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REVIEW

Efficacy and Safety Profile of Tuberculin Protein Purified Derivative Injection As Immunotherapy For the Treatment of Cutaneous and Anogenital Warts: A Review Article

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Introduction: Various treatments available today for anogenital and cutaneous warts have limitations, including time-consuming, challenging to perform, and the risk of scarring. A new treatment using tuberculin purified protein derivative (PPD) has been developed, which is expected to generate cellular immunity against HPV.

Objective: To assess the evidence for the efficacy and safety of PPD treatment for cutaneous and anogenital warts.

Materials and methods: A literature search was performed with the keyword-based search on digital libraries, including the National Library of Medicine, Cochrane Controlled Register of Trial, and Google Scholar, using the following terms: anogenital warts, condyloma acuminata, cutaneous warts, human papillomavirus, immunotherapy, and tuberculin purified protein derivative. Original studies on treating cutaneous or anogenital warts with PPD were included. The results were 47 clinical trials and 4 case reports. Most of the research was done in countries with common *Mycobacterium tuberculosis* infection. The treatment showed good efficacy. Comparative studies showed that the treatment has similar efficacy with other immunotherapies. No significant side effects were reported, with evidence of the safety use on the pregnant population.

Conclusion: Based on good efficacy and safety, PPD can be considered an alternative therapy, especially in countries where tuberculosis is frequent.

Keywords: anogenital warts, condyloma acuminata, cutaneous warts, human papillomavirus, immunotherapy, tuberculin purified protein derivative

Introduction

Cutaneous and anogenital warts (AGWs) are manifestations of infection caused by human papillomavirus (HPV) on the skin and mucous membranes.[1–3] It has been estimated that 7–10% of the population were affected by HPV infection.[4] Furthermore, HPV is also the most frequent sexually transmitted infection worldwide, with an estimated global incidence of 160–289 cases per 100.000 persons per year.[2,5] Warts can significantly impair a patient's quality of life due to physical discomfort and cosmetic disfigurement.[2,3] In two-thirds of patients, warts can undergo spontaneous resolution within two years; however, they can also resolve slowly and persist for many years with a high recurrence rate.[6] Various modalities are available and being used in the treatment of warts, including destructive treatments (eg, cryotherapy, electrosurgery,

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ablative laser, or surgical removal), pharmacological treatments (eg, salicylic acid, trichloroacetic acid, podophyllin, 5-fluorouracil, bleomycin, imiquimod),[2,3,7,8] and photodynamic therapy.[7] Topical treatments are more tolerable to patients but require frequent applications.[2] Meanwhile, destructive modalities require fewer treatment sessions, but they are destructive, frequently cause pain, and may lead to scarring. Furthermore, treatment modalities available to date showed variable effectiveness and are often associated with recurrence.[3] Conventional treatment approaches are limited to local application and lack systemic effect; therefore, they are unfavorable for patients with multiple lesions and difficult-to-reach locations.[2,9] Cell-mediated immunity (CMI) is paramount in the clearance of HPV infection and subsequent wart resolution.[3] Virus-induced CMI has been shown to cause warts to regress spontaneously.[4] Immunotherapeutic agents increase recognition of HPV by the patient's immune system by stimulating CMI at the site of the wart,[1] therefore helping to eradicate the virus rather than only removing visible skin lesions.[1,3] Cytokines released from T helper 1 cells, such as interleukin (IL)-2 and interferon (IFN)-γ are predominantly increased in response to immunotherapeutic agent injection.[2] Through the induction of delayed-type hypersensitivity and activation of cytotoxic and natural killer cells against the virus, intralesional immunotherapy can increase the host immunity to HPV.[4] Due to its non-destructive action and low recurrence rates, immunotherapy has recently received growing interest in the treatment of warts.[3] Various immunotherapeutic agents have been studied to stimulate the host immune response, including *Candida albicans*; measles, mumps, and rubella (MMR); *Trichophyton*; purified protein derivative (PPD); *Mycobacterium w* (*Mw)*, and Bacillus Calmette-Guerin (BCG) with variable outcome.[2,3]

Purified protein derivative contained extract of *Mycobacterium tuberculosis*, routinely used to test for tuberculin protein, either acquired from previous vaccination or environmental exposure.[4] The first standardized preparation of PPD was produced in 1944, known as PPD-Standard (PPD-S). This was later adopted as the international standard of tuberculin by the World Health Organization (WHO). All formulations of PPD produced after that must show potency equivalent to PPD-S. One tuberculin unit (TU) equals the biological activity contained in 0.02 µg of PPD-S. PPD-RT23 is the most widely used PPD product globally. It is stated that 2.5TU of PPD-RT23 containing Tween 80 had similar potency to 5TU of PPD-S.[10] PPD is a ubiquitously available antigen and has shown promising results for treating warts in different studies.[11,12] It was first introduced by Kus et al[13] in 2005 to eighteen patients with recalcitrant cutaneous warts in Turkey, where tuberculosis vaccination is routinely performed. PPD was chosen for this reason. The study protocol involved intralesional injection of PPD RT23-5TU with 3-week intervals into each target wart. Complete clearance was reported in 29.4% of patients, and overall improvement (>50% reduction in wart size) was achieved in 58%. Additionally, two patients underwent complete clearance of distant untreated warts. This study demonstrated a promising result of PPD injection in treating warts, particularly in countries where tuberculosis vaccination is performed routinely.[13] Based on this finding, numerous studies have increasingly developed ever since.

Injection of antigen to which the patient was previously sensitized induces the elicitation phase of the immune response to recognize HPV antigens.[14] Intralesional PPD is known to stimulate the production of T helper 1 cytokines, such as interleukin IL-4, 5, 8, 12, IFN-γ and tumor necrosis factor (TNF)-α which drive cytotoxic and natural killer cells to develop an immune response against HPV. A study by Azab et al[15] documented an increase in the serum level of IL-17 after PPD injection. Abd-Elazeim et al[16] reported that wart clearance was related to the relative increase of IL-12, another Th1 cytokine. In addition to IL-12, Shaheen et al[17] also reported a higher level of serum IL-4 after PPD injection compared to baseline level. Interferon-γ was found to be increased after PPD injection in a study by Abou-Taleb et al.

Furthermore, this study compared cytokine levels after PPD and vitamin D3 injection. The PPD group demonstrated an increase of both IL-12 and IFN-γ, while the latter only showed an increase of serum IFN-γ level. These findings suggested that PPD induces a higher Th1 immune response than vitamin D3.[18] Conversely, Sil et al[19] reported that IL-10, a Th2 cytokine, was downregulated after immunotherapy with PPD, Mw vaccine, Measles, and MMR vaccine. In this study, a decline in IL-10 was associated with a decrease in size and warts. Its level was found to be significantly low in complete responders of the PPD group compared to the partial responders at the end of the study period, indicating its essential role in the total clearance of lesions. The production pattern of the abovementioned cytokines might explain the mechanism of action of PPD in inducing wart clearance.

This study aims to evaluate the evidence regarding the efficacy and safety of PPD for treating cutaneous and anogenital warts.

Methods

We performed a literature search on digital libraries, including the National Library of Medicine, Cochrane Controlled Register of Trial, and Google Scholar. Original studies on the treatment of cutaneous or anogenital warts using purified protein derivatives from 2011 (2022) were included, as well as comparative studies and case reports. The search used the following terms: warts, verruca, condyloma, anogenital warts, cutaneous warts, purified protein derivative, and immunotherapy. Only English-language articles involving human subjects were included. After performing this initial filtering process, we further reviewed the remaining articles for relevance to our subject.

Results

We initially discovered 279 articles through a literature search of the abovementioned platforms. After reviewing the full-text articles for relevance to our subject, 228 were excluded. A total of 47 clinical trials, including 26 comparative studies and 4 case reports, were included in the final analysis (Figure 1). The selected articles should at least report the efficacy of the treatment. These studies were distributed over countries where *Mycobacterium tuberculosis* infection is common and BCG vaccination is mandatory, namely Egypt, India, Nepal, Iran, Iraq, Saudi Arabia, Pakistan, Malaysia, Philippines, and Indonesia. The intervention applied in each study is detailed in Tables 1 and 2 below. Most studies evaluated treatment outcomes on the size and number of lesions. Complete clearance was defined as total resolution of lesion(s) and return of the typical skin markings, partial if the clearance occurred in some of the lesions (varied between studies, ranging from 25–99%), and no response. Treatment outcome was primarily assessed on the injected lesion, and several studies also evaluated the outcome on distant-site lesions.

Discussion

Efficacy

We assessed the efficacy based on the complete clearance rate in each study. Immunotherapy showed variable efficacy across these studies, ranging from 13.3% to 96%. Figure 2 shows the complete clearance rate reported in all studies in the present work. Twelve studies (25.6%) reported an efficacy rate of 70–79%, followed by 60–69% in 11 studies (23.4%). There were nine studies (19.1%) that reported an efficacy of 50–59%, while a similar number of other studies (9; 19.1%) had an efficacy below 50%. The efficacy in 5 studies (10.6%) was 80–89%, and in 1 study (2.2%), it had efficacy >90%. The overall mean complete clearance rate is 61.5%.

The highest complete clearance rate (96%) was reported in a comparative study by Elela et al. This randomized-controlled trial, involving 110 patients with different cutaneous warts, was conducted in Egypt. Patients were divided into

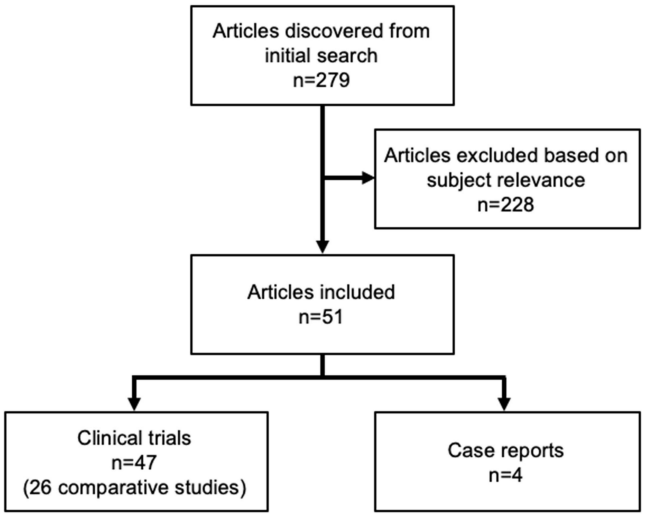

Figure 1 Flowchart of the article selection process.

Table 1 Clinical Trials Using PPD Immunotherapy in Cutaneous and Anogenital Warts

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Abd- Elazeim et al[16] 2014 (Egypt)	RCT	• PPD (A) • Saline (B)	A: 20 B: 20	Recalcitrant; common	• Group A: ○ Test dose: 0.1 mL PPD, intradermal on forearm ○ Treatment: volume injected determined by the size of skin test reactivity according to Johnson et al[20] 0.3; 0.2; and 0.1 mL if the reaction diameter was 5–20, 21–40, and >40 mm (intralesion on largest wart) • Group B: 0.3 mL normal saline, intralesion on largest wart • Weekly interval, max. 6 sessions	Target warts: A: 75 B: 0 Distant warts: A: 25 B: 0	10	6	Pain, mild erythema, swelling, transient post-hypopigmentation
Abou-Taleb et al[18] 2019 (Egypt)	RCT	• PPD (A) • Vitamin D3 (B)	A: 22 B: 23	Simple, recalcitrant; common, plantar	• Group A: ○ Test dose: 0.1 mL PPD-5TU, intradermal ○ Treatment: volume injected determined by the size of skin test reactivity according to Kus et al[13] 0.3; 0.2; and 0.1 mL if the reaction diameter was 5–9, 10–15, and >15 mm (intralesion, max. 3 lesions) • Group B: • Injection of 0.1 mL lignocaine (20 mg/mL) followed by injection of 0.6 mL vitamin D3 (intralesion on max. 3 lesions) • 3 weeks interval, max. 3 sessions	Target warts: A: 72.7 B: 43.5 Distant warts: A: 59.1 B: 21.7	0	3	• A: tolerable pain, erythema, edema • B: severe pain (needed anesthesia), erythema, edema, itching
Ahmed et al[21] 2020 (India)	RCT	• Vitamin D3 (A) • MR (B) • PPD (C)	A: 15 B: 15 C: 15	Simple; common, plane, palmoplantar, filiform	• Group A: 2 units of vitamin D3 600.000 (15 mg/mL) • Group B: 2 units of MR vaccine (0.5 mL/dose) • Group C: 2 units of PPD-5TU (0.1 mL/dose) • Injected into 2 largest warts • 2-weeks interval, min. 3 injections	A: 25.5 B: 9.3 C: 23.2	A: 6.66 B: 0 C: 6.66	6	• A: mild pain, persistent swelling, necrosis at injection site • C: mild swelling, fever, erythema, itching

Alajlan,[22] 2020 (Saudi Arabia)	Open label study	• PPD (A) • Saline (B)	A: 62 B: 20	Recalcitrant; common	• Test dose: ○ Group A: 0.1 mL PPD-5TU, intradermal on forearm ○ Group B: 0.1 mL normal saline, intradermal on forearm • Treatment: ○ Group A: 0.1 mL PPD-5TU, intradermal on 1 or 2 warts ○ Group B: 0.1 mL normal saline, intradermal on 1 wart • 3 weeks interval, max. 3 sessions	A: 79 B: 10	0	3	Pain at injection sites
Amirnia et al[11] 2015 (Iran)	RCT	• PPD (A) • Saline (B) • Cryo-therapy (C)	A: 35 B: 34 C: 33	Recalcitrant; common, plantar, anogenital/ mucous membrane	• Group A: ○ Test dose: 0.1 mL PPD, intradermal on forearm ○ Treatment: volume injected determined by the size of skin test reactivity according to Johnson et al[20] (intralesion on largest wart) • Group B: 0.3 mL of saline, intralesion on largest wart • Group C: liquid nitrogen spray applied perpendicularly to the largest wart at a distance of 2 cm, 2 mm margin (3 freeze-thaw cycles) • 2-weeks interval, max. 6 sessions	Target warts: A: 77.1 B: 0 C: 18.2 Distant warts: A: 85.7	A: 8.6 B: 5.9 C: 24.2	6	• C: pain, blister, erythema, swelling, hyperpigmented scar • None observed on PPD and placebo group
Awad et el.[23] 2022 (Egypt)	RCT	• PPD (A) Cryo-therapy + PPD (B)	A: 25 B: 25	Simple, recalcitrant; common	• Group A: ○ Test dose: 0.1 mL PPD-5TU, intradermal on forearm ○ Treatment: volume injected determined by the size of skin test reactivity according to Kus et al[13] (intralesion on largest wart) • Group B: cryotherapy applied for all lesions using liquid nitrogen spray at a distance of 1 cm, margin 1–2 mm (single freezing cycle) followed by intralesional PPD injection into the largest wart • 2-weeks interval, max. 4 sessions	A: 48 B: 44	A: 20 B: 0	2	• Both groups: pain, redness, edema • B: blistering, hypopigmentation

(*Continued*)

Table 1 (Continued).

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Awad et al[24] 2022 (Egypt)	RCT	• PPD (1) • Zinc sulfate 2% (2)	1: 60 2: 60 (pediatric)	Simple, recalcitrant; common, plantar, anogenital	• Group 1: 0.1 mL PPD, intralesion on largest wart • Group 2: Zinc sulfate 2%, intralesion on largest wart • 2-weeks interval, max. 5 sessions	Target warts: 1: 83.3 2: 93.4 Distant warts: 1: 81.7 2: 81.7	1: 1.7 2: 10	6	• 1: pain, itching, fever, acute urticaria • 2: pain, inflammation, necrosis, ulceration, necrosis, scar, itching, fever, scarring alopecia
Azab et al[15] 2022 (Egypt)	RCT	• PPD (1) • Control (2)	1: 63 2: 50	Simple, recalcitrant; ano-genital	• Test dose: 0.1 mL PPD, intradermal on forearm • Group 1: PPD-10TU, intralesion on largest wart, 2-weeks interval for 6 sessions • Group 2: included healthy individuals, no treatment given • Measurements of IL-17 in all patients before and after PPD injection in group 1, and to all control subjects in group 2	Target warts: 1: 58.7 Distant warts: 2: 66.7	1: 23.3	3	Pain, edema, systemic symptoms, erythema, swelling, hypo or hyper-pigmentation
Bhalala et al[25] 2022 (India)	RCT	• PPD (A) • MMR (B) • Saline (C)	A: 27 B: 25 C: 21	Simple, recalcitrant; common, plane, palmoplantar, periungual, anogenital	• Group A: 0.1 mL PPD, intralesion on largest wart • Group B: 0.1 mL MMR, intralesion on largest wart • Group C: 0.1 mL normal saline, intralesion on largest wart • 2-weeks interval, max. 4 sessions	A: 51.85 B: 56 C: 0	A: 1 patient	6	• All groups: pain • A: scarring, swelling • B: flu-like symptoms
Bharga-va et al[26] 2021 (India)	RCT	PPD	40	Simple, recalcitrant; common, plantar, palmar, plane, periungual	• 0.01 mL PPD 5-TU, intralesion on the largest wart • Weekly interval for 4 weeks	65	N/A	N/A	N/A

Chandra et al[27] 2019 (India)	RCT	• PPD (A) • *Mw* (B)	A: 32 B: 32	Simple, recalcitrant; common, plane, palmo-plantar, periungual	• Test dose on all patients: 0.1 mL PPD-10TU, intra-dermal on forearm • Group A: 0.1 mL PPD-10TU, intradermal on deltoid region • Group B: 0.1 mL *Mw* vaccine, intradermal on deltoid region • 2-weeks interval, max. 6 sessions	A: 50 B: 68.8	0	3	• A: hyper-pigmentation, erythema, scaling, pruritus • B: indurated nodule after every injection that healed with scarring, ulceration, erythema, scaling, pruritus
Chou-dhary et al[12] 2018 (Nepal)	Open label study	PPD	52	Simple, recalcitrant; common, plantar, plane, periungual	• PPD-2.5TU into each wart until lesions blanched, max. 25 TU in 1 session • 2-weeks interval, max. 5 sessions	78.8	0	6	Erythema, pain, edema, low-grade fever
Diab et al[4] 2021 (Egypt)	RCT	PPD	20	Simple, recalcitrant; common	• 0.01 mL PPD-5TU, intra-lesion on largest wart • 2-weeks interval, max. 6 sessions	35	0	6	Pain, myalgias, fever, erythema, edema, skin pigmentation
Diab et al[28] 2021 (Egypt)	RCT	• PPD (A) • PPD + iso-tretinoin (B)	A: 20 B: 20	Simple, recalcitrant; common, plantar	• Group A: 0.1 mL PPD, intralesion on largest wart, 2-weeks interval, max. 6 sessions • Group B: PPD as given in group A + low dose iso-tretinoin (0.2–0.4 mg/kg/day) for 3 months	A: 35 B: 55	A: 0 B: 9.1	3	• All groups: erythema, edema, pain, dis-pigmentation, fever, myalgias • B: cheilitis, dry skin
Durga-devi et al[29] 2018 (India)	Open label study	• PPD (1) • Topical 5% 5-fluoroura-cil (2)	1: 25 2: 25	Simple, recalcitrant; peri-ungual, warts in other areas (not mentioned in detail)	• Group 1: PPD-1TU, volume injected deter-mined by size of skin test reactivity according to Johnson et al[20] intralesion on one randomly selected lesion, 3-weeks interval, max. 6 sessions • Group 2: topical 5% 5-FU applied on the lesion(s) selected by investigator, under occlusion daily during the night and left for 12 hours, for 3 months	1: 88 2: 20	0	3	• 1: none • 2: paronychia, edema, pain, erythema

(*Continued*)

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Table 1 (Continued).

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Eassa et al[30] 2011 (Egypt)	RCT	• PPD (A) • Distilled water (B)	A: 20 B: 20 (preg-nant)	Recalcitrant; ano-genital	• Tuberculin test on all patients: 0.1 mL PPD-2TU, intradermal on forearm • Group A: 0.1 mL PPD, intradermal on middle third of ventral aspect of both forearm, repeated weekly for 12 weeks • Group B: 0.1 mL distilled water at similar site as in Group A, repeated weekly for 4 weeks then shifted to 0.1 mL PPD weekly for 12 weeks	A: 50 B: 45	0	>6	Pain, erythema, tenderness
Elela et al[31] 2011 (Egypt)	RCT	• PPD intra-lesion (1) • PPD intra-dermal (2) • Saline (3)	1: 40 2: 50 3: 20	Simple, recalcitrant; common, plantar, plane	• Group 1: 0.1 mL PPD, intralesion • Group 2: 0.1 mL PPD, intradermal into the right forearm • Group 3: 0.1 mL normal saline, intralesion • 2-weeks interval, max. 10 injections	1: 94.1 2: 96 3: 15	N/A	N/A	N/A
Farhana et al[32] 2018 (India)	RCT	• Vitamin D3 (A) • PPD (B)	A: 10 B: 10	Simple, recalcitrant; common, plantar, periungual	• Group A: 0.2 mL (15 mg/mL) vitamin D3, intralesion per wart • Group B: 0.2 mL PPD-5TU, intralesion per wart • 2-weeks interval until complete clearance	A: 70 B: 80	A: 10 B: 0	3	Pain, erythema, swelling, itching
Fatima et al[33] 2019 (Pakistan)	Quasi experi-mental	• PPD (A) • Cryo-therapy (B)	A: 30 B: 30	Cutaneous warts	• Group A: 0.1 mL PPD-5TU, intralesion on largest wart • Group B: cryotherapy using liquid nitrogen by direct application using orange stick with cotton tip for (2 freeze-thaw cycles) • 2-weeks interval, max. 6 sessions	A: 70 B: 30	N/A	3	N/A

Fawzy et al[34] 2020 (Egypt)	RCT	• PPD (1) • *Candida* (2) • MMR (3)	1: 40 2: 40 3: 40	Simple, recalcitrant; plane	• Group 1: 0.1 mL PPD, intralesion on largest wart • Group 2: 0.1 mL of 1/1000 solution of *Candida* antigen, intralesion on largest wart • Group 3: 0.1 mL MMR vaccine, intralesion on largest wart • 2-weeks interval, max. 5 sessions	1: 55 2: 70 3: 62.5	1: 7.5 2: 0 3: 0	6	All groups: pain, erythema, edema, flu-like symptoms
Ghaly et al[35] 2020 (Egypt)	RCT	• PPD (1) • Vitamin D3 (2) • Saline (3)	1: 20 2: 20 3: 20	Simple; plantar	• Group 1: PPD-5TU, volume injected determined by the size of skin test reactivity according to Kus et al[13] intralesion on largest wart, 2-weeks interval, max. 3 sessions • Group 2: 0.2 mL (300.000 IU 7.5 mg/mL) vitamin D3, intralesion on largest wart after prilocaine injection, 4-weeks interval, max. 3 sessions • Group 3: 0.3 mL normal saline, intralesion on largest wart, 2-weeks interval, max. 3 sessions	Target wart: 1: 50 2: 70 3: 0 Distant wart: 1: 37.5 2: 25 3: 0	0 in all groups	6	• 1: pain, hyper-pigmentation, flu-like symptoms, erythematous edema • 2: hyper-pigmentation, pain • 3: none
Ibrahim et al[36] 2021 (Egypt)	RCT	• Cryo-therapy (A) • PPD (B) • Cryo-therapy + PPD (C)	A: 25 B: 25 C: 25	Simple, recalcitrant; common	• Group A: cryogun sprayed at distance of 1 cm, margin 1–5 mm (single freeze-thaw cycle) • Group B: 0.1 mL PPD-10TU, intralesion on largest wart • Group C: 0.1 mL PPD-10TU, intralesion on largest wart followed by spraying all warts with cryogun • 2-weeks interval, max. 4 sessions	A: 24 B: 48 C: 84	N/A	2 weeks	• A: pain, edema, hypopigmentation, bullae formation • B: pain, erythema, edema, flu-like symptoms • C: pain, edema, bullae, hypo-pigmentation, erythema, flu-like symptoms
Jain et al[37] 2021 (India)	Open label study	• Vitamin D3 (1) • MMR (2) • PPD (3)	1: 20 2: 20 3: 20	Recalcitrant; common, plane, palmoplantar, periungual, subungual	• Group 1: 0.2 mL (15 mg/mL) vitamin D3, intralesion on largest wart or 2 warts after lignocaine injection • Group 2: 0.5 mL MMR vaccine, intralesion on largest wart or 2 warts • Group 3: 0.1 mL PPD-10TU, intralesion on largest wart or 2 warts • 2-weeks interval, max. 4 sessions	Target wart: 1: 80 2: 90 3: 85 Distant wart: 1: 70 2: 85 3: 75	1: 8.3 None in other groups	3	• 1: itching, swelling with itching, swelling with pain, dys-pigmentation • 2: acute urticaria exacerbation, itching, swelling, swelling with pain, dyspigmentation • 3: itching, swelling with exfoliation, swelling with itching, swelling with pain, dyspigmentation

(*Continued*)

Table 1 (Continued).

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Jaiswal et al[38] 2019 (India)	RCT	PPD	51	Simple, recalcitrant; common, palmoplantar, plane, periungual, anogenital	• 0.01 mL PPD-5TU, intralesion on largest wart • Weekly interval, max. 6 sessions	68.6	N/A	3	Pain, swelling, erythema
Kaimal et al[39] 2020 (India)	Open label study	PPD	28	Cryotherapy-resistant; common, palmo-plantar, periungual	• 0.01 mL PPD-2TU, intralesion into index wart (oldest and/or largest wart) • 2-weeks interval, max. 6 sessions	50	0	3	Pain, edema
Milante et al[40] 2019 (Philip-pines)	Randomized, open-label, superiority trial	• Single injection PPD (1) • Multiple injection PPD (2)	1: 29 2: 29	Simple, recalcitrant; common	• Test dose: 0.1 mL PPD-5TU, intradermal on forearm • Group 1: PPD-5TU, volume injected determined by by the size of skin test reactivity according to Kus et al[13] intralesion on largest wart • Group 2: PPD–5TU, intralesion on all lesions, volume injected determined as maximum 88 TU or 1.76 mL • 2-weeks interval, max. 6 sessions	1: 58.6 2: 79.3	0 in all groups	6	• 1: pain, fever, malaise, edema, pain • 2: fever, malaise, edema, vesiculation, more painful than group 1
Mishra et al[14] 2022 (Nepal)	Open label study	PPD	54	Simple, recalcitrant; palmo-plantar, periungual	• 0.01 mL PPD, intralesion on the largest wart • 2-weeks interval, max. 6 sessions	66.7	11	3	• 2 cases of local site reaction: intense swelling, pain, and edema requiring therapy discon-tinuation • Other: mild erythema, edema, pain
Moham-med et al[41] 2020 (Egypt)	RCT	• PPD (A) • MMR (B) • Saline (C)	A: 30 B: 30 C: 30	Recalcitrant; common, plane, plantar, periungual, ano-genital	• Test dose: PPD 0.1 mL or MMR 0.1 mL, intradermal on forearm • Group A: 0.2 mL PPD (10 TU), intralesion on largest wart • Group B: 0.2 mL MMR (20 IU), intralesion on largest wart • Group C: 0.2 mL saline, intralesion on largest wart • 2-weeks interval, max. 5 sessions	Target warts: A: 60 B: 80 C: 0 Distant warts: A: 60 B: 40 C: 0	N/A	N/A	• All groups: minimal pain • B: minimal erythema, transient induration

Mohta et al[8] 2022 (India)	Randomized, open-label study	• *Mw* (A) • PPD (B)	A: 55 B: 47	Simple, recalcitrant; extra-genital	• Group A: 0.1–0.2 mL *Mw* vaccine, intralesion on the largest wart • Group B: 0.1–0.2 mL PPD-5TU, intralesion on the largest wart • 4-weeks interval, max. 3 sessions	A: 76.3 B: 65.9	0	6	• Most common: pain, erythema • Rare: fever, nodule formation, transient urticaria
Mohta et al[42] 2022 (India)	RCT	• PPD (A) • *Mw* (B)	A: 46 B: 51	Recalcitrant; extra-genital	• Group A: 0.1 mL PPD, intralesion on largest wart • Group B: 0.1 mL *Mw* vaccine, intralesion on largest wart • 4-weeks interval, max. 5 sessions	Target wart: A: 63 B: 76.5 All warts: A: 52.17 B: 62.75	0 in all groups	3	• A: erythema, swelling, pruritus, mild fever, generalized urticaria • B: mild fever, painful nodule, ulceration, erythema, pruritus
Mou-basher et al[43] 2021 (Egypt)	RCT	• PPD (A) • Cryo-therapy (B) • PPD + cryo-therapy (C)	A: 15 B: 15 B: 15	Simple, recalcitrant; anogenital	• Group A: PPD, volume injected determined by the size of skin test reactivity according to Johnson et al[20] intralesion, evaluation was done at 2 weeks • Group B: liquid nitrogen using cryogun at a distance of 2 cm, margin 2 mm (3 freeze-thaw cycle), 2-weeks interval for 4 sessions	A: 13.3 B: 26.7 C: 46.7	N/A	N/A	• A: pain, flu-like symptoms, erythema • B: pain, erosion, hypopigmentation • C: pain, flu-like symptoms, erythema, hypopigmentation
Nada et al[44] 2020 (Egypt)	RCT	PPD	59	Simple, recalcitrant; anogenital	• Tuberculin test: 0.1 mL PPD-5TU, intradermal on forearm • Treatment: 0.2 mL PPD-5TU, intralesion on the largest wart • 2-weeks interval, max. 6 sessions	69.5	32.6	3	Pain, mild erythema, swelling, hypopigmentation
Nimbal-kar et al[45] 2022 (India)	RCT	PPD	45	Simple, recalcitrant; common, palmoplantar, filiform, periungual	• PPD 10 TU, intralesion on the largest wart • 2-weeks interval, max 6 sessions	62.2	0	4	Localized hair loss around injected wart over the scalp, pain and abscess at injection site, hyperpigmentation, urticaria

(*Continued*)

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Table 1 (Continued).

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Nofal et al[46] 2020 (Egypt)	RCT	• PPD (1) • *Candida* antigen (2) • PPD / *Candida* antigen alternate (3) • Saline (4)	1: 36 2: 38 3: 34 4: 35	Simple, recalcitrant; common, plantar, filiform, periungual	• Group 1: 0.1 mL PPD, intralesion on largest wart • Group 2: 0.1 mL of 1/1000 solution of *Candida* antigen, intralesion on largest wart • Group 3: alternating therapy of intralesional PPD and intralesional *Candida* antigen on largest wart • Group 4: 0.1 mL normal saline, intralesion on largest wart • 2-weeks interval, max. 6 sessions	1: 61.1 2: 36.8 3: 70.6 4: 8.6	1: 9.1 4: 33.3	N/A	N/A
Nofal et al[47] 2021 (Egypt)	RCT	• PPD (1) • *Candida* antigen (2) • MMR (3)	1: 50 2: 50 3: 50	Simple, recalcitrant; periungual	• Test dose: 0.1 mL of each antigen, intradermal on forearm • Group 1: 0.1 mL PPD, intralesion on largest wart • Group 2: 0.1 mL of 1/100 solution of *Candida* antigen, intralesion on largest wart • Group 3: 0.1 mL MMR • 2-weeks interval, max. 5 sessions	Target warts: 1: 70 2: 80 3: 74 Distant warts: 1: 70 2: 86.7 3: 83.3	0 in all groups	6	All groups: pain, erythema, edema, flu-like symptoms
Nofal et al[48] 2022 (Egypt)	RCT	• PPD (A) • *Candida* antigen (B) • MMR (C) • PPD + *Candida* antigen + MMR (D)	A: 40 B: 40 C: 40 D: 40	Recalcitrant; common, palmar, plantar, plane, filiform, subungual	• Group A: 0.3 mL PPD 0.3 mL, intralesion on largest wart • Group B: 0.3 mL of 1/100 solution of *Candida* antigen, intralesion on largest wart • Group C: 0.3 mL MMR, intralesion on largest wart • Group D: 0.1 mL PPD + *Candida* antigen 0.1 mL + MMR 0.1 mL (combined in the same syringe), intralesion on largest wart • 2-weeks interval, max. 5 sessions	Target warts: A: 57.5 B: 72.5 C: 62.5 D: 77.5 Distant warts: A: 48 B: 61.5 C: 55.5 D: 65	A: 8.7 B: 13.8 C: 12 D: 6.45	6	All groups: pain, erythema and desquamation, blister, edema, flu-like symptoms, hypopigmentation
Podder et al[49] 2016 (India)	RCT	• BCG (A) • PPD (B)	A: 33 B: 27	Simple, recalcitrant; common, plane, palmo-plantar	• Group A: 0.1 mL BCGI, intradermal on right arm • Group B: 0.1 mL PPD-5TU, intradermal on right arm • 4-weeks interval, max. 3 sessions	A: 48.5 B: 18.5	0 in both groups	1	• More adverse events in group A: pain, abscess, scar • B: pain, scar

Pundir et al[50] 2018 (India)	RCT	PPD	40	Simple, recalcitrant; plane warts on face	• PPD-2TU, intralesion on each wart, max. 10 TU each session • 2-weeks interval, total 4 sessions	65.75	10	6	Erythema, swelling, pain, fever, body ache
Puri,[51] 2019 (India)	RCT	PPD	25	Recalcitrant; common, plane, palmoplantar, ano-genital	• PPD-2.5TU, intralesion on each wart, max 25 TU each session • 3-weeks interval, total 3 sessions	72	8	6	Erythema, edema, pain, fever
Raveen-dra et al[52] 2021 (India)	RCT	• PPD (A) • Vitamin D3 (B)	A: 50 B: 50	Simple, recalcitrant; common, plane, palmo-plantar, periungual, facial	• Group A: PPD-2.5TU, intralesion on each lesion, max. 10 lesions or 25 TU each session • Group B: 0.1 mL vitamin D3, intralesion on each lesion, max. 10 lesions or 1 mL each session • 2-weeks interval for 4 sessions	A: 76 B: 84	A: 4 B: 8	– 1 –6 via tele-phone	Minimal-moderate pain
Saoji et al[53] 2016 (India)	Open uncontrolled trial	PPD	55	Simple, recalcitrant; common, plane, plantar	• PPD-2.5TU intralesion on each wart, max 10 lesions and 25 TU each session • 2 weeks interval, total 4 sessions	76	1.8	6	Erythema, edema, pain, low grade fever, body ache
Sha-heen et al[17] 2015 (Egypt)	RCT	• MMR (1) • PPD (2) • Saline (3)	1: 10 2: 10 3: 10	Simple, recalcitrant; common, plane, plantar, periungual, ano-genital	• Test dose: 0.1 mL MMR or PPD-5TU, intradermal on forearm • Group 1: volume of MMR injected determined by the size of skin test reactivity: 0.3; 0.2; and 0.1 mm of intralesional if the reaction diameter was 5–20 mm, 21–40 mm, and >40 mm (intralesion on largest wart) • Group 2: volume of PPD injected determined by the size of skin test reactivity according to Kus et al[13] (intralesion on largest wart only) • Group 3: 0.3 mL normal saline, intralesion on largest wart • 3-weeks interval, max. 3 sessions	Target wart: 1: 80 2: 60 3: 0 Distant wart: 1: 40 2: 60 3: 0	0	3	• All groups: pain • 1: erythema, swelling, vasovagal attack • 3: vasovagal attack

(*Continued*)

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Table 1 (Continued).

Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Shar-quie et al[54] 2016 (Iraq)	RCT	• PPD (A) • Distilled water (B)	30	Simple, recalcitrant; common, plane, plantar	• Test dose: 0.1 mL PPD-2TU, intradermal on forearm • Group A: PPD-2TU, intralesion on each wart located in the right side of the body until the lesion gets blanched • Group B: Distilled water, intralesion on each wart located in the left side of the body until the lesion gets blanched • 2-weeks interval, max. 3 sessions	- A: 23.33 - B: 0	0	2	Mild pain
Sil et al[19] 2020 (India)	Co-hort	• PPD (A) • *Mw* (B) • MMR (C)	A: 9 B: 11 C: 12	Simple, recalcitrant; non-genital	• Group A: 0.1 mL PPD, intradermal on deltoid region • Group B: 0.1 mL *Mw* vaccine, intradermal on deltoid region • Group C: 0.3 mL MMR vaccine, intradermal on deltoid region • 2-weeks interval, max. 6 sessions	A: 44.44 B: 45.45 C: 41.66	N/A	N/A	N/A
Sukanya et al[55] 2020 (India)	RCT	PPD	25	Simple, recalcitrant; common	• PPD-2.5TU, intralesion into into all warts, max. 5 lesions • 2-weeks interval, max. 6 sessions	56	N/A	6	Pain, erythema, inflammation, itching

Tawfik et al[56] 2022 (Egypt)	RCT	• PPD (A) • *Candida* antigen (B)	A: 40 B: 40	Simple; anogenital	• Test dose: 0.1 mL PPD and 0.1 mL *Candida* antigen, intradermal on forearm • Group A: PPD-5TU, volume injected determined by the size of skin test reactivity according to Kus et al[13] intralesion on largest wart • Group B: *Candida* antigen 1/1000, volume injected determined by the size of skin test reactivity: 0.3; 0.2; and 0.1 mL if the reaction diameter was 5–20 mm, 21–40 mm, and >40 mm, intralesion on largest wart • 2-weeks interval, max. 4 sessions	A: 72.5 B: 85	A: 3.4 B: 2.9	6	• All groups: mild pain, burning sensation after injection • A: itching, erythema • B: erythema, edema
Wan Ahmad Kammal et al[57] 2021 (Malay-sia)	RCT	• Cryo-therapy (1) • PPD (2)	1: 15 2: 15	Simple, recalcitrant; common,	• Group 1: liquid nitrogen sprayed perpendicularly at a distance of 2 cm to all warts, margin 2 mm (2 freeze-thaw cycle) • Group 2: PPD-2.5TU, intralesion on largest wart • 2-weeks interval, max. 6 sessions	1: 73.3 2: 86.7	1: 27.3 2: 13.4	4	• 1: blister, hypo-pigmentation, hyper-pigmentation, compartment-like syndrome-like symptoms and sign with swelling, cyanosis, and hypoaesthesia at the tip of the finger • 2: pain, edema, erythema

Table 2 Case Reports Using PPD Immunotherapy in Cutaneous and Anogenital Warts

Authors, Years, Country	Study Design	Treatment Arms(s)	Partici-Pants	Type of Warts	Follow-up Duration (Months)	Protocols	Complete Response (%)	Recurrences (%)	Side Effects
Achdiat et al[58] 2022 (Indo-nesia)	Case report	PPD	1	Simple; anogenital	• Tuberculin skin test revealed 15 mm induration • Treatment: 0.2 mL PPD-2TU, intralesion on one lesion • Weekly interval, 3 sessions	Complete clearance on day 46th	0	24	Pain
Alha-shimi et al[59] 2021 (Egypt)	Case report	PPD	1	Simple, anogenital	• 0.2–0.3 mL PPD, intralesion on 2–3 different lesions at least 2 cm apart • 2-weeks interval, 7 sessions	98% clearance after 7 sessions	0	10	Mild discomfort
Manoj et al[60] 2019 (India)	Case series	PPD	5	Simple, cutaneous	• PPD, intradermal (not mentioned in detail) • 2-weeks interval, max. 6 sessions	80	N/A	3–6	Mild pain
Nofal et al[61] 2020 (Egypt)	Case series	• *Candida* antigen • MMR • PPD	2	Recalcitrant; cutaneous	• Case 1: 0.3 mL MMR, intralesion on largest wart, 2-weeks interval, for 5 sessions then switched to 0.3 mL *Candida* antigen solution 1/1000, intralesion on largest wart, 2-weeks interval • Case 2: 0.3 mL PPD, intralesion, 2-weeks interval, for 5 sessions then switched to 0.3 mL *Candida* antigen solution 1/1000, intralesion on largest wart, 2-weeks interval	Both cases: complete clearance after 2nd session	1: 0 2: 0	1: 24 2: 6	Case 1: pain, erythema, edema, exfoliation, influenza-like symptoms

three groups: the first group received 0.1 mL intralesional PPD, the second group received 0.1 mL PPD given intradermally on the right forearm, and the third group (control) received 0.1 mL intralesional saline. A complete clearance rate was achieved in 96% of patients in group 2, compared to 94.1% in group 1. However, this difference was not statistically significant. The clearance in the control group was 15%. Treatment was done every two weeks for a maximum of 10 sessions. The longer treatment duration might explain the high clearance rate observed in this study.[31] Meanwhile, the lowest complete clearance (13.3%) was reported by Moubasher et al, in which 15 patients with anogenital warts were given PPD-5TU intralesional injection into the largest wart and evaluated at two weeks. The injection volume was determined by the size of skin test reactivity conducted prior to treatment, ie, 0.3, 0.2, and 0.1 mL of PPD if the size of induration was 5–20 mm, 21–40 mm, and >40 mm, respectively. This study was performed in Egypt. This finding might be related to the shorter treatment duration and the fewer participants in this study.[43]

In addition, we included four case reports which also evaluated the efficacy of PPD. Achdiat et al used 0.2 mL PPD-2TU given weekly for three sessions as an intralesional injection in a case of AGWs in a 30-year-old homosexual man. Clinical improvement was observed starting on day 18th and complete resolution on day 46th.[58] Despite the various treatment modalities available for AGWs, large recalcitrant lesions tend to be more resistant to treatments and carry a high risk of pain, scarring, and recurrence. Alhashmi et al reported a case of giant condyloma acuminata successfully treated with intralesional PPD in a dose of 0.2–0.3 mL, injected on 2 or 3 different lesions at least 2 cm apart, given at 2-week intervals. After seven sessions, more than 98% of the lesions were cleared. Then, four sessions of cryotherapy and topical podophyllin were added to clear the remaining small lesions. Ten months of follow-up revealed no recurrence.[59] Manoj et al further reported the efficacy of PPD in a case series involving five patients with multiple cutaneous warts. Significant improvement was noticed in 80% of patients at the end of 3 months.[60] Moreover, Nofal et al evaluated the effect of switching between intralesional antigens in 2 cases of multiple recalcitrant cutaneous warts that demonstrated complete clearance with intralesional *Candida* antigen after failure of treatment with five sessions of MMR and PPD. Differences in the injected antigens' processing, presentation, and cytokine production may affect the variable responses observed in these cases.[61]

As depicted in Figure 2, most studies (25%) reported an efficacy rate of 70–79%. The efficacy of PPD was further confirmed in placebo-controlled studies. A statistically significant difference was constantly demonstrated between the PPD and placebo group, implying its significant role in inducing wart clearance.[15,16,22,54]

Furthermore, Abd-Elazeim et al[16] and Azab et al[15] evaluated the effect of PPD on the clearance of distant non-injected warts. In the former study, complete clearance of distant wart(s) was observed in 25% of patients in the PPD group compared to 0 in the placebo group.[16] Azab et al[15] reported an even higher complete clearance rate (66.7%) in the

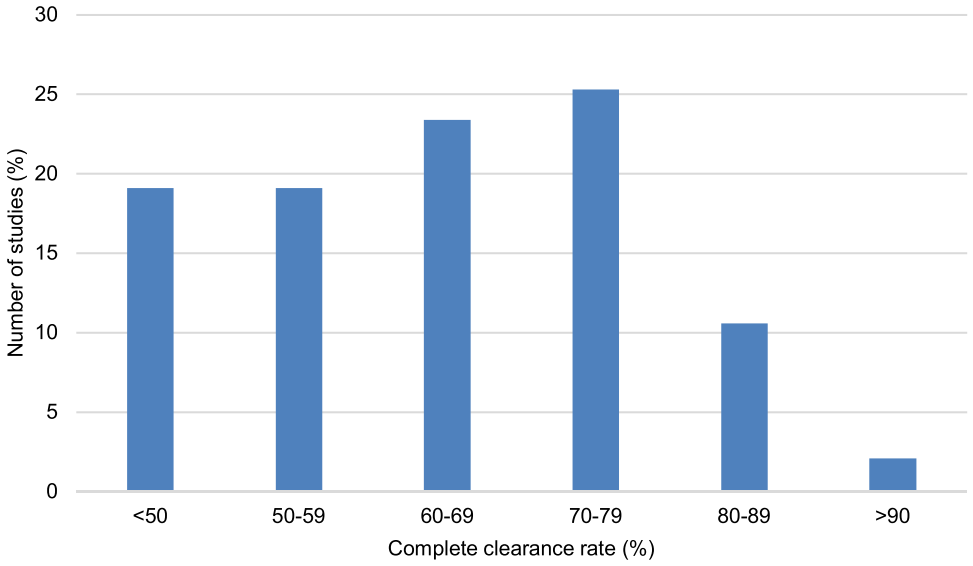

Figure 2 Efficacy of Purified Protein Derivative in all studies.

PPD group. This further adds to another beneficial effect of PPD, which is not seen with conventional treatments, suggesting its preferable use for multiple and difficult-to-reach lesions.[15–17]

Regarding time to resolution, complete clearance was achieved as early as two weeks after PPD injection in several studies.[50,53,55] Pundir et al used intralesional injection of PPD-2TU on 40 patients with plane warts on the face. Injection was done on each wart, with a maximum of 10TU in each session. Treatment was performed every two weeks for a total of 4 sessions. Complete clearance was observed in 3 patients after two weeks. The mean age of patients in this study was 25.3 years old (range 15–40). The number of lesions ranged from 15–to 40, with an average of 25.85 lesions. Disease duration ranged from 6 to 24 months, with a mean duration of 7.05 months.[50] The higher dose of PPD used in this study might contribute to the faster resolution of lesions. Nevertheless, Nimbalkar et al reported that complete clearance of lesions was first observed at the end of 6 weeks. This study involved 45 patients with single or multiple warts of different types, treated with intralesional injection of PPD-10TU on the largest wart, every two weeks for a maximum of 6 sessions.[45]

Safety

Adverse events (AEs) related to PPD injections were most frequently reported in the form of local reactions. Figure 3 shows the variable local AEs following PPD injection.

Among the 44 studies reporting AEs of PPD, pain at the injection site was the most frequently reported local AEs. However, it was mild and tolerable. Significant local AEs were reported by Mishra et al in which intense swelling, pain, and edema requiring discontinuation of therapy occurred in 2 cases. The characteristics of patients experiencing these AEs were not mentioned in detail. In this study, patients received an intralesional injection of 0.1 mL PPD into the most prominent wart every two weeks, with a maximum of 6 sessions.[14] In a study by Nimbalkar et al, abscess and localized hair loss at the injection site were noted in 1 patient each. Patients in this study received PPD-10TU injected intralesionally into the most prominent wart every two weeks for a maximum of 6 sessions.[45]

A few patients experienced systemic AEs in the form of fever, flu-like symptoms, myalgia, acute urticaria, and malaise, as depicted in Figure 4. Rare AEs in the form of acute urticaria were reported in 3 studies.[8,24,45] The mechanisms underlying such events are still unknown.

In several studies, the study participants included a pediatric age group as young as four.[22,30,34,45,50] There was no dose-adjustment according to age in these studies, and all study participants received similar interventions. Unfortunately, the outcomes of this particular population were also not explicitly reported, and the data was presented along with that of the other study participants. One study compared the efficacy and safety of PPD and zinc sulfate 2%, specifically in pediatric warts, and no serious AEs were reported in any of the study participants.[45]

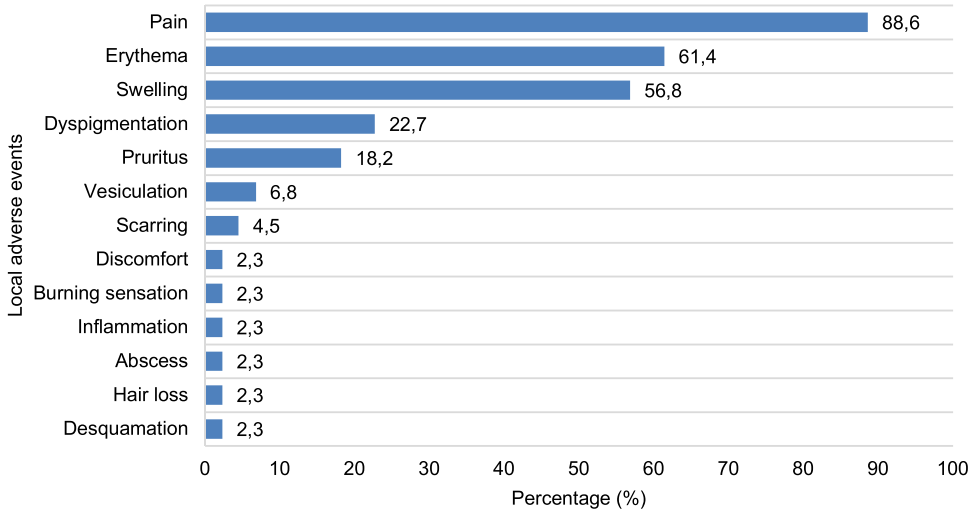

Figure 3 Local adverse events following Purified Protein Derivative injection.

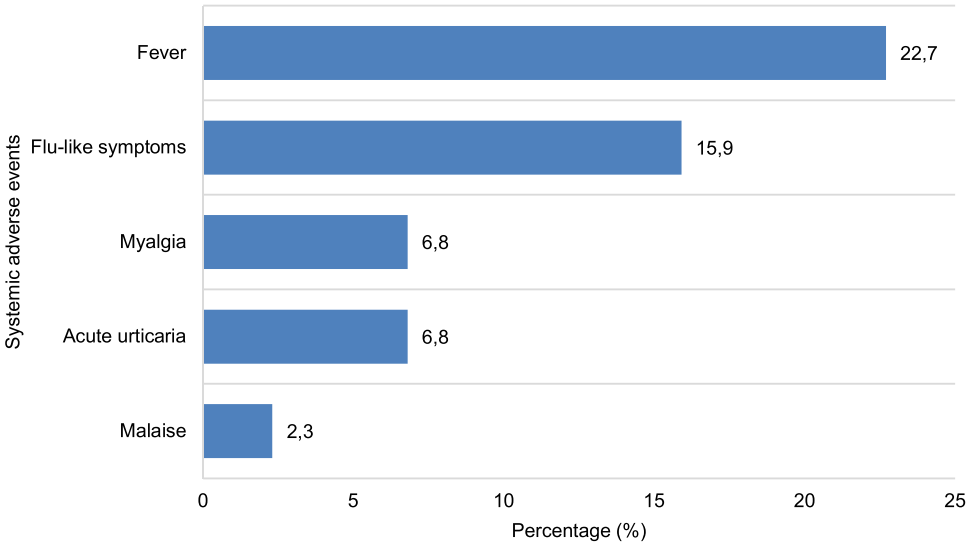

Figure 4 Systemic adverse events following Purified Protein Derivative injection.

Pregnant Population

During pregnancy, due to altered immunity and increased blood flow, genital warts may multiply quickly. They can present in either clinical or subclinical form. The risk of transmission from mother to child with subsequent disease development has been estimated to be around 1:80 and 1:1500, respectively. It is worthwhile to consider giving this modality of treatment to pregnant women because AGWs in this population are frequently challenging to treat, and this type of treatment is classified as category C in pregnancy. Despite lacking animal studies, the Advisory Council for the Elimination of Tuberculosis states that tuberculin skin testing is considered valid and safe throughout pregnancy. Eassa et al conducted a randomized clinical trial involving 40 pregnant Egyptian women with recalcitrant AGWs. Twenty patients received intradermal injection of 0.1 mL PPD repeated weekly for 12 weeks, while another 20 patients received intradermal injection of 0.1 mL distilled water (placebo) for four weeks and then shifted to 0.1 mL PPD weekly for 12 weeks. At the end of 12 weeks, 50% of patients in the PPD group achieved complete resolution.

Meanwhile, in the placebo group, none of the patients experienced any improvement in the first four weeks; nonetheless, 45% of patients reported complete resolution after treatment shifted to PPD injections for 12 weeks. All patients showing complete resolution were followed up for over six months, and no recurrence was reported. Adverse effects were mild and manifested locally at the injection site as pain, erythema, and tenderness. No systemic AEs were noted. In this study, PPD showed good efficacy and safety profile in the treatment of AGWs in pregnant women.[30]

Influencing Factors

Dosage

The dose of PPD used in these studies was variable. Some studies administered a fixed dose for all patients. In contrast, in some others, the dose was based on the size of skin test reactivity conducted before treatment. Among the fixed-dose studies using single injection, the administered dose ranged from 2–15TU. Of 32 studies, the most frequently administered dose in a single injection was 5TU. Figure 5 shows the variable doses used in fixed-dose studies using single injection. The mean complete clearance rate among studies using 5TU was 59.9%. Meanwhile, studies using 10TU reported a higher mean complete clearance rate (67.25%). One study using 2TU reported a complete clearance of 50%;[39] another study using 2.5 TU achieved an 86.7% clearance rate.[57] A dosage of 4TU was reported in one study by Achdiat et al[58] in a case of AGWs, and complete clearance was achieved on day 46th. Two studies by Alhashimi et al[59] and Nofal et al[61] using 15TU demonstrated a 98% clearance rate after seven sessions and 100% complete clearance after two sessions, respectively.

It has been hypothesized that response to PPD may be dose-dependent. Therefore, multiple injections are thought to be more effective and potentially require less time to clear warts. Among the fixed-dose studies using multiple injections,

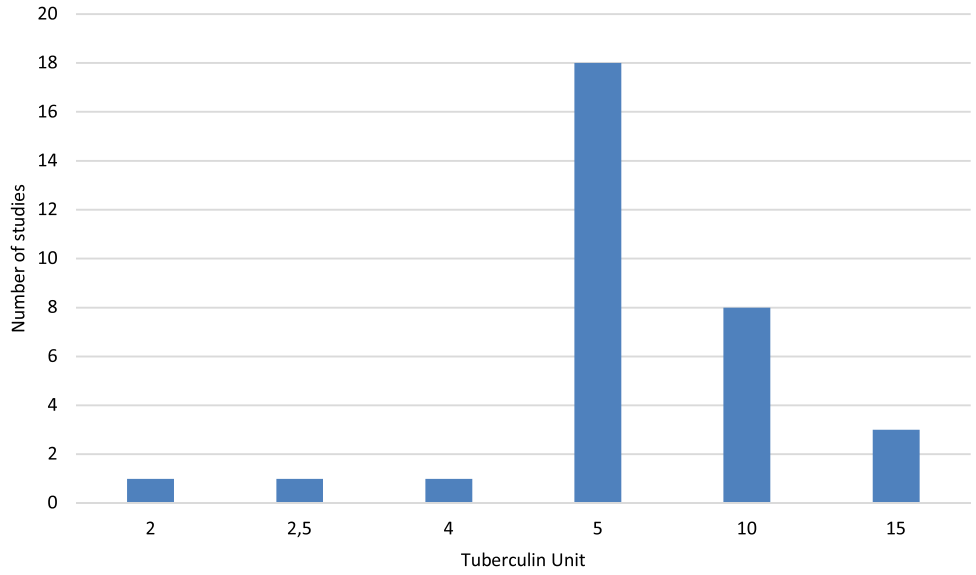

Figure 5 Purified Protein Derivative dosage among fixed-dose studies using single injection.

the maximum administered dose ranged from 10–25TU. Twenty-five TU was determined as the maximum dose of injection per session in 3 studies, followed by 10 TU in 2 studies and 12.5 TU in one study. A study by Milante et al comparing single versus multiple intralesional injections of PPD in 58 patients with common warts showed a superior clearance rate in the multiple injection group (79.3%) compared to the single injection group (58.6%). This difference was statistically significant (p=0.0236). PPD 5TU was injected into the most prominent wart in the single injection group. The injection volume was determined by the size of tuberculin skin test reactivity conducted before treatment. Meanwhile, in the multiple injection group, PPD-5TU was injected into all lesions with a maximum of 88TU or 1.76 mL. Injection was done every two weeks until clearance for a maximum of 6 sessions. The highest clearance was observed in week 12 for the single injection group and week 10 for the multiple injection group. However, multiple injections were reported to be significantly more painful than single injections. Late AEs, including constitutional symptoms and vesiculation, also occurred more frequently in the multiple injection group. There was no recurrence reported in both groups.[40] One study by Sharquie et al[54] performed multiple injections using PPD-2TU on multiple warts until the lesions blanched but did not specify the maximum volume administered in each session. The highest dose of PPD administered among these studies was 88TU. However, the related article did not mention in detail the number of patients who received this dose and whether there were associated AEs.

Nine studies determined the volume of PPD injection based on the size of skin test reactivity conducted before treatment. Five studies administered the dose according to Johnson et al[20] in which 0.3; 0.2; and 0.1 mL of PPD were injected if the size of induration was 5–20; 21–40; and >40 mm, respectively. In four studies, the dose administered was determined based on Kus et al,[13] in which 0.3; 0.2; and 0.1 mL of PPD was injected if the induration size was 5–9; 10–15; and >15 mm, respectively. The treatment outcome varied between the two groups. The prior sensitization status will be discussed more in the following section.

Interval

Regarding treatment interval, the shortest interval used in these studies was weekly, while the longest was four weeks. Thirty-seven out of 50 studies (74%) determined two weeks as the minimum interval between treatments, as shown in Figure 6. This interval was chosen as this is the usual time for an induration to heal following a Mantoux test (7–12 days).[12] Among these studies using a 2-week interval, the mean complete clearance rate was 61.8%. This rate was lower than studies using weekly (64.6%) and 3-week intervals (74.3%). The lowest mean complete clearance rate was demonstrated in studies using a 4-week interval (18.5%).

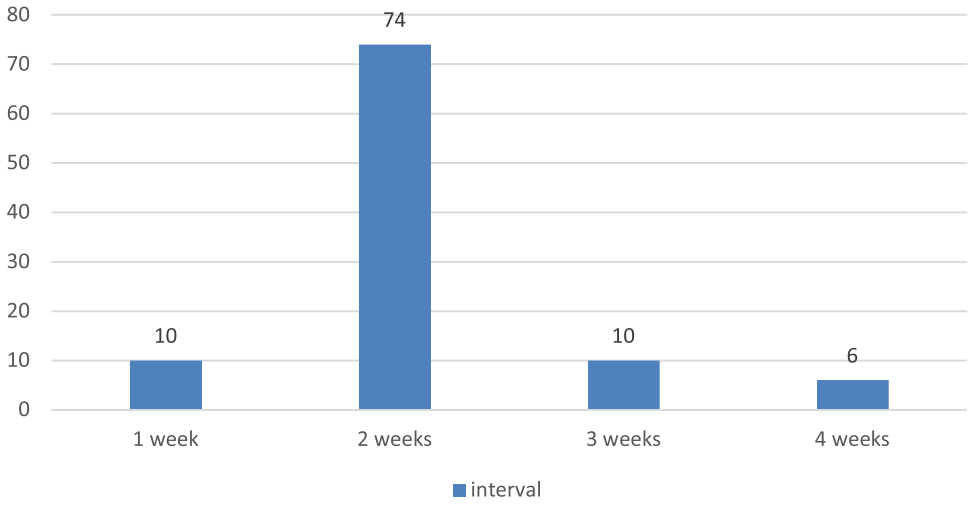

Figure 6 Different treatment intervals between studies.

Routes of Administration

In the present work, 43 studies applied an intralesional injection. In comparison, five studies used intradermal injection either on the forearm or deltoid region. The remaining studies did not mention the method of injection. Elela et al evaluated the effect of intradermal versus intralesional injection of PPD in 110 patients with various cutaneous warts. Patients were divided into three groups: group 1 included 40 patients treated with intralesional injection of 0.1 mL PPD, group 2 included 50 patients treated with intradermal injection of 0.1 mL PPD in the right forearm, and group 3 included 20 patients as control group treated with intralesional injection of 0.1 mL normal saline. Treatment was given every two weeks, with a maximum of 10 injections for the whole treatment duration. Complete cure was comparable between the two groups receiving PPD injection (94.1% in group 1 and 96% in group 2), and the difference was not statistically significant. These findings suggest that PPD can provide an excellent clinical outcome for wart treatment through any approach. However, local site reaction should be considered when intradermal injection is performed on healthy, uninvolved skin.[31]

Prior Sensitization Status

All of the studies included in the present work were conducted in countries where BCG vaccination is mandatory: Egypt (22), India (20), Nepal (2), Iran (1), Iraq (1), Saudi Arabia (1), Pakistan (1), Malaysia (1), Philippines (1), and Indonesia (1); hence, these populations were expected to have developed immunity against *M. tuberculosis*. Considering this, several studies straightly proceed to treatment with PPD in the intervention group. In contrast, some others performed a PPD sensitization test prior to intervention.[11,20,22,24,30,39,40,44,45,50,53–55,57]

A study by Alajlan involving 82 patients with multiple common warts divided patients in the intervention group into two further different groups, namely those with positive and negative PPD skin tests. A skin test was done by injecting 0.1 mL PPD-5TU intradermally. The result was read 48 hours after injection, and induration of ≥5 mm was considered positive. This study revealed that 76% of patients who were PPD-positive and 82% of patients who were PPD-negative in the intervention group achieved clearance of one or more warts. Moreover, among the responders in the positive-PPD group, distant wart clearance was observed in 38% of patients, compared to 78% in the negative-PPD group. The result of this study suggested that a positive PPD skin test is not required to induce PPD efficacy.[22]

On the other hand, Sharquie et al reported that 10 out of the 14 responders in the intervention group were tuberculin-positive, and 13 out of 16 non-responders in the intervention group were tuberculin-negative, with a statistically significant difference. An intradermal injection of 0.1 mL PPD-2TU was used for the sensitization test. In this study, patients who tested positive for tuberculin skin test demonstrated better responses to PPD treatment. Furthermore, a better outcome was observed in patients with previous BCG vaccination, suggesting prior sensitization to *M. tuberculosis* bacilli.[54] These variable findings called for further study regarding the effect of prior sensitization status on the treatment outcome of PPD.

Other Factors

Most studies found no statistically significant relationship between baseline characteristics of the study participants, such as age, duration, number, and type of warts, with the therapeutic response to PPD. However, Awad et al[23] and Jaiswal et al[38] reported younger age of patients among the good responders compared to the minimal or non-responders. The weaker immunological response with increasing age might cause this.[11] Abd-Elazeim et al,[16] Elela et al[31] and Nada et al[44] observed that longer-duration warts were less responsive to treatment. Abd Elazeim et al[16] also reported that the mean size of warts was significantly higher in minimal and non-responders than in complete and partial responders. Mohta et al[8] reported a negative correlation between the number of warts and treatment outcomes in which patients showing complete clearance had a mean of 9.13 lesions compared to 17.26 lesions in patients with moderate to no clearance. Jain et al[37] reported that plane warts showed the optimal response to PPD, compared to palmoplantar and periungual warts, which best responded to MMR.

Comparative Studies

Comparison to Destructive Treatments

Cryotherapy is a commonly used destructive treatment option for warts. A study by Amirnia et al compared intralesional PPD to cryotherapy using liquid nitrogen spray in 3 freeze-thaw cycles with 2-week intervals and a maximum of 6 sessions. Complete clearance was achieved in 77.1% of participants in the PPD group compared to 18.2% in the cryotherapy group. Furthermore, the PPD group revealed less recurrence after six months of follow-up than the cryotherapy group (8.6% versus 24.2%, respectively).[11] Studies by Fatima et al[33] on 60 cutaneous warts patients, of which 30 patients were under treatment with cryotherapy (6 sessions), also reported comparable results with a clearance rate of 70% in the PPD group versus 30% in the cryotherapy group. Wan Ahmad et al[57] reported a higher clearance rate in the PPD group than in the cryotherapy group (86.7% versus 73.3%, respectively) compared to other comparative studies. However, this study involved fewer participants. Awad et al compared the combination of PPD and cryotherapy to PPD only. In the cryo-immunotherapy group, a single freezing cycle of cryotherapy for four sessions was followed by intralesional injection of PPD on the most prominent wart. While the clearance rate was comparable between the two groups, combination treatment showed less recurrence than PPD monotherapy (0 versus 20%, respectively).[23] Meanwhile, Moubasher et al[43] compared a combination of PPD and cryotherapy to each treatment alone for AGWs. Cryotherapy was given in 3 freeze-thaw cycles for four sessions. The cryo-immunotherapy group showed the highest clearance rate compared to PPD or cryotherapy alone (46.7% versus 13.3% and 26.7%, respectively). However, higher AEs were also observed in this group, with blistering and hypopigmentation as the most significant AEs.[43] Ibrahim et al[36] reported an even higher complete clearance rate in patients receiving combination therapy of intralesional PPD and cryotherapy (84%) than both monotherapy alone (24% in the cryotherapy group and 48% in the PPD group), with only a single freeze-thaw cycle.

Comparison to Other Immunotherapies

Mycobacterium w Vaccine

Mycobacterium w vaccine contained killed nonpathogenic atypical mycobacterium belonging to Runyon Group IV, currently known as *Mycobacterium indicus pranii*.[27] Mohta et al compared the efficacy of PPD to the *Mw* vaccine given intralesionally in 102 patients with extragenital warts. This study achieved complete clearance in 76.3% of patients in the *Mw* group and 65.9% of patients in the PPD group. No recurrence was observed during the six-month follow-up period. Besides a faster clearance rate, the *Mw* group demonstrates a better safety profile. Significant AEs like injection site granuloma, atypical mycobacterial infection, and generalized urticarial rash were reported in the PPD group.[8] In contrast, similar research by Chandra et al, which compared PPD to the *Mw* vaccine injected intradermally on a deltoid region for extragenital warts, reported that 32 patients in the *Mw* group experienced indurated nodules following every injection that later healed with scarring. Of these, 12 patients reported significant pain requiring analgetic treatment with paracetamol 650 mg, given twice daily until resolution; 11 patients developed ulceration in the nodule, and four patients reported discharge leaking from the nodule.[27] Another study by Mohta et al reported similar findings, with higher AEs in the *Mw* group compared to the PPD group. Severe AEs, including painful nodules, nodule site ulceration, and scarring, were observed only in the *Mw* group.[42]

Measles, Mumps, Rubella

A study by Shaheen et al compared PPD, MMR vaccine, and normal saline injected intralesionally on 30 patients with cutaneous and anogenital warts, given in 3-week intervals and a maximum of 3 sessions. Before treatment, sensitization tests were performed in both groups by intradermal injection of each antigen. Only responders were later included in the study.[17] For the MMR group, treatment dose was determined based on criteria by Johnson et al.[20] In contrast, in the PPD group, dosing was given according to criteria by Kus et al.[13] This study reported the highest clearance rate in the MMR group compared to PPD and placebo (80% versus 60% and 0, respectively). No severe side effects nor recurrence were reported during the three-month follow-up in either group.[17] Studies by Fawzy et al.[34] Bhalala et al.[25] Jain et al[37] and Nofal et al[47] reported similar results. However, the difference was not statistically significant in these studies.[25,34,47] In contrast, a study by Ahmed et al[21] reported a higher complete clearance rate in the PPD compared to the measles and rubella (MR) group (23.2% versus 9.3%, respectively). This finding follows a study by Sil et al[19] in which the clearance rate was reported as 44.4% in the PPD group and 41.66% in the MMR group. Being composed of more than one antigen might explain the higher clearance rate observed in former studies in the MMR group. However, regarding the effect on distant warts, Shaheen et al[17] and Mohammed et al[41] reported a higher clearance rate in the PPD compared to the MMR group (60% versus 40%, respectively, in both studies). This might reflect the less systemic effect of MMR compared to PPD, implying that MMR might be better used to treat single warts or to be injected in each wart.[17]

Candida

Fawzy et al compared intralesional PPD to *Candida* antigen and MMR in 120 patients with multiple plane warts. Forty patients received 0.1 mL PPD, while another 40 patients were given 0.1 mL of 1/1000 solution of *Candida* antigen, both injected intralesionally on the most prominent wart, two weeks apart and continued until a maximum of 5 sessions. Seventy percent of patients in the *Candida* antigen group achieved complete clearance, compared to 55% in the PPD group. Adverse events were comparable between the *Candida* antigen and PPD group, with edema and erythema reported more frequently in the former.[34] This finding aligns with Tawfik et al, in which complete clearance was observed in 85% of patients in the *Candida* antigen group compared to 72.5% in the PPD group. In this study, PPD-5TU and 1/1000 solution of *Candida* antigen were used. However, skin test results conducted previously determined the volume of solution injected.[56] Similarly, Nofal et al compared intralesional PPD to *Candida* antigen and MMR in 150 patients with periungual warts. Before treatment, a sensitization test was done by injecting 0.1 mL of each antigen intradermally. Only responders were later included in the study. Unlike the former, this study used 0.1 mL of 1/100 solution of *Candida* antigen given to 50 patients. In comparison, another 50 patients were given 0.1 mL PPD. Both injections were given intralesionally on the most prominent wart, with 2-week intervals and a maximum of 5 sessions. Complete clearance was achieved in 80% of participants of the *Candida* antigen group, compared to 70% in the PPD group. Moreover, complete clearance of distant warts was also higher in the Candida antigen than in the PPD group (86.7% versus 70%, respectively).[47] The ability to induce stronger local inflammatory reactions might explain *Candida* antigen's relative superiority over PPD. Another explanation could be the higher sensitivity to *Candida* antigen brought on by the widespread exposure to candidal infection, particularly in the early years of life.[34] Furthermore, Nofal et al[46] conducted a randomized placebo-controlled clinical trial comparing intralesional PPD and *Candida* antigen alternatingly versus either agent alone towards 160 patients presenting with multiple common warts. Patients were assigned to 4 groups: group 1 received 0.1 mL of intralesional PPD, group 2 received 0.1 mL of 1/1000 solution of *Candida* antigen, group 3 received alternating therapy of PPD and *Candida* antigen, and group 4 received 0.1 mL normal saline (control group). Injections were given into the most prominent wart every two weeks for six group sessions. Complete clearance was observed in 70.6% of participants in the alternating therapy group, 61.1% in the PPD group, 36.8% in the *Candida* antigen group, and 8.6% in the regular saline group, with a statistically significant difference. The synergistic effect of both agents might explain the better outcome observed in the alternating therapy group. Each antigen may trigger the cell-mediated immune response through a separate pathway, therefore augmenting one another.[46]

Bacillus Calmette-Guerin

Bacillus Calmette-Guerin contained a live attenuated form of *Mycobacterium bovis* introduced as a prophylactic agent against tuberculosis and other mycobacterial infections.[49,62] Podder et al conducted a double-blind, randomized controlled-trial comparing PPD to BCG in 60 patients with cutaneous warts. Thirty-three patients in the BCG group received 0.1 mL of BCG, while 27 patients in the PPD group received 0.1 mL of PPD-5TU. Both antigens were injected intradermally on the right arm. Treatment was given at a 4-week interval and a maximum of 3 sessions. In this study, both immunotherapies showed significant responses after four weeks onward.

Nonetheless, at the end of the study, complete clearance was achieved in 48.5% of patients in the BCG group compared to 18.5% of patients in the PPD group. This outcome might be explained by the more significant number of cross-reacting epitopes existing on the whole bacterial antigen of M. bovis than in PPD. However, AEs were also observed more frequently in the BCG group, including pain and abscess on the injection site, scar formation.[49]

Combination Antigen

Nofal et al compared the efficacy and safety of triple intralesional immunotherapy composed of PPD, *Candida* antigen, and MMR versus each agent alone in 160 patients with multiple cutaneous recalcitrant warts. Patients were randomly assigned into four groups: group A received 0.3 mL PPD, group B received 0.3 mL of 1/100 solution of *Candida* antigen, group C received 0.3 mL MMR, while group D received 0.3 mL combination of the three antigens (0.1 mL each, combined in the same syringe), injections were done intralesionally into the most prominent wart every two weeks, for a maximum of 5 sessions. Although both target and distant warts' complete clearance was reported to be highest in the triple immunotherapy (77.5% and 65%, respectively), this effectiveness was not significantly different compared to other groups that received mono immunotherapy. There was also a statistically significant difference in AEs observed between all groups; the most common AE was pain during injection, which was observed in all groups. Although it is expected that triple immunotherapy activates different immune pathways induced by various microbial antigens and different vaccine natures, each of which acts on a certain arm of the immune response, resulting in robust stimulation of CMI. However, in this study, triple immunotherapy produced nonsignificant difference in effectiveness compared to monotherapy. It also has disadvantages, such as difficulty obtaining all three antigens simultaneously.[48]

Comparison to Other Treatments

Vitamin D3

Although the mechanism of action of vitamin D3 in the treatment of warts has not yet been fully understood, some have suggested that in addition to regulating cell proliferation and proliferation, it also exhibits immunoregulatory properties.[63] It has been proposed that vitamin D3 can activate toll-like receptors on human macrophages, leading to increased expression and production of antimicrobial peptides and alteration of innate immunity.[32,63] In a study by Farhana et al comparing PPD to vitamin D3 in 20 patients with cutaneous warts, the complete clearance rate was higher in the PPD compared to the vitamin D3 group (80% versus 70%, respectively). This study used 0.2 mL of 15 mg/mL (600.000) vitamin D3 and 0.2 mL of PPD-5TU, given intralesionally into each wart every two weeks until complete clearance was achieved. The number of sessions required to achieve complete clearance in the PPD group was 3–4 sessions compared to 6 sessions in the vitamin D3 group.[32] Study by Jain et al[37] also reported similar findings in which complete clearance was achieved in 85% of patients in the PPD group compared to 80% in the vitamin D3 group. In addition to complete clearance of injected warts, distant warts clearance was also higher in the PPD group, supporting its superiority in inducing systemic effects.[17,37] On the contrary, Ahmed et al.[21] Ghaly et al[35] and Raveendra et al[52] reported a higher complete clearance rate in the vitamin D3 group. However, a study by Ghaly et al[35] demonstrated the more favourable effect of PPD in the clearance of distant warts compared to vitamin D3 (37.5% versus 25%, respectively).

Zinc

Zinc sulfate is hypothesized to work by modulating macrophage and neutrophil functions, NK cell/phagocyte activity, and different types of inflammatory cytokines. When injected intradermally, it causes significant infiltration of inflammatory cells, consisting of eosinophils followed by lymphocytes and fibroblasts, into the injection site. Awad et al

compared the efficacy of PPD to zinc sulfate 2% in 120 pediatric warts patients. Patients were randomized into two groups; one group received 0.1 mL of PPD, while another received zinc sulfate 2%; treatment was given as an intralesional injection on the most prominent wart with two-week intervals and a maximum of 5 sessions. Despite the higher complete clearance rate in the zinc sulfate group, the PPD group demonstrated a better safety profile. Significant AEs were common in the zinc sulfate group, including pain (70%), inflammation (26.7%), ulceration (8.3%), and scars (16.7%), compared to only injection site itching (13.3%) in the PPD group. Furthermore, after six months of follow-up, recurrence was observed more frequently in the zinc sulfate group (10%) compared to the PPD group (1.7%).[24]

5-Fluorouracil

5-fluorouracil (5-FU) is an antimetabolite, a pyrimidine analogue that enhances the production of Th1 cytokines, activating the natural killer and cytotoxic cells to eliminate HPV. Durgadevi et al compared the efficacy of intralesional PPD using PPD-1TU and topical 5% 5-FU in 50 patients with periungual warts. The volume of PPD injected was determined by the size of the skin test reactivity conducted before treatment. In the PPD group, treatment was given in 3-week intervals with a maximum of 6 sessions. In contrast, topical 5% 5-FU was given under occlusion daily at night and left for 12 hours for three months. Complete clearance was significantly higher in the PPD group (88%) compared to the 5-FU group (20%). The different treatment approaches in each group may explain this finding. Patients in the PPD group received intralesional injections exclusively delivered by an investigator. In contrast, treatment in the 5-FU group was self-applied. Therefore, the results highly depended on the patient's motivation and adherence to the treatment protocol. Moreover, faster time to resolution was observed in the PPD group compared to the 5-FU group (6.6 weeks versus 9.8 weeks, respectively). No AE was reported in the PPD group, while 8% of patients in the 5-FU group reported paronychia, erythema, and itching.[29]

Isotretinoin

Retinoids are known to promote the proliferation of basal cells and the number of cells expressing differentiation markers like involucrin, loricrin, filaggrin, and epidermal transglutaminase, which results in increased epidermal desquamation. Oral retinoids also demonstrate an anti-angiogenic mechanism by inhibiting vascular endothelial growth factor synthesis by keratinocytes, causing clearance of angiogenesis-dependent warts. Furthermore, it is also known as a potent immunomodulator capable of inducing apoptosis and suppressing viral transcription in the affected keratinocytes. Diab et al conducted a randomized clinical trial in which low-dose oral tretinoin combined with intralesional PPD was compared to PPD monotherapy for treating multiple common warts. Forty patients were equally divided into two groups. One group received 0.1 mL of intralesional PPD and an oral placebo given to the most prominent wart every two weeks for a maximum of 6 sessions. In contrast, another group received intralesional PPD, as previously mentioned, plus low-dose isotretinoin (0.2–0.4 mg/kg/day) for three months. Complete clearance was achieved in 35% of patients in the PPD monotherapy group and 55% in the combination group. Nevertheless, the difference was statistically insignificant. This finding might be explained by the dose of isotretinoin in this study, which may not have been high enough to create a potent synergistic effect and preserve the immune response after PPD injection. Beside cheilitis and dry skin, which was more pronounced in the combination group, other side effects were comparable between both groups. In this study, the low-dose isotretinoin did not add a therapeutic value for treating common warts.[28]

Conclusion

PPD immunotherapy demonstrated promising efficacy and safety in treating cutaneous and anogenital warts, including in the pediatric population. Although previous research on PPD showed good efficacy and safety profile in treating AGWs in pregnant women, a comparison study with other modalities has not been done, which needs to be confirmed in future research. Clearance of distant, uninjected warts provides an additional benefit of PPD, particularly in cases involving multiple lesions and challenging locations. These studies were performed in countries with prevalent tuberculosis infection, and BCG vaccination is obligatory. Therefore, it sensitized such population to *M. tuberculosis*, and the subsequent wart treatment with PPD injection may result in easier stimulation of CMI responses. However, for this reason, the result of our study is not yet applicable to the general population.

Furthermore, trials studying the effect of prior sensitization status on treatment response still demonstrated inconsistent results. Intralesional and injection from distant sites showed comparable results. Variable treatment outcomes demonstrated in these studies may be related to the difference in dosing, interval, and frequency of treatments. Therefore, clinical trials with larger sample sizes are needed to determine the optimal dosing and frequency of treatment to standardize the treatment protocols, also adding into consideration countries in which the prevalence of tuberculosis is low. Studies with longer follow-up duration are also necessary to further evaluate recurrences and long-term AEs. Comparative studies showed comparable results with other immunotherapies. Future research on combination therapy of currently available procedural therapy such as electrocautery with PPD injection and both the effectiveness and safety on special populations such as the elderly, immunocompromised individuals, those on immunosuppressants, and patients with HIV or autoimmune diseases can be considered.

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Disclosure

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