Intralesional immunotherapy for the treatment of warts: A network meta-analysis

Samar Salman, MSc,[a,b] Mohamed Shehata Ahmed, MedSci,[c] Ahmed Mohamed Ibrahim, MBBCh,[b,d] Omar Mohamed Mattar, MedSci,[b,e] Hassan El-Shirbiny, MedSci,[b,f] Sameh Sarsik, MSc,[a] Ahmed M. Afifi, MBBCh,[g] Ruba Marwan Anis, MedSci,[b,e] Nadim Aiman Yakoub Agha, MedSci,[b,e] and Abdelrahman Ibrahim Abushouk, MBBCh[g]

Tanta, Zagazig, Cairo, and Kafrelsheikh, Egypt

Background: Without clear evidence, selecting among the existing immunotherapeutic options for warts remains challenging.

Objective: Through network meta-analyses, we aimed to evaluate the comparative efficacy of different intralesional immunotherapeutic modalities.

Methods: We included randomized controlled trials comparing intralesional immunotherapeutic modalities to cryotherapy, placebo, or imiquimod. All outcomes were presented as odds ratios (ORs) with 95% confidence intervals. Both conventional and network meta-analyses (with a frequentist approach) were conducted on R software. The P-score was used to rank different treatments.

Results: Network meta-analysis of 17 randomized controlled trials (1676 patients) showed that PPD (purified protein derivative vaccine, OR 39.56), MMR (measles, mumps, rubella vaccine, OR 17.46) and interferon β (OR 15.55) had the highest efficacy in terms of complete recovery at the primary site compared with placebo. Regarding complete recovery at the distant site, autoinoculation (OR 79.95), PPD (OR 42.95), and MMR (OR 15.39) were all statistically superior to placebo. According to the P-score, MMR was more effective than other modalities in reducing the recurrence rate at the same site.

Limitations: Relatively small sample size in some comparisons and variability in baseline characteristics.

Conclusion: PPD and MMR were the most effective in achieving complete primary and distant recovery (along with autoinoculation for distant recovery) and reducing the recurrence rate at the same site compared with cryotherapy and other immunotherapeutic modalities. (J Am Acad Dermatol 2019;80:922-30.)

Key words: cryotherapy; HPV; immunotherapy; network meta-analysis; warts.

Warts are common benign epidermal tumors, caused by human papilloma virus (HPV) infection.[1,2] Due to its highly infectious nature, most people experience HPV infection at some point in their life.[3,4] According to the form and anatomic site, warts are classified into verruca vulgaris, plane, plantar, filiform or digitate, myrmecia, mosaic, genital, and periungual warts. They are usually asymptomatic, but tenderness might exist with certain types of warts, such as plantar, subungual warts, or when warts are fissured.[5,6]

From the Department of Dermatology and Venereology, Tanta University Hospital, Faculty of Medicine, Tanta University[a]; Medical Research, Education, and Practice Association[b]; Faculty of Human Medicine, Zagazig University[c]; Faculty of Medicine, Al-Azhar University, Cairo[d]; Kasr Al-Ainy Faculty of Medicine, Cairo University[e]; Faculty of Medicine, Kafrelsheikh University[f]; and Faculty of Medicine, Ain Shams University, Cairo.[g]

Funding sources: None.

Conflicts of interest: None disclosed.

Accepted for publication July 3, 2018.

Reprint requests: Abdelrahman Ibrahim Abushouk, MBBCh, Faculty of Medicine, Ain Shams University, 11566 Ramsis St, Abbasia, Cairo, Egypt. E-mail: abdelrahman.abushouk@med.asu.edu.eg.

Published online July 10, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.07.003

Although spontaneous resolution occurs in about 60%-65% of warts within 2 years, most patients seek treatment because warts are cosmetically unacceptable.[3] Several management modalities are available, including medical agents (eg, high concentrations of salicylic acid, podophyllotoxin, 5-flurouracil, and oral zinc sulfate); physical destructive methods (eg, electrocautery, cryotherapy, and photodynamic therapy); or surgical excision. However, these methods might be associated with pain, scarring, and high recurrences rates.[7,8] In contrast, immunotherapeutic approaches act by enhancing the host cell-mediated immunity to eliminate the virus rather than just clearing the skin lesions.[8,9]

Nowadays, dermatologists commonly use intralesional immunotherapy for cutaneous and genital verruca, especially refractory types.[9] However, selecting between its different modalities remains a clinical challenge in the absence of clear evidence favoring one modality over the other. Network meta-analysis (NMA) is a statistical technique that allows comparison of multiple treatments simultaneously. It can synthesize direct, indirect, and mixed evidence. Typical outputs of NMA are relative intervention effects for all comparisons and ranking of interventions.[10] Through NMA approach, we aimed to evaluate the comparative safety and efficacy of different intralesional immunotherapeutic modalities in the treatment of warts.

CAPSULE SUMMARY

- Although intralesional immunotherapy is commonly used for wart treatment, selection among existing immunotherapeutic modalities remains challenging.
- Purified protein derivative vaccine and measles, mumps, and rubella vaccine are the most effective modalities for lesion clearance at primary and distant sites (along with autoinoculation), and also reduce recurrence.
- Purified protein derivative vaccine and measles, mumps, and rubella vaccine may be considered as first-line treatments for warts.

MATERIALS AND METHODS

We reported this study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines. The protocol of this review was registered on PROSPERO (CRD42017067775).

Literature search strategy

An electronic search of 4 databases (Medline via PubMed, Cochrane Central, Web of Science, and Scopus) was performed during May 2017 with the search terms ((intralesional) AND (immunotherapy OR PPD [purified protein derivative] OR trichophyton antigen OR BCG [bacilli Calmette-Guerin] OR MMR [measles, mumps, rubella] OR *Candida* OR *Mycobacterium indicus pranii* OR *Mycobacterium* w OR autoinoculate OR autoimplant OR vitamin D OR *Corynebacterium parvum* OR INF [interferon]-α OR INF-γ OR *Propionibacterium parvum* OR *Propionibacterium acne* OR tuberculin OR vaccine OR vaccination)) AND (warts OR verruca OR human papilloma virus). We used no filters by language or publication period. Two independent reviewers screened the retrieved reports for eligibility through title and abstract and full-text screening. Discrepancies were solved through discussion with a third reviewer.

Criteria for study eligibility

We included all randomized controlled trials (RCTs) that evaluated the use of any intralesional immunotherapeutic modality for the treatment of skin warts. No restrictions were made with regard to age, sex, or race of the participants. We excluded studies with unreliable data for extraction, overlapping data sets, or unavailable full-texts. Theses, case reports, in vitro studies, nonhuman trials, and secondary analyses were also excluded.

Data extraction and outcomes

Two reviewers developed the extraction sheet on Microsoft Excel (Redmond, WA) and pilot-testing was performed by all authors. Data were extracted by 2 independent reviewers and double-checked by a third reviewer. Disagreements were settled by consensus with senior researchers. The extracted data included patients' demographic characteristics, cure rates, and adverse events. Complete recovery from the primary wart was defined as complete lesion clearance and a return to normal skin markings at the injection site, and complete recovery at distant sites was defined as complete recovery of all noninjected warts. Immediate and late adverse effects were evaluated after each treatment session.

Risk of bias assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias.[11] Three reviewers assessed the risk of bias independently and discrepancies were resolved by discussion. The risk of bias in included studies was assessed in terms of random

Abbreviations used:

CI: confidence interval
HPV: human papilloma virus
INF: interferon
MMR: measles, mumps, and rubella vaccine
Mw: *Mycobacterium w* vaccine
NMA: network meta-analysis
OR: odds ratio
PPD: purified protein derivative vaccine
RCT: randomized controlled trial

sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other sources of bias.

Statistical analysis

First, we performed pairwise meta-analyses using R software (version 3.4.3). Then, NMA was conducted by using a frequentist approach and the R package netmeta. All outcomes were presented as odds ratios (ORs) with 95% confidence intervals (CIs). We used the P-score to rank different treatments. The P-score is a value between zero and one, where a larger value indicates better performance. It is based on frequentist point estimates and standard errors.[12] We used the net split function in R package netmeta to assess the consistency and inconsistency between direct and indirect evidence. Net heat plots were also used to assess heterogeneity. Warmer or cooler colors both indicated a significant inconsistency. Moreover, we used the chi-squared test, where a P value $<.1$ indicated significant heterogeneity. In case of significant heterogeneity, a random effects model was employed. Otherwise, the fixed effect model was adopted. A P value $<.05$ indicated a significant difference. Subgroup analysis for individual adverse events and sensitivity analysis were conducted.

RESULTS

Literature search and study characteristics

Initially, 924 records were retrieved form electronic database searches. After removing duplicates and excluded studies, 17 RCTs (1676 patients) were finally eligible (Fig 1).[13-29] The network plots illustrating direct evidence between the interventions are shown in Fig 2. The follow-up duration in the included studies ranged 1-8 months. The design, main findings, and baseline characteristics of patients in these studies are summarized in Supplemental Table I (available at http://www.jaad.org).

Doses of 0.1-0.3 mL of PPD, MMR, *Candida*, Mw vaccine, or *Propionibacterium parvum* showed effectiveness after 2-6 sessions (with 1–3-week intervals between sessions) for PPD[13,14,29] and 1-5 sessions (with 2–3-week intervals) for MMR and *Candida* antigen vaccines.[14-16,18,20,22,25] Only 1 trial[21] reported effectiveness with a higher dose of MMR (0.5 mL) after 3 sessions (with 2-week intervals). *Propionibacterium parvum* and Mw vaccine were used for 1-12 sessions (with 1–2-week intervals).[15,20,22] A dose of 1×10^6 IU of INF-α and INF-β for 3-12 sessions (with 3–7-day intervals) induced lesion clearance in most patients.[17,24-27] One trial reported effectiveness with only 1 session of INF-α using the same dose.[19] Autoinoculation was assessed after 3 sessions (with 4–8-week intervals) and showed significant reduction in the number of warts from the first follow-up visit.[28]

Assessment of risk for bias

Several included studies did not adequately report on their methods of randomization (8 studies) or allocation concealment (12 studies). Six studies were double-blinded, and 4 studies were single-blinded (outcome assessors only). Nine studies had a high risk of attrition bias, and most studies had a low risk of reporting bias.

Outcomes

Complete recovery in initial site. *Conventional meta-analysis.* The effect size favored MMR (OR 11.37, 95% CI 5.46-23.67), PPD (OR 96.08, 95% CI 17.2-536.6), INF-β (OR 15.55, 95% CI 6.08-39.77), INF-γ (OR 3.64, 95% CI 1.29-10.29), and *Propionibacterium* (OR 71.4, 95% CI 3-1696.74) over placebo. Moreover, the effect size favored PPD over cryotherapy (OR 15.19, 95% CI 4.64-49.69), while no significant differences were observed among other treatments.

Network meta-analysis. PPD (OR 39.56, 95% CI 7.13-219.42), *Propionibacterium* (OR 71.4, 95% CI 2.03-2515.91), MMR (OR 17.46, 95% CI 5.02-60.74), and INF-β (OR 15.55, 95% CI 2.37-101.85) were significantly superior to placebo. These results were consistent with the results of the conventional meta-analysis. In addition, PPD was superior to INF-α (OR 18.99, 95% CI 2.93-123.1), INF-γ (OR 10.83, 95% CI 1.2-97.68), and cryotherapy (OR 10.21, 95% CI 1.55-67.3), and MMR was significantly superior to INF-α (OR 8.38, 95% CI 1.96-35.86) (Table I). A sensitivity analysis was conducted by excluding the study by Nasser[15] that compared *Propionibacterium* with placebo. NMA showed that PPD, MMR, and INF-β were significantly superior to placebo, while other comparisons held similar effect sizes.

Complete recovery in distant sites. *Conventional meta-analysis.* The effect size favored MMR

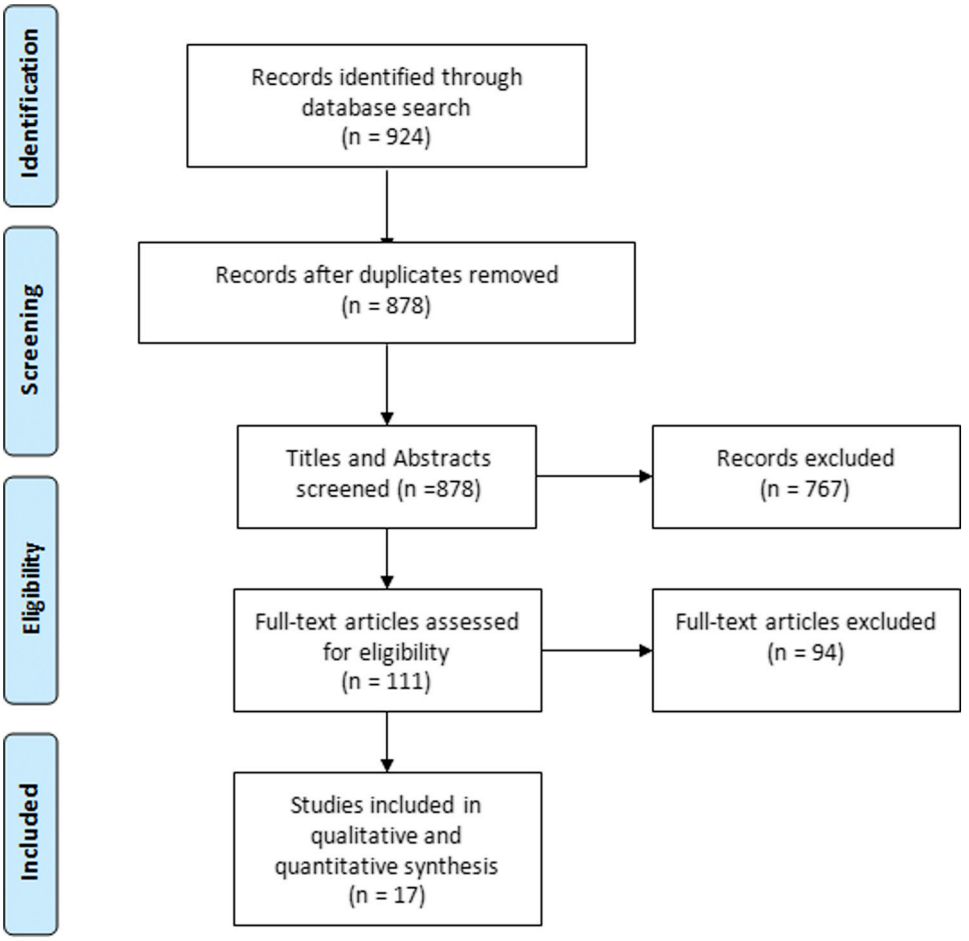

Fig 1. Warts PRISMA flow diagram of literature search and study selection. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

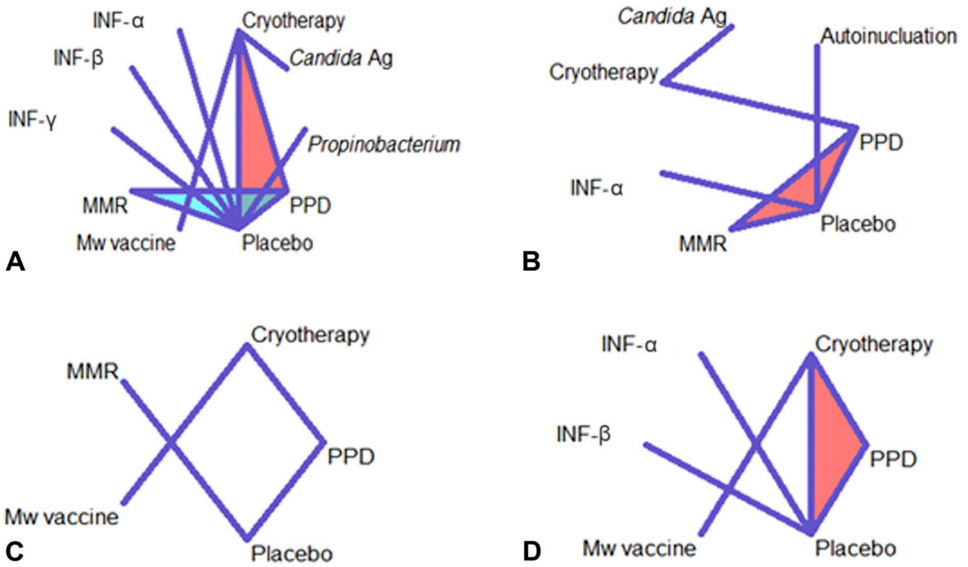

Fig 2. Warts network plots showing direct evidence between the assessed interventions in terms of complete recovery at initial site (**A**), complete recovery at distant site (**B**), recurrence (**C**), and all adverse events (**D**). The treatments are equally spaced on the perimeter of the circle. Any 2 treatments are connected by a line when there is at least 1 study comparing them. The shading indicates a 3-arm study. *Ag*, Antigen; *INF*, interferon; *MMR*, measles, mumps, rubella vaccine; *Mw*, *Mycobacterium* w; *PPD*, purified protein derivative vaccine.

Table I. Results of complete recovery at initial site according to network meta-analysis

Treatment	*Propionibacterium*	MMR	INF-β	*Candida* antigen	Mw vaccine	INF-γ	Cryotherapy	INF-α	Placebo
PPD	0.55 (0.01-28.85)	2.27 (0.37-13.93)	2.54 (0.20-32.37)	4.03 (0.26-63.72)	7.95 (0.53-118.83)	**10.83 (1.20-97.68)**	**10.13 (1.47-69.89)**	**18.99 (2.93-123.10)**	**39.56 (7.13-219.42)**
Propionibacterium		4.09 (0.09-178.12)	4.59 (0.08-257.80)	7.28 (0.07-811.70)	14.35 (0.13-1549.04)	19.54 (0.43-891.18)	18.29 (0.25-1323.70)	34.28 (0.90-1305.13)	**71.40 (2.03-2515.91)**
MMR			1.12 (0.12-10.72)	1.78 (0.07-42.74)	3.51 (0.15-80.30)	4.78 (0.74-30.68)	4.47 (0.37-54.10)	**8.38 (1.96-35.86)**	**17.46 (5.02-60.74)**
INF-β				1.59 (0.04-58.87)	3.12 (0.09-111.25)	4.25 (0.41-43.81)	3.98 (0.19-82.39)	7.46 (0.99-56.41)	**15.55 (2.37-101.85)**
Candida antigen					1.97 (0.13-30.34)	2.68 (0.09-78.98)	2.51 (0.35-18.05)	4.71 (0.20-112.84)	9.81 (0.45-215.01)
Mw vaccine						1.36 (0.05-38.32)	1.28 (0.19-8.47)	2.39 (0.10-54.58)	4.98 (0.24-103.86)
INF-γ							0.94 (0.06-14.60)	1.75 (0.37-8.42)	1.75 (0.37-8.42)
Cryotherapy								1.87 (0.16-22.61)	3.90 (0.36-42.00)
INF-α									2.08 (0.99-4.40)

The results are odds ratios with 95% confidence intervals when comparing the column-defined treatments with the row-defined treatments. Bold items are statistically significant.
INF, Interferon; *MMR*, measles, mumps, rubella vaccine; *Mw*, *Mycobacterium* w vaccine; *PPD*, purified protein derivative vaccine.

Table II. Results of complete recovery at distant site according to network meta-analysis

Treatment	PPD	MMR	*Candida* antigen	Placebo	INF-α	Cryotherapy
Autoinoculation	1.86 (0.06-54.98)	5.20 (0.20-136.18)	52.48 (0.54-5088.11)	**79.95 (4.34-1473.59)**	**103.37 (5.17-2066.92)**	**131.85 (1.56-11,144.27)**
PPD		2.79 (0.61-12.78)	**28.19 (1.30-610.93)**	**42.95 (7.66- 240.67)**	**55.53 (8.66- 355.92)**	**70.83 (4.02-1246.56)**
MMR			10.10 (0.33-312.35)	**15.39 (3.52-67.25)**	**19.89 (3.90-101.52)**	25.38 (0.99-652.08)
Candida antigen				1.52 (0.04-51.78)	1.97 (0.05-71.63)	2.51 (0.83-7.64)
Placebo					1.29 (0.65-2.59)	1.65 (0.06-46.82)
INF-α						1.28 (0.04-38.88)

The results are odds ratios with 95% confidence intervals when comparing the column-defined treatments with the row-defined treatments. Bold items are statistically significant.
INF, Interferon; *MMR*, measles, mumps, rubella vaccine; *PPD*, purified protein derivative vaccine.

(OR 12.11, 95% CI 2.48-59.19), PPD (OR 60.68, 95% CI 7.15-514.77), and autoinoculation (OR 86.01, 95% CI 10.27-720.37) over placebo. Moreover, the effect size favored PPD over cryotherapy (OR 70.83, 95% CI 4.02-1246.56), and no significant differences were noted among other treatments.

Network meta-analysis. Autoinoculation (OR 79.95, 95% CI 4.34-1473.59), PPD (OR 42.59, 95% CI 7.66-240.67), and MMR (OR 15.39, 95% CI 3.52-67.25) were significantly superior to placebo. These results were consistent with those of the conventional meta-analysis. Moreover, autoinoculation (OR 103.37, 95% CI 5.17-2066.92), PPD (OR 55.53, 95% CI 8.66-355.92), and MMR (OR 19.89, 95% CI 3.90-101.52) were significantly superior to INF-α. In addition, autoinoculation (OR 131.85, 95% CI 1.56-11,144.27) and PPD (OR 70.83, 95% CI 4.02-1246.56) were significantly superior to cryotherapy, and PPD was superior to *Candida* antigen (OR 28.19, 95% CI 1.30-610.93) (Table II).

Adverse events. *Conventional meta-analysis.* PPD and Mw vaccines were associated with lower overall rates of adverse events compared with cryotherapy, and no significant difference was noted when comparing INF-α with placebo or comparing Mw vaccine with imiquimod. Regarding initial site outcomes, the effect size showed that MMR had lower rates of partial recovery than placebo. Moreover, MMR, PPD, INF-α, and *Propionibacterium* had significantly lower nonresponse rates than placebo. Data on other adverse events are illustrated in Table III.

Network meta-analysis. The overall rate of adverse events was significantly higher with cryotherapy (OR 104.78, 95% CI 4.85-2262.88), INF-β (OR 24.85, 95% CI 1.17-529.16), and INF-α (OR 4.89, 95% CI 2.30-10.38) than placebo. There was no significant difference between Mw vaccine (OR 0.57, 95% CI 0.01-44.84) or PPD (OR 7.43, 95% CI 0.31-180.72) and placebo (Table IV). Subgroup NMA showed that in comparison with MMR, cryotherapy was associated with higher rates of recurrence at the same site (OR 44.61, 95% CI 1.18-1683.53), and no significant differences were detected between other treatments (Table V).

Ranking of treatments using P-score

According to the P-score, PPD, MMR, and INF-β were the top-ranked treatments in achieving complete primary recovery. Regarding complete distant recovery, autoinoculation, PPD, and MMR were the top-ranked treatments. Further, MMR was associated with the maximum reduction in recurrence at the same site compared with other treatments.

Table III. Results of conventional meta-analysis for all assessed outcomes

Category	MMR vs placebo	PPD vs placebo	INF-α vs placebo	INF-β vs placebo	INF-γ vs placebo	*Propioni-bacterium* vs placebo	Auto-inoculation vs placebo	*Candida* antigen vs placebo	PPD vs cryotherapy	Mw vaccine vs cryotherapy	*Candida* antigen vs cryotherapy	Mw vaccine vs imiquimod
Complete recovery at initial site	**11.37 (5.46-23.67)**	**96.08 (17.20-536.60)**	2.11 (0.95-4.70)	**15.55 (6.08-39.77)**	**3.64 (1.29-10.29)**	**71.40 (3.00-1696.74)**	—	—	**15.19 (4.64-49.69)**	1.27 (0.48-3.35)	2.51 (0.83-7.64)	1.38 (0.58-3.28)
Partial recovery at initial site	**0.40 (0.17-0.93)**	1.46 (0.60-3.57)	1.60 (0.79-3.24)	—	0.80 (0.41-1.57)	4.49 (0.21-93.30)	—	—	0.59 (0.20-1.73)	0.78 (0.30-2.06)	1.0 (0.06-16.76)	0.72 (0.24-2.13)
Nonresponse at initial site	**0.09 (0.04-0.21)**	**0.01 (0-0.09)**	**0.47 (0.25-0.89)**	—	0.34 (0.05-2.17)	**0.01 (0-0.05)**	—	—	**0.01 (0-0.26)**	—	0.38 (0.12-1.19)	0.48 (0.29-2.42)
Complete recovery at distant site	**12.11 (2.48-59.19)**	**60.68 (7.15-514.77)**	0.76 (0.36-1.59)	—	—	—	**86.01 (10.27-720.37)**	—	**70.83 (4.02-1246.56)**	—	2.51 (0.83-7.64)	—
Partial recovery at distant site	**30.33 (1.39-660.76)**	1.83 (0.06-53.01)	2.44 (1.0-5.94)	—	—	—	**30.03 (1.63-553.55)**	—	**35.64 (2.01-632.01)**	—	—	—
Nonresponse at distant site	**0 (0-0.13)**	**0.01 (0-0.21)**	1.19 (0.45-3.17)	—	—	—	—	—	**0 (0-0.05)**	—	—	—
Pain	—	—	0.91 (0.47-1.78)	—	—	—	—	—	**0.01 (0-0.16)**	**0.01 (0-0.10)**	—	1.05 (0.46-2.42)
Erythematous swelling at lesional sites	3.32 (0.12-91.60)	—	**2.94 (1.48-5.84)**	—	—	—	—	2.32 (0.72-7.41)	0.09 (0-1.79)	1.94 (0.65-5.81)	13.16 (0.69-249.48)	**0.23 (0.07-0.78)**
Fever for 24 hr and myalgia	—	—	**14.10 (2.54-78.17)**	—	—	—	—	—	—	—	—	—
Fever 2-3 d	—	—	2.93 (0.75-11.43)	—	—	—	—	3.10 (0.12-79.23)	—	**45.51 (2.54-814.02)**	—	2.39 (0.86-6.65)
Inflammatory papulonodular swelling	—	—	—	—	—	—	—	2.32 (0.72-7.41)	—	**3599.00 (69.13-187,377.27)**	**3721.00 (71.51-193,624.43)**	—
Blistering	—	—	—	—	—	—	—	—	**0.03 (0-0.49)**	**0.02 (0-0.39)**	**0.02 (0-0.29)**	—
Recurrence in same site	0.08 (0-1.51)	0.99 (0.22-4.39)	—	—	—	—	—	—	0.29 (0.07-1.22)	0.31 (0.01-7.96)	—	—

The results are odds ratios with 95% confidence intervals. Bolded values are statistically significant.
INF, Interferon; *MMR*, measles, mumps, rubella vaccine; *Mw*, *Mycobacterium* w; *PPD*, purified protein derivative vaccine.

Table IV. Results of total adverse events according to network meta-analysis

	INF-β	PPD	INF-α	Placebo	Mw vaccine
Cryotherapy	4.22 (0.06-321.83)	**14.10 (2.60-76.55)**	21.43 (0.91-507.00)	**104.78 (4.85-2262.88)**	**184.87 (8.26-4138.95)**
INF-β		3.34 (0.04-277.96)	5.08 (0.22-118.61)	**24.85 (1.17-529.16)**	43.85 (0.21-9093.21)
PPD			1.52 (0.06-40.36)	7.43 (0.31-180.72)	13.11 (0.38-451.48)
INF-α				**4.89 (2.30-10.38)**	8.62 (0.10-727.69)
Placebo					1.76 (0.02-139.57)

The results are odds ratios with 95% confidence intervals when comparing the column-defined treatments with the row-defined treatments. Bolded values are statistically significant.
INF, Interferon; *Mw*, *Mycobacterium* w; *PPD*, purified protein derivative vaccine.

Table V. Results of recurrence at the same site according to network meta-analysis

	Mw vaccine	Placebo	PPD	MMR
Cryotherapy	3.21 (0.13-82.07)	3.39 (0.43-26.60)	3.41 (0.82-14.21)	**44.61 (1.18-1683.53)**
Mw vaccine		1.06 (0.02-49.15)	1.06 (0.03-36.68)	13.89 (0.11-1805.16)
Placebo			1.01 (0.23-4.45)	13.16 (0.66-261.58)
PPD				13.07 (0.46-368.36)

The results are odds ratios with 95% confidence intervals when comparing the column-defined treatments to the row-defined treatments. Bolded values are statistically significant.

Consistency analysis

The net heat plot and net split methods were used to conduct homogeneity and consistency analyses. Only complete recovery at the initial site showed heterogeneity and inconsistency. Other outcomes showed moderate-to-high degrees of homogeneity, indicating that their results are highly consistent and reliable.

DISCUSSION

To the best of our knowledge, this is the first NMA to compare the efficacy of all available forms of intralesional immunotherapy for wart treatment in different body sites. All modalities showed statistically significant efficacy compared with placebo. The P-score ranking revealed that PPD and MMR were the most effective treatments, either for complete primary or distant recovery, along with autoinoculation for distant recovery. Moreover, MMR was the most effective in reducing the recurrence rate at the primary site after 3-6 sessions of treatment.

Although intralesional immunotherapy is now more popular,[16] controlled trials are lacking on some modalities, such as Mw vaccine, trichophyton, autoinoculation, *Corynebacterium parvum*, and *Propionibacterium parvum*. Through our search, we could identify only 1 study evaluating the latest[15]; however, its quality was poor and the effect estimate was too large to skew the treatment ranking. Therefore, a sensitivity analysis was done for the complete recovery outcome. Similarly, autoinoculation appears promising for evoking the immune response to eliminate warts, even at distant sites; however, only 1 RCT evaluated its efficacy.[28] Therefore, we recommend future investigators to further assess the efficacy of the aforementioned modalities.

Furthermore, we suppose that combining intralesional immunotherapy with a destructive treatment method might enhance the efficacy, shorten the treatment duration, and reduce the possible side effects. Of note, only 1 trial[17] studied the efficacy of intralesional INF-β in epidermodysplasia verruciformis (ie, autosomal-recessive disease characterized by increased susceptibility for HPV infection and disseminated warts).[30] This study reported that injecting all warts over 6 sessions caused visible lesion clearing. However, further research is still needed.

Our study provides evidence of the efficacy of intralesional immunotherapeutic modalities, especially PPD and MMR, favoring them over some destructive modalities, such as cryotherapy, that require even more sessions until complete response.[18] Although cryotherapy is being used widely, our study showed that it has a lower efficacy and higher overall recurrence rates than intralesional immunotherapy.[31] In contrast to PPD, the MMR vaccine is not recommended during pregnancy.[32]

The variability in baseline characteristics, such as wart site, size, disease duration, and outcome of treatment (reluctant or not), might affect the accuracy of our results. Moreover, some comparisons in our NMA relied on 1 study and should be further investigated. Further, some included trials were unblinded or did not adequately report on their randomization and allocation concealment

processes. Due to the lack of data, we did not compare the assessed arms in terms of cost-effectiveness and patient satisfaction with treatment.

Conclusion

PPD and MMR were the most effective in achieving complete primary and distant recovery (along with autoinoculation for the latter) compared with cryotherapy and other immunotherapeutic modalities. Moreover, intralesional immunotherapy had less frequent adverse events and recurrence at the same site than cryotherapy. Further studies should provide additional data about combination regimens and other intralesional immunotherapy modalities that were not sufficiently assessed.

Data availability

The patients' baseline characteristics and findings of included studies are summarized in Supplementary Table I (available at http://www.jaad.org). Other Supplementary Tables and Figures for this article are available at: http://dx.doi.org/10.17632/nsfrj565v5.1.

REFERENCES

1. Formana D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012; 30(SUPPL.5):F12-F23.
2. Gonçalves MAG, Donadi EA. Immune cellular response to HPV: current concepts. *Braz J Infect*. 2004;8(1):1-9.
3. Sterling JC, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. *Br J Dermatol*. 2001;144(1):4-11.
4. Tyring SK. Human papillomavirus infections: epidemiology, pathogenesis, and host immune response. *J Am Acad Dermatol*. 2000;43(1):S18-S26.
5. HippelÄinen MI, HippelÄinen M, Saarikoski S, Syrjänen K. Clinical course and prognostic factors of human papillomavirus infections in men. *Sex Transm Dis*. 1994;21(5):272-279.
6. Monk BJ, Tewari KS. The spectrum and clinical sequelae of human papillomavirus infection. *Gynecol Oncol*. 2007;107(2):S6-S13.
7. Bacelieri R, Johnson SM. Cutaneous warts: an evidence-based approach to therapy. *Am Fam Physician*. 2005;72(4):647-652.
8. Rivera A, Tyring SK. Therapy of cutaneous human papillomavirus infections. *Dermatol Ther*. 2004;17(6):441-448.
9. Thappa D, Chiramel M. Evolving role of immunotherapy in the treatment of refractory warts. *Indian Dermatol Online J*. 2016; 7(5):364.
10. Salanti G, Higgins JP, Ades A, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res*. 2008; 17(3):279-301.
11. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343.
12. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15(1):58.
13. Amirnia M, Khodaeiani E, Fouladi DF, et al. 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 Dermatol Treat*. 2016;27(2): 173-178.
14. Shaheen MA, Salem SAM, Fouad DA, El-Fatah AAA. Intralesional tuberculin (PPD) versus measles, mumps, rubella (MMR) vaccine in treatment of multiple warts: a comparative clinical and immunological study. *Dermatol Ther*. 2015;28(4):194-200.
15. Nasser N. Treatment of common warts with the immune stimulant Propionium bacterium parvum. *An Bras Dermatol*. 2012;87(4):585-589.
16. Nofal A, Nofal E. Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. *J Eur Acad Dermatol Venereol*. 2010;24(10):1166-1170.
17. Niimura M. Application of beta-interferon in virus-induced papillomas. *Soc Invest Dermatol*. 1990;95(6):149-151.
18. Khozeimeh F, Jabbari Azad F, Mahboubi Oskouei Y, et al. Intralesional immunotherapy compared to cryotherapy in the treatment of warts. *Int J Dermatol*. 2017;56(4):474-478.
19. Aksakal AA, Ozden MG, Atahan C, Onder M. Successful treatment of verruca plantaris with a single sublesional injection of interferon-α2a. *Clin Exp Dermatol*. 2008;34(1):16-19.
20. 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*. 2015;20(2): 123-129.
21. 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.
22. Kumar P, Dar L, Saldiwal S, et al. Intralesional injection of Mycobacterium w vaccine vs imiquimod, 5%, cream in patients with anogenital warts: a randomized clinical trial. *JAMA Dermatol*. 2014;150(10):1072-1078.
23. Lee SW, Houh D, Kim HO, Kim CW, Kim TY. Clinical trials of interferon-gamma in treating warts. *Ann Dermatol*. 1990;2(2): 77-82.
24. Eron LJ, Judson F, Tucker S, et al. Interferon therapy for condylomata acuminata. *New Engl J Med*. 1986;315(17):1059-1064.
25. 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(5):589-594.
26. Vance JC, Bart BJ, Hansen RC, et al. Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. *Arch Dermatol*. 1986;122(3):272-277.
27. Varnavides CK, Henderson CA, Cunliffe WJ. Intralesional interferon: ineffective in common viral warts. *J Dermatol Treat*. 1997;8(3):169-172.
28. Lal NR, Sil A, Gayen T, Bandyopadhyay D, Das NK. Safety and effectiveness of autoinoculation therapy in cutaneous warts: a double-blind, randomized, placebo-controlled study. *Indian J Dermatol Venereol Leprol*. 2014;80(6):515.
29. 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 Dermatol Treat*. 2014;25(3):264-267.
30. Rajagopalan K, Loo DSC, Tay CH, Chin KN, Tan KK. Familial epidermodysplasia verruciformis of lewandowsky and lutz. *Arch Dermatol*. 1972;105(1):73-78.
31. Sharma N, Sharma S, Singhal C. A comparative study of liquid nitrogen cryotherapy as monotherapy versus in combination with podophyllin in the treatment of condyloma acuminata. *J Clin Diagn Res*. 2017;11(3):WC01-WC05.
32. Eassa BI, Abou-Bakr AA, El-Khalawany MA. Intradermal injection of PPD as a novel approach of immunotherapy in anogenital warts in pregnant women. *Dermatol Ther*. 2011; 24(1):137-143.

Supplemental Table I. Summary of trials evaluating wart immunotherapies

Study ID	Arm	Age, y	N	Warts before injection, n	Duration of warts, mo	Mean size of warts before injection	Site of warts	No. immunotherapy sessions	Interval between sessions	Main findings
Zamanian et al, 2014[21]	MMR, 0.5 mL	18.9 ± 12	24	4.4 ± 2	–	–	–	3	2 wk	Therapeutic response in the MMR group was 80% higher than in the saline group
	Saline	20.1 ± 10	22	4.1 ± 2.5						
Nofal A and Nofal E, 2010[16]	MMR, 0.1 mL	32.4 ± 9.3	70	Single (n = 18); multiple (n = 52)	8.3 ± 5.1	–	Extragenital mostly extremities	Maximum 5	2 wk	Intralesional immunotherapy with MMR vaccine was an effective and safe treatment modality for common warts, particularly the multiple ones
	Saline	30.2 ± 7.8	40	Single (n = 11); multiple (n = 29)	9.4 ± 6.3					
Shaheen et al, 2015[14]	PPD, 0.1-0.3 mL based on IRT	23 ± 12	10	11 ± 6	6.5 ± 3	–	Common (n = 7), periungual (n = 3), plantar (n = 1), genital (n = 2)	≥2	3 wk	Intralesional PPD and MMR showed comparable safety and efficacy in the treatment of multiple warts
	MMR, 0.1-0.3 mL based on IRT	18 ± 10	10	11 ± 7	5.7 ± 2		Common (n = 6), periungual (n = 6), plantar (n = 2), plane (n = 2)			
	Saline	26 ± 12	10	10 ± 6	5.8 ± 1.3		Common (n = 3), periungual (n = 2), plantar (n = 3), plane (n = 2), genital (n = 1)			
Abd-Elazeim et al, 2014[29]	PPD, 0.1 mL	10-39	20	Complete resolution (13.6 ± 12.3), partial resolution (18.5 ± 9.2), minimal resolution (12 ± 0), no response (5 ± 1.4)	19 ± 20.9	Complete resolution (3.0 ± 1.0 mm), partial resolution (4.4 ± 3.4 mm), minimal resolution (8.1 ± 0 mm), no response (8.2 ± 4.7 mm)	Extragenital	3-6	1 wk	Intralesional immunotherapy by PPD is a safe and effective treatment for recalcitrant multiple common warts in previously immunized patients

Continued

Supplemental Table I. Cont'd

Study ID	Arm	Age, y	N	Warts before injection, n	Duration of warts, mo	Mean size of warts before injection	Site of warts	No. immunotherapy sessions	Interval between sessions	Main findings
	Saline		20	Complete resolution (0), partial resolution (15.5 ± 7.2), minimal resolution (0), no response (11 ± 9.4)		Complete resolution (0 mm), partial resolution (3.3 ± 3.5 mm), minimal resolution (0 mm), no response (9.2 ± 3.7 mm)				
Amirnia et al, 2016[13]	PPD, 0.1-0.3 mL based on IRT	21.1 ± 8.5	35	Mean ± SEM (12.2 ± 1.3)	Mean ± SEM (37.4 ± 3.7)	≤0.5 mm (n = 14), ≤0.5 and ≤1 mm (n = 19), >1 mm (n = 2)	Upper limb (6), lower limb (2), genitalia and mucous membrane (11), head and neck (6), upper and lower limbs (10)	6	2 wk	Intralesional immunotherapy with PPD antigen is highly effective and safe for treating recalcitrant warts
	Cryotherapy	24.6 ± 8.2	33	Mean ± SEM (11.9 ± 1.7)	Mean ± SEM (35.9 ± 2.5)	≤0.5 mm (n = 20), ≤0.5 and ≤1 mm (n = 13)	Upper limb (5), lower limb (3), genitalia and mucous membrane (11), head and neck (3), upper and lower limbs (11)			
	Saline	25.9 ± 9.5	34	Mean ± SEM (15.3 ± 2.2)	Mean ± SEM (36.9 ± 2.5)	≤0.5 mm (n = 18), ≤0.5 and ≤1 mm (n = 14), >1 mm (n = 2)	Upper limb (6), lower limb (9), genitalia and mucous membrane (8), head and neck (2), upper and lower limbs (9)			

Continued

Supplemental Table I. Cont'd

Study ID	Arm	Age, y	N	Warts before injection, n	Duration of warts, mo	Mean size of warts before injection	Site of warts	No. immunotherapy sessions	Interval between sessions	Main findings
Horn et al, 2005[25]	Antigen (mumps, *Candida*, and trichophyton), 0.3 mL	Mean 37	54	Patients with single and multiple warts were included	—	—	—	Maximum 5	—	Intralesional immunotherapy using injections of *Candida*, mumps, or trichophyton skin test antigens is an effective treatment for warts
	Antigen + IFN-α2b	Mean 38	41							
	IFN-α2b, 1×10^6 IU	Mean 40	46							
	Saline	Mean 34	60							
Eron et al, 1986[24]	Interferon-α2b, 1×10^6 IU	Mean 30	124	Mean 7	—	26 ± 4 mm^2	Genital warts	3X/wk for 3 wk	1 wk	Direct injection of IFN-α2b into the genital warts appears to be an effective and fairly well-tolerated form of therapy.
	Placebo		128			32.9 ± 4.3 mm^2				
Niimura, 1990[17]	IFN-β, 1×10^6 IU	10-50	64	—	<12 (n = 11), <36 (n = 39) or >36 years (n = 14)	—	Extremities	Maximum 10	1 wk	Intralesional IFN-β was relatively effective for benign epidermodysplasia verruciformis lesions, but systemic treatment was not effective
	Placebo									
Vance et al, 1986[26]	IIFN-α2, 1×10^6 IU	NR	30	Single	—	34 mm^2	Condyloma acuminatum or verruca plantaris	3X/wk for 3 wk or 9 times	1 wk	Intralesional INF-α2 is beneficial in the treatment of single condylomas; however, its role in multiple condyloma and verruca plantaris remains to be verified
	IFN-α2, 1×10^5 IU		32			37 mm^2				
	Placebo		29			24 mm^2				
Varnavides et al, 1997[27]	IFN-α, 0.3 mL, 10 IU/m	16-60	23	—	12	—	Palmar and plantar warts	12	1 wk	Treatment with human lymphoblastoid INF offered no significant advantage over placebo in patients with palmar and plantar warts
	Placebo		19							
Aksakal et al, 2008[19]	IFN-α2a, 4.5 MU	Mean 22.6	45	Single (n = 24), multiple (n = 11)	6-36	5-40 mm	Plantaris and vulgaris	1	—	A single sublesional dose of INF-α may be beneficial in the treatment of verruca patients, especially in those with single verruca plantaris lesions
	Saline		8	Single (n = 8)						
Lee et al, 1990[23]	IFN-γ, 5×10^5 IU	>5	36	—	≤12 (n = 29), ≤36 (n = 31), >36 (n = 14)	—	Periungual warts, planter warts, or warts in other sites	6	3 d	High-dose INF-γ showed significantly better response than low-dose IFN and placebo (but with more frequent adverse events)
	IFN-γ, 1×10^5		53							
	Placebo		36							

Continued

Supplemental Table I. Cont'd

Study ID	Arm	Age, y	N	Warts before injection, n	Duration of warts, mo	Mean size of warts before injection	Site of warts	No. immunotherapy sessions	Interval between sessions	Main findings
Khozeimeh et al, 2017[18]	*Candida* antigen, 0.1-0.3 mL based on IRT	23.4 ± 6.6	30	8.2 ± 4.9	1-6	429.7 ± 115.9 mm^2	Verruca vulgaris and plantar warts	1-3	3 wk	Immunotherapy led to a better therapeutic response in the first two-thirds of the treatment period compared with cryotherapy
	Cryotherapy	28.7 ± 13.8	30	6.4 ± 3.8		325.8 ± 133.2 mm^2				
Kumar et al, 2014[22]	Mw vaccine, 0.1 mL	29.4 ± 1.1	44	1-5 warts (n = 3), 6-10 warts (n = 8), 11-20 warts (n = 14), >20 warts (n = 19)	Median 4.5	≥10 mm^2	Genital in 36 patients, perianal in 4, genital and perianal in 4	8	2 wk	Although invasive and associated with local immunologic reactions, intralesional Mw vaccine was as effective as imiquimod in the treatment of genital warts
	Imiquimod 5%	26 ± 8.4	45	1-5 warts (n = 6), 6-10 warts (n = 7), 11-20 warts (n = 9), >20 warts (n = 23)	Median 4	≥11 mm^2	Genital in 36 patients, perianal in 2, genital and perianal in 7			
Dhakar et al, 2015[20]	Mw vaccine, 0.1 mL	<30 (n = 27), ≥30 (n = 6)	33	Single (n = 7), multiple (n = 26)	<6 (n = 23), ≥6 (n = 10)	—	Extragenital (palm, sole, multiple sites)	1-12	1 wk	Both treatments were able to completely clear the lesions at the primary site; however, this was faster in the immunotherapy group
	Cryotherapy	<30 (n = 26), ≥30 (n = 7)	33	Single (n = 12), multiple (n = 20)	<6 (n = 24), ≥6 (n = 9)					
Lal et al, 2014[28]	Autoinoculation	24.3 ± 8.4	24	14.8 ± 12.6	17.4 ± 5.2	4.5 ± 2.3 mm	Palmoplantar, face, periungual and subungual, trunk and extremities	3	4 or 8 wk	Significant reduction in the number of warts in the autoinoculation group was noticed from the first follow-up visit
	Placebo	30.9 ± 11.7	24	10 ± 5.8	16.1 ± 3.5	5.4 ± 1.4 mm				
Nasser, 2012[15]	*Propionibacterium*, 0.5 mL given 1-3 times	—	10	—	—	—	Hand (fingers and nail bed), lower limb (leg and feet)	6	30 d	The immune stimulant *Propionibacterium parvum* destroyed the warts without scars and cured 90% of the patients
	Placebo		10							

INF, Interferon; *IRT*, immunotherapy reaction test; *MMR*, measles, mumps, rubella vaccine; *Mw*, *Mycobacterium* w; *NR*, not reported; *PPD*, purified protein derivative vaccine; *SEM*, standard error of the mean.