfied" with the treatment [46].

However, there have also been reports of severe reactions to intralesional bleomycin therapy including Raynaud phenomenon, cutaneous toxicity, and pulmonary/lung toxicity following injection [47-50]. These reactions, in addition to the increased complaints of burning sensations compared to other agents, cause some hesitation in medical practitioners in choosing this particular agent for intralesional use.

Intralesional injection may also be a good alternative to surgery for patients with warts in challenging locations. A patient was initially referred for surgical excision for warts in his ears bilaterally that caused him dizziness, hearing loss, and pain. The patient was treated successfully with bleomycin injections, with complete clearance after two injections of bleomycin at a one-month interval [51].

*Pingyangmycin*

One study tested pingyangmycin, an anti-tumor antibiotic in the same family as bleomycin. In 66 patients, four treatment sessions showed 58 (87.88%) had a complete response and 8 (12%) had a partial response [52].

*Vincristine*

Vincristine, a vinca alkaloid antiblastic, was successfully used in three patients with warts on the feet after patients failed several treatments with cryotherapy. Vincristine sulphate, 0.03 ml, at a concentration of 1µg/ml was administered in an amount proportional to the diameter of the nodule. After two treatments, there was a decrease in lesion size for the treated warts compared with the other lesions. Adverse effects included pain at injection site for several days [53].

**Other intralesional agents**

*Vitamin D*

Two studies investigated intralesional vitamin D to stimulate the immune system. In a study of 64 patients with recalcitrant warts, a dose of 0.2-0.5ml of 600,00IU (15mg/ml) was injected at 3-week

intervals with a maximum of 5 warts injected per session. Of the 60 patients that completed the study, 54 patients (90%) reported complete resolution of their warts and 5 (6.66%) had a partial response [54]. In another study of intralesional vitamin D, 20 patients received injections of 7.5 mg/ml of vitamin D along with an injection of 0.1ml (20mg/ml) of prilocaine. The injections were given at 4-week intervals for two sessions. A complete response was obtained in 16 patients (80%) and one (5%) had a partial response. Although the study size was smaller, the difference in the number of treatments or dosage could account for the differences in response rates between the two studies [55].

*5-aminolevulinic acid*

One study reported intralesional 5-aminolevulinic acid used as an adjunct to photodynamic therapy for viral warts in 8 patients. 5-aminolevulinic acid used acts as a photosensitizing agent, creating reactive oxygen species in pathological tissues at certain wavelengths. Half the patients showed a good response with complete remission in two patients. There were no adverse reactions and this may be a good option for patients with thick resistant warts [56].

*Interferon alpha*

Interferon- α (IFNα) has also been used for treatment of plantar warts. Interferons are glycoproteins that have antiproliferative effects [2]. One study compared IFNα to placebo in 53 patients with plantar warts. A single treatment of intralesional IFNα was given to 45 patients and 8 received placebo [57]. A complete response was achieved in 19 patients, two patients had a partial response, and three patients had no response. In the control group, only two patients (25%) experienced partial response to treatment. Other studies have shown intralesional IFNα to have mild side effects such as pain at the injection site, headache, and flu like symptoms [2].

**Comparison Studies**

In a prospective randomized study comparing mycobacterium vaccine to cryotherapy in 66 patients, there were roughly equal rates of clearance seen in either treatment group. Of patients given *Mycobacterium* vaccine injections, 20/30 (66.7%) had complete resolution of their verruca versus 19/29 patients (65.5%) treated with cryotherapy. However, those treated with intralesional *Mycobacterium* noted a significant reduction in distant warts (P=0.04), [58].

In a randomized clinical trial in 73 patients comparing bleomycin to cryotherapy, intralesional bleomycin was more effective than cryotherapy treatment for cutaneous warts. Bleomycin injections had a complete response in 94.9% of patients and 97% of total warts compared with cryotherapy, which yielded complete response in 76.5% of patients and 82% of total warts (P<0.05 for both), [56].

A double-blind, randomized control trial evaluated *Mycobacterium* vaccine injections and imiquimod in 89 patients with anogenital warts. Imiquimod monotherapy was used in 44 patients and 45 received both imiquimod and *Mycobacterium* vaccine injections. Imiquimod monotherapy had a 59% complete response, whereas the combination of imiquimod and *Mycobacterium* had a 67% complete response. There were no recurrences in any patients with complete resolution at the three-month follow up [26].

A study evaluated intralesional PPD, MMR, and saline placebo in 30 total patients, with 10 patients each receiving one of the three treatments. Measles, mumps and rubella vaccine was the most effective in clearing the local wart with an 80% complete response rate; PPD produced a 60% complete response rate. However, PPD was more effective in treating distant warts, with a 60% complete response, whereas MMR had a 40% complete response. Both treatments were more effective than saline placebo, with which no patient had a complete response [59].

## Discussion

The treatment choice for cutaneous warts should be determined on an individual patient basis, guided by number, size, location of warts, and comorbidities [2]. In comparison studies intralesional agents for wart therapy have equal or superior efficacy (66%-

94.9%) compared to first-line salicylic acid or cryotherapy (65.5-76.5% efficacy), (**Table 1**). One key benefit of intralesional wart therapy is that the agents stimulate the immune system so that even with a single lesion injected, patients may benefit by having distant warts also improve. Intralesional wart therapy may be considered particularly for patients with multiple warts, warts that have been refractory to treatment, or warts that are in difficult-to-treat places (ears, anogenital region, sole).

Although the side effects of intralesional injections are most often mild pain and erythema following the injection, there have been rare cases of vitiligo, lymphangitis, nevi regression, and Raynaud phenomenon [36], (**Table 2**). Many of the studies followed patients for up to 6 months following the injection and there were limited recurrences.

Of the 43 articles reviewed, 30 were studies which included more than 10 participants, three of these were double-blind randomized controlled studies, one was a single blind randomized control study, and the remainder were open label studies, case studies, or reports. When reviewing these articles, it is important to note that randomized controlled trials are innately stronger study designs than open-label studies, case series, and reports. Randomized controlled trials and several comparative studies show intralesional wart injection to be as effective or slightly more effective than current first-line treatments such as cryotherapy, but placebo controlled intralesional wart studies tend to show less benefit than the open label studies (**Table 1**).

Variation between study design, previous treatments, intralesional agents, treatment dosages, length of study, and follow up make it difficult to directly compare the different types of intralesional agents head-to-head for efficacy. Study results may also be affected by the possibility of spontaneous resolution but several of those reviewed strictly included patients with refractory warts that had failed previous first line treatments, making this less likely. Articles covered in this review with weaker study designs such as case reports and retrospective studies are inherently limited in their significance and generalizability. This study was limited by the fact that articles that tend to show benefit are more likely to be published. Data was gathered by only searching one database, PubMed, so articles may have been missed that were only indexed elsewhere.

There have been several randomized controlled trials, comparative studies, cohort studies, and case reports completed over the past several years demonstrating the safety and efficacy of intralesional wart injections with candida, MMR, vitamin D, bleomycin, cidofovir, vincristine, and IFNα. Limited case reports suggest that using intralesional therapy for numerous or refractory warts in immunosuppressed patients may be safe. However, there have not been larger studies in this population. Intralesional injections are also being studied as treatment for molluscum, suggesting that intralesional injections with immunotherapeutic agents may help to treat other viral skin diseases.

## Conclusion

Intralesional wart injections are safe, affordable, and efficacious treatments for warts. Intralesional agents that have been used to treat warts include *Candida*, cidofovir, MMR, TB, bleomycin, vitamin D, and several others. Physicians should consider intralesional injections for patients with refractory warts, multiple warts, or warts in sensitive areas given the potential benefit of distant wart resolution.

## Potential conflicts of interest

Dr. Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Mikel Muse, Katherine Stiff, Katelyn Glines, Abigail Cline have no conflicts to disclose.

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**Table 1**. *Intralesional wart injection therapy comparison studies.*

| Study Factors | Study Design | Authors | Number Patients Total Per Treatment | Dose | Number Sessions | Treatment Intervals | Complete Response | Partial Response |
|---|---|---|---|---|---|---|---|---|
| MMR vs. Placebo | RCT | Nofal A and Nofal E [15] | 110<br>70 MMR<br>40 NS | 0.3ml if reaction diameter <20mm<br>0.2ml if reaction diameter 21-40mm<br>0.1ml if reaction diameter >40mm | Up to 5 | 2 weeks | MMR: 57 (81.4%)<br>NS: 11 (27.5%) | MMR: 7 (10%)<br>NS: 6 (15%) |
| MMR vs. Placebo | Single blind RCT | Awal and Kaur [16] | 122<br>72 MMR<br>50 Saline Injection | 0.5mL of MMR vs. 0.5mL of NS | Up to 5 | 2 weeks | MMR: 49 (68%)<br>NS: 5 (10%)<br>P <0.00001 | MMR: 18 (24%)<br>NS: 15 (30%) |
| MMR vs Saline | Double blind RCT | Agrawal et al [17] | 60<br>30 MMR<br>30 Saline | 0.3ml | Up to 3 | 3 weeks | MMR: 18 (60%)<br>NS: 7 (23.3%) | MMR: 6 (20%)<br>NS: 13 (43.3%) |
| Mycobacterium injection vs. imiquimod cream | Double blind RCT | Kumar et al [26] | 89<br>44 Imiquimod 5% cream<br>45 Mw intralesional | - | - | - | Imiquimod cream: 26 (59%)<br>Imiquimod + MW: 30 (67%)<br>No statistical difference between groups | - |
| Bleomycin injection vs microneedling-assisted topical bleomycin + Occlusion | Comparison | Al-Naggar et al [46] | 60<br>30 intralesional bleomycin<br>30 spray bleomycin + occlusion | - | 1 | 0 | 21 (70%) intralesional<br>25 (83%) microneedling | - |
| Bleomycin vs cryotherapy | RCT | Dhar SB [56] | 73<br>39 bleomycin<br>34 cryotherapy<br><br>155 total warts<br>87 Bleomycin<br>68 Cryotherapy | 0.1% Bleomycin solution w/ local anesthetic<br><br>Double freeze cycle cryotherapy | Up to 3 | 4 weeks | Bleomycin:<br>37 (94.9%) patients<br>97% of total warts<br><br>Cryotherapy:<br>26 76.5% patients<br>82% total warts<br><br>P < 0.05 by x(2) analysis and RR = 7.67 | - |

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| Interferon-alpha 2a vs placebo in patients with verruca plantaris | Comparison | Aksakal et al [57] | 53<br>45 IFN Alpha<br>8 NS | 4.5 MU IFN - $\alpha$ 2a | 1 | - | IFN: 19 (42%)<br>Placebo: 0 (0%) | IFN: 2 (8.3%)<br>Placebo: 2 (25%) |
| Mycobacterium vs. Cryotherapy | Prospective randomized comparative study | Dhakar et al [58] | 66 | - | - | - | Mycobacterium: 66.7% (20/30)<br>Cryotherapy: 65.5% (19/29) | - |
| PPD vs MMR vs. NS | Comparison | Shaheen et al [59] | 30<br>10 PPD<br>10 MMR<br>10 NS | - | Up to 3 | 3 weeks | PPD:<br>6 (60%) local warts<br>6 (60%) distant warts<br>MMR:<br>8 (80%) local wart<br>4 (40%) distant wart<br>NS- 0% | - |

**Table 2.** *Intralesional wart injection studies and case report response rates and adverse effects*

| Type | MOA | Author | Number of Patients | Dose | Number of Sessions | Treatment Intervals | Complete Response | Partial Response | Distant Wart Response | Adverse Effects |
|---|---|---|---|---|---|---|---|---|---|---|
| MMR | Nonspecific CMI stimulator | Saini et al [12] | 86 | 0.3ml | Up to 3 | 3 weeks | 40 (46.5%) | 18 (20.9%) | 82% | Pain at injection site, erythema, post-inflammatory hyperpigmentation |
| | | Nofal et al [13] | 65 | 0.3ml | Up to 5 | 2 weeks | 41 (63%) | 9 (14%) | 74.5% | Injection site pain, itching, erythema, edema at injection site, flu-like symptoms |
| | | Na et al [14] | 136 | Dose dependent on size of injection reaction* | Up to 6 | 2 weeks | 36 (26.5%) | 34 (25%) | 24.5% | Pain with injection, mild pruritis and burning at injection site |
| Mycobacterium Vaccine | Nonspecific CMI stimulator | Meena et al [18] | 37 | 0.11mL | Up to 10 | 1 week | 33 (83%) | 1 (2.7%) | 23/33 (70%) | Tender erythematous papules &/or pustules, erythema, edema, superficial ulceration, low-grade fever, swollen lymph nodes |
| | | Singh et al [20] | 44 | 0.1mL | Up to 10 | 2 weeks | 24 (54.5%) | 17 (38.6%) | 38 (86.3%) | Intradermal nodule/granuloma on shoulder, intralesional nodule/granuloma, low grade fever, pain with injection, paresthesias, atrophic scarring |
| | | Garg and Baveja [21] | 30 | 0.1mL | Up to 10 | 4 weeks | 28 (93.3%) | 0 (0%) | 28 (93.33%) | Fever, myalgias, headache, vomiting, redness, swelling, induration of injection site, |

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| | | | | | | | | | | spontaneous ulceration |
| PPD BCG | Nonspecific CMI stimulator | Abd-Elazeim et al [23] | 20 NS 20 PPD | PPD: Dose dependent on size of injection reaction* NS: 0.3mL | Up to 6 | 1 week | PPD: 12 (60%) NS: 0 (0%) | 3 (15%) 2 (10%) | 25% | Pain, mild erythema, swelling, post-hypopigmentation |
| | | Saoji et al [24] | 55 | 2.5 TU | 4 | 2 weeks | 42 (76%) | 0 (0%) | - | Erythema, edema, pain, low grade fever, eczematous reaction |
| | Nonspecific CMI stimulator | Gupta [25] | 2 | 0.1ml/2cm$^2$ (max of 0.5mL & 0.4mL in pts 1 & 2, respectively) | 1 | N/A | 2 (100%) | 0 (0%) | - | Pain, inflammation at injection site |
| | | Kumar et al [26] | 1 | 0.1 mL | 3 | 2 week | 100% | | | |
| | | Nofal et al [27] | 1 | 0.1mL | 5 | 2 week | 100% | | 1 (100%) | Erythema, pain |
| Candida | Stimulate cell-mediated immune response Stimulate immunogenic response Stimulates anti-HPV t-cell response Immune modulator Th1 promotion and dectin-1 stimulation | Munoz [28] | 220 children | - | 2.73 | 3 weeks | 156 (70.9%) | 37 (18.8%) | 21.3% | Discomfort at time of injection |
| | | Alikhan et al [29] | 100 | - | - | N/A | 39 (39%) | 41(41%) | - | Minimal and short-lived |
| | | Kim KH [31] | 11 | 0.3 mL | 4 | 3 weeks | 9 (82%) | 1 (9%) | 6/8 (75%) | Pain and erythema at injection site |
| | | Nofal et al [32] | 54 | - | Up to 5 | 2 weeks | 61.1% | - | - | Insignificant |
| | | Vlahovic et al [33] | 80 with plantaris verrucae | 0.1-0.3 mL | - | - | 52 (65% | - | - | Minimal, noted 4x greater response to injections in Females > Males |
| | | Wong and Crawford [34] | 7 HIV+ | - | - | - | 3 (42.85%) | - | - | Redness, pruritis, and pain at injection site |
| | | Summers P et al [35] | 1 HIV+ | - | - | - | 1 (100%) | 0 (0%) | - | N/A |
| | | Kollman et al [36] | 1 | - | - | - | - | - | - | Regression of Nevi, halo nevi, vitiligo |
| | | Wilmer et al [37] | 1 | - | - | - | - | - | - | 1$^{st}$ Vitiligo case |

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| | | Zubritsky et al [38] | 1 | - | - | - | - | - | - | Lymphangitis |
| Propionium bacterium parvum | Immune modulator/stimulant Produces antibodies | Nasser et al [39] | 20 10-placebo 10-propium | 0.1 ml | 3-5 | 1 month | 9 (90%) (P < 0.001) | 1 (10%) | - | None |
| Cidofovir | Antiviral nucleotide analog Potent antiviral agent against viral DNA, including HPV | Broganelli et al [40] | 280 | 15mg/mL | 3.2 | 4 weeks | 276 (98.6%) | 4 (1.4%) | - | Pain, burning during injection, itching, erythema, post-inflammatory hyperpigmentation |
| | | Blouin et al [41] | 1 renal transplant | - | 7 | 4 weeks | 1 (100%) | 0 (0%) | - | - |
| | | Moore E, Kovarik C [42] | 1 lymphoma | 75mg/m:, 0.75 ml of cidofovir in 2.25 ml of saline for total 3 mL | 3 | 8 weeks | 1 (100%) | 0 (0%) | - | - |
| Bleomycin | Antibiotic, breakages in DNA strands preventing cell replication Antitumor, antibacterial, antiviral | AlGhamdi KM, Khurram H [43] | 23 | 0.1 U/ml | - | 4 weeks | 17 (74%) | 1 (4.3%) | - | Pain for 2-3 days following injection 2 recurred at 3 month follow up, 1 went away with additional injection at 6 month follow up |
| | | Kruter et al [44] | 46 | - | 1.7 | - | 34 (74%) | - | - | 70% had pain that lasted less than 2 days following injection |
| | | Singh et al [50] | 50 | 0.2 ml, 1mg/ml | 2 | 2 weeks | 40 (80%) | 7 (145) | - | Pain at injection site |
| | | Lee et al [51] | 1 | - | 2 | 1 month | 1 (100%) | N/A | - | None noted |
| Vitamin D | Immune modulator | Raghukumar, Ravikumar et al [54] | 64 | 0.2-0.5ml 600,00 IU 15mg/mL | 3.66 | 3 weeks | 54/60 (90%) | 2/60 (6.66%) | (64) 100% | - |
| | | Aktas, Ergin et al [55] | 20 | Vitamin D(3) (0.2 mL, 7.5 mg/mL) after prilocaine (0.1 mL, 20 | 2 | 4 weeks | 16/20 80% | 1/20 (5%) | - | None noted |

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| | | | | mg/mL) injection | | | | | | |
| Pingyangmycin | Antitumor antibiotic | Yang et al [52] | 66 | - | 4 | - | 58 (87.88%) | 8 (12%) | - | No serious side effects noted |
| Vincristine | Vinca alkaloid antiblastic | Lee et al [53] | 3 | 0.03 mL at 1ug/mL | 3 | - | 0 (0%) | 3 (100%) | - | Pain at site of injection for several days |
| Intralesional 5-aminolevulinic acid | Photosensitizing agent, creates reactive oxygen species in pathological tissues | Kim et al [56] | 8 | 5 ALA + PDT Light Treatment | - | 2-3 weeks | 4 (50%) | | - | No severe adverse reactions reported |