Systematic Reviews and Meta-analyses

Intralesional immunotherapy for non-genital warts: A systematic review and meta-analysis

Hyun Jeong Ju, Hye Ree Park[1], Ji Yoon Kim, Gyong Moon Kim, Jung Min Bae, Ji Hae Lee

Departments of Dermatology, St. Vincent's Hospital, Paldal-gu, Suwon, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Abstract

Background: Intralesional immunotherapy has been reported to be effective for warts and to show good safety profiles, but this has not yet been systematically studied.

Aims: To determine the efficacy and safety of intralesional immunotherapy for treating non-genital warts.

Methods: We comprehensively searched the MEDLINE, Embase, Web of Science and Cochrane Library databases from the times of their inception to January 3, 2020. The primary outcome was the rate of complete response of all lesions. The distant complete response rate of warts located in an anatomically different body part and the recurrence rate were also analyzed.

Results: A total of 54 prospective studies was ultimately included. The immunotherapeutic agents used were *Mycobacterium w* vaccine, measles, mumps and rubella vaccine, purified protein derivative, *Candida* antigen, interferon, bacillus Calmette-Guérin vaccine and others. The pooled rate of complete response among all patients with non-genital warts treated using intralesional immunotherapy was 60.6% (95% confidence interval 54.8–66.5%). The pooled recurrence rate was 2.0% (95% confidence interval, 1.1–2.9%). All reported adverse events were mild and transient.

Limitations: The heterogeneity among studies

Conclusion: Intralesional immunotherapy is suggested for use in patients with multiple warts, given its promising results, good safety profile and low recurrence rate.

Key words: Intralesional immunotherapy, immunotherapy, non-genital wart, systematic review, warts

Plain Language Summary

Intralesional immunotherapy has been reported to be effective for warts, but this has not been systematically studied. In this meta-analysis, intralesional immunotherapy demonstrated significant therapeutic effects on non-genital warts with high safety profiles and low recurrence rates and can be recommended for use in patients with multiple non-genital warts.

Introduction

Warts are the most common clinical manifestation of human papillomavirus on the skin and mucous membranes. They can greatly affect a patient's quality of life by causing embarrassment, fear of negative appraisal by others, and frustration due to persistent recurrence.[1,2] Various treatment methods are available, such as physical destruction (e.g., cryotherapy, electrosurgery, ablative laser, or surgical removal), chemical destruction (e.g., salicylic acid or trichloroacetic acid), and anti-proliferative agents (e.g., podophyllin, 5-fluorouracil or bleomycin). Unfortunately, no treatment has yet shown 100% effectiveness as a cure. Furthermore available modalities may cause pain, scarring, and is associated with high recurrence rates.[3]

Immunotherapeutic agents act by enhancing the host cell-mediated immunity that helps to eliminate the virus rather than simply destroying visible skin lesions[4] and have recently

How to cite this article: Ju HJ, Park HR, Kim JY, Kim GM, Bae JM, Lee JH. Intralesional immunotherapy for non-genital warts: A systematic review and meta-analysis. Indian J Dermatol Venereol Leprol 2022;88:724-37.

Corresponding author: Dr. Ji Hae Lee, Department of Dermatology, St. Vincent's Hospital, Paldal-gu, Suwon, South Korea. l.jihaemd@gmail.com

Received: December, 2020 **Accepted:** February, 2022 **EPub Ahead of Print:** July, 2022 **Published:** November, 2022

DOI: 10.25259/IJDVL_1369_20 **PMID:** 35962514

received increasing attention for the treatment of warts because of their non-destructive action, high safety profiles, promising results, and low recurrence rates. Contact immunotherapy using contact sensitizers (diphenylcyclopropenone or dinitrochlorobenzene), topical imiquimod, oral cimetidine or intralesional immunotherapy has been attempted as viable immunotherapeutic options for treatment of warts, and their therapeutic effects vary from study to study.

Intralesional immunotherapy has been assessed as an alternative therapeutic approach, particularly for cases of recalcitrant or multiple warts, since it may facilitate the clearance of not only the injected wart but also surrounding non-injected warts. Various immunotherapeutic agents including skin test antigens (mumps, *Candida*, and *Trichophyton*); the combined measles, mumps, and rubella vaccine; the tuberculin purified protein derivative; *Mycobacterium w* vaccine; and bacillus Calmette–Guérin vaccine have been assessed. A recent study used network meta-analysis to examine the comparative efficacy and safety of different modalities in the treatment of warts,[5] but the treatment response rate has not been studied systematically. Therefore, we performed a systematic review and meta-analysis of all relevant prospective studies available to evaluate the treatment responses, safety and recurrence rate of each type of intralesional immunotherapy for the management of non-genital warts.

Methods

Protocol and registration

We conducted a single-arm meta-analysis of prospective studies on the treatment response of intralesional immunotherapy for treating non-genital warts. We reported this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[6] and this study was registered with PROSPERO, an international database of prospectively registered systematic reviews (https://www.crd.york.ac.uk/PROSPERO/, CRD42020163379).

Databases

We performed a comprehensive search using predefined search terms in MEDLINE, EMBASE, Web of Science, and Cochrane Library databases from the respective dates of database inception to January 4, 2020. The main keywords used were "intralesional," "immunotherapy," "purified protein derivative," "*Trichophyton*," "BCG," "bacillus Calmette-Guerin," "MMR," "measles-mumps-rubella," "candida," "*Mycobacterium*," "vitamin D," "*Corynebacterium*," "INF," "interferon," "Propionium," "*Propionibacterium*," "tuberculin," "vaccine," "vaccination," "wart" and "verrucae." All prospective and experimental studies were included and the reference lists of identified relevant review articles were scanned manually as well. All articles identified using this search process were screened independently by two reviewers (H. J. J. and H. R. P.). In cases of discrepancy between the two main reviewers, a final decision was reached by consensus with two other reviewers (J.M.B. and J.H.L).

Study selection

All relevant clinical studies that reported the treatment response of intralesional immunotherapy by a single injection of the immunotherapeutic agent into the largest lesion in each treatment session were examined. The inclusion criteria were[1] prospective study design (randomized or non-randomized controlled trials and open trials);[2] participants of all age groups with a diagnosis of a non-genital wart;[3] at least one intralesional immunotherapy or control (saline or sterile water injection) group;[4] at least 10 participants in each treatment arm, regardless of dropout rate; and,[5] outcomes measured based on complete response or no response (0 or <25%). Conversely, the exclusion criteria were[1] retrospective or observational study design;[2] different outcome measures;[3] other interventions or combined; and[4] unavailability of the corresponding authors. We excluded studies involving genital warts, as the causative virus and conventional therapeutic modalities are different from those of non-genital warts.

Data extraction, quality assessment and outcome measures

For the meta-analysis, two reviewers extracted the following predefined variables: authors, country, year of publication, study type, the immunotherapeutic agent used, numbers of treated patients, treatment protocols and outcome. Quality assessment of the analytic studies was performed.

The primary outcome was the treatment response rate of intralesional immunotherapy in patients with non-genital warts. Complete response was defined as the complete disappearance of all lesions including both the injected and nearby satellite lesions. The treatment response rate was calculated as the number of participants who achieved complete response divided by the total number of participants who completed the individual study. The no response rate was assessed by dividing the total number of patients who had no or minimal treatment response (<25%) by the total number of participants who had completed the individual study. Because the immune reaction to the intralesional injection can be effective not only for adjacent warts but also for anatomically distant warts, a secondary outcome, defined as distant complete response, was the clearance of distant warts located in an anatomically different body part, away from the injection site. In addition, the recurrence rate was analysed by compiling the studies that reported recurrence. Studies with fewer than 10 patients showing complete response after treatment were excluded.

Meta-regression for age and sex

Meta-regression analyses were conducted to determine whether the estimated treatment response rates varied according to age or sex of patients and were performed by setting the mean age and female to male ratio of participants in each study as moderator variables, respectively.

Safety profiles

We noted all reported adverse events. We recorded common events and their frequencies for each study and searched for serious adverse events.

Statistical analyses

The rates of corresponding treatment responses of the included studies were pooled by generic inverse variance weighting and were combined using a random-effects model.[7] Heterogeneity was assessed using the I^2 value and subset analyses.[8] We used a funnel plot of sample size against log odds to determine publication bias because conventional funnel plots can be asymmetric in the absence of publication bias, especially in studies for extreme proportional metrics.[9] Meta-analyses were conducted using R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) software with "metagen" and "metafor" packages.

Results

Search results

We initially identified a total of 1,348 records through database searching and six additional records from the reference lists of related articles; 727 duplicates were removed and 494 were deleted after reviewing the titles and abstracts [Figure 1]. A total of 133 full-text articles was assessed in terms of eligibility; of these, 79 were excluded after full-text evaluation. The remaining 54 studies fulfilled the inclusion criteria and were included in the final analysis [Table 1].

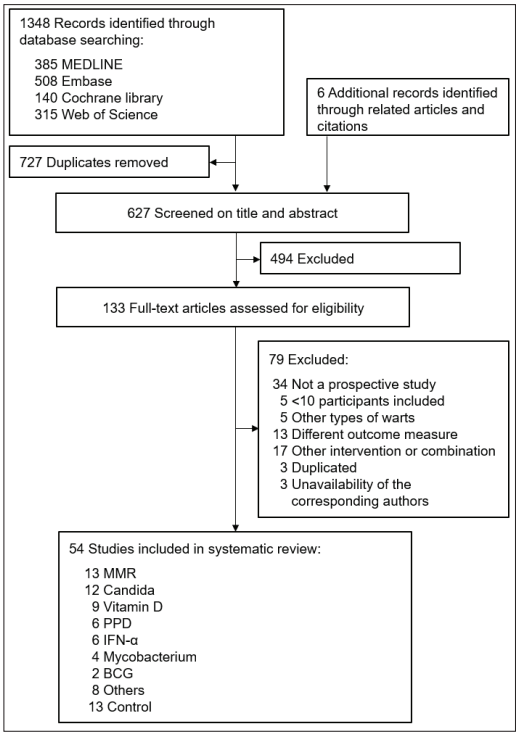

Figure 1: Flow diagram showing how eligible studies were identified in the present review

Characteristics of included studies

A total of 54 studies of 3,446 enrolled patients was deemed finally eligible [Table 2]. Overall, 13 studies with 747 patients in the MMR group[10-22]; 12 studies with 436 patients in the *Candida* group[23-34]; nine studies with 311 patients in the Vitamin D group[25,35-42]; six studies with 235 patients in the PPD group[38,43-47]; six studies with 197 patients in the interferon-α group[48-53]; four studies with 127 patients in the Mw group[54-57]; two studies with 49 patients in the BCG group[13,58]; and one study each of other therapeutic agents of smallpox vaccine,[59] mumps antigen,[34] mumps or *Candida* antigen,[60] mumps or *Candida* or *Trichophyton* antigen,[52] HPV,[61] Propionium,[62] and zinc[37] were included. As a control group, 13 studies with 470 patients who received saline or sterile water injection were included.[10,15,16,20,22,25,40,43,49,52,53,59,62] The mean treatment duration was 8.2 ± 6.0 weeks, and the mean follow-up duration was 4.6 ± 3.5 months (range, 1–25 months).

Treatment response of injected and nearby lesions

The overall complete response rate was 60.6% (95% confidence interval: 54.8–66.5%) among 53 studies with 2,548 patients [Figure 2a]. The complete response ratio of the Mw group was 73.1% (95% confidence interval: 55.6–90.6%) in four studies,[54-57,63] the *Candida* group was 62.6% (95% confidence interval: 53.3–71.9%) in 11 studies,[23,24,26-34] MMR group was 63.2% (95% confidence interval: 53.1–73.4%) in 13 studies,[10-22] PPD group was 62.7% (95% confidence interval: 42.4–83.0%) in six studies,[38,43-47] Vitamin D group was 54.2% (95% confidence interval: 32.7–76.0%) in eight studies,[35-42] interferon-α group was 51.9% (95% confidence interval: 27.0–76.9%) in six studies,[48-53] and BCG group was 50.9% (95% confidence interval: 5.0–96.8%) in two studies.[13,58] There was no significant difference depending on the immunotherapeutic agent used (p-value, 0.88). In the control group receiving saline/sterile water injection, the complete response rate was 17.3% (95% confidence interval: 10.0–24.5%) in 12 studies.[10,15,16,20,22,40,43,49,52,53,59,62]

Overall no response rate of intralesional immunotherapy was 16.6% (95% confidence interval: 12.4–20.8%) in 38 studies including a total of 1,719 patients. The no response rate was highest in the IFN-α group (48.1% [95% confidence interval: -2.2–98.4%] in two studies[49,52]), followed by in the MMR group (20.9% [95% confidence interval: 7.5–34.2%] in six studies[12,14,17,18,21,22]) and *Candida* group (14.6% [95% confidence interval: 8.8–20.3%] in eight studies[24,25,28,29,31-34]), whereas the no response rate of the control group was 79.7% (95% confidence interval: 66.2–93.2%) in seven studies.[22,25,40,43,49,52,62]

Treatment response of distant lesions

Among the studies included in this analysis, 15 described the treatment response of distant lesions located away from the mother wart. The overall distant complete response rate of the intralesional immunotherapy was 51.6% (95% confidence interval: 37.9–65.3%) [Figure 2b]. The distant

Table 1: Clinical characteristics of studies included in this review

Study, yr	Country	Study design[a]	Population	Enrolled patients, n	Age, yr (range)[b]	Male/female	Type of warts[c]	Immunotherapeutic agent[d]
Israel *et al.*, 1969	US	PD RCT	NA	T: 50 C: 50	NA	NA	NA	T: Smallpox vaccine C: Saline
Gibson *et al.*, 1986	UK	PD OT	Adults	T: 16	35 (19–54)	7/5	NA	T: IFN-α
Vance *et al.*, 1986	US	PD RCT	NA	T: 80 C: 42	NA	NA	PW	T: IFN-α C: Sterile water
Brodell *et al.*, 1995	US	SA OT	All	T: 22	21.9 (7–48)	9/13	PW	T: IFN-α
Johnson *et al.*, 2001	US	PD RCT	All	T1: 54 T2: 10	31.3	NA	CW	T1: Mumps antigen T2: Candida antigen
Park *et al.*, 2002	Korea	PD RCT	All	T: 10	18.6 (5–37)	6/4	PW	T: IFN-α
Signore *et al.*, 2002	US	PD OT	All	T: 100	23.7	35/52	CW, PW	T: Candida
Clifton *et al.*, 2003	US	SA OT	Children	T: 47	12.9 (4–18)	25/22	NA	T: Mumps or Candida antigen
Arcaute et al., 2004	Mexico	SA OT	All	T: 30	NA (5–67)	16/14	NA	T: Candida
Johnson *et al.*, 2004	US	SA OT	All	T: 260	21.4 (2–70)	98/108	NA	T: Mumps, Candida and Trichopyton antigen
Horn *et al.*, 2005	US	PD RCT	NA	T1: 58 T2: 43 T3: 48 C: 61	37 (23–31) 38 (12–29) 40 (21–25) 34 (28–32)	23/31 12/29 21/25 28/32	NA	T1: Mumps or Candida or Trichophyton antigen T2: Antigen plus IFN-α T3: IFN-α C: Saline
Aksakal *et al.*, 2008	Turkey	PD OT	All	T: 45 C: 8	25.1 24.6	22/23 4/4	CW, PW	T: IFN-α C: Saline
Kim *et al.*, 2010	US	SA OT	Adults	T: 18	30.18 (18–46)	6/5	CW	T: Candida
Nofal *et al.*, 2010	Egypt	PD RCT	Adults	T: 85 C: 50	32.4 (14–57) 30.2 (16–52)	31/39 17/23	CW	T: MMR C: Saline
Choi *et al.*, 2012	Korea	SA OT	Children	T: 40	NA	NA	NA	T: MMR
Nasser *et al.*, 2012	Brazil	PD DB RCT	All	T: 14 C: 14	NA	NA	CW, PW	T: Propionium C: Saline
Majid *et al.*, 2013	India	SA OT	Adults	T: 40	24.3 (14–36)	20/14	CW, PW	T: Candida
Meena *et al.*, 2013	India	SA OT	Adults	T: 40	25.2 ± 7.18 (13–48)	36/4	CW, FW, PW	T: Mycobacterium
Abd-Elazeim *et al.*, 2014	Egypt	PD RCT	All	T: 20 C: 20	22.7 ± 8.4	18/22	CW, PW	T: PPD C: Saline
Dogra *et al.*, 2014	India	PD RCT	NA	T: 33	NA	NA	CW	T: Mycobacterium
Garg *et al.*, 2014	India	SA OT	All	T: 30	22.5 ± 11.1 (6–45)	19/11	PW	T: Mycobacterium
Zamanian *et al.*, 2014	Iran	PD DB RCT	All	T: 30 C: 30	18.9 ± 12 20.1 ± 10	13/11 12/10	NA	T: MMR C: Saline
Nofal *et al.*, 2015	Egypt	SA OT	Adults	T: 70	38.9 (18–55)	35/30	CW	T: MMR
Dhakar *et al.*, 2016	India	PD RCT	Adults	T: 33	22.8	18/15	PW	T: Mycobacterium
El-Samahy *et al.*, 2016	Egypt	SA OT	All	T: 52	24.6 ± 10.1 (5-43)	12/13	NA	T: PPD
Kerure *et al.*, 2016	India	SA OT	Adults	T: 110	24 (12–52)	NA	CW	T: PPD
Parmar *et al.*, 2016	India	SA OT	Children	T: 44	NA (4–17)	17/23	CW	T: MMR
Saini *et al.*, 2016	India	SA OT	All	T: 100	24.8 ± 7.7 (10–45)	54/32	CW, FW, PW	T: MMR
Saoji *et al.*, 2016	India	SA OT	All	T: 61	28.3 (4–57)	40/15	CW, FW, PW	T: PPD
Kavya *et al.*, 2017	India	SA OT	Adults	T: 42	20 ± 9.7 (12–66)	27/15	CW, PW, filiform wart	T: Vitamin D3
Khozeimeh *et al.*, 2017	India	PD RCT	Adults	T: 30	23.4 ± 6.7	19/11	CW, PW	T: Candida
Nofal *et al.*, 2017	India	SA OT	All	T: 54	25.9 ± 13.8 (3–64)	21/33	CW	T: Candida

Table 1: *Continued...*

Study, yr	Country	Study design[a]	Population	Enrolled patients, n	Age, yr (range)[b]	Male/female	Type of warts[c]	Immunotherapeutic agent[d]
Raghukumar *et al.*, 2017	India	SA OT	All	T: 64	23.9 (8–66)	32/28	CW, PW, FW, filiform wart	T: Vitamin D3
Agrawal *et al.*, 2018	India	PD DB RCT	All	T: 50 C: 50	25 ± 9.5 (10–45) 27 ± 8.9 (10–44)	19/11 17/13	CW	T: MMR C: Saline
Awal *et al.*, 2018	India	PD RCT	Adults	T: 75 C: 75	28.9 ± 9.4 (15–48) 33.6 ± 9.2 (17–50)	40/32 27/23	CW	T: MMR C: Saline
Mohtashim *et al.*, 2018	India	SA OT	Adults	T: 200	26.26 ± 8.8	NA	CW, PW	T: MMR
Munnangi *et al.*, 2018	India	PD OT	Adults	T1: 15 T2: 15	21.96 ± 6.79	17/13	CW	T1: MMR T2: BCG
Nofal *et al.*, 2018	Egypt	PD OT	Adults	T: 36	NA	NA	CW, PW	T1: Candida and acitretin T2: Candida
Sabry *et al.*, 2018	Egypt	SA OT	NA	T: 60	21.93 ± 14.24	24/34	CW, PW, FW, filiform wart	T: Candida
Abd El-Magid *et al.*, 2019	Egypt	PD RCT	NA	T1: 39 T2: 39	NA (10–60) NA (16–57)	18/2 16/4	PW	T1: Vitamin D3 T2: Zinc
Abou-Taleb *et al.*, 2019	Egypt	PD RCT	Adults	T1: 24 T2: 24	31.13 ± 6.86 32.13 ± 13.34	18/4 13/10	CW, PW	T1: Vitamin D3 T2: PPD
Chauhan *et al.*, 2019	India	SA OT	Adults	T: 110	31.31 ± 1.15 (19–62)	61/49	CW, PW	T: MMR
ElGhareeb *et al.*, 2019	Egypt	PD OT	Adults	T: 40	NA	NA	NA	T: MMR
El-Taweel *et al.*, 2019	Egypt	SA OT	Adults	T: 20	28.8 (15–50)	14/6	CW, PW	T: Vitamin D
Hodeib *et al.*, 2019	Egypt	PD OT	All	T: 20	18.9 ± 7.7 (5–40)	7/13	FW	T: Candida
Jaisinghani *et al.*, 2019	India	SA OT	Adults	T: 40	25.5 (18–46)	34/0	CW	T: BCG
Kareem *et al.*, 2019	Egypt	PD OT	Adults	T: 30 C: 20	NA (12–50)	NA	CW	T: Vitamin D C: Saline
Milante *et al.*, 2019	Philippines	PD RCT	Adults	T: 29	30.66 ± 1.49	16/13	CW, PW	T: PPD
Fathy *et al.*, 2019	Egypt	PD OT	NA	T1: 20 T2: 20 C: 20	29.2 26.15 NA	9/11 15/5 NA	NA	T1: Candida T2: Vitamin D C: Saline
Nasr *et al.*, 2019	Egypt	SA OT	All	T: 48	NA (9–45)	16/32	NA	T: Candida
Rezai *et al.*, 2019	Iran	PD RCT	NA	T: 30 C: 30	27.2 ± 8.73 25.37 ± 9.23	12/18 11/19	PW	T: MMR C: Saline
Naresh *et al.*, 2019	India	PD RCT	All	T: 60	31 (10–60)	40/20	CW, PW, filiform wart	T: Vitamin D
Verma *et al.*, 2019	India	SA OT	Adults	T: 36	20 (12–60)	24/12	CW, PW, filiform wart	T: Vitamin D
Nofal *et al.*, 2020	Egypt	PD OT	Adults	T: 22	29.27 ± 8.7 (16–45)	12/10	CW, PW	T: HPV vaccine

[a]Study design: SA, single arm; PD, parallel design; OT, open trial; DB, double-blind; RCT, randomized controlled trial, [b] Reported as mean (range) unless otherwise indicated, [c]Type of warts: CW: common warts, FW: flat warts, PW: plantar warts, [d]Immunotherapeutic agent: HPV: human papilloma virus, INF: Interferon, MMR: measles, mumps, rubella vaccine, Mw: *Mycobacterium w* vaccine, PPD: purified protein derivative vaccine, C: Control group, T: treatment group, NA: not available

Table 2: Clinical outcomes and adverse events in the studies included in this review

		Intervention						Clinical outcomes[b], n				
Study, yr	Country	Injected site[a]	Session, n*	Interval, wk	Duration, wk†	Follow up, month†	Enrolled patients, n	CR	DCR	NR	Recurrence	Adverse events (%)
1. MMR												
A Nofal and E Nofal, 2010	Egypt	MW	5	2	8	6	85	57	17	6	0	Flu-like symptom (8.6%), pain(85.7%)
Choi *et al.*, 2012	Korea	MW	6	2	10	1	40	8	NA	16	NA	Flu-like symptom (2.5%), pain(100%)
Zamanian *et al.*, 2014	Iran	EW	3	2	4	6	30	18	NA	NA	NA	Flu-like symptom(30%), pain(100%)
Nofal *et al.*, 2015	Egypt	MW	5	2	8	6	70	41	38	NA	2	Edema(1.5%), erythema(4.6%), flu-like symptoms(12.3%), pain(100%), pruritus(6.1%)
Parmar *et al.*, 2016	India	MW	5	3	12	6	44	35	NA	0	0	Erythema, pain, urticaria
Saini *et al.*, 2016	India	MW	3	3	6	6	100	40	NA	28	3	Erythema(8.1%), pain(53.5%), post-inflammatory hyperpigmentation(5.8%)
Agrawal *et al.*, 2018	India	MW	3	3	6	6	50	18	16	NA	3	Erythema(13.3%), pain(60%)
Awal and Kaur, 2018	India	MW	5	2	8	4	75	49	NA	NA	2	Edema/erythema/pruritus(4%), flu-like symptom(6%), pain(90%)
Mohtashim *et al.*, 2018	India	MW	5	2	8	6	200	120	NA	63	NA	Pain
Munnangi *et al.*, 2018	India	MW	5	2	8	3	15	5	3	NA	NA	Erythema(6%), hyperpigmentation(4%)
Chauhan *et al.*, 2019	India	MW	5	2	8	2	110	42	NA	7	0	Pain(100%)
ElGhareeb *et al.*, 2019	Egypt	MW	4	2	6		40	29	8	NA	NA	Flu-like symptoms(12.5%)
Rezai *et al.*, 2019	Iran	MW	5	2	8	6	30	14	NA	NA	0	Edema, erythema, flu-like symptom, pain, pruritus
2. Candida												
Johnson *et al.*, 2001	US	MW	3	3	6	4	10	7	NA	1	NA	Flu-like symptom, pain, pruritus
Signore, 2002	US	MW	3	5	8	25	100	44	NA	8	NA	Digital edema(2%), flu-like symptom(5%), headache(1%), herpes zoster(1%), localized wheal(3%), milia(1%), pain(2%), tenderness for 1 week(1%)
Arcaute *et al.*, 2004	Mexico	NA	2	4	4	NA	30	13	NA	6	NA	NA
Kim *et al.*, 2010	US	MW	10	3	NA	6	18	9	NA	1	1	Erythema, pain
Majid *et al.*, 2013	India	MW	3	3	6	6	40	19	3	NA	0	Flu-like symptom(7.5%), pain
Khozeimeh *et al.*, 2017	Iran	MW	3	3	6	NA	30	23	NA	6	NA	Erythema(16.7%), flu-like symptom (3.3%), pain(100%)

(Contd...)

Table 2: (*Continued...*)

Study, yr	Country	Intervention					Enrolled patients, n	Clinical outcomes[b], n			Recurrence	Adverse events (%)
		Injected site[a]	Session, n*	Interval, wk	Duration, wk†	Follow up, month†		CR	DCR	NR		
Nofal *et al.*, 2017	Egypt	MW	5	2	8	6	54	37	9	5	0	Burning sensation(7.4%), edema(37%), erythema(9.3%), flu-like symptom(7.4%), pain(100%), pruritus(12.9%)
Nofal *et al.*, 2018	Egypt	MW	5	2	8	6	36	12	NA	NA	NA	Cheilitis, edema, flu-like symptom, pain, pruritus
Sabry *et al.*, 2018	Egypt	MW	6	2	10	6	60	44	6	NA	4	Edema/erythema/pruritus(44.8%), fever(6.9%)
Fathy *et al.*, 2019	Egypt	MW	3	3	6	6	20	NA	NA	4	2	Edema/erythema(25%), pain(100%)
Hodeib *et al.*, 2019	Egypt	MW	4	2	6	2	20	12	NA	8	0	Edema(35%), fever(20%), flu-like symptom(25%), hypopigmentation(5%), pain(100%), pain within the day of injection(20%)
Nasr *et al.*, 2019	Egypt	NA	6	2	10	6	48	30	NA	NA	0	Burning sensation(10.4%), edema(20.8%), erythema(41.7%), flu-like symptom(7.4%), pain(100%), pruritus(20.8%)
3. PPD												
Abd-Elazeim *et al.*, 2014	Egypt	MW	6	1	5	6	20	9	NA	1	1	Edema (5%), erythema and pain(15%), post-hypopigmentation(10%)
El-Samahy *et al.*, 2016	Egypt	MW	3	3	6	NA	52	9	NA	2	NA	Edema/erythema/pain(32.7%), pain required the intake of NSAID(3.8%)
Kerure *et al.*, 2016	India	MW	6	2	10	3	110	84	NA	5	0	Pain
Saoji *et al.*, 2016	India	EW	4	2	6	6	61	42	NA	NA	1	Edema/erythema(21.3%), flu-like symptom(1.6%), eczema(1.6%)
Abou-Taleb *et al.*, 2019	Egypt	MW	3	3	6	3	24	13	13	0	0	Edema(63.6%), erythema(68.2%), pain(81.8%)
Milante *et al.*, 2019	Philippines	MW	6	2	12	6	66	17	NA	NA	0	Constitutional symptoms(9.1%), edema(10.6%), vesiculation(1.5%)
4. IFN-a												
Gibson *et al.*, 1986	UK	MW	35	1	12	1.5	16	11	NA	NA	NA	Pain, swelling and redness, headache, tiredness, fever, shivering and sweating, aching, stiffness in muscles and joints, sore throat, dizziness, depression, diarrhea, vomiting
Vance *et al.*, 1986	US	MW	3	5	3	3	80	11	NA	14	NA	Pain(33.8%)

(Contd...)

Table 2: (*Continued...*)

Study, yr	Country	Intervention					Enrolled patients, n	Clinical outcomes[b], n				Adverse events (%)
		Injected site[a]	Session, n*	Interval, wk	Duration, wk†	Follow up, month†		CR	DCR	NR	Recurrence	
Brodell and Bredle, 1995	US	MW	32	5	8	9.5	22	16	NA	NA	3	Mild discomfort(13.6%), lymphangitis(4.5%)
Park *et al.*, 2001	Korea	MW	9	5	3	6	10	5	NA	NA	1	Flu-like symptom(50%), pain(100%)
Horn *et al.*, 2005	US	MW	5	3	12	0	48	12	3	34	NA	Edema/erythema(23.9%), flu-like symptom(19.1%)
Aksakal *et al.*, 2008	Turkey	MW	1	0	0	12	45	25	NA	NA	0	Flu-like symptom(71.1%)
5. Vitamin D												
Kavya *et al.*, 2017	India	MW	4	2	6	6	42	33	NA	0	1	Edema(78.57%), dyspigmentation (2.4%),
Raghukumar *et al.*, 2017	India	EW	4	3	9	6	64	54	NA	NA	2	Edema(3.33%), erythema(5%), pain(100%)
Abd El-Magid *et al.*, 2019	Egypt	EW	4	2	8	3	39	2	NA	0	0	Hematoma(5%), pain(5%), vasovagal attack(40%)
Abou-Taleb *et al.*, 2019	Egypt	MW	3	3	6	3	24	5	NA	3	0	Edema(13%), erythema(17.4%), pain(87%), pruritus(34.8%)
El-Taweel *et al.*, 2019	Egypt	EW	2	4	4	3	20	8	3	3	0	Edema/erythema(90%), erosion(5%), lymphadenopathy(5%), pain(100%)
Fathy *et al.*, 2019	Egypt	MW	3	3	6	6	20	NA	NA	6	1	Pain(100%)
Kareem *et al.*, 2019	Egypt	MW	2	4	4	3	30	12	2	11	0	Pain(23.3%), pruritus(26.7%), both pain and pruritus(10%)
Naresh, 2019	India	EW	3	4	9	6	60	48	NA	NA	4	Edema(60%), Pain(100%)
Verma *et al.*, 2019	India	MW	2	4	6	6	36	25	NA	NA	NA	Edema(55.5%), dyspigmentation(5.6%)
6. Mycobacterium												
Meena *et al.*, 2013	India	EW	10	1	12	NA	40	23	NA	3	3	Edema(16%), erythema(70%), fever(5%), superficial ulceration(2.5%), tenderness and swelling of submandibular lymph nodes(5%)
Dogra *et al.*, 2014	India	MW	12	1	11	NA	33	20	NA	NA	NA	NA
Garg and Baveja, 2014	India	MW	10	4	36	6	30	28	NA	2	4	Edema/erythema(33.33%), fever(66.67%), headache(10%), myalgia(23.33%), spontaneous ulceration (6.67%), vomiting(6.67%)

(Contd...)

Table 2: (*Continued...*)

Study, yr	Country	Intervention					Enrolled patients, n	Clinical outcomes[b], n			Recurrence	Adverse events (%)
		Injected site[a]	Session, n*	Interval, wk	Duration, wk†	Follow up, month†		CR	DCR	NR		
Dhakar *et al.*, 2016	India	MW	12	1	11	4	33	20	12	7	0	Cellulitis of lower limb(6.6%), erythematous swelling(73.3%), fever(43.3%), pain(23.3%), regional lymphadenopathy(10%), swelling at the sensitization site(100%)
7. BCG												
Munnangi *et al.*, 2018	India	MW	5	2	8	3	15	4	1	NA	NA	Flu-like symptoms(30%), hyperpigmentation(53.3%), Ulceration(60%)
Jaisinghani *et al.*, 2019	India	MW	3	3	6	3	40	25	9	1	0	BCGitis(2.9%), edema(5.9%), erythema(8.8%), flu-like symptom(100%), hypopigmentation(5.9%), nodule/granuloma(11.8%), pain(100%), pruritus(38.2%), scarring(14.7%), ulceration(5.9%)
8. Others												
HPV vaccine												
Nofal *et al.*, 2020	Egypt	MW	6	2	10	6	22	18	8	2	0	Drowsiness or fatigue(9.1%), pain(100%), pruritus(90.9%)
Mumps												
Johnson *et al.*, 2001	US	MW	3	3	6	4	45	22	14	4	0	Flu-like symptom, pain, pruritus
Mumps or Candida												
Clifton *et al.*, 2003	US	MW	3	3	6	0	47	22	19	9	NA	Edema/erythema(10%), pruritus(50%)
Mumps or Candida or Trichophyton												
Horn *et al.*, 2005	US	MW	5	3	12	0	58	29	15	25	NA	Edema/erythema(26.1%), flu-like symptom(14.9%)
Mumps and Candida and Trichophyton												
Johnson and Horn, 2004	US	MW	10	4	36	0	260	146	112	33	NA	Edema/erythema/pruritus (20.4%), flu-like symptom(13.6%)
Mumps or Candida or Trichophyton and IFN-a												
Horn *et al.*, 2005	US	MW	5	3	12	0	43	28	20	13	NA	Edema/erythema(26.1%), flu-like symptom(63.8%),
Smallpox vaccine												
Israel, 1969	US	MW	1	0	0	2	50	26	NA	NA	2	Erythema/tenderness(40%), lymphangitis(8%), lymphadenitis(8%), malaise and fever(12%)

Table 2: (*Continued...*)

Study, yr	Country	Intervention					Enrolled patients, n	Clinical outcomes[b], n			Recurrence	Adverse events (%)
		Injected site[a]	Session, n*	Interval, wk	Duration, wk†	Follow up, month†		CR	DCR	NR		
Propionium												
Nasser, 2012	Brazil	MW	5	4	20	0	14	8	NA	1	NA	NA
Zinc												
Abd El-Magid *et al.*, 2019	Egypt	EW	4	2	8	3	39	4	NA	0	2	Edema(15%), hematoma(55%), pain(100%), post-treatment hyperpigmentation(10%), superficial necrosis(15%)
9. Control												
Israel, 1969	US	MW	1	0	0	2	50	21	NA	NA	0	Edema/erythema(2%)
Vance *et al.*, 1986	US	MW	3	5	3	3	42	8	NA	17	NA	None
Horn *et al.*, 2005	US	MW	5	3	12	0	61	13	9	47	NA	Edema/erythema(23.9%), flu-like symptom(2.1%)
Aksakal *et al.*, 2008	Turkey	MW	1	0	0	3	8	0	NA	NA	0	None
A Nofal and E Nofal, 2010	Egypt	MW	5	2	8	6	50	11	3	13	3	None
Nasser, 2012	Brazil	MW	5	4	20	0	14	0	NA	9	NA	NA
Abd-Elazeim *et al.*, 2014	Egypt	MW	6	1	5	6	20	0	NA	18	2	Edema (5%), erythema and pain(15%), post-hypopigmentation(10%)
Zamanian *et al.*, 2014	Iran	EW	3	2	4	6	30	6	NA	NA	NA	Pain(100%)
Agrawal et al, 2018	India	MW	3	3	6	6	50	7	0	NA	4	Erythema, pain
Awal and Kaur, 2018	India	MW	5	2	8	4	75	5	NA	NA	3	Flu-like symptom(2%), pain(88%)
Fathy *et al.*, 2019	Egypt	MW	3	3	6	6	20	NA	NA	20	NA	Pain(100%)
Kareem *et al.*, 2019	Egypt	MW	2	4	4	3	20	1	0	19	0	Pain(20%)
Rezai *et al.*, 2019	Iran	MW	5	2	8	6	30	5	NA	NA	0	Edema, erythema, flu-like symptom, pain, pruritus

[a]Injection site: EW: every single wart, MW: mother wart, [b]Clinical outcomes: CR: complete response, DCR: distant complete response, NR: no response, *maximum, †mean, NA, not available

complete response rate of the MMR group was 62.0% (95% confidence interval: 31.1–93.0%) and that of the *Candida* group was 42.0% (95% confidence interval: 7.3–76.7%). The distant complete response rate of Vitamin D (17.6%, [95% confidence interval: −0.5–35.8%]) and IFN-α (8.8%, [95% confidence interval: −0.7–18.4%]) showed no significant difference from that of the control group with saline injection (14.2% [95% confidence interval: −1.9–30.2%]).

Meta-regression for age and sex

There were no significant linear interactions between mean age and sex (female to male ratio) with changes in treatment response, and the coefficients for the variables were not statistically significant (*p*-value, 0.61 for age; 0.43 for sex).

Rate of recurrence among patients who have achieved complete response

A total of 47 studies reported recurrence after treatment, and the median follow-up period was six months (range, 0–12 months). The recurrence rates among studies were reported from 0 to 16.7%. The pooled recurrence rate was 2.0% (95% confidence interval: 1.1–2.9%).

Safety of intralesional immunotherapy

Of the 54 clinical studies included in this analysis, 51 reported occurrence of adverse events, and 41 presented the specific frequency of adverse events. The most common adverse event was pain, reported in 35 of 51 studies regardless of the immunotherapeutic agent used, with frequency varying

from 2 to 100%. Flu-like symptoms were reported in 22 of the 51 studies, ranging in frequency from 2.5 to 100%. Other adverse events including erythema, oedema, and pruritus have been reported frequently, and lymphadenopathy, vasovagal syncope, dyspigmentation, eczematous reaction and ulceration have been noted as rare adverse events.

Discussion

In this systematic review and meta-analysis, the overall treatment response rate for the complete response of intralesional immunotherapy was 60.6% (95% confidence interval: 54.8–66.5%) [Figure 3]. The complete response rate for each immunotherapeutic agent was observed from 50.9 to 73.1%, but the difference was not statistically significant. The treatment response rate of distant lesions was 51.6% (95% confidence interval: 37.9–65.3%), and all agents except vitamin D and IFN-α showed similar results.

Intralesional immunotherapy is thought to target the CMI response by introducing antigens at the wart site, inducing a T cell-mediated systemic response. All intralesional immunotherapy methods share some common mechanism of action, regardless of the agent used, so it is presumed that they showed similar efficacy in this study. Horn *et al*. reported that increased proliferation of peripheral blood mononuclear cells to autologous HPV antigens after initiation of intralesional immunotherapy using mumps, *Candida*, and *Trichophyton* skin test antigens was more likely to be observed among responders than non-responders.[52] Kim *et al*. in their trial of intralesional injection of *Candida* antigen reported an immune response to HPV-57 L1 peptide among responders, suggesting that L-1–specific T-cells may be involved in wart regression.[31] The strong proinflammatory signals against Mw attract antigen-presenting cells with the production of helper T-cell type 1 cytokines and activation of cytotoxic and natural killer T cells that probably also recognize and process low-profile HPV particles in the infected tissue.[64] Vitamin D is thought to be effective in the treatment of warts as a mechanism that regulates cytokine production through its action on Vitamin D receptors at the same time controlling differentiation and proliferation of epidermal cells.[65,66]

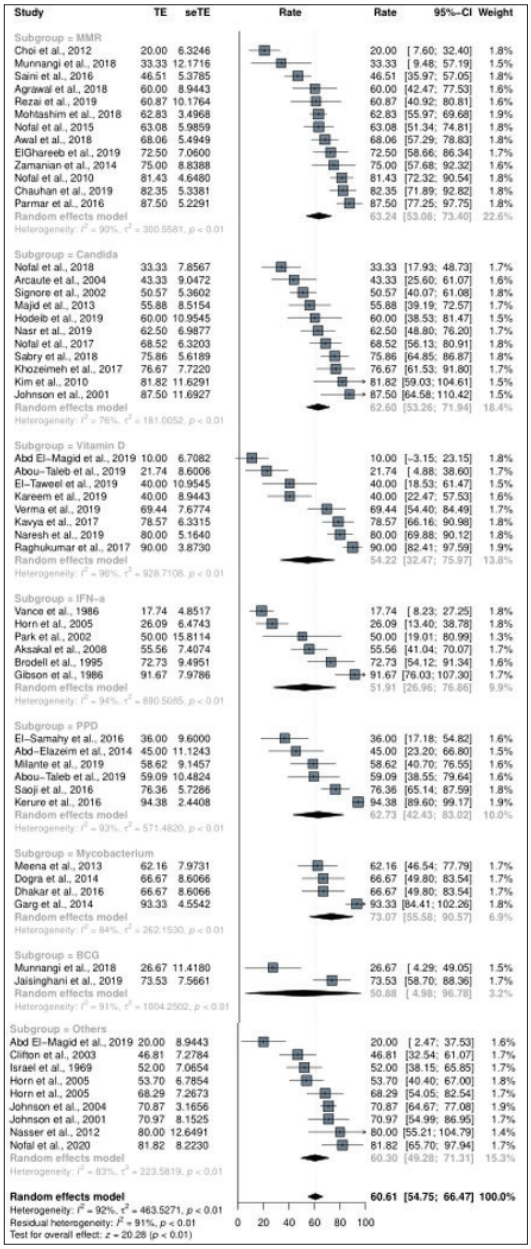

Figure 2a: Treatment response of intralesional immunotherapy. The complete response rate of intralesional immunotherapy on injected and adjacent warts

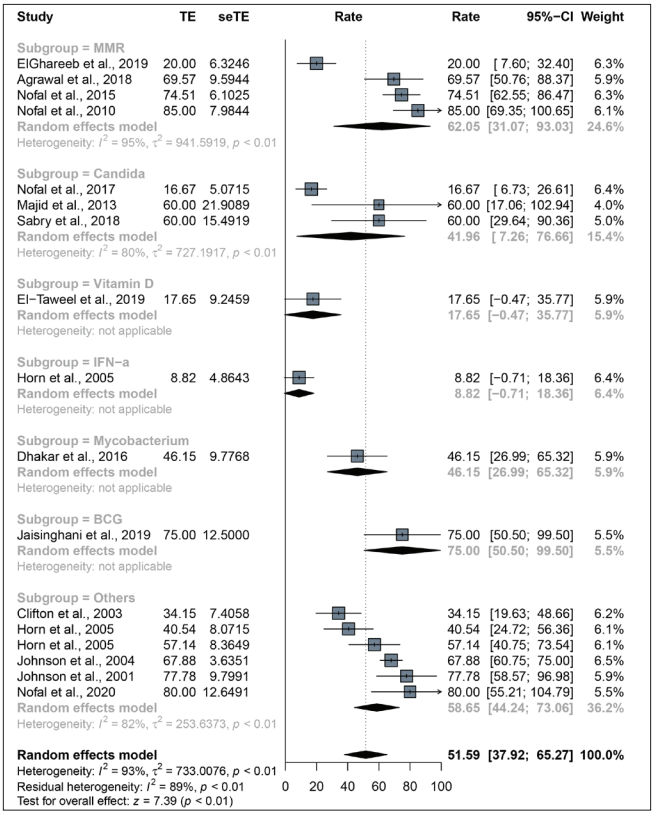

Figure 2b: Treatment response of intralesional immunotherapy. The complete response of intralesional immunotherapy on distant warts located in other body parts

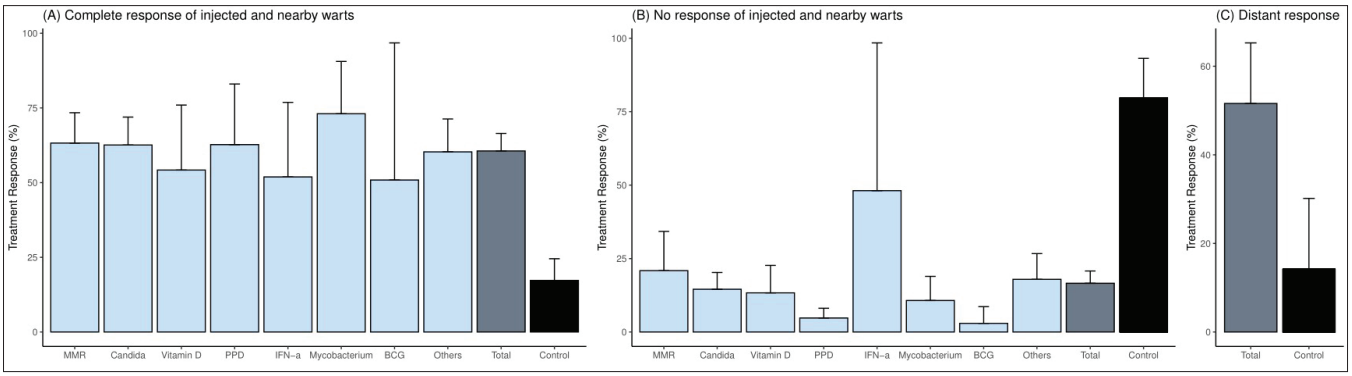

Figure 3: The pooled treatment response of intralesional immunotherapy

Reports of distant wart resolution suggested a systemic immune response resulting from intralesional immuno therapy. The immunity acquired through the use of an immunotherapeutic method could exert a positive effect with a higher response rate in the treatment of patients with numerous distant warts. An evoked delayed-type hypersensitivity response to both the used antigens and the wart tissue, as well as an instigated cellular immunity through activation of cytotoxic and natural killer cells against HPV have been suggested as aspects of this phenomenon.[67] Based on this assumption, the effectiveness of intralesional immunotherapy in eradicating distant warts and the occurrence of better outcomes in patients with previous sensitization to the employed antigens could be justified.[22,31,34,60,64]

The most troublesome factor in the management of warts is the high recurrence rate of at least 30% after apparently successful treatment, which is possibly driven by the recrudescence of the virus from the surrounding tissue reservoir.[68] In the present systematic review, the median follow-up duration among assessed studies was six months, and the pooled recurrence rate was 2.0%, which is remarkably lower than the recurrence rate reported in correlation with conventional treatments. It is assumed that the immune response acquired by intralesional immunotherapy may have played a role in preventing recurrence.

Intralesional immunotherapy is a safe treatment option. The adverse events appeared either in the form of local immunologic or irritant reactions or systemic and constitutional symptoms, such as fever and flu-like symptoms. Pain at the injection site was mentioned in most studies but was rarely prolonged in duration. However, painful indurated nodules, discharges, and scars may occur at the injection site of the Mw vaccine and there was one case report of a severe adverse event of a painful purple finger after injection of *Candida albicans* antigen for the treatment of a periungual wart,[69] so awareness of all possible complications is important.

Intralesional immunotherapy is useful for treatment of non-genital warts, especially in patients with multiple lesions, as it is simple to perform, has a short downtime, rare mild adverse effects, favorable treatment response, and low recurrence rate. Conventional therapies for warts with a destructive mechanism might similarly be effective against conspicuous lesions;[70] however, adverse events and high recurrence rates are often major limitations inherent in these approaches.[71] For example, the recurrence rate of warts after cryotherapy is as high as 30%.[72] Adverse events that follow use of destructive modalities such as infection, ulceration, scarring and hypo- or hyperpigmentation seldom occur when using intralesional antigen immunotherapy.

This study was limited by substantial heterogeneity of the included studies, which may be attributable to variations in treatment regimen, study population race, and disease severity (number, location, and duration of warts) across studies.

Conclusion

We systematically reviewed the response to intralesional immunotherapy in the management of non-genital warts. Intralesional immunotherapy, compared with conventional therapeutic methods, showed favorable treatment outcomes, lower incidence of side effects, and lower recurrence rate. With its efficacy in clearing distant warts, intralesional immunotherapy is a promising treatment approach for patients with multiple or recalcitrant warts.

Abbreviations

BCG: Bacillus Calmette-Guerin
CI: Confidence interval
CMI: Cell-mediated immunity
HPV: Human papillomavirus
MMR: Measles, mumps, and rubella
Mw: Mycobacterium w
PPD: Purified protein derivative

Declaration of patient consent

Patient consent is not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Forman D, Martel de C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L *et al.* Global burden of human papillomavirus and related diseases. Vaccine 2012;30:12–23.
2. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australas J Dermatol 2003;44:169–73.
3. Rivera A, Tyring SK. Therapy of cutaneous human papillomavirus infections. Dermatologic Ther 2004;17:441–8.
4. Thappa DM, Chiramel MJ. Evolving role of immunotherapy in the treatment of refractory warts. Indian Dermatol Online J 2016;7:364–70.
5. Salman S, Ahmed MS, Ibrahim AM, Mattar OM, El-Shirbiny H, Sarsik S *et al.* Intralesional immunotherapy for the treatment of warts: A network meta-analysis. J Am Acad Dermatol 2019;80:922–30.
6. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
7. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
9. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol 2014;67:897–903.
10. Rezai MS, Ghasempouri H, Marzidareh O, Cherati JY, Rokni GH. Intralesional injection of the measles-mumps-rubella vaccine into resistant palmoplantar warts: A randomized controlled trial. Iran J Med Sci 2019;44:10–17. .
11. ElGhareeb MI. Comparative study of autoimplantation therapy and intralesional injection of MMR vaccine in warts treatment. Dermatol Ther 2019;32:e13135.
12. Chauhan PS, Mahajan VK, Mehta KS, Rawat R, Sharma V. The efficacy and safety of intralesional immunotherapy with measles, mumps, rubella virus vaccine for the treatment of common warts in adults. Indian Dermatol Online J 2019;10:19–26.
13. Munnangi P, Kishore KLP, Devi VN. Comparative study between intralesional MMR and intralesional BCG in treatment of verruca vulgaris. IOSR J Dent Med Sci 2018;17:44–50.
14. Mohtashim M, Amin SS, Adil M, Arif T, Singh M, Bansal R *et al.* Efficacy of intralesional MMR vaccine in treatment of single or multiple refractory cutaneous warts. Przeglad Dermatologiczny 2018;105:498–508.
15. Awal G, Kaur S. Therapeutic outcome of intralesional immunotherapy in cutaneous warts using the mumps, measles, and rubella vaccine: A randomized, placebo-controlled trial. J Clin Aesthet Dermatol 2018;11:15-20.
16. Agrawal C, Vyas K, Mittal A, Khare AK, Gupta LK. A Randomized double blind controlled study comparing the efficacy of intralesional MMR vaccine with normal saline in the treatment of cutaneous warts. Indian Dermatol Online J 2018;9:389–93.
17. Saini P, Mittal A, Gupta LK, Khare AK, Mehta S. Intralesional mumps, measles and rubella vaccine in the treatment of cutaneous warts. Indian J Dermatol Venereol Leprol 2016;82:343–5.
18. Parmar N, Kuruvila S. Intralesional measles, mumps and rubella vaccine for the treatment of multiple and recalcitrant nongenital cutaneous warts in children: A prospective, uncontrolled open-label study. BJD 2016;175:160.
19. Nofal A, Nofal E, Yosef A, Nofal H. Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: A promising approach. Int J Dermatol 2015;54:667–71.
20. Zamanian A, Mobasher P, Jazi GA. Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with wart. Adv Biomed Res 2014;3:107.
21. Choi H, Kim HR, Na CH, Kim MS, Shin BS, Choi KC. Intralesional immunotherapy of warts with mumps, measles and rubella vaccine. J Dermatol 2012;39:63–4.
22. Nofal A, Nofal E. Intralesional immunotherapy of common warts: Successful treatment with mumps, measles and rubella vaccine. J Eur Acad Dermatol Venereol 2010;24:1166–70.
23. Nasr M, Marie A, Boghdadi G, Elsaid R, Salah E. Role of mannose binding lectin in response to candida antigen immunotherapy of warts. J Dermatolog Treat 2021;32:376–80.
24. Hodeib AAE, Al-Sharkawy BG, Hegab DS, Talaat RAZ. A comparative study of intralesional injection of candida albicans antigen, bleomycin and 5-fluorouracil for treatment of plane warts. J Dermatolog Treat 2021;32:663–8.
25. Fathy G, Sharara MA, Khafagy AH. Intralesional vitamin D3 versus candida antigen immunotherapy in the treatment of multiple recalcitrant plantar warts: A comparative case–control study. Dermatol Ther 2019;32:e12997.
26. Sabry HH, Hamed AM, Salem RM, Marei AM, El Sebaey RM. Peripheral blood toll-like receptor 4 correlates response to candida immunotherapy of warts. Dermatol Ther 2018;31:e12691.
27. Nofal A, Khattab F, Nofal E, Elgohary A. Combined acitretin and Candida antigen versus either agent alone in the treatment of recalcitrant warts. J Am Acad Dermatol 2018;79:377–8.
28. Nofal A, Marei A, Amer A, Amen H. Significance of interferon gamma in the prediction of successful therapy of common warts by intralesional injection of Candida antigen. Int J Dermatol 2017;56: 1003–9.
29. Khozeimeh F, Jabbari Azad F, Mahboubi Oskouei Y, Jafari M, Tehranian S, Alizadehsani R *et al.* Intralesional immunotherapy compared to cryotherapy in the treatment of warts. Int J Dermatol 2017;56:474–8.
30. Majid I, Imran S. Immunotherapy with intralesional Candida albicans antigen in resistant or recurrent warts: A study. Indian J Dermatol 2013;58:360–5.
31. Kim KH, Horn TD, Pharis J, Kincannon J, Jones R, O'Bryan K *et al.* Phase 1 clinical trial of intralesional injection of candida antigen for the treatment of warts. Arch Dermatol 2010;146:1431–3.
32. Arcaute LAB, Páramo AV, Aguilar REB, Collado CM. Experience with intralesional candidin in the treatment of viral warts. Dermatologia Revista Mexicana 2004;48:307–10.
33. Signore RJ. Candida albicans intralesional injection immunotherapy of warts. Cutis 2002;70:185–92.
34. Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or candida skin test antigens: A novel immunotherapy for warts. Arch Dermatol 2001;137:451–5.
35. Kavya M, Shashikumar BM, Harish MR, Shweta BP. Safety and efficacy of intralesional vitamin D3 in cutaneous warts: An open uncontrolled trial. J Cutan Aesthet Surg 2017;10:90–4.
36. Raghukumar S, Ravikumar BC, Vinay KN, Suresh MR, Aggarwal A, Yashovardhana DP. Intralesional Vitamin D3 injection in the treatment of recalcitrant warts: A novel proposition. J Cutan Med Surg 2017;21:320–4.
37. Abd El-Magid WM, Nada EEA, Mossa RA. Intralesional injection of vitamin D3 versus zinc sulfate 2% in treatment of plantar warts: A comparative study. J Dermatolog Treat 2021;32:355–60.
38. Abou-Taleb DAE, Abou-Taleb HA, El-Badawy O, Ahmed AO, Thabiet Hassan AE-D, Awad SM. Intralesional vitamin D3 versus intralesional purified protein derivative in treatment of multiple warts: A comparative clinical and immunological study. Dermatol Ther 2019;32:e13034.
39. El-Taweel A, Salem RM, Allam AH. Cigarette smoking reduces the efficacy of intralesional vitamin D in the treatment of warts. Dermatol Ther 2019;32:e12816
40. Kareem IMA, Ibrahim IM, Mohammed SFF, Ahmed AAB. Effectiveness of intralesional vitamin D3 injection in the treatment of common warts: Single-blinded placebo-controlled study. Dermatol Ther 2019;32:e12882.

41. Naresh M. A study of effectiveness of intralesional vitamin D3 in treatment of multiple cutaneous warts. IOSR J Dent Med Sci 2019;18:84–7.
42. Verma A, Bishnoi S, Bagri M, Agarwal S. Intralesional vitamine-D3 in multiple skin warts. IOSR J Dent Med Sci 2019;18:74–8.
43. Abd-Elazeim FMA, Mohammed GFA, Fathy A, Mohamed RW. Evaluation of IL-12 serum level in patients with recalcitrant multiple common warts, treated by intralesional tuberculin antigen. J Dermatolog Treat 2014;25:264–7.
44. El-Samahy MH, El-Shennawy DA, Labib SMW, Abdallah MA. Evaluation of serum interleukin-12 and interferon-y in patients with multiple warts treated with intralesional tuberculin injection. J Egypt Women's Dermatol Soc 2016;13:23–8.
45. Kerure AS, Nath AK, Oudeacoumar P. Intralesional immunotherapy with tuberculin purified protein derivative for verruca: A study from a teaching hospital in South India. Indian J Dermatol Venereol Leprol 2016;82:420–2.
46. Saoji V, Lade NR, Gadegone R, Bhat A. Immunotherapy using purifiied protein derivative in the treatment of warts: An open uncontrolled trial. Indian J Dermatol Venereol Leprol 2016;82:42–6.
47. Milante RR, Venida-Tablizo A, King-Ismael D. Efficacy and safety of single versus multiple intralesional immunotherapy with purified protein derivative (PPD) in the treatment of multiple verruca vulgaris. Int J Dermatol 2019;58:1477–82.
48. Gibson JR, Harvey SG, Kemmett D, Salisbury J, Marks P. Treatment of common and plantar viral warts with human lymphoblastoid interferon-α - Pilot studies with intralesional, intramuscular and dermojet injections. Br J Dermatol 1986;115:76–9.
49. Vance JC, Bart BJ, Hansen RC, Reichman RC, McEwen C, Hatch KD. Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. Arch Dermatol 1986;122:272–7.
50. Brodell RT, Bredle DL. The treatment of palmar and plantar warts using natural alpha interferon and a needleless injector. Dermatol Surg 1995;21:213–8.
51. Choi GS, Park JH, Kim YK, Choi GS. Combination therapy with intralesional interferon a-2b and pulsed dye laser for the treatment of periungual warts. Ann Dermatol 2002;14:82–7.
52. Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: A single-blinded, randomized, and controlled trial. Arch Dermatol 2005;141:589–94.
53. Aksakal AB, Ozden MG, Atahan C, Onder M. Successful treatment of verruca plantaris with a single sublesional injection of interferon-alpha2a. Clin Exp Dermatol 2009;34:16–9.
54. Meena JK, Malhotra AK, Mathur DK, Mathur DC. Intralesional immunotherapy with mycobacterium w vaccine in patients with multiple cutaneous warts: Uncontrolled open study. JAMA Dermatol 2013;149:237–9.
55. Dogra S, Kumar A, Kanwar AJ. Efficacy and safety of intralesional mycobacterium w vaccine and cryotherapy in the treatment of refractory extragenital warts: A randomized open-label comparative study. Br J Dermatol 2014;171:55–6.
56. Garg S, Baveja S. Intralesional immunotherapy for difficult to treat warts with Mycobacterium w vaccine. J Cutan Aesthet Surg 2014;7:203–8.
57. Dhakar AK, Dogra S, Vinay K, Sarangal R, Kanwar AJ, Singh MP. Intralesional Mycobacterium w Vaccine Versus cryotherapy in treatment of refractory extragenital warts: A randomized, open-label, comparative study. J Cutan Med Surg 2016;20:123–9.
58. Jaisinghani A, Dey V, Suresh M, Saxena A. Bacillus Calmette-Guerin immunotherapy for recurrent multiple warts: An open-label uncontrolled study. Indian J Dermatol 2019;64.
59. Israel RM. Treatment of warts by vaccination. Arch Dermatol 1969;100:222–3.
60. Clifton MM, Johnson SM, Roberson PK, Kincannon J, Horn TD. Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens. Pediatr Dermatol 2003;20:268–71.
61. Nofal A, Marei A, Ibrahim SM, Nofal E, Nabil M. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. J Am Acad Dermatol 2020;82:94–100.
62. Nasser N. Treatment of common warts with the immune stimulant Propionium bacterium parvum. An Bras Dermatol 2012;87:585–9.
63. Chandra S, Sil A, Datta A, Pal S, Das NK. A double-blind, randomized controlled trial to compare the effectiveness and safety of purified protein derivative of tuberculin antigen with mycobacterium w vaccine in the treatment of multiple viral warts. Indian J Dermatol Venereol Leprol 2019;85:355–66.
64. Gupta S, Malhotra AK, Verma KK, Sharma VK. Intralesional immunotherapy with killed Mycobacterium w vaccine for the treatment of ano-genital warts: An open label pilot study. J Eur Acad Dermatol Venereol 2008;22:1089–93.
65. Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: Is this relevant to malignant melanoma? Br J Dermatol 2002;147:197–213.
66. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770–3.
67. Amirnia M, Khodaeiani E, Fouladi DF, Masoudnia S. Intralesional immunotherapy with tuberculin purified protein derivative (PPD) in recalcitrant wart: A randomized, placebo-controlled, double-blind clinical trial including an extra group of candidates for cryotherapy. J Dermatolog Treat 2016;27:173–8.
68. Chandrashekar L. Intralesional immunotherapy for the management of warts. Indian J Dermatol Venereol Leprol 2011;77:261–3.
69. Perman M, Sterling JB, Gaspari A. The painful purple digit: An alarming complication of Candida albicans antigen treatment of recalcitrant warts. Dermatitis 2005;16:38–40. .
70. Bourke JF, Berth-Jones J, Hutchinson PE. Cryotherapy of common viral warts at intervals of 1, 2 and 3 weeks. Br J Dermatol 1995;132:433–6.
71. Goihman-Yahr M, Goldblum OM. Immunotherapy and warts: A point of view. Clin Dermatol 2008;26:223–5.
72. Lipke MM. An armamentarium of wart treatments. Clin Med Res 2006;4:273–93.