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# TRAITEMENTS LOCAUX DES CONDYLOMES ANO-GENITAUX EXTERNES (REVUE SYSTEMATIQUE, META-ANALYSES, ANALYSE POOLEE ET META-ANALYSE EN RESEAU)

**Local management of anogenital warts in non-immunocompromised adults: a systematic review with meta-analyses, pooled analysis and network meta-analysis of randomized controlled trials**

**Directeur de thèse**
Monsieur le Docteur Christian DERANCOURT

**Jury**

| | |
|---|---|
| Monsieur le Professeur François AUBIN | **Juge et Rapporteur** |
| Monsieur le Professeur André CABIE | **Juge** |
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| Madame le Professeur Simone MATHOULIN-PELISSIER | **Juge** |
| Monsieur le Professeur Mathieu NACHER | **Juge** |
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## Résumé

***Contexte :*** Il existe plusieurs traitements pour les condylomes ano-génitaux externes (CAE) cependant, aucune hiérarchie de traitement claire, n'est mentionnée dans les dernières recommandations. ***Objectifs :*** Comparer l'efficacité des traitements topiques et des traitements ablatifs pour la prise en charge des CAE. ***Méthodes :*** Douze bases de données électroniques ont été consultées. Tous les essais cliniques comparatifs et randomisés (ECR) comparant des adultes immunocompétents avec des CAE ayant reçu au moins un traitement administré par le médecin ou auto appliqué par le patient dans au moins un groupe parallèle ont été inclus. L'évaluation du risque de biais a suivi les recommandations Cochrane. Les critères d'évaluation de l'étude étaient la clairance, la récurrence, les effets secondaires (ES) et la réponse lésionnelle complète (RLC) après évaluation du traitement. Des méta-analyses, des analyses poolées puis une méta-analyse réseau ont été réalisées. ***Résultats :*** Soixante-dix ECR (9 931 patients) ont été inclus. Tous les ECR, sauf quatre présentaient un risque élevé de biais. En comparaison directe : Le laser CO2 était légèrement plus efficace que la cryothérapie (rapport de risque (RR) 2,05 ; intervalle de confiance à 95% (IC) 1,61-2,62), avec moins de récidives à 3 mois (RR 0,28 ; IC95% 0,09-0,89). L'électrochirurgie était légèrement plus efficace que la cryothérapie. Aucune différence d'efficacité ou d'effets secondaires n'a été observée entre la cryothérapie et l'imiquimod ou l'acide trichloroacétique. La podophyllotoxine 0.5% gel était légèrement plus efficace que la podophyllotoxine 0.5% crème. Dans l'analyse poolée : le taux d'élimination total était plus élevé avec les traitements administrés par le médecin (TAM) (56 à 92%) qu'avec les traitements auto-appliqués (TAP), mais le taux de récurrence était plus faible pour les TAP (6 à 29%) que pour les TAM. La chirurgie était douloureuse dans 48% des cas et le laser CO2 était associé à un taux de récidive de 31%. L'acide trichloroacétique (TCA) comparativement à la cryothérapie, était associé à un taux de clairance plus élevé, un taux de récurrence plus faible et moins d'ES. La solution/crème de podophyllotoxine 0,5% semblait aussi efficace que la cryothérapie et l'imiquimod, mais elle causait plus d'ES généraux. Méta-analyse en réseau (évaluation du RLC seule) : une géométrie de réseau était construite à partir de 49 des 70 ECR. Les traitements les plus efficaces comparativement au placebo étaient la chirurgie (RR 10,54 ; IC95% 4,53-24,52), une combinaison de traitement ablatif et d'imiquimod (RR 7,52 ; IC95% 4,53-24,52) et l'électrochirurgie (RR 7,10 ; IC95% 3,47-14,53). Les valeurs de SUCRA confirmaient la supériorité de la chirurgie (90,9%), d'une combinaison d'un traitement ablatif avec de l'imiquimod (79,8%) et de l'électrochirurgie (77,1%). Les TAP les plus efficaces étaient la podophyllotoxine 0,5 % solution (63,5%) et la podophyllotoxine à 0,5 % crème (62,2%). ***Conclusions :*** La majorité des ECR inclus sont à faible niveau de preuve. La chirurgie et l'électrochirurgie semblent être supérieures aux autres traitements. La podophyllotoxine 0,5 % semble s'avérer le TAM le plus efficace, mais elle semble causer plus d'ES généraux que les autres. Les traitements combinés devraient faire l'objet d'une évaluation plus précise dans le cadre des ECR à venir.

## Abstract

***Background:*** While several treatments exist for anogenital warts (AGWs), no clear treatment hierarchy is mentioned in the latest guidelines. ***Objectives:*** To compare the efficacy of topical treatments and ablative procedures for the management of AGWs. ***Methods:*** Twelve electronic databases were systematically searched. All randomized controlled trials (RCTs) comparing immunocompetent adults with AGWs who received at least 1 provider-administered or patient-administered treatment in at least 1 parallel group were included. Risk of bias assessment followed the Cochrane Handbook. Study endpoints were clearance, recurrence, side effects (SE) and complete lesion response (CLR) after treatment assessment. Meta-analyses, pooled analysis then network meta-analysis were performed. ***Results:*** Seventy RCTs (9,931 patients) were included. All but 4 RCTs had a high risk of bias. In direct comparison: $CO_2$ laser was slightly more efficacious than cryotherapy (risk ratio (RR) 2.05; 95% confidence interval (CI) 1.61-2.62), with fewer recurrences at 3 months (RR 0.28; CI95% 0.09-0.89). Electrosurgery was slightly more efficacious than cryotherapy. No differences in efficacy or side effects were found between cryotherapy and imiquimod or trichloroacetic acid. Podophyllotoxin gel was slightly more efficacious than podophyllotoxin cream. In pooled analysis: the complete clearance rate was higher for provider-administered therapy (ProT) (56 to 92%) than patient-administered therapy (PaT), but the recurrence rate was lower for PaTs (6 to 29%) than ProTs. Surgery was painful in 48% of cases, and $CO_2$ Laser was associated with a recurrence rate of 31%. Trichloroacetic acid (TCA) was associated with a high clearance rate, a low recurrence rate, and few SEs compared to cryotherapy. Podophyllotoxin 0.5 solution/cream seemed as effective as cryotherapy and imiquimod, but caused more general SEs. In network meta-analysis (only CLR assessment)***:*** a network geometry was constructed based on 49 of the 70 RCTs. The most efficacious treatments compared to placebo were surgery (RR 10.54; CI95% 4.53-24.52), association of ablative therapy and imiquimod (RR 7.52; CI95% 4.53-24.52), and electrosurgery (RR 7.10; CI95% 3.47-14.53). SUCRA values confirmed the superiority of surgery (90.9%), association of ablative therapy and imiquimod (79.8%), and electrosurgery (77.1%). The most efficacious patient-administered treatments were podophyllotoxin 0.5% solution (63.5%) and podophyllotoxin 0.5% cream (62.2%). ***Conclusions:*** Most included RCTs have low-level evidence. Surgery and electrosurgery seem to be superior to other treatments. Podophyllotoxin 0.5% was the most efficacious PaT but caused more general SEs than others. Combined therapy should be more evaluated in future RCT.

# TABLE DES MATIERES

## Abréviations:

| | |
|---|---|
| 5-FU: | 5-fluorouracil |
| AGW: | Anogenital wart |
| CI: | Confidence interval |
| CAE: | Condylomes ano-génitaux externes |
| CLR: | Complete lesion response |
| ECR: | Essai clinique randomisé |
| ES: | Effet secondaire |
| GRADE: | Grading of Recommendation Assessment, Development, and Evaluation |
| HPV: | Human papillomavirus |
| INF: | Interferon |
| ITT: | Intention-to-treat |
| IC: | Intervalle de confiance |
| KOH: | Potassium hydroxide |
| QOL: | Quality of life |
| NMA: | Network meta-analysis |
| PaT: | Patient-administered treatment |
| PDT: | Photodynamic therapy |
| PVH: | Papillomavirus Humain |
| ProT: | Provider-administered treatment |
| RCT: | Randomized controlled trial |
| RLC: | Réponse lésionnelle complète |
| RR: | Relative risk / risque relatif |
| SE: | Side effect |
| SUCRA: | Surface Under the Cumulative RAnking curve |
| TAM: | Traitement administré par le médecin |
| TAP: | Traitement administré par le patient |
| TCA: | Trichloroacetic acid |

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- A. Bertolotti, C. Ferdynus, B. Milpied, N. Dupin, L. Huiart, C. Derancourt. Local management of anogenital warts in non-immunocompromised adults: a network meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol, (soumis) IF 5.113

# I. INTRODUCTION

## I.1. Etiologie et épidémiologie des condylomes

Les condylomes sont des lésions prolifératives bénignes que l'on peut identifier sur l'épithélium de toutes les parties des organes génitaux, de l'anus ou de la région péri-anale. Ils peuvent également concerner les régions inguinales, péri-anales et pubiennes. Ils sont causées par les génotypes 6 et 11 du virus du papillome humain (VPH) dans plus de 95 % des cas(1). Cependant, plusieurs types de VPH peuvent être présents dans les condylomes y compris les génotypes oncogènes "à risque élevé" tels que 16 et 18(1,2).

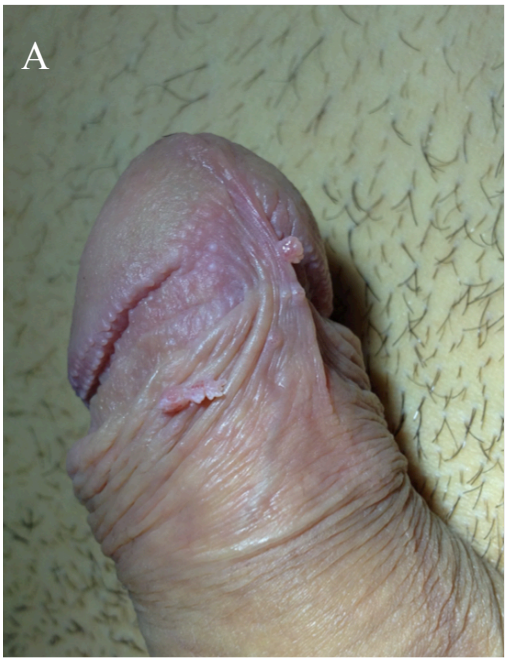
Les condylomes constituent un problème de santé publique important, avec des estimations mondiales de 160 à 289 cas pour 100 000 personnes-année(3). Leur prévalence globale d'après des bases de données administratives rétrospectives et des cohortes prospectives variait de 0,13 % à 0,56 %, et de 0,2 % à 5,1 % lors d'examen génitaux systématiques(3).

La transmission du VPH entre partenaires sexuels est de près de 50% et peut se produire en l'absence de condylome visible(4). A partir des analyses de col de l'utérus, la prévalence mondiale du VPH (tout génotype confondu) est estimée à 11.7%. Les lésions cliniques à type de condylomes se développent dans 14,6 à 64,2% des cas selon les études(5-7). La période d'incubation entre l'incident et l'infection par le VPH 6 ou 11 est plus courte chez les femmes (médiane de 2,9 mois) que chez les hommes (médiane de 11,0 mois)(5, 6). L'élimination virale naturelle spontanée s'effectue en quelques mois et dans plus de 90 % des cas dans les 24 mois. Le mode de contamination des condylomes est le plus souvent sexuel, mais une transmission non sexuelle indirecte peut être évoquée lors d'utilisation d'objets de toilette souillés, de sauna, jacuzzi…(8) Les condylomes de l'enfant témoignent le plus souvent de contaminations non sexuelles (verrues des mains), mais la recherche de sévices doit être envisagée.

## I.2. Clinique des condylomes

Le diagnostic des condylomes est clinique. On distingue trois types de condylomes :

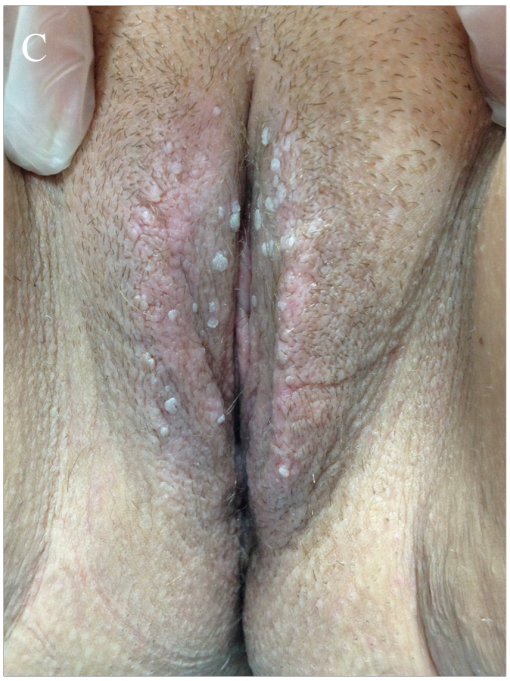
- les condylomes acuminés (Figures A et B) : exophytiques, plus ou moins kératosiques, blanchâtres, papillomateux, souvent multiples, parfois confluents dits en « crête de coq »

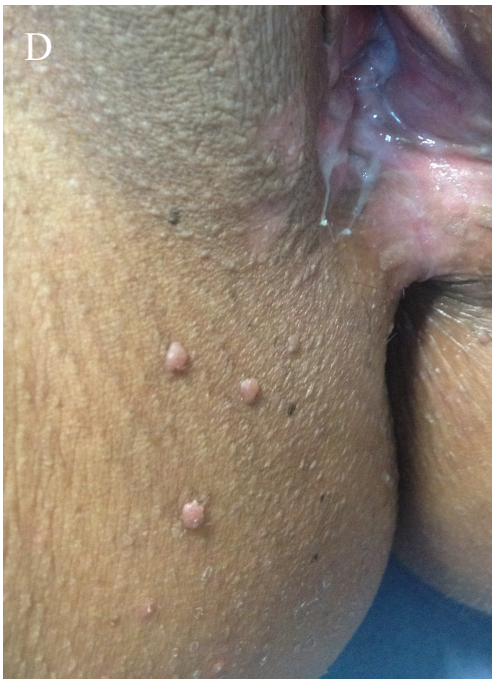




**Figures A et B : condylomes acuminés**

- Les condylomes papuleux (Figure C et D) : petites papules infra centimétriques, couleur chair




**Figures C et D : condylomes plans**

- Les condylomes plans : lésions à peine visibles, mais mieux identifiées après application d'acide acétique à 5 %, sous forme de macules blanches.

Forme particulière :

- condylome géant de Buschke-Lowenstein : associé aux PVH 6 et 11, d'aspect clinique tumoral inquiétant, mais évolution généralement bénigne.

## I.3 Terrain particulier

Les condylomes chez les patients immunodéprimés (VIH, greffé d'organe, sous immunosuppresseurs, corticothérapie longue…) sont souvent plus extensifs, plus fréquents, multifocaux et associés à d'autres infections sexuellement transmissibles.

La prévalence des lésions infra-cliniques est plus élevée. Le risque de lésions dysplasiques et d'infections à PVH oncogènes est plus important. Chez les patients séropositifs au VIH, les trithérapies seules ne suffisent souvent pas à permettre la régression nette des lésions.

Ces patients immunodéprimés, doivent donc être informés des risques infectieux et les femmes doivent bénéficier d'une surveillance gynécologique régulière(8).

## I.4 Complications des condylomes

### I.4.a Impact psychosexuel

Les condylomes entraînent un fort impact psychosexuel sur la qualité de vie(9,10). L'anxiété, la culpabilité, la colère et la perte de l'estime de soi, mènent à des préoccupations concernant le risque de transmission, la fertilité et les cancers chez les patients(11,12).

### I.4.b Précancer et cancer

Les condylomes sont par définition des lésions bénignes qui ne présentent aucun risque de transformation en néoplasie. Cependant, des lésions précancéreuses (néoplasie intra épithéliale vulvaire, anale et pénienne, c.-à-d. VIN, AIN et PIN) ou malignes peuvent coexister(13,14). La suspicion clinique d'un changement néoplasique doit être éveillée par

une hémorragie, une ulcération ou une infiltration cutanée palpable en particulier chez des patients immunodéprimés.

## I.5 Bilan

Devant un condylome, il convient de :

- rechercher d'autres localisations (frottis cervico vaginal, +/- anuscopie, +/- urétroscopie) chez le patient et ses partenaires en fonction des pratiques sexuelles,
- rechercher une étiologie sous jacente (immunodépression…),
- réaliser un bilan d' infection sexuellement transmissible,
- réaliser une biopsie en cas de doute clinique ou de suspicion d'une néoplasie.

## I.6 Traitement des condylomes

### I.6.a Généralités

Il n'existe pas de traitement antiviral efficace spécifiquement contre les PVH. L'objectif est la disparition macroscopique des lésions pour les condylomes. L'information du patient sur l'histoire évolutive naturelle de la maladie est essentielle.

Il existe 3 grandes formes de traitement :

- les traitements auto-administrés par le patient (PAP ou Patient administered Treatment – PaT):
  - l'imiquimod : molécule immunomodulatrice qui en se fixant sur les récepteurs Toll-like de type 7 permet la synthèse de cytokines pro-inflammatoires anti-virales.
  - la podophyllotoxine : traitement anti-mitotique extrait de rhizome et de racine de Podophyllum.
- Les traitements employés par le médecin (PAM ou Provider administered Treatment - ProT):
  - la cryothérapie à l'azote liquide
  - l'acide trichloracétique (TCA)

- la chirurgie
- l'électrocoagulation
- laser $CO_2$

- Les traitements préventifs :
  - le port du préservatif et l'absence de contact pour les zones non couvertes par le préservatif,
  - la vaccination : elle est préconisée chez les jeunes femmes entre 11 et 14 ans avec un rattrapage avant 19 ans possible pour éviter les cancers du col de l'utérus, et chez les homosexuels masculins de moins de 26 ans pour éviter les cancers anaux. Ce vaccin a montré, dans les pays (Australie, USA, Angleterre, Danemark, Suède) où il est très largement employé et étendu à la population masculine, une nette diminution des condylomes, des dysplasies cervicales et des cancers du col(15,16).

### I.6.b Hiérarchie thérapeutique

Il n'existe pas de recommandation qui hiérarchise les différents traitements disponibles dans la prise en charge des condylomes.

Les recommandations européennes en 2012 proposaient que les médecins définissent leur propre algorithme de traitement en incluant leurs pratiques locales et les recommandations. Un examen toutes les 4 semaines était encouragé. Un changement de traitement, en cas de réponse inadéquate était sollicité(17).

Les recommandations américaines en 2015 proposaient que le traitement soit guidé par le nombre, la taille et le site anatomique où se situait le(s) condylome(s). Le choix du traitement devait également prendre en compte les préférences du patient, les effets secondaires envisagés, son coût et l'expérience du praticien envers ce traitement proposé. Elles encourageaient aussi le développement d'algorithme propre à chaque équipe avec une surveillance de l'évolution et une réadaptation thérapeutique. Pour les condylomes ano-génitaux externes, elles proposaient principalement l'emploi de l'imiquimod 3,75% ou 5%, de

la podophyllotoxine 0.5% en gel ou solution, de la polyphenone 15%, de la cryothérapie, de la chirurgie, du laser, de l'électrochirurgie ou encore du TCA(18).

Les recommandations françaises en 2016 proposaient un choix thérapeutique selon les mêmes suggestions que les recommandations américaines de 2015 (type, localisation, souhait du patient, expérience du médecin). Elles spécifiaient cependant de traiter par de la cryothérapie, de l'imiquimod ou de la podophyllotoxine, les patients présentant des lésions limitées en nombre et en taille. Ceux présentant des lésions nombreuses (>10) ou étendues (>1cm$^2$) pouvaient être traités lors du premier épisode par de l'imiquimod ou un traitement ablatif (laser, chirurgie, électrocoagulation), puis en cas de récidive par l'association des deux(8).

En 2016, le National Institute for Health Research en Grande Bretagne publiait une revue systématique de la littérature avec méta-analyse en réseau et analyse médico-économique. Elles concluaient que la meilleure solution thérapeutique, coût-efficacité, était la succession de la podophyllotoxine 0.5% en solution, suivie par l'utilisation du laser $CO_2$ en cas d'échec ou de récidive(19).

Les recommandations allemandes de 2018 reprenaient les mêmes préconisations que celles du CDC en 2015. Elles les complétaient par l'absence d'avis dans l'utilisation de la podophyllotoxine 0.15% en crème, l'imiquimod 3,75% en crème, le 5-fluoro-uracyl 5% en crème ou encore l'interféron alpha en topique ou en intra-lésionnel. Elles se positionnaient contre la podophylline solution et l'utilisation du cidofovir 1% en crème ou gel(20).

Enfin, les dernières recommandations européennes en 2019, ajoutent l'utilisation en seconde ligne du 5-fluoro-uracyl 5% en crème, de l'interféron alpha en topique ou en intra-lésionnel et de la photothérapie dynamique(21).

La vaccination, jusqu'à ce jour, n'est pas recommandée en adjuvant.

## I.7 Synthétiser la littérature

### I.7.a Revue systématique de la littérature

Le nombre d'essai clinique, visant à améliorer la qualité d'une prise en charge d'une maladie, est en constante augmentation. Il est ainsi de plus en plus difficile de pouvoir accéder à toute l'information disponible sur un sujet. La revue systématique est un outil permettant de fournir une information exhaustive et objective aux professionnels de santé.
La revue systématique repose sur une méthodologie rigoureuse et complète. Elle ne doit pas être confondue avec une « revue générale » qui représente bien plus souvent l'opinion d'un expert(22).

La rédaction d'une revue systématique répond aux mêmes règles que toute étude menée dans le cadre de la recherche. Elle nécessite dans un premier temps, la rédaction d'un protocole afin de limiter les biais et d'assurer la meilleure objectivité du travail. Les recommandations Cochrane permettent d'aider les auteurs à la rédaction(23). Dès la fin de l'écriture du protocole, il est préconisé de l'enregistrer dans la base PROSPERO comme c'est le cas pour les essais cliniques randomisés dans *clinicaltrials.gov*(24). Un numéro est alors émis, permettant d'afficher et de garantir la rigueur méthodologique *à priori* lors des publications en rapport avec ce protocole.

La recherche des études est réalisée à travers plusieurs bases de données (MEDLINE, CENTRAL,…) car aucune base ne contient tous les articles. Chaque base propose un système d'interrogation spécifique. Désormais, l'utilisation de moteurs de recherche plus généraux tels que Google Scholar peuvent aussi améliorer l'exhaustivité de la recherche et permettre d'explorer la littérature grise(22).

La stratégie de la recherche employée, à travers l'élaboration des mots clefs et des synonymes, doit permettre la recherche la plus complète en diminuant les biais de sélection.

Lorsque la recherche des articles est terminée, certains logiciels permettent de trier les articles et d'éliminer à travers les différentes bases consultées, les doublons. La lecture des titres et des résumés doit permettre de réaliser une première phase de sélection selon la question de recherche. Puis, les textes des articles restants doivent être examinés en détails afin de confirmer leur inclusion. Ce travail doit être réalisé de manière indépendante par au moins deux investigateurs afin de garantir la robustesse méthodologique de cette étape. Des

réunions de résolution des désaccords sont nécessaires lors de résultats discordants. Les raisons d'exclusion des études doivent être notifiées et rapportées lors de la rédaction finale du travail. Cette phase est illustrée à travers un diagramme de flux.

Une grille de recueil de données est élaborée pour la réalisation de l'extraction des études incluses. Cette grille doit être réalisée, à l'aide d'un groupe d'expert de la thématique abordée et des méthodologistes expérimentés en revue systématique de la littérature. L'extraction des données est effectuée également de manière indépendante par au moins deux investigateurs. En l'absence d'accord, une réunion de résolution des désaccords est nécessaire.

Une évaluation de la qualité méthodologique des études doit systématiquement accompagner l'analyse des résultats(22). Elle évaluera l'aveugle, la randomisation, la comparabilité des groupes, le traitement des données incomplètes et les conflits d'intérêts.

### I.7.b Méta-analyse

La méta-analyse est un mode de synthèse des données selon une analyse quantitative consistant à surmonter les limites des essais individuels à l'aide des données agrégées ou des données individuelles de plusieurs études. Elle réduit alors l'incertitude de l'effet du traitement qui est combiné au même traitement dans les autres essais et permet d'explorer l'hétérogénéité, c'est à dire la variabilité des effets du traitement d'un essai à l'autre.

Les données brutes des études sont à nouveau analysées. L'effet de l'intervention est alors quantifiée par l'indice d'effet qui s'exprime de manière différente en fonction du type de données collectées (dichotomique, continue)(22). L'estimation de l'effet commun et de sa variance pour l'ensemble des études incluses, s'effectue en combinant les effets de chaque étude, pondérés en fonction, de leur précision ou de la taille de leur échantillon. Lorsque les indices d'effets pondérés sont calculés, un test d'hétérogénéité est réalisé. Il permet d'apprécier si les différences entre les effets des interventions pourraient être attribuées au hasard. Il existe différentes façons d'évaluer l'hétérogénéité : (i) visuellement sur les

graphiques de type forest plot, (ii) par des test statistiques tels que du $Chi^2$, (iii) par le calcul du $I^2$ qui correspond à une estimation du pourcentage de la variabilité en lien avec l'hétérogénéité(25).

Lors d'une méta-analyse, il est préconisé de réaliser des analyses de sensibilité, car au cours du travail de revue de la littérature, certaines décisions doivent être prises dans la sélection des études et des données à recueillir. Ces analyses de sensibilités consistent à vérifier que les résultats restent alors les mêmes si l'on répète les analyses en remplaçant certains paramètres découlant des décisions prises (choix du sexe, choix de l'âge, choix de la ligne thérapeutique…)(22).

Les résultats sont présentés sous la forme d'un forest plot. Cette figure, se présente par : une ligne verticale correspondant à l'absence d'effet de l'intervention au centre; un rectangle symbolisant l'effet de chaque étude; et une ligne horizontale pour chaque étude correspondant à son intervalle de confiance. Le losange inférieur représente l'effet commun, c'est à dire, la combinaison pondérée des résultats individuels.

Le funnel plot est un autre graphique dont la présentation permet de détecter un éventuel biais de publication par l'affichage des résultats des études individuellement(26). L'ordonnée correspond ici, à la taille de la population de l'étude et l'abscisse correspond à l'effet de l'intervention. Une ligne verticale présente l'effet commun de l'intervention.

### I.7.c Méta-analyse en réseau

Les méta-analyses permettent des comparaisons deux à deux des traitements, mais nécessitent que toutes les comparaisons entre deux traitements aient été déjà réalisées. Devant le prix de réalisation d'un essai clinique randomisé et le faible intérêt que peuvent porter les revues scientifiques sur les anciens traitements, de nombreuses thérapeutiques n'ont jamais pu et ne seront jamais comparées directement entre elles. Ainsi il est difficile de permettre une hiérarchisation des traitements dans certaines pathologies où il existe plusieurs alternatives médicales ou chirurgicales. Depuis le début du XXIème siècle une nouvelle forme de méta-analyse est apparue : la méta-analyse en réseau. Cette dernière

permet de réaliser des comparaisons indirectes, c'est-à-dire de comparer tous les essais randomisés comparant les différentes interventions disponibles pour traiter une maladie donnée, les uns contre les autres ou contre d'autres comparateurs(27-28).

La méta-analyse en réseau est présentée par l'intermédiaire de graphes non orientés multi bras, dans lequel les nœuds représentent les interventions et deux nœuds sont liés par une ligne si au moins un essai clinique randomisé a comparé les deux interventions correspondantes. L'épaisseur des lignes est proportionnelle au nombre d'essais. La taille du nœud est proportionnelle au nombre de sujets qui ont reçu l'intervention correspondante. En l'absence d'essai clinique randomisé entre l'intervention A et l'intervention B, une comparaison indirecte ajustée est réalisée, s'il existe des essais comparant A à C et B à C, où C est un comparateur commun (par exemple, un placebo). Alors, l'effet de A relativement à B sera estimé par :

$$\theta_{indirecteAB} = \theta_{directeAC} - \theta_{directeBC}$$

et la variance associée par :

$$var(\theta_{indirecteAB}) = var(\theta_{directeAC}) + var(\theta_{directeBC})$$

La non hétérogénéité des données doit être vérifiée, leur similarité également et enfin la cohérence des données est estimée (statistique $I^2$ de Higgins) avec absence attendue de différence entre les résultats des comparaisons directes et indirectes(29).

Cet outil statistique, devant son intérêt pratique, est employé de plus en plus par les organismes de réglementation des médicaments et les agences nationales d'évaluation des technologies de santé(30-32).

## II. OBJECTIF

Comparer l'efficacité des traitements locaux et interventionnels dans la prise en charge des condylomes ano-génitaux externes.

# III. METHODES & RESULTATS

Le travail a débuté par l'apprentissage des techniques de revue systématique de la littérature et des comparaisons directes. Notre première analyse a permis d'identifier l'absence de méta-analyse permettant de comparer la cryothérapie aux autres thérapies alors qu'il s'agissait d'un des outils thérapeutiques les plus employés par les dermatologues. Ce travail a fait l'objet d'une publication dans *Journal American Academy of Dermatology* en 2017 et a déjà été cité 12 fois.

# Cryotherapy to treat anogenital warts in nonimmunocompromised adults: Systematic review and meta-analysis

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***Background:*** Cryotherapy is one of the most commonly used therapeutic modalities to treat anogenital warts (AGWs), but this treatment was not clearly established in the recent international recommendations.

***Objective:*** To compare the efficacy and safety of cryotherapy versus other AGW treatments.

***Methods:*** Through a systematic search of 12 electronic databases, we identified 11 randomized controlled trials, screened from database inception through October 2016, that met the inclusion criteria (including immunocompetent adults with AGWs receiving cryotherapy in 1 of the comparison groups). Primary endpoint was complete clearance of AGW. Risk-for-bias assessment was based on Cochrane Handbook recommendations. Meta-analyses used Review Manager v5.3 software.

***Results:*** Cryotherapy efficacy did not appear to differ from that of trichloroacetic acid, podophyllin, or imiquimod. Electrosurgery was weakly associated with better AGW clearance than cryotherapy (risk ratio [RR] 0.80, 95% confidence interval [CI] 0.65-0.99). Cryotherapy was associated with more immediate low-level adverse events (erythema, stinging, or irritation; RR 3.02, 95% CI 1.38-6.61) and immediate pain requiring oral analgesics (RR 2.11, 95% CI 1.07-4.17) but fewer erosions (RR 0.57, 95% CI 0.36-0.90).

***Limitations:*** All but 1 randomized-controlled trial had a high risk for bias.

***Conclusion:*** With low-level quality of the evidence, cryotherapy is an acceptable first-line therapy to treat AGWs. (J Am Acad Dermatol 2017;77:518-26.)

***Key words:*** anogenital warts; condyloma; cryotherapy; genital; HPV; infection; meta-analysis; penile; sexually transmitted disease; STD; systematic review; vulvar.

Anogenital warts (AGWs) are one of the most frequent reasons for consultation in sexually transmitted disease clinics[1]; they come in second, after the potential for infection with nononcogenic human papillomaviruses (HPVs; eg, HPV types 6 and 11) and oncogenic HPVs.[2] Annual AGW incidence is around 1%-2%, depending on the world region considered.[1] The AGW burden remains relatively high, affecting quality of life[3,4] and health care costs,[4] despite HPV vaccination campaigns.[5] AGWs may be monitored with many different therapeutic options, which can be divided into

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Conflicts of interest: None declared.

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provider-administered (ie, bi- or trichloroacetic acid [TCA] application, podophyllin resin, $CO_2$ laser surgery, cryotherapy, surgical excision, and electrosurgery) and patient-administered treatments (ie, podophyllotoxin, imiquimod, sinecatechins, and 5-fluorouracil cream). The efficacies of these agents vary, and notable adverse events (AEs) of patient-administered therapies might affect treatment adherence and follow-up in clinics.

**CAPSULE SUMMARY**

- International recommendations do not prioritize first-line anogenital wart treatments.
- Low-level quality of the evidence indicated that cryotherapy was neither superior nor inferior to trichloroacetic acid or imiquimod; cryotherapy was slightly less efficacious than electrosurgery.
- Cryotherapy is an acceptable first-line therapy for anogenital warts.

Cryotherapy, an inexpensive and simple provider-administered procedure using liquid nitrogen in a spray or cryoprobe, is frequently used in many countries.[6-9] It destroys warts by cold-induced cytolysis. In the most recent versions of European and American guidelines,[10,11] first-line treatments for AGWs in immunocompetent adults are listed without priority as follows: provider-administered cryotherapy, TCA or surgery (scissor, electrosurgery, curettage, or laser) and patient-applied products (imiquimod, podophyllotoxin, or sinecatechins). Expert consensuses concluded that the decision should take into account the patient's preference, physician's experience, cost, anatomic site, and AGW size and number. Use of locally developed and monitored treatment algorithms was encouraged because no conclusive evidence suggests that any recommended treatment is superior to another.[11]

A recent systematic review of randomized controlled trials (RCTs) on local treatments for immunocompetent and HIV-infected patients (inclusion ended September 2014) globally concluded that ablative techniques are immediately clinically more effective at completely clearing AGWs posttreatment.[12] The results of several new RCTs examining cryotherapy for AGWs have become available since that review. Moreover, no specific systematic review of cryotherapy efficacy with meta-analysis has been published. The objectives of this systematic review and meta-analysis were to assess cryotherapy efficacy and safety compared with either placebo or other interventions to treat AGWs.

## METHODS

### Protocol

This review was registered on PROSPERO (no. CRD42015025827). PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement recommendations were followed.[13]

### Data sources and search strategy

Two independent reviewers (Drs Bertolotti and Derancourt) systematically and individually searched 12 databases, which were screened from inception of each database to October 1, 2016. We used a search strategy adapted to specific descriptor-based logic (English language) linked to the Boolean operators (AND and OR). Search terms included 3 synonym groups (AGW, cryotherapy, or RCT) with adjustments made for each database. Attempts were made to locate unpublished and ongoing trials through correspondence with authors, pharmaceutical laboratories, and trial registers. Reference lists in review articles[14-16] were searched to identify any additional studies. No language restriction was imposed.

### Selection

The same 2 reviewers independently selected studies initially on the basis of title and abstract. Study inclusion selection criteria were 1) being an RCT; 2) having original data providing risk ratio (RR) estimates with confidence intervals (CIs) or enough data to calculate them; 3) including immunocompetent men and nonpregnant women >16 years old who were clinically diagnosed with AGWs; 4) cryotherapy reported in at least 1 comparison treatment group; and 5) 1 provider-administered therapy (TCA, electrosurgery, $CO_2$ laser surgery, surgical excision, podophyllin, or bleomycin) or patient-administered treatment (imiquimod or KOH) in the other group. Studies not satisfying these criteria were excluded at this stage. Selected studies were further screened for suitability by reading the full text.

### Data extraction, outcomes, and risk for within-trial bias

An extraction grid was developed after collegial discussion. After consulting public hospital and private-practice dermatologists at regional and national meetings Drs Milpied, Bertolotti, and Derancourt initially retained primary (clearance at 3 months, recurrence 3 months later) and secondary outcomes (AEs, time to complete clearance, percentage

*Abbreviations used:*

| | |
|---|---|
| AE: | adverse event |
| AGW: | anogenital wart |
| CI: | confidence interval |
| GRADE: | grading of recommendation assessment, development, and evaluation |
| HPV: | human papillomavirus |
| ITT: | intention-to-treat |
| KOH: | potassium hydroxide |
| OR: | odds ratio |
| PRISMA: | preferred reporting items for systematic reviews and meta-analyses |
| RCT: | randomized controlled trial |
| RR: | risk ratio |
| TCA: | trichloroacetic acid |

of partial clearance, percentage of recurrence at 6 months, patient satisfaction, quality of life during treatment, and cost-effectiveness ratio). For each study, the 2 reviewers independently extracted these details and the following information: first author's last name; publication year; country of origin; inclusion criteria; exclusion criteria; sample-size determination; baseline demographic data (age, AGW duration, number of AGWs, total AGW area, and sex); number of participants randomized; losses to follow-up and reasons for loss to follow-up; final number of participants assessable; treatment modalities; and treatment doses, frequencies, and durations.

The 2 experienced reviewers independently assessed the risk for bias in the selected RCT reports using the Cochrane Collaboration Risk of Bias tool,[17] according to 6 specific domains: random-sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (including supposed financial support). Each domain was evaluated for low, high, or unclear risk for bias.

Any data collection discrepancies were resolved through consensus, and a third reviewer (Dr Milpied) was consulted as necessary. Investigators were contacted to collect complementary information as needed. For any studies involving the same patient cohort, we retained the article with its longest follow-up period.

Intention-to-treat (ITT) analysis was performed whenever possible for collection of information on the number of participants, except for recurrence, for which a per-protocol analysis was used.

### Data synthesis and analysis

The patient was the unit of analysis for all studies. When studies comparing similar interventions reported the same outcome measures, their data were combined for meta-analysis. Review Manager v5.3 (http://ims.cochrane.org/revman) was used to analyze the data with the Mantel-Haenszel method for dichotomous outcomes according to a fixed-effect or random-effects model. Estimates of the intervention's effects are expressed as RR (95% CI). Heterogeneity was estimated clinically and methodologically, and when Higgins'[18] $I^2$ exceeded 50%, a random-effects model was used.

The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of the Cochrane test for heterogeneity and the $I^2$ statistic. The grading of recommendation assessment, development, and evaluation (GRADE) approach was used to rate the quality of evidence and summarize the recommended treatments compared in ≥2 RCTs (data not shown).[19]

## RESULTS

### Description of studies and risk for bias

The searches led to the retrieval of 1281 references after removing duplicates. Thirty full-text articles were obtained, and from them, 11 RCTs were included in this review (Fig 1; Table I).[8,20-29] Eight studies with 2 arms, 2 studies with 3 arms,[24,28] and 1 study with 5 arms[22] used a parallel design.

Those 11 RCTs included 1639 participants with a mean of 149 subjects per study. Cryotherapy was compared with TCA in 4 trials,[22,23,25,29] with podophyllin in 3 others,[22,24,28] with imiquimod[21,28] or electrosurgery[24,26] in 2 trials each, and to $CO_2$ laser[20] or 5% potassium hydroxide solution (KOH)[8] in 1 RCT each. One study compared 2 combination therapies: cryotherapy with podophyllin and bleomycin with placentrex.[27]

Fig 2 summarizes the risk-for-bias assessment of the studies included. Nine studies had >1 domain assessed as having uncertain bias or having a high risk for bias (no blinding of outcome assessor, incomplete outcome data, selective reporting, or another risk) and are therefore described as having a high risk for bias. The study by Mahajan et al[27] was deemed as having a low risk for bias. One trial using industry-provided drugs[25] and 4 trials comparing home therapy versus cryotherapy[8,22,24,28] gave no information about financial support and were classed as having an unclear risk. Four studies[20,23,26,29] comparing provider-administered cryotherapy without information about financial support were classed as having a low risk for bias (low probability of financial influence).

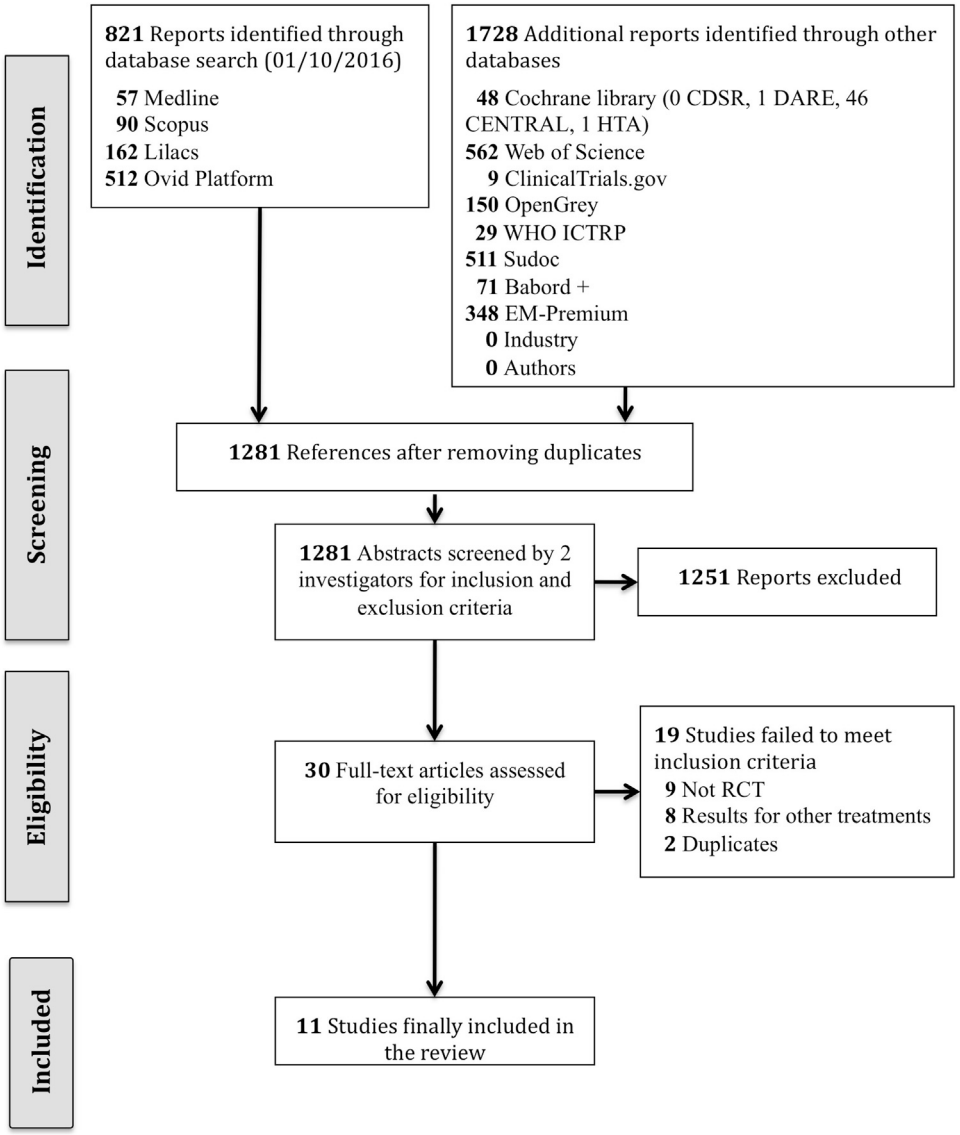


**Fig 1.** Flowchart showing the selection of randomized controlled trials (*RCTs*) on cryotherapy for anogenital warts. *CDSR*, Cochrane Database of Systematic Reviews; *DARE*, Database of Abstract of Reviews of Effects; *HTA*, health technology assessment; *WHO ICTRP*, World Health Organization International Clinical Trials Registry Platform; *EM*, Elsevier Masson.

**AGW clearance postintervention: Cryotherapy versus others**

Four studies that included 453 patients compared the effects of cryotherapy versus TCA.[22,23,25,29] Meta-analysis of this data estimated the pooled RR at 1.09 (95% CI 0.91-1.32) with substantial heterogeneity ($\chi^2$ = 7.58, df = 3, $P$ = .06, $I^2$ = 60%).

Three studies that enrolled 542 patients compared the effects of cryotherapy versus podophyllin.[22,24,28] Meta-analysis of this data estimated the pooled RR at 1.41 (95% CI 0.79-2.54) with substantial heterogeneity ($\chi^2$ = 36.13, df = 2, $P$ < .01, $I^2$ = 94%).

Two trials conducted on 204 patients compared the effects of cryotherapy versus imiquimod.[21,28] Meta-analysis of this data estimated the pooled RR at 0.90 (95% CI 0.73-1.12) without heterogeneity ($\chi^2$ = 0.55, df = 1, $P$ = .46, $I^2$ = 0%).

Two studies including 348 patients compared the effects of cryotherapy versus electrosurgery.[24,26] Meta-analysis of this data estimated the pooled RR at 0.80 (95% CI 0.65-0.99), slightly favoring electrosurgery, without heterogeneity ($\chi^2$ = 0.05, df = 1, $P$ = .83, $I^2$ = 0%).

One study that included 48 patients compared the effects of cryotherapy versus KOH.[8] No significant

**Table I.** Characteristics of the randomized controlled trials included in the meta-analysis

| Study | Country | First treatment | Intervention | Patients randomized (analyzed), n | Frequency | Modalities | Follow-up, mo | Outcome measures |
|---|---|---|---|---|---|---|---|---|
| Azizjalali et al, 2012[20] | Iran | No | $CO_2$ laser | 80 (80) | Once every 2 wk for a maximum of 6 wk | Local anesthesia, 30 W, 10,600 nm, 4.5 J/cm$^2$ | 3 | Clearance after 6 wk; recurrence after 3 mo; AEs |
| | | | Cryo | 80 (80) | — | 2 freezing cycles | | |
| Stefanaki et al, 2008[21] | Greece | Yes | Imiquimod | 60 (35) | 3 times/wk for a maximum of 12 wk | NR | 12 | Clearance after 4, 8, 12 and 24 wk; recurrence after 9 mo; AEs |
| | | | Cryo | 60 (45) | Once every 3 wk for a maximum of 12 wk | Frozen once for 10-20 s | | |
| Sherrard et al, 2007[22] | UK | No | Podo (25%) | 79 (56) | Times per week NR but a maximum of 8 wk | NR | 2 | Clearance after 8 wk; AEs |
| | | | TCA | 88 (58) | — | — | | |
| | | | Cryo | 81 (66) | — | — | | |
| | | | TCA + podo | 85 (65) | — | — | | |
| | | | Cryo + podo | 76 (59) | — | — | | |
| Abdullah et al, 1993[23] | UK | Yes | Cryo | 53 (43) | Once a week for a maximum 6 wk | Applied twice with a cotton Q-tip until wart is frozen with 1-mm margin | 3 | Clearance after 6 wk; AEs |
| | | | TCA | 33 (30) | — | A pointed plastic probe | | |
| Stone et al, 1990[24] | US | No | Podo (dose NR) | 144 (53) | Times per week NR but for a maximum of 6 wk | NR | 5 | Clearance after 6 wk; recurrence after 3 mo; AEs |
| | | | Cryo | 154 (60) | Once weekly for a maximum of 6 wk | Each AGW was frozen once | | |
| | | | Electro | 152 (51) | — | 1% lidocaine anesthesia | | |
| Godley et al, 1987[25] | UK | No | TCA | 69 (57) | Once weekly for a maximum of 10 wk | Applied with an orange stick | 4.5 | Clearance after 10 wk; recurrence after 2 mo; AEs; time to complete clearance |
| | | | Cryo | 61 (49) | — | Freeze twice for 15 s | | |
| Lotfabadi et al, 2015[29] | Iran | No | Cryo | 34 (34) | Every 2 wk, maximum 12 wk | Freeze with 1-mm margin, 10-15 s | 6 | Clearance 1 mo after 12 wk of treatment; recurrence after 2 mo; AEs |
| | | | TCA | 34 (34) | — | Applied with an applicator then washed | | |
| Simmons et al, 1981[26] | UK | No | Cryo | 24 (16) | Once every 2 wk for a maximum of 12 wk | Product ice-balls 2-mm larger than the wart | 3 | Clearance after 12 wk |
| | | | Electro | 18 (11) | Once every 2 wk for a maximum of 12 wk | 2% lignocaine anesthesia | | |
| Camargo et al, 2014[8] | Brazil | Yes | KOH | 24 (20) | Once daily for a maximum of 12 wk | Applied with a cotton wrapped toothpick | 3 | Clearance after 12 wk; recurrence after 1 mo; AEs; time to complete clearance |
| | | | Cryo | 24 (2) | Every 2 wk, maximum 12 wk | Freezing once 5-20 s | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mahajan et al, 2014[27] | India | No | Cryo + podo 20% | 30 (24) | Cryo once & Podo every 2 wk | Cryo: freezing with a 5-mm margin from 2-mm away<br>Podo: wash 3 h after therapy | 6 | Clearance after 8, 12, 24 wk; recurrence after 1 mo; AEs; time for complete clearance |
| | | | Bleomycin + placentrex | 30 (25) | Bleomycin every 2 wk for a maximum of 10 wk; placentrex every night | After bleomycin, ice water soaks BID for 4 d | | |
| Akhavan et al, 2014[28] | Iran | Yes | Podo (20%) | 42 (38) | Once weekly for a maximum of 8 wk | NR | 8 | Clearance after 8 wk; recurrence after 3 mo; recurrence after 6 mo |
| | | | Imiquimod | 42 (37) | Thrice weekly for a maximum of 8 wk | — | | |
| | | | Cryo | 42 (56) | Once; no other information given | — | | |

*AEs*, Adverse events; *AGW*, anogenital wart; *cryo*, cryotherapy; *electro*, electrosurgery; *KOH*, potassium hydroxide; *NR*, not reported; *podo*, podophyllin; *TCA*, trichloroacetic acid.

clinical improvement difference was found (RR 1.08, 95% CI 0.65-1.78).

One RCT enrolled 160 patients and compared the effects of cryotherapy versus $CO_2$ laser.[20] Clinical improvement differed significantly favoring the $CO_2$ laser (RR 0.49, 95% CI 0.38-0.62).

The effects of cryotherapy combined with podophyllin versus bleomycin combined with placentrex were compared in a trial on 60 patients.[27] No significant clinical improvement difference was found (RR 0.72, 95% CI 0.52-1.00).

Using 155 patients, 1 trial compared the effects of cryotherapy combined with podophyllin versus podophyllin alone[22]; a statistically significant difference in clinical improvement supported the use of combination therapy (RR 1.33, 95% CI 1.07-1.67).

### Cryotherapy AEs and AGW recurrence

Weak evidence from studies at high risk for bias suggested that cryotherapy might be associated with more low-grade local AEs (erythema, stinging, or irritation; RR 3.02, 95% CI 1.38-6.61)[8,25] or pain requiring oral analgesics (RR 2.11, 95% CI 1.07-4.17),[8,21,22,24,29] but the treatment was less associated with minor bleeding, erosion, or infection (RR 0.57, 95% CI 0.36-0.90)[8,22,24,25] than other treatments. No statistical evidence supported that cryotherapy caused more ulceration (data not shown) or that it was followed by more recurrences than other treatments, except when compared with $CO_2$ laser treatment[20] (RR 3.59, 95% CI 1.12-11.51).

### Other outcomes

Patient satisfaction, quality of life during treatment, and the cost-effectiveness ratio were not addressed in RCT publications.

### GRADE approach

For all assessable results, the GRADE approach rated the quality of evidence of the comparison between treatments (cryotherapy, TCA, imiquimod, and electrosurgery) low (data not shown).

## DISCUSSION

This systematic review with meta-analysis of cryotherapy efficacy and safety for patients with AGWs enabled us to conclude, with low-level quality of evidence, that no evidence supports cryotherapy superiority or inferiority when compared with TCA, imiquimod, or podophyllin and that cryotherapy appears slightly less effective than electrosurgery. A statistically significant clinical effect favoring $CO_2$ laser over cryotherapy was found in 1 trial[20] at high risk for bias. Cryotherapy caused fewer erosions than

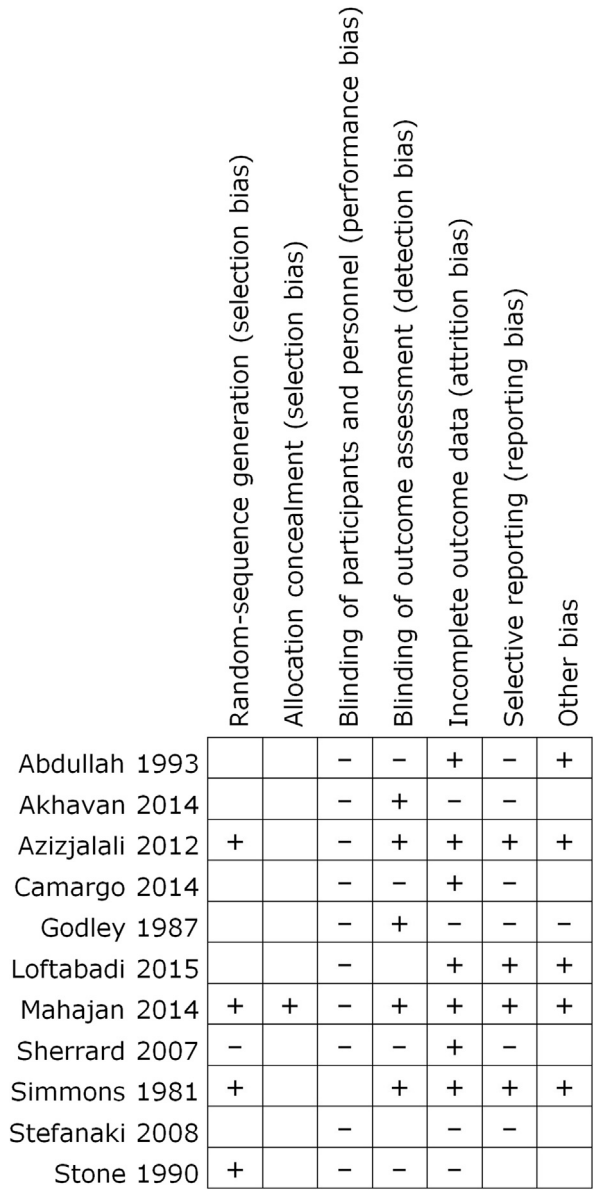


**Fig 2.** Risk-for-bias assessment of randomized controlled trials evaluating cryotherapy in the treatment of anogenital warts. +, low bias; −, high bias; blank square, uncertain.

other treatments. Low-grade AEs (erythema and pain) occurring immediately after cryotherapy usually did not require treatment discontinuation and are common AEs of provider-administered therapies. The limits of our conclusions mainly reflect the high risk for bias from the 10/11 RCTs retained, mostly because of missing information. Moreover, the lack of uniformity of the outcome assessment period in the different RCTs prompted us to evaluate clearance 4-12 weeks posttreatment, instead of 3 months, as decided collegially in our protocol. Therefore, because AGWs disappear rapidly but tend to reappear relatively shortly thereafter, it seems important that future RCTs evaluate the clearance rate after 3 months, and recurrence after 6 and 12 months. Moreover, the different AGW locations should be specified in future RCTs to enable subgroup analyses to determine whether cyto-destructive methods are more effective on keratinized epithelia and whether imiquimod or podophyllotoxin are more effective on mucosal epithelia.

We observed that AEs, eg, pain and ulceration, were not systematically described in RCT reports concerning patient-administered agents, even though therapeutic compliance is highly dependent on them. Unfortunately, partial clearance, patient satisfaction, quality of life during treatment, and cost-effectiveness ratios were rarely reported, although they could be informative. Risk for bias was evaluated based on AGW clearance, but other judgement criteria had similarly assessed risks for bias (data not shown).

Another limit of our conclusions is that cryotherapy efficacy, like all provider-administered procedures, is operator-dependent. Cryotherapy delivery (intensity [aggressive vs gentle], delivery duration, and spray or cryoprobe use) was not sufficiently standardized in RCTs. Furthermore, operator blinding is difficult to obtain for nondrug treatment,[30] but strategies could be developed in future RCTs with interventional treatment to decrease bias,[31,32] eg, providing patients the study goals only at the end of the study was proposed by some authors.[32-34] In contrast, blinded participants and personnel do not ensure successful blinding in practice; drug AEs enable the possible identification of the assigned intervention.[35,36]

As for numerous systematic reviews with meta-analyses, contacting authors and pharmaceutical companies[37-39] to obtain unpublished information was unsuccessful, as was access to the Chinese databases. Because of the paucity of RCTs included in each comparison, quantitative estimation of publication bias[40] was not possible.

From a statistical point of view, we used ITT analysis to assess clearance and AE outcomes but a per-protocol analysis for recurrence because this approach best reflects real-life practice. The low number of studies included precluded sensitivity analyses, as recommended by PRISMA guidelines.[13] Similarly, subgroup analyses of different well-documented locations or numbers of AGWs could not be computed because of the small number of patients with data included in the studies.

According to Thurgar et al's analysis,[12] cryotherapy efficacy versus placebo efficacy was assessed with an odds ratio (OR) of 71.05 (95% CI

10.44-274.10). However, they used a 25-month longer inclusion period and a different selection procedure to retrieve articles, and 5 additional RCTs[8,26-29] were included in this report. We obtained different results when comparing cryotherapy with electrosurgery (our calculated ORs vs Thurgar et al's, 1.55 [95% CI 1.01-2.36] vs 1.52 [95% CI 0.97-2.39], respectively) or podophyllin (2.10 [95% CI 0.97-4.53] vs 2.98 [95% CI 1.97-4.51]). Moreover, the inclusion of more studies and hence more data contributes to better accuracy about AEs, especially those Thurgar et al did not consider, such as local mild-grade pain requiring analgesics. These significant results enable the practitioner to better inform their patients and better adapt the therapeutic choice.

The results of our analyses suggest that cryotherapy could be used as a first-line therapy for AGWs. Electrosurgery could be used but seems more aggressive (requiring local anesthesia), even though it is slightly more effective, and $CO_2$ laser could be used but is less available, particularly in developing countries.

In the future, conducting low-risk-for-bias RCTs with appropriate blinding procedures[31,32] could help clarify our conclusion. Moreover, standardizing the cryotherapy procedure should also be discussed to optimize comparability, with direct comparisons between cryotherapy and podophyllotoxin, $CO_2$ laser, or imiquimod. Furthermore, the high cost of managing AGWs[3,41] requires economic analyses to specify the cost-effectiveness of cryotherapy in comparison with those of other topical therapies and provider-administered procedures, including HPV vaccination.

We would like to thank Professor Rodolphe Thiebaut for continuous support; Evelyne Mouillet, research librarian; dermatologists from the French National Group of Sexually Transmitted Diseases of the Société Française de Dermatologie and l'Association des Dermatologues des Alpes du Sud; and Janet Jacobson for editorial assistance.

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Dans les suites, nous avons étendu notre requête à l'ensemble des thérapies locales et interventionnelles. Nous avons également mis à jour les dates d'extraction au fur et à mesure de l'avancée de la thèse. Le premier résultat le plus important de notre travail fut la mise en évidence du nombre très élevé d'essais clinique à haut risque de biais dans ce domaine. Ce résultat spécifique a fait l'objet d'une publication dans *Journal American Academy of Dermatology* en 2019.

diagnosed as anti-p200/lamγ1 pemphigoid. In addition, 13 sera (9.2%) contained AAbs exclusively reactive with Col7, and 4 (2.8%) contained AAbs exclusively reactive with lam332. In 9 of the cohort of 141 sera (6.4%), no target antigen was identified (Fig 2).

In summary, anti-p200/lamγ1 pemphigoid was by far the most frequent pemphigoid disease, with 78.7% of the 141 patients having dermal binding AAbs, followed by EBA in 11.4% of patients and anti-lam332 MMP in 3.5% of patients.

Dual reactivity with different antigens may be explained either by cross-reactive AAbs or by epitope spreading, which is a phenomenon that describes the generation of AAbs with different antigen specificities in the same patient.[1] Our data suggest that epitope spreading may occur more frequently in anti-p200/lamγ1 pemphigoid than in EBA and anti-lam332 MMP.

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*Reprints not available from the authors.*

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## Methodologic gaps and risk of bias in randomized controlled trials of local anogenital wart treatments

*To the Editor:* The latest guidelines for first-line treatment of anogenital warts (AGWs) in immunocompetent adults failed to establish a therapeutic hierarchy[1,2] because of methodologic gaps in research and insufficient randomized controlled trial (RCT) evidence. This section of our systematic review (Prospero no. CRD42015025827) addresses these insufficiencies and provides recommendations for future RCTs of AGW treatments.

A search was conducted through 12 databases from their inception to August 1, 2018 (supplemental material available at https://www.mendeley.com/community/journal-of-the-american-academy-of-dermatology/). RCTs were included when a provider- or patient-administered treatment was reported in ≥1 parallel treatment group; the other inclusion criteria were reported in a previous paper.[3] The primary outcomes were percentage of clearance and percentage of recurrence, and the Cochrane Collaboration risk of bias tool and its methodology[4] were used.

In total, 70 unique RCTs involving 9931 individual patients (mean 142 participants/study) fulfilled the inclusion criteria (Appendix S2). The overwhelming majority of included RCTs (66/70) were found to be of poor quality (Appendix S3). A risk of performance bias due to knowledge of the allocated intervention by participants and personnel (excluding outcome assessor) was detected in 31 of 70 RCTs (row 3, Appendix S3). The risk of detection bias due to knowledge of the allocated intervention by outcome assessors was high in 10 of 70 and unclear in 35 of 70 RCTs (row 4, Appendix S3). The risk of selection bias due to inadequate generation of a randomized sequence was high in 7 of 70 and unclear in 38 of 70 RCTs (row 1, Appendix S3). Other biases corresponded mainly to pharmaceutical funding or to conflicts of interest; the risk was high in 25 of 70 RCTs and unclear in 35 of 70 RCTs (row 7,

Appendix S3). A selection bias was suspected in many RCTs (57/70) (row 2, Appendix S3). High risk of attrition bias and reporting bias was evident in 19 of 70 and 20 of 70 RCTs, respectively (rows 5 and 6, Appendix S3). Thirty-five RCTs were published since the first CONSORT (Consolidated Standards of Reporting Trials) statement was released (1996)[5]; among these, 12 had a high or uncertain risk of reporting bias. AGW clearance was assessed from immediately after treatment (mainly for provider-administered therapies) up to 4 months later, depending on the study. Recurrence was occasionally assessed (15/70 RCTs) 1-12 months after clearance.

The following should be considered in future RCTs. Participants and physicians should be systematically blinded to the allocated intervention, and both AGW clearance and recurrence should be assessed at fixed time points (a consensus is lacking on this point) by an independent expert unaware of the allocated intervention. Proper randomization procedures should be strictly followed. The CONSORT statement must imperatively be employed. Systematic information on previous therapies and on AGW location and characteristics should be provided to enable efficacy analyses. The unit of analysis must always be the patient, as the primary goal is full recovery. Split studies should be avoided for statistical reasons but also because of the risk of performance bias. In future RCTs, the percentage of AGW recurrence, which is an important yet often neglected outcome, should also be evaluated. Nevertheless, RCT assessment of recurrence raises important methodologic problems, including a high rate of loss to follow-up and recontamination.

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## Association between prurigo nodularis and malignancy in middle-aged adults

*To the Editor:* Prurigo nodularis (PN) is an extremely pruritic, inflammatory skin disease associated with multiple underlying comorbidities.[1] Case reports have noted an association between PN and malignancies, including lymphoma[2,3] and solid organ tumors.[4] The goal of this cross-sectional study was to evaluate an association between PN and a variety of malignancies in a diverse patient population.

Institutional review board approval was waived for this study because only anonymous aggregate-level data were used. The study population consisted of 695 patients aged 40-69 years who presented to the Johns Hopkins Health System during 2013-2017

# Methodological gaps and risk of bias in randomized controlled trials of local anogenital warts treatments

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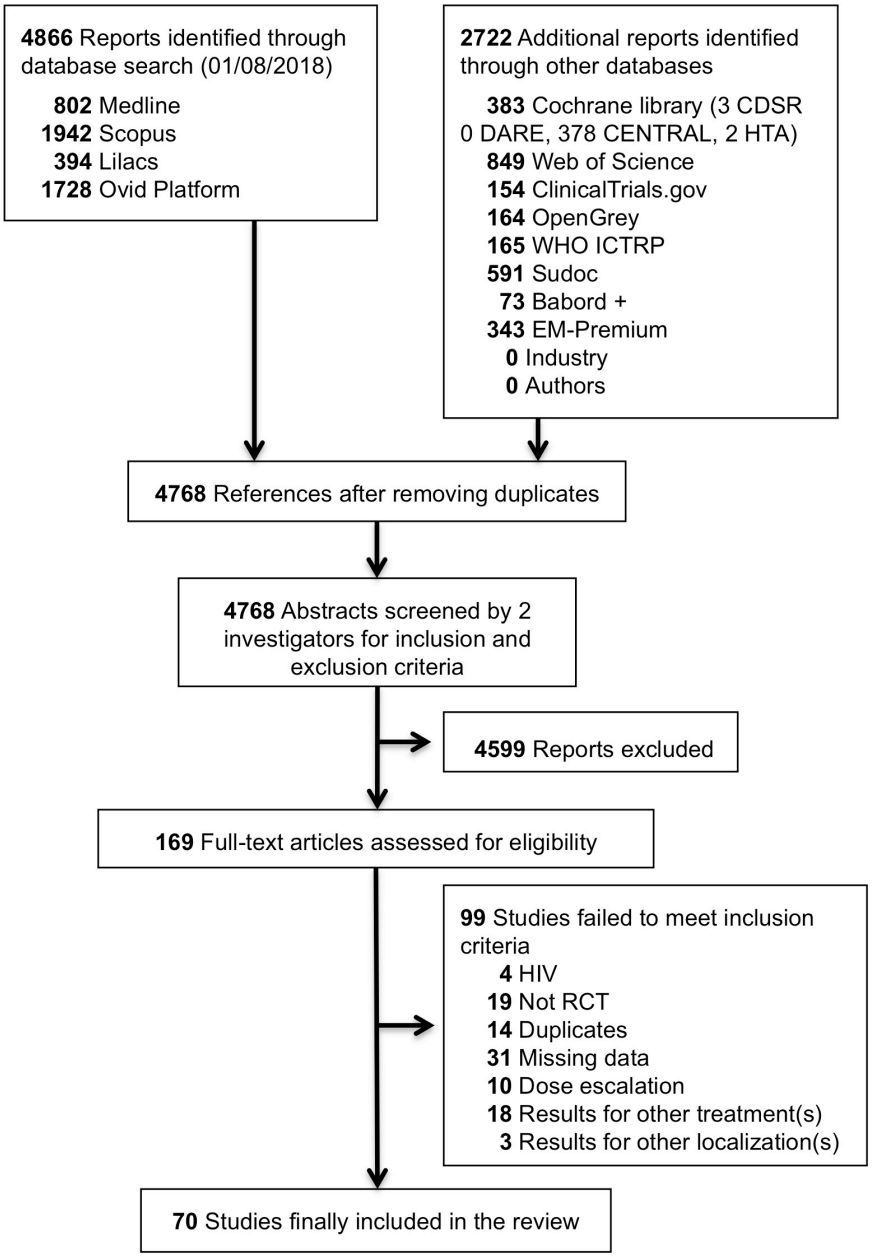
**Appendix S1.** Flow diagram of selected randomized controlled trials (RCTs) of local anogenital warts treatments.



**Appendix S2:** Characteristics of RCTs included in the meta-analysis

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Abdullah 1993[1] | UK | Cryo | 53 (43) | 1×/wk, maximum 6 wk | Applied with a cotton Q-tip until wart is frozen with 1-mm margin, 2× | 3 | Clearance after 6 wk, side effects | 1st treatment |
| | | TCA | 33 (30) | Same | A pointed plastic probe | | | |
| Akhavan 2014[2] | Iran | Podophyllin 20% | 42 (38) | 1×/wk, maximum 8 wk | NR | 8 | Clearance after 8 wk, recurrence after 3 mo, recurrence after 6 mo | 1st treatment, only women |
| | | Imiquimod | 42 (37) | 3×/wk, maximum 8 wk | Same | | | |
| | | Cryo | 42 (36) | 1×; no other information given | Same | | | |
| Arican 2004[3] | Turkey | Imiquimod 5% | 34 (33) | 3×/wk, maximum 12 wk | Applied with the tip of the stick and then cleaned with abundant amounts of water | 9 | Clearance after 3 mo, recurrence after 6 mo, side effects | ITT modified |
| | | Placebo | 11 (10) | Same | Same | | | |
| Azizjalali 2012[4] | Iran | $CO_2$ laser | 80 (80) | 1× every 2 wk, maximum 6 wk | Local anesthesia, 30 W, 10,600 nm, 4.5 J/cm$^2$ | 3 | Clearance after 6 wk, recurrence after 3 mo, side effects | ITT |
| | | Cryo | 80 (80) | Same | 2 freezing cycles | | | |
| Baker 2011[5] | USA | Imiquimod 2.5% | 202 (139) | 1×/d for 8 wk | Wash after 8 hr | 4 | Clearance after 4 mo, side effects | ITT, only women |
| | | Imiquimod 3.75% | 204 (149) | Same | Same | | | |
| | | Placebo | 105 (77) | Same | Same | | | |
| Benedetti Panici 1989[6] | Italy | Electro | 51 (51) | Until apparent elimination of the genital wart, interval: 3 wk | Local anesthesia, diathermocoagulation with bipolar electrodes | 12 | Clearance after 1 mo, recurrence after 2.6 mo, side effects | ITT, only women, some patients with AGWs on cervix; IFN arm (data not shown) |
| | | Placebo | 48 (48) | NR | NR | | | |
| Beutner 1989[7] | USA | Podophyllotoxin 0.5% gel | 56 (56) | 2×/d, 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 6 wk, recurrence after 10 wk, side effects, new warts | ITT, only men |
| | | Placebo | 53 (53) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Beutner 1998[8] | USA | Imiquimod 5% | 94 (69) | 1×/d, maximum 16 wk | Wash after 8 hr with soap and water | 7 | Clearance after 8, 12, 16 wk, recurrence after 3 mo, side effects, partial clearance, time for complete clearance, new warts | ITT |
| | | Imiquimod 1% | 90 (71) | Same | Same | | | |
| | | Placebo | 95 (67) | Same | Same | | | |
| Bilensoy 2011[9] | Turkey | Placebo | 6 (6) | 3×/wk, 1 wk/2, maximum 12 wk | Applied with a cotton-tipped swab | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance | ITT, only women; both 5-FU arms used with cyclodextrin thermosensitive gel |
| | | 5-FU cream | 14 (14) | Same | Same | | | |
| | | Placebo intra-lesional | 6 (6) | Same | NR | | | |
| | | 5-FU intra-lesional | 18 (18) | Same | Same | | | |
| Bornstein 1997[10] | Israel | IFNβ-1a intra-lesional 1 MIU | 30 (30) | 3×/wk, maximum 3 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance, time to complete clearance | ITT |
| | | Placebo intra-lesional | 30 (30) | Same | Same | | | |
| Camargo 2014[11] | Brazil | KOH | 24 (20) | 1×/d, maximum 12 wk | Applied with a cotton wrapped toothpick | 3 | Clearance after 12 wk, recurrence after 1 mo, side effects, time to complete clearance | 1st treatment, only men |
| | | Cryo | 24 (22) | Every 2 wk, maximum 12 wk | Freezing 1× 5-20 s | | | |
| Carpiniello 1988[12] | NR | $CO_2$ laser | 41 (NR) | NR | | 4 | Clearance after treatment, recurrence after 4 mo | Only men |
| | | $CO_2$ laser + 5-FU | 27 (NR) | 5-FU every night maximum 30 d | 5-FU initiated 1 wk after $CO_2$ laser | | | |
| Chen 2007[13] | China | $CO_2$ laser | 21 (21) | 1×/wk for 3 wk if not removed | topical anesthesia with 2% lidocaine | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | ITT, no quantification for side effects |
| | | PDT | 65 (65) | Same | ALA dissolved in sterile 0.9% NaCl just before application, 3 hr before light illumination (632 nm) | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Claesson 1996[14] | Sweden, Finland, France | Podophyllotoxin 0.15% cream | 60 (60) | 2×/d for 3 consecutive d, maximum 4 wk | | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT |
| | | Podophyllotoxin 0.3% cream | 60 (60) | Same | | | | |
| | | Podophyllotoxin 0.5% sol | 60 (60) | Same | | | | |
| Duus 1985[15] | Denmark | $CO_2$ laser | 25 (21) | 1×, maximum 2× | Continuous wave (5-20 W), spot diameter of 0-7 mm | 6 | Clearance after treatment, recurrence after 3 mo, side effects | |
| | | Ablative treatment (surgery, Electro) | 25 (23) | 1×, maximum 2× | NR | | | |
| Edwards 1998[16] | Multicentric: Hawaii, New York, Pennsylvania & Canada | Imiquimod 5% | 109 (90) | 3×/wk for 16 wk | Wash after 6-10 hr with soap and water | 7 | Clearance after 4 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Imiquimod 1% | 102 (71) | Same | Same | | | |
| | | Placebo | 100 (73) | Same | Same | | | |
| Edwards 1988[17] | UK | Podophyllotoxin 0.5% sol | 32 (32) | 2×/d for 3 consecutive d, maximum 6 wk | Self-applied | 6 | Clearance after 6 wk, side effects | ITT, only men |
| | | Podophyllin 20% | 19 (19) | 1×/wk, maximum 6 wk | Provider-applied | | | |
| Eron 1986[18] | USA | IFNα-2b (1 MIU) intra-lesional | 147 (125) | NR | NR | 7 | Clearance after 4,16 wk; recurrence after 3 mo, side effects | |
| | | Placebo intra-lesional | 149 (132) | Same | Same | | | |
| Gabriel 1983[19] | UK | Podophyllin 25% | 38 (29) | 1×/wk, maximum 6 wk | Applied with the tip of the stick | 3 | Clearance after 6 wk, recurrence after 6 wk, side effect, time to complete clearance | Only men |
| | | Podophyllin 25% + TCA 50% | 35 (31) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Gilson 2009[20] | UK | Cryo + placebo | 75 (40) | Cream 2×/d for 3 consecutive d, maximum 4 wk, Cryo: 45-s freezing/wk, maximum 12 wk | NR | 9 | Clearance after 3 mo, recurrence after 3 mo, side effects | ITT modified |
| | | Cryo + podophyllotoxin 0.15% cream | 74 (31) | Same | Same | | | |
| Godley 1987[21] | UK | TCA | 69 (57) | 1×/wk maximum 10 wk | Applied with an orange stick | 4,5 | Clearance after 10 wk; recurrence after 2 mo, side effects, time to complete clearance | Only men |
| | | Cryo | 61 (49) | Same | Freeze for 15 sec twice | | | |
| Greenberg 1991[22] | USA | Podophyllotoxin 0.5% sol & cream | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with a cotton tip | | Clearance after 4 wk; recurrence after 2 mo, distinctive side effects for gel & cream, new warts | ITT modified, only women |
| | | Placebo | 24 (21) | Same | Same | | | |
| Gross 2007[23] | Germany & Russia | Polyphenon 15% | 80 (46) | 3×/d, maximum 16 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, side effects | |
| | | Polyphenon 10% | 79 (36) | Same | Same | | | |
| | | Placebo | 83 (31) | Same | Same | | | |
| Hellberg 1995[24] | Sweden | Podophyllotoxin 0.5% cream | 30 (28) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | Only women |
| | | Podophyllin 20% | 30 (27) | 1×/wk, maximum 4 wk | Wash 4 hr after application | | | |
| Isik 2014[25] | Turkey | KOH | 30 (30) | 1×/d for 12 wk | Perilesional application of Vaseline | 6 | Clearance after 3 mo, recurrence after 3 mo, partial clearance | ITT |
| | | 5-FU + salicylic acid | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Jensen 1985[26] | Denmark | Podophyllin 25% | 30 (30) | 1×/wk, maximum 6 wk | Wash after 6 hr | 12 | Clearance after 4 wk; recurrence after 1.5, 4.5, 10.5 mo; side effects, time to complete clearance | ITT |
| | | Surgery | 30 (30) | Same | Local anesthesia with lignocaine | | | |
| Keay 1988[27] | USA | IFNα cream | 32 (31) | 3×/d, maximum 4 wk | Applied topically by gentle 30-s rubbing | 4 | Clearance after 4, 16 wk, side effects | ITT modified, only women |
| | | Placebo | 33 (30) | Same | Same | | | |
| Khawaja 1989[28] | UK | Podophyllin 25% | 19 (19) | 1×/wk, maximum 6 wk | Wash after 6 hr | 10.5 | Clearance after 6 wk, recurrence after 3, 9 mo; side effect, time to complete clearance | ITT, 1st treatment |
| | | Surgery | 18 (18) | 1× | Local anesthesia with lignocaine | | | |
| Kinghorn 1993[29] | UK | Podophyllotoxin 0.5% sol | 168 (138) | 2×/d for 3 consecutive d, maximum 5 wk | | 3 | Clearance after 54 wk; recurrence after 2 mo, side effects | |
| | | Podophyllin 25% | 84 (62) | 2×/wk, maximum 5 wk | Wash off after 4 hr | | | |
| Kirby 1990[30] | USA | Podophyllotoxin 0.5% sol | 19 (19) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT |
| | | Placebo | 19 (19) | Same | Same | | | |
| Komericki 2011[31] | Austria | Podophyllotoxin 0.5% sol | 26 (25) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk for podophyllotoxin and 16 wk for imiquimod, side effects | 1st treatment |
| | | Imiquimod 5% | 25 (20) | 3×/wk maximum 16 wk | Same | | | |
| Kumar 2014[32] | India | Imiquimod 5% | 44 (41) | 3×/wk, maximum 16 wk | Intradermal injections of the Mw vaccine and vehicle on both shoulders at baseline to sensitize and improve local immune response to intralesional therapy | 8 | Clearance after 20 wk; recurrence after 3 mo, side effects, time to complete clearance, partial clearance | ITT |
| | | *Mycobacterium* intra-lesional | 45 (39) | Every 2 wk, maximum 16 wk | – | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Lacey 2003[33] | UK | Podophyllin 25% | 116 (96) | 2×/wk, maximum 4 wk | In the clinic | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects, cost/efficacy ratio | |
| | | Podophyllotoxin 0.15% cream | 118 (82) | 2×/d for 3 consecutive d, maximum 4 wk | NR | | | |
| | | Podophyllotoxin 0.5% sol | 120 (98) | Same | Same | | | |
| Lassus 1987[34] | Finland | Podophyllotoxin 0.5% sol | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | At home | 3 | Clearance after 4 wk; recurrence after 2 mo | ITT, only men |
| | | Podophyllin 20% | 52 (52) | 1×/wk, maximum 4 wk | In the clinic | | | |
| Lotfabadi 2015[35] | Iran | Cryo | 34 (34) | Every 2 wk, maximum 12 wk | Freeze with 1-mm margin, 10-15 s | 6 | Clearance 1 mo after 12 wk of treatment; recurrence after 2 mo; side effects | |
| | | TCA | 34 (34) | Same | Applied by an applicator then washed | | | |
| Mahajan 2014[36] | India | Cryo + podophyllin 20% | 30 (24) | Cryo once & podo every 2 wk | Cryo: freezing with a 5-mm margin from a distance of 2-mm<br>Podo: Wash 3 hr after therapy | 6 | Clearance after 8,12, 24 wk; recurrence after 1 mo; side effects; time to complete clearance | |
| | | Bleomycin + placentrex intra-lesional | 30 (25) | Bleomycin every 2 wk, maximum 10 wk; placentrex every night | After bleomycin, ice water soaks twice daily for 4 d | | | |
| Mazurkiewicz 1990[37] | Poland | Podophyllin 20% | 16 (13) | Once/wk, maximum 6 wk | Doctor-applied | 1,5 | Clearance after 6 wk, side effects | |
| | | Podophyllotoxin 0.5% sol | 16 (14) | 2×/d for 3 consecutive d, maximum 6 wk | Patient-applied | | | |
| | | Podophyllotoxin 0.5% cream | 22 (16) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Nath 1990[38] | India | Podophyllin 25% | 50 (47) | 1×/wk, maximum 12 wk | Wash after 2 hr | 6 | Clearance after 3 mo, recurrence after 3 mo, time to complete clearance | Incompletely randomization (pregnant women got TCA) |
| | | TCA 50% | 50 (48) | Same | Applied with a swab stick | | | |
| On 2014[39] | USA | Polyphenon 15% + cryo | 21 (NR) | Polyphenon: 2×/d, maximum 16 wk; Cryo: 1× | Cryo: 2 5-s cycles/5-s interval rest | 16 | Clearance after 9 & 17 wk, side effects, partial clearance | ITT |
| | | Cryo | 21 (NR) | 1× | Same | | | |
| Ormerod 2015[40] | Germany, UK, Holland, Switzerland, Poland: 40 centers | Placebo | 75 (74) | 2×/d for 12 wk | Sodium nitrite was applied first, then citric acid, & the 2 creams were mixed. | 6 | Clearance after 3 mo, recurrence after 3 mo, side effects, time to complete clearance | |
| | | Sodium nitrite 3% + citric acid 4.5% | 74 (72) | 2×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 77 74) | 1×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 73 (70) | 2×/d for 12 wk | Same | | | |
| Padhiar 2006[41] | India | Imiquimod 5% | 30 (30) | 3×/wk, maximum 16 wk | Wash after 6-10 hr | 10 | Clearance after 4 mo, recurrence after 3 & 6 mo, side effects, partial clearance, time to complete clearance | ITT |
| | | Podophyllin 20% | 30 (30) | 1×/wk, maximum 6 wk | Applied with a swab stick, wash after 4-6 hr | | | |
| Petersen 1995[42] | Denmark | Podophyllotoxin 0.5% sol | 18 (18) | 2×/d for 3 consecutive d, maximum 4 wk | Fingertip application | 3 | Clearance after 6 wk, recurrence after 6 wk, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 18 (18) | Same | Same | | | |
| Reichman 1988[43] | USA | IFNα-n1 intra-lesional | 17 (15) | 3×/wk, maximum 4 wk | NR | 12 | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | IFNβ (1 MIU) intra-lesional | 20 (20) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Reichman 1988[43](continued) | | IFNα-2b intra-lesional | 23 (23) | Same | Same | | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | Placebo intra-lesional | 19 (18) | Same | Same | | | |
| Relakis 1996[44] | Brazil & Greece | $CO_2$ laser | 71 (71) | 1× | Applied Vaseline & $ZnO_2$ 10% cream | 12 | Clearance after 3 mo, recurrence after 3, 6 & 9 mo, side effects | ITT, only men |
| | | 5-FU | 218 (218) | 5×/wk, maximum 4 wk | Applied Vaseline 5% $ZnO_2$, before 5-FU | | | |
| | | $CO_2$ laser + 5-FU | 47 (47) | Both | Both | | | |
| Schofer 2006[45] | Germany | Ablative procedure (Electro, Cryo, laser, surgery) | 100 (100) | 1×/wk, maximum 4 wk | NR | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | ITT |
| | | Imiquimod 5% | 155 (155) | 3×/d, maximum 16 wk | Same | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | |
| | | Ablative procedure + imiquimod | 103 (103) | Both | Same | | | |
| Sherrard 2007[46] | UK | Podophyllin 25% | 79 (56) | Times/wk NR, but maximum 8 wk | NR | 2 | Clearance after 8 wk, side effects | |
| | | TCA | 88 (58) | Same | Same | | | |
| | | Cryo | 81 (66) | Same | Same | | | |
| | | TCA + Podophyllin | 85 (65) | Same | Same | | | |
| | | Cryo + Podophyllin | 76 (59) | Same | Same | | | |
| Simmons 1981[47] | UK | Cryo | 24 (16) | 1× every 2 wk, maximum 12 wk | Produced 2-mm ice-balls larger than wart | 3 | Clearance after 12 wk | |
| | | Electro | 18 (11) | 1× every 2 wk, maximum 12 wk | 2% lignocaine anesthesia | | | |
| Snoeck 2001[48] | Belgium | Cidofovir | 19 (19) | 1×/d, 5 d/wk, 1 wk/2 for 12 wk | Applied with a cotton tipped swab or a rubber glove | | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Placebo | 11 (11) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Stefanaki 2008[49] | Greece | Imiquimod | 60 (35) | 3×/wk, maximum 12 wk | NR | 12 | Clearance after 4, 8,12 & 24 wk, recurrence after 9 mo, side effects | 1st treatment |
| | | Cryo | 60 (45) | 1× every 3 wk, maximum 12 wk | Frozen 1× for 10-20 s | | | |
| Stockfelth 2008[50] | Multicentric (Europe, South Africa) | Polyphenon 15% | 201 (161) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | ITT modified |
| | | Polyphenon 10% | 199 (170) | Same | Same | | | |
| | | Placebo | 103 (80) | Same | Same | | | |
| Stone 1990[51] | USA | Podophyllin (dose NR) | 144 (53) | Times/week NR, but maximum 6 wk | NR | 5 | Clearance after 6 wk, recurrence after 3 mo, side effects | |
| | | Cryo | 154 (60) | 1×/wk, maximum 6 wk | Each AGW was frozen 1× | | | |
| | | Electro | 152 (51) | Same | 1% lidocaine anesthesia | | | |
| Strand 1995[52] | Sweden | Podophyllotoxin 0.15% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with an applicator | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT, only men |
| | | Podophyllotoxin 0.3% cream | 31 (31) | Same | Same | | | |
| | | Podophyllotoxin 0.5% sol | 29 (29) | Same | NR | | | |
| Swinehart 1997[53] | USA | 5-FU injection intra-lesional | 80 (78) | 1×/wk, maximum 6× over 8 wk | NR | 5 | Clearance after 8 wk, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | Individual lesion analysis |
| | | 5-FU | 80 (76) | NR | Same | | | |
| | | Placebo | 40 (33) | Same | Same | | | |
| Syed 1998[54] | Pakistan | Imiquimod 2% | 30 (30) | 2×/d for 5 consecutive d, maximum 6 wk | Wash & dry warts before each application and apply | 4 | Clearance after 6 wk, recurrence after 2.5 mo, side effects | ITT, only women, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Syed 1995 (a)[55] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, recurrence after 9 mo, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1995 (b)[56] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1994[57] | Pakistan | Podophyllotoxin 0.3% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Let dry for at least 1 min without washing | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 30 (30) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 2000[58] | Pakistan | Imiquimod 2% | 30 (30) | 3 consecutive d, maximum 4 wk | Applied with a finger cot | 18 | Clearance after 16 wk, recurrence after 18 mo, side effects | ITT, only men, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |
| Szeimies 2009[59] | Germany | PDT + $CO_2$ laser | 84 (84) | 1× | PDT: 100 J/cm$^2$, 100 mW/cm$^2$ (640-740 nm) occlusion for 4-6 hr | 12 | Clearance after treatment, recurrence after 1, 2, 3, 6 & 12 mo, side effects, satisfaction | ITT |
| | | $CO_2$ laser | 91 (91) | Same | Continuous wave, defocused beam (2-mm diameter), 10-20 W, general or local anesthesia | | | |
| Tabari 2010[60] | Iran | Podophyllin 20% | 60 (60) | 2×/wk | Wash after 20 min | 6 | Clearance after 4 or 8 wk, recurrence after 3 mo, side effects | ITT |
| | | TCA 30% | 60 (60) | NR | With a topical cotton soap and washed after 1 min | | | |

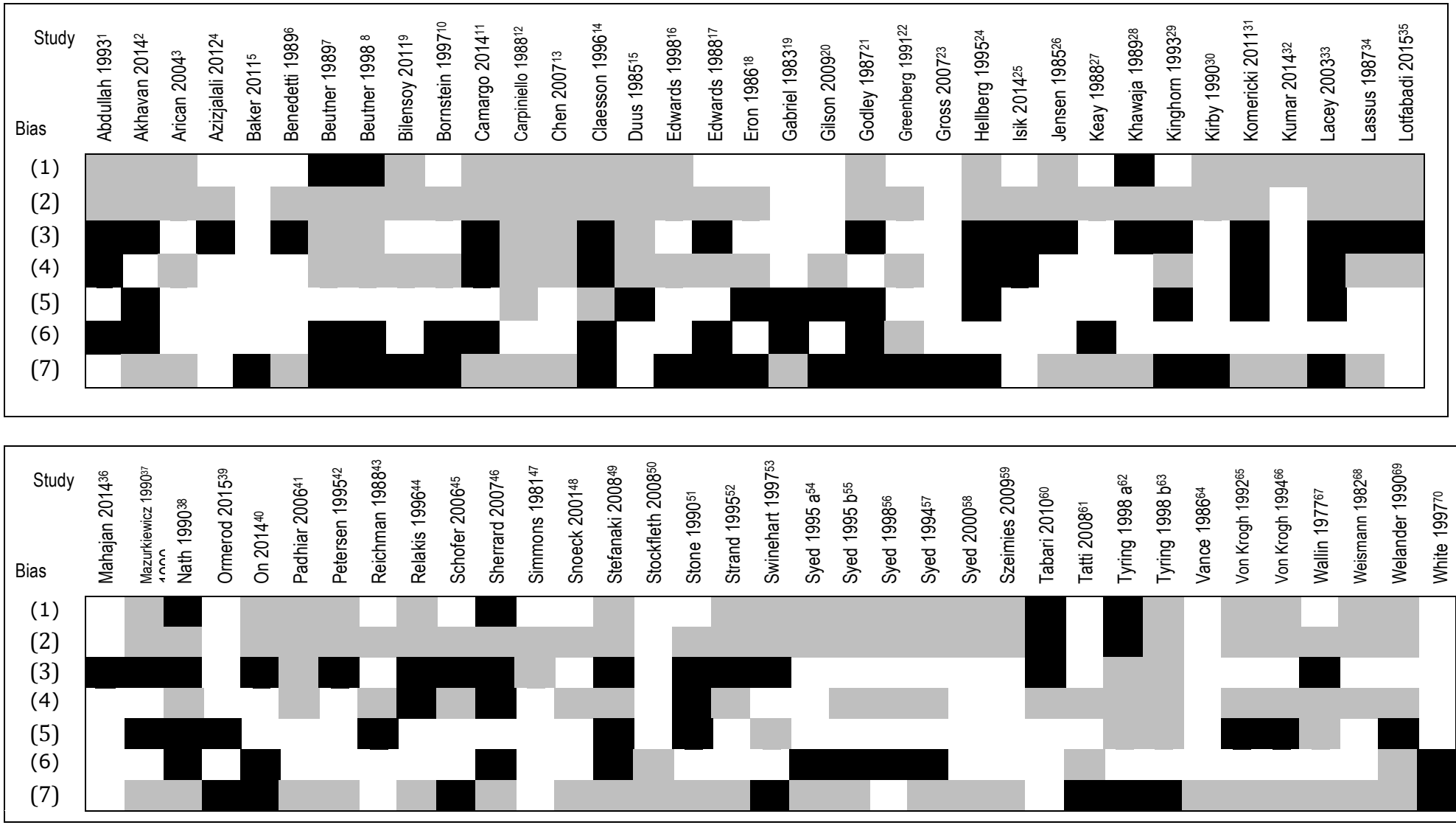
Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Tatti 2008[61] | USA, Europe, S Africa multicenter | Polyphenon 15% | 196 (159) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 16 wk, recurrence after 3 mo, side effects, partial clearance | ITT modified |
| | | Polyphenon 10% | 202 (162) | Same | Same | | | |
| | | Placebo | 104 (83) | Same | Same | | | |
| Tyring 1998[62] | USA | Imiquimod 5% | 18 (16) | 3×/wk, maximum 16 wk | Applied with cotton swab tip | 4 | Clearance after 16 wk, side effects, partial clearance | |
| | | Placebo | 4 (3) | Same | Same | | | |
| Tyring 1998[63] | USA | Placebo | 107 (95) | 2×/d for 3 consecutive d, maximum 8 wk | NR | 4 | Clearance after 4 & 8 wk, recurrence after 3 mo, side effects | |
| | | Podophyllotoxin 0.5% gel | 219 (197) | Same | Same | | | |
| Vance 1986[64] | USA | IFNα-2b (1 MIU) intra-lesional | 37 (30) | 3×/wk, maximum 3 wk | NR | 3 | Clearance after 4, 5, 7 & 12 wk, side effects, partial clearance | ITT |
| | | IFNα-2b (0.1 MIU) intra-lesional | 38 (32) | Same | Same | | | |
| | | Placebo intra-lesional | 39 (29) | Same | Same | | | |
| von Krogh 1992[65] | Sweden | Placebo | 12 (11) | 2×/d, 3 d/wk for 2 wk | NR | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | |
| | | Podophyllotoxin 0.5% cream | 48 (44) | Same | Same | | | |
| von Krogh 1994[66] | Sweden | Podophyllotoxin 0.25% sol | 19 (18) | 2×/d, 3 d/wk for 2 wk | Applied with wool swabs | 6 | Clearance after 3 wk, recurrence after 2 & 6 mo, side effects | 1st treatment |
| | | Podophyllotoxin 0.5% sol | 19 (16) | Same | Same | | | |
| | | Placebo | 19 (17) | Same | Same | | | |
| Wallin 1977[67] | Sweden | 5-FU | 21 (18) | 1×/d for 2 wk | Applied with cotton swab tip | 9 | Clearance after 4 wk, recurrence after 6 mo, side effects | Only men |
| | | Podophyllin 25% sol | 21 (19) | 1×/wk for 4 wk | Provider-applied, wash 4-6 hr later | | | |

Appendix S2: Characteristics of RCTs included in the meta-analysis (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Weismann 1982[68] | Denmark | 5-FU | 30 (30) | 2×/wk for women, once/d for men | NR | 2 | Clearance after 8 wk, side effects, partial clearance, time to complete clearance | ITT |
| | | Placebo | 29 (29) | Same | Same | | | |
| Welander 1990[69] | USA | IFNα-2b (1 MIU) intra-lesional | 20 (16) | 3×/wk, maximum 3 wk | NR | NR | Clearance after 4 or 15 wk, side effects | |
| | | Placebo intra-lesional | 22 (21) | Same | Same | | | |
| White 1997[70] | UK | Podophyllotoxin 0.5% sol | 106 (77) | 2×/d for 3 consecutive d, maximum 12 wk | NR | 3 | Clearance after 5 wk, side effects | ITT, only men, 1st treatment |
| | | Podophyllin 0.5% | 103 (86) | Same | Same | | | |
| | | Podophyllin 2% | 106 (81) | Same | Same | | | |

Abbreviations: ITT, intention-to-treat; NR, not reported; KOH, potassium hydroxide; ALA, 5-aminolaevulinic acid; Mw, *Mycobacterium* w; Sol, solution; PDT, photodynamic therapy; Electro, electrosurgery; Cryo, cryotherapy; IFN, interferon.




Appendix S3. Assessment of risk of bias. White square: low; grey square: uncertain; black square: high; (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); (7) Other bias.

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Afin de parvenir à proposer une première hiérarchie thérapeutique, nous avons réalisé une analyse en données poolées sur l'ensemble des critères de jugement. Cette analyse a permis d'afficher un peu mieux les caractéristiques et particularités de chaque thérapie. Ce résultat a fait l'objet d'une publication dans *Journal American Academy of Dermatology* en 2019.

## Local management of anogenital warts in immunocompetent adults: Systematic review and pooled analysis of randomized-controlled trial data

*To the Editor:* Although several treatments exist for anogenital warts, no clear treatment hierarchy is mentioned in the latest guidelines.[1,2] We conducted a pooled analysis of randomized-controlled trials (RCTs) of anogenital wart treatments (provider-administered therapies and patient-administered treatments reported in at least 1 parallel treatment group). Our analysis covered a large number of patients and supplements meta-analyses performed with studies that included only 2 treatment groups.

Our systematic review included RCTs of anogenital wart treatments published up to August 1, 2018, following the methodology described in our systematic review protocol (Prospero no. CRD42015025827).[3]

In total, 70 RCTs involving 9931 individual patients were included. A high risk of bias was identified in 66 RCTs.[4]

Our main pooled analysis results are summarized in the Table I.[1,5] The complete clearance rate was higher for provider-administered therapies (92%) than patient-administered treatments (56%), but the recurrence rate was lower for patient-administered treatments (6%) than provider-administered therapies (29%). Surgery was painful in 48% of cases, and $CO_2$ laser was associated with a recurrence rate of 31%. For electrosurgery, the recurrence rate was high, side effects were low, and the clearance rate was low due to the high number of patients lost to follow-up in the study by Stone et al;[5] it would have been 79% with a per-protocol analysis. Trichloroacetic acid was associated with a high clearance rate, a low recurrence rate, and few side effects compared with cryotherapy.[3] The latest guidelines[1] include 5-fluorouracil cream but fail to mention potassium hydroxide. Our analysis yielded a high clearance rate and a low recurrence rate for both treatments, suggesting that potassium hydroxide could also be included as first-line treatment in future guidelines; besides, 5-fluorouracil cream caused more low- and medium-grade local side effects than potassium hydroxide. Podophyllotoxin 0.5% solution or cream seemed as effective as cryotherapy or imiquimod but caused more general side effects. Cryotherapy, $CO_2$ laser, and podophyllotoxin 0.5% solution or cream caused less high-grade local side effects than other treatments. High-grade local side effects were rarely reported for provider-administered therapies with local anesthesia. They seemed equivalent in number between patient-administered treatments and provider-administered therapies but involved different consequences. Recurrent pain or burns after application of patient-administered treatments (eg, imiquimod) can lead to nonadherence, unlike after provider-administered therapies requiring only a single application (eg, $CO_2$ laser).

Although the risk of bias was high in many of the included studies (unpublished data), our results complement the latest guidelines.[1] Therapies could be selected on the basis of anogenital wart duration

**Table I.** Pooled-analysis of potential first-line local AGW treatments* for all judgment criteria

| Treatment | No. RCTs (total no. ITT patient population) | Clearance | % with type of side effect/outcome quartile† | | | | |
|---|---|---|---|---|---|---|---|
| | | | Recurrence | LGL | MGL | HGL | LGG |
| Patient-administered | | | | | | | |
| 5-Fluorouracil cream | 6 (393) | 68/Q2 | 13/Q2 | 84/Q4 | 68/Q4 | 8/Q2 | 16/Q2 |
| Potassium hydroxide* | 2 (54) | 63/Q2 | 6/Q1 | 17/Q1 | 50/Q3 | NR | 17/Q2 |
| Podophyllotoxin 0.5% solution | 13 (829) | 59/Q2 | 29/Q3 | 62/Q3 | 46/Q3 | 10/Q2 | 45/Q4 |
| Podophyllotoxin 0.5% cream | 8 (294) | 57/Q3 | 11/Q2 | 22/Q2 | 25/Q2 | 1/Q1 | 48/Q4 |
| Imiquimod 5% | 10 (611) | 57/Q3 | 13/Q2 | 50/Q3 | 26/Q2 | 13/Q3 | 24/Q3 |
| Polyphenon 15% | 3 (477) | 54/Q3 | 7/Q1 | 60/Q3 | 8/Q1 | 7/Q2 | 11/Q1 |
| Provider-administered without local anesthesia | | | | | | | |
| Trichloroacetic acid | 6 (334) | 72/Q2 | 14/Q2 | 26/Q2 | 17/Q2 | 8/Q2 | 18/Q2 |
| Cryotherapy | 12 (709) | 58/Q3 | 27/Q3 | 24/Q2 | 15/Q1 | 4/Q1 | 29/Q3 |
| Provider-administered with local anesthesia | | | | | | | |
| Surgery | 2 (48) | 92/Q1 | 20/Q2 | NR | 42/Q3 | NR | 48/Q4 |
| $CO_2$ laser | 6 (329) | 88/Q1 | 31/Q4 | 57/Q3 | 43/Q3 | 0/Q1 | 10/Q1 |
| Electrosurgery | 3 (221) | 56‡/Q3 | 35/Q4 | NR | 8/Q1 | NR | 16/Q2 |

*AGW*, Anogenital wart; *HGL*, high-grade local (blisters and ulcerations); *ITT*, intention-to-treat; *LGG*, low-grade general (pain requiring analgesics); *LGL*, low-grade local (stinging, irritation, erythema); *MGL*, medium-grade local (skin burn, soiling, minor bleeding, erosion, infection); *NR*, not reported; *Q*, quartile; *RCT*, randomized-controlled trial.

*First-line treatments mentioned in current international recommendations.[1] Potassium hydroxide is not included in those guidelines, but our pooled-analysis results indicate that it could be.

†Outcomes are graded best (Q1) to worst (Q4) by quartile.

‡Clearance was 79% after performing a per-protocol analysis of the data provided by Stone et al.[5]

and history of recurrence. Indeed, we found in our pooled analysis that recurrence at 12 months was lower for patient-administered treatments, making these more relevant than provider-administered therapies as a global therapeutic response—although such recurrence is difficult to evaluate because of the methodologic limitations (eg, lost to follow-up, recontamination). Although provider-administered therapies presented the best clearance before 3 months, their reproducibility remains difficult to compare both among RCTs and among treatments (eg, lack of standardization of freezing or surgical procedures). Given the need for local anesthesia, the use of surgery, $CO_2$ laser, and electrosurgery seem justified when other treatments have failed. Last, knowledge of treatment side effects can assist physicians with adjusting anogenital wart management to the tolerance of the patient.

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## Pitfalls and proposed solutions for patient communication about erythropoietic protoporphyria: A survey of parents and adult patients

*To the Editor:* Erythropoietic protoporphyria (EPP) is a rare inherited defect of heme metabolism resulting in painful photosensitivity.[1] A 1987 survey of 17 EPP

**Table I.** Demographics and clinical characteristics of EPP patients

| Characteristic | Children with EPP, n = 13 | Adults with EPP, n = 46 |
|---|---|---|
| Mean age, y | 14.3 | 49.7 |
| Sex, n (%) | | |
| Male | 8 (61.5) | 22 (47.8) |
| Female | 5 (38.5) | 24 (52.2) |
| Age at diagnosis, y, mean (range) | 6.5 (3-10) | 17 (2-57) |
| Sensitive to indoor lights, n (%) | 3 (23.1) | 18 (39.1) |
| Sunlight exposure limit, n | | |
| 0-10 min | 4 | 18 |
| 10-30 min | 4 | 17 |
| 30 min-1 hr | 2 | 8 |
| 1-2 hr | 2 | 2 |
| 2-3 hr | 0 | 1 |
| ≥3 hr | 1 | 0 |
| Words used to describe EPP, % | | |
| Allergy | 46 | 52 |
| Burn | 46 | 50 |
| Internal sunburn | 31 | 28 |
| Photosensitive | 54 | 35 |
| Phototoxic reaction | 23 | 20 |
| Sensitive to the sun | 77 | 83 |
| Other | 31 | 26 |

Demographics and clinical characteristics were acquired via survey. For EPP patients who were children (<18 years of age), questions were answered by their parents. EPP diagnosis was patient reported or parent reported (for children) and accompanied by the survey participant's description of the method of diagnosis.
*EPP*, Erythropoietic protoporphyria.

Cependant les analyses poolées correspondent à la somme des sujets guéris, divisée par la somme des sujets traités par une même thérapie. Aucune analyse comparative statistique n'a été réalisée. Nous avons donc réalisé l'ensemble des comparaisons directes 2 à 2 des traitements et avons réalisé des méta-analyses dès lors que 2 essais cliniques randomisés comparaient des traitements similaires. Ainsi il était pris en compte la puissance de chaque essai mais aussi l'hétérogénéité clinique et statistique observées entre chaque étude. Ces analyses permettaient ainsi d'avoir une estimation plus précise de l'effet du traitement que celles réalisées dans les données poolées. Ces résultats ont fait l'objet d'un refus du *Journal American Academy of Dermatology*, puis du *Canadian Medical Association Journal.* Il a été accepté dans *Dermatology and Therapy* en septembre 2019.

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ORIGINAL RESEARCH

# Local Management of Anogenital Warts in Non-immunocompromised Adults: A Systematic Review and Meta-analyses of Randomized Controlled Trials

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## ABSTRACT

***Introduction***: Several therapeutic options are available to manage anogenital warts (AGWs). However, no hierarchy of treatments is provided in the latest European and American recommendations. This study aimed to determine the efficacy and safety of local treatments for the management of AGWs.

***Methods***: A search was conducted through 12 databases from inception to August 2018. All randomized controlled trials (RCTs) in which at least one parallel treatment group composed of immunocompetent adults with AGWs received at least one provider-administered or patient-administered treatment were included. Risk of bias assessment and meta-analyses of aggregated study data were performed on the basis of the Cochrane Handbook, and quality of evidence evaluation followed the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Primary endpoints were complete clearance and recurrence at 3 months.

***Results***: Seventy RCTs (9931 patients) were included. All but four RCTs had a high risk of bias. $CO_2$ laser was slightly more efficacious than cryotherapy [risk ratio (RR) 2.05; 95%

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confidence interval (CI) 1.61–2.62], with fewer recurrences at 3 months (RR 0.28; 95% CI 0.09–0.89). Electrosurgery was slightly more efficacious than cryotherapy. No differences in efficacy or side effects were found between cryotherapy and imiquimod or trichloroacetic acid. Podophyllotoxin gel was slightly more efficacious than podophyllotoxin cream. 5-Fluorouracil (5-FU) was slightly more efficacious and caused less erosion than $CO_2$ laser (RR 1.37; 95% CI 1.11–1.70).

***Conclusion***: The vast majority of included RCTs had a low level of evidence, thereby preventing the establishment of a hierarchy of treatments. Nevertheless, our results provide an overview of the main AGW treatments available for general practitioners and specialists. While provider-administered treatments are superior, patient-administered treatments (e.g., imiquimod, podophyllotoxin) are useful solutions for compliant patients.

***Protocol registration***: PROSPERO-CRD42015025827.

**Keywords:** Anogenital warts; Condyloma; Cryotherapy; Genital; Meta-analysis; Systematic review

## INTRODUCTION

Anogenital warts (AGWs) are benign epithelial skin lesions that typically occur on the external genitalia. They are one of the most common sexually transmitted diseases [1], with an overall prevalence rate of around 1–5% depending on world region [1]. AGWs are usually painless, but are often physically uncomfortable. Their burden is relatively high, as they affect quality of life (QOL) and incur significant healthcare costs [2, 3]. Different options are available for first-line management of AGWs, including (1) provider-administered treatments [trichloroacetic acid (TCA), electrosurgery, $CO_2$ laser, surgical excision, podophyllin, bleomycin, intracondyloma injection] and (2) patient-administered treatments [imiquimod, potassium hydroxide (KOH), 5-fluorouracil (5-FU), sinecatechins, podophyllotoxin], which can be prescribed by general practitioners.

The efficacy of these various therapies is variable, and in the case of patient-administered treatments, notable side effects may impact compliance. Vaccination campaigns, which focus mainly on oncogenic anti-human papillomavirus, have been too narrow in scope to control these infections [4]. In addition, evidence-based indications of AGW treatment efficacy are limited. The latest European and American guidelines do not provide a hierarchy of first-line treatments for AGWs in immunocompetent adults [5, 6]. According to these guidelines, therapeutic decisions should take into account patient preference, physician experience, treatment costs, anatomic site, and the size and number of AGWs. The latest systematic review, which includes randomized controlled trials (RCTs) up to September 2014, concludes that ablative techniques are clinically more efficacious at completely clearing AGWs, but that they cannot prevent recurrence. This review also found podophyllotoxin 0.50% solution to be the most cost-effective treatment from the perspective of the UK National Health Service [7]. It should be noted, however, that several RCTs of AGW treatments have since been published.

Our recent pooled analysis provided an overview of available treatments, but did not include any comparative statistical analysis; consequently, our results were less robust than they would have been using direct comparisons [8].

The aim of the present meta-analyses was to assess the efficacy and safety of local treatments and ablative procedures for the management of AGWs.

## METHODS

This systematic review was registered with Prospero (No. CRD42015025827). Recommendations of the PRISMA statement for systematic review and meta-analyses were followed [9].

### Search Strategy, Study Selection, Risk of Bias Assessment, and Data Synthesis

The methodology of this systematic review, including registration, databases, search

strategy (reference lists of review articles [5–7, 10–12] were searched to identify additional studies), study selection, outcomes of interest, bias assessment [13], data extraction, and data synthesis, was described in a previous article [14]. Inclusion criteria were then extended to include studies that compared provider-administered treatments, patient-administered treatments, or both, and in which at least one treatment arm received the treatment of interest.

### Statistical Analyses

Dichotomous outcomes were analyzed according to a fixed effects or random effects model with the Mantel–Haenszel method using Review Manager v5.3 (http://ims.cochrane.org/revman). Estimates of the effects of interventions were given as risk ratios (RR) (95% CI). A random effects model was used when heterogeneity was detected. Heterogeneity was estimated clinically (e.g., age, sex, location and number of AGWs, etc.), methodologically (blinding, randomization, etc.), and statistically when Higgins' $I^2 > 50\%$ [15]. Subgroup analyses were performed to explore the potential sources of heterogeneity. Cochrane's test for heterogeneity and the $I^2$ statistic were used to evaluate the significance of estimated discrepancies in treatment efficacy between the various trials. The Grading of Recommendation Assessment, Development and Evaluation (GRADE) [16] approach was applied.

### Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## RESULTS

### Study Screening

After duplicates were removed, queries of our 12 computerized databases retrieved 4768 references (Fig. 1). A total of 169 full-text articles remained after screening of titles and abstracts. Finally, after the full papers were read, 70 unique RCTs involving 9931 individual patients with a mean of 142 participants per study fulfilled the inclusion criteria of our systematic review [17–86] (Appendices S2–S3 in the supplementary material).

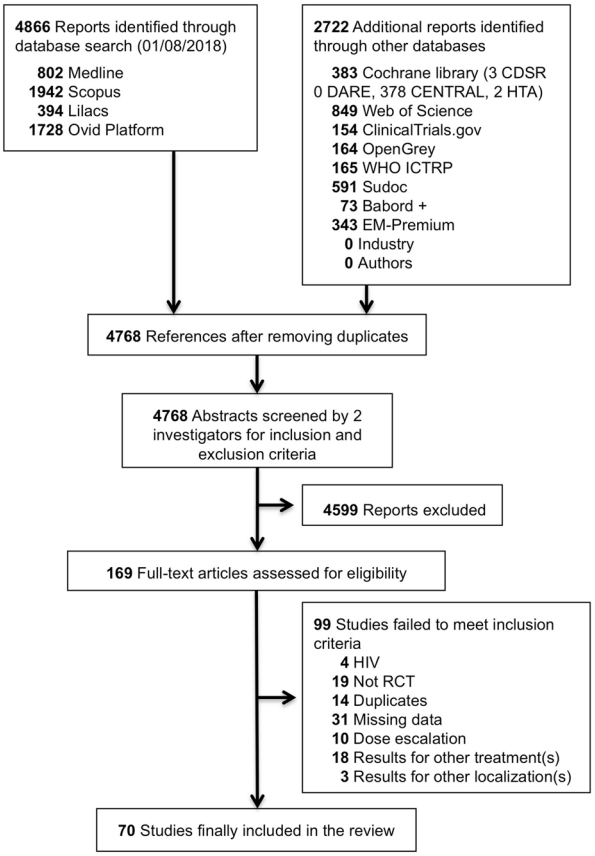
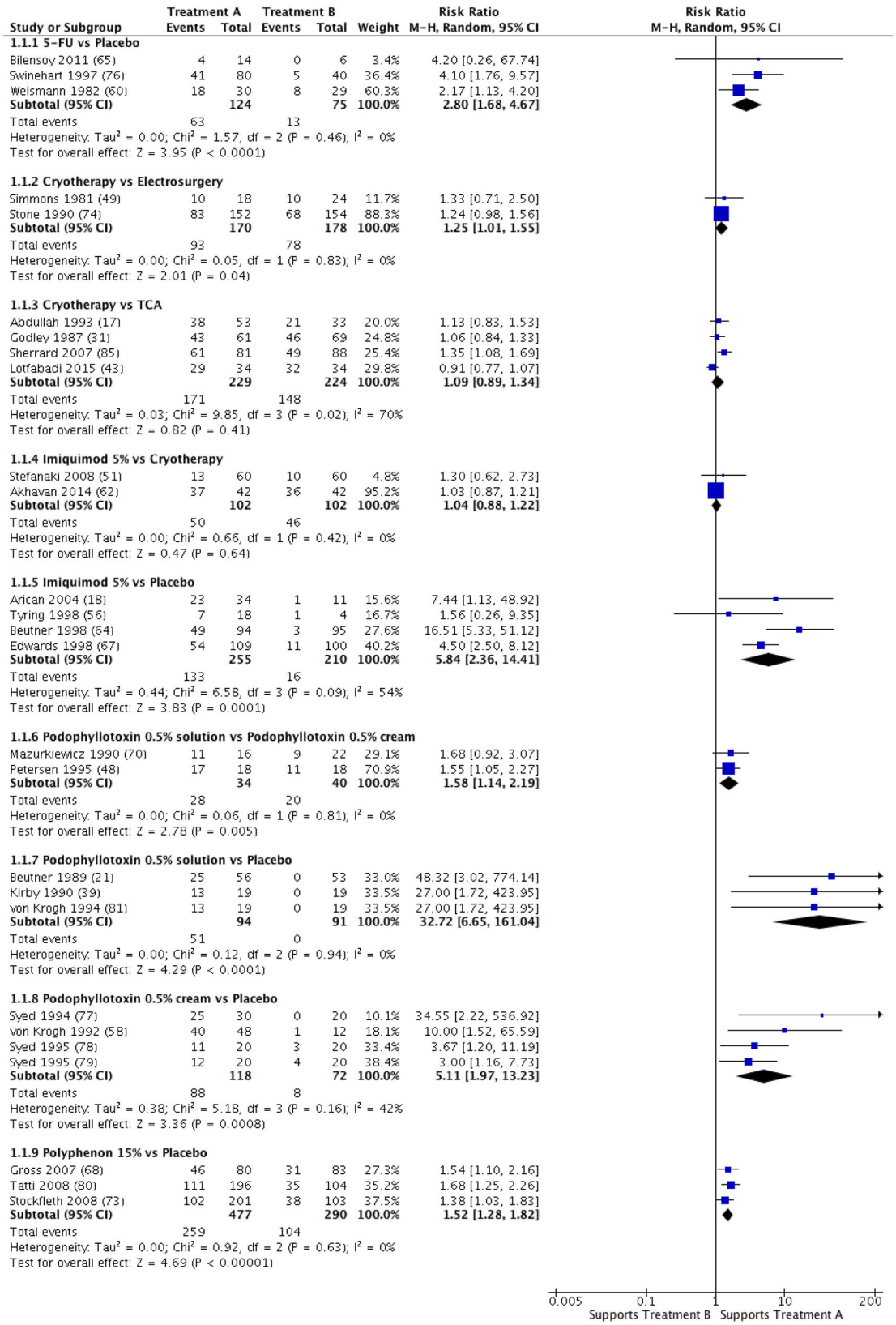



**Fig. 1** Flow diagram of randomized controlled trials (RCTs) selected for treatment of anogenital warts. *CDSR* Cochrane Database of Systematic Reviews, *DARE* Database of Abstract of Reviews of Effects, *HTA* Health Technology Assessment, *WHO ICTRP* World Health Organization International Clinical Trials Registry Platform, *EM* Elsevier Masson, *HIV* human immunodeficiency virus

### Description of Included Studies

The 70 included RCTs assessed 46 provider-administered or patient-administered treatments. Parallel design was used in 45 studies with 2


Treatment A
Treatment B
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 5-FU vs Placebo
Bilensoy 2011 (65) 4 14 0 6 3.4% 4.20 [0.26, 67.74]
Swinehart 1997 (76) 41 80 5 40 36.4% 4.10 [1.76, 9.57]
Weismann 1982 (60) 18 30 8 29 60.3% 2.17 [1.13, 4.20]
Subtotal (95% CI) 124 75 100.0% 2.80 [1.68, 4.67]
Total events 63 13
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 3.95 (P < 0.0001)
1.1.2 Cryotherapy vs Electrosurgery
Simmons 1981 (49) 10 18 10 24 11.7% 1.33 [0.71, 2.50]
Stone 1990 (74) 83 152 68 154 88.3% 1.24 [0.98, 1.56]
Subtotal (95% CI) 170 178 100.0% 1.25 [1.01, 1.55]
Total events 93 78
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
1.1.3 Cryotherapy vs TCA
Abdullah 1993 (17) 38 53 21 33 20.0% 1.13 [0.83, 1.53]
Godley 1987 (31) 43 61 46 69 24.8% 1.06 [0.84, 1.33]
Sherrard 2007 (85) 61 81 49 88 25.4% 1.35 [1.08, 1.69]
Lotfabadi 2015 (43) 29 34 32 34 29.8% 0.91 [0.77, 1.07]
Subtotal (95% CI) 229 224 100.0% 1.09 [0.89, 1.34]
Total events 171 148
Heterogeneity: Tau² = 0.03; Chi² = 9.85, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 0.82 (P = 0.41)
1.1.4 Imiquimod 5% vs Cryotherapy
Stefanaki 2008 (51) 13 60 10 60 4.8% 1.30 [0.62, 2.73]
Akhavan 2014 (62) 37 42 36 42 95.2% 1.03 [0.87, 1.21]
Subtotal (95% CI) 102 102 100.0% 1.04 [0.88, 1.22]
Total events 50 46
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
1.1.5 Imiquimod 5% vs Placebo
Arican 2004 (18) 23 34 1 11 15.6% 7.44 [1.13, 48.92]
Tyring 1998 (56) 7 18 1 4 16.7% 1.56 [0.26, 9.35]
Beutner 1998 (64) 49 94 3 95 27.6% 16.51 [5.33, 51.12]
Edwards 1998 (67) 54 109 11 100 40.2% 4.50 [2.50, 8.12]
Subtotal (95% CI) 255 210 100.0% 5.84 [2.36, 14.41]
Total events 133 16
Heterogeneity: Tau² = 0.44; Chi² = 6.58, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 3.83 (P = 0.0001)
1.1.6 Podophyllotoxin 0.5% solution vs Podophyllotoxin 0.5% cream
Mazurkiewicz 1990 (70) 11 16 9 22 29.1% 1.68 [0.92, 3.07]
Petersen 1995 (48) 17 18 11 18 70.9% 1.55 [1.05, 2.27]
Subtotal (95% CI) 34 40 100.0% 1.58 [1.14, 2.19]
Total events 28 20
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
1.1.7 Podophyllotoxin 0.5% solution vs Placebo
Beutner 1989 (21) 25 56 0 53 33.0% 48.32 [3.02, 774.14]
Kirby 1990 (39) 13 19 0 19 33.5% 27.00 [1.72, 423.95]
von Krogh 1994 (81) 13 19 0 19 33.5% 27.00 [1.72, 423.95]
Subtotal (95% CI) 94 91 100.0% 32.72 [6.65, 161.04]
Total events 51 0
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.29 (P < 0.0001)
1.1.8 Podophyllotoxin 0.5% cream vs Placebo
Syed 1994 (77) 25 30 0 20 10.1% 34.55 [2.22, 536.92]
von Krogh 1992 (58) 40 48 1 12 18.1% 10.00 [1.52, 65.59]
Syed 1995 (78) 11 20 3 20 33.4% 3.67 [1.20, 11.19]
Syed 1995 (79) 12 20 4 20 38.4% 3.00 [1.16, 7.73]
Subtotal (95% CI) 118 72 100.0% 5.11 [1.97, 13.23]
Total events 88 8
Heterogeneity: Tau² = 0.38; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 3.36 (P = 0.0008)
1.1.9 Polyphenon 15% vs Placebo
Gross 2007 (68) 46 80 31 83 27.3% 1.54 [1.10, 2.16]
Tatti 2008 (80) 111 196 35 104 35.2% 1.68 [1.25, 2.26]
Stockfleth 2008 (73) 102 201 38 103 37.5% 1.38 [1.03, 1.83]
Subtotal (95% CI) 477 290 100.0% 1.52 [1.28, 1.82]
Total events 259 104
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.69 (P < 0.00001)
0.005
0.1
1
10
200
Supports Treatment B
Supports Treatment A

◀**Fig. 2** Forest plot of anogenital wart clearance after two first-line treatments. Random effects analysis. *CI* confidence interval, *TCA* trichloroacetic acid, *M–H* Mantel–Haenszel method. Reference numbers are given in parentheses

arms [17–61], 21 studies with 3 arms [62–82], 3 studies with 4 arms [65, 83, 84], and 1 study with 5 arms [85]. The risk of bias assessment of included studies is described in a previous study [87]. The 66 RCTs that presented more than one criterion for uncertain or high risk of bias (based on the Cochrane Risk of Bias Tool) were described as having a high risk of bias. The remaining four studies [44, 63, 68, 86] were classified as having a low risk of bias. The 25 trials that received drugs from pharmaceutical laboratories were classified as having a high risk of bias [21, 22, 28–33, 38, 39, 46, 56, 57, 63–69, 72, 76, 80, 82, 83]. The 35 trials that provided no information on financial support were classified as having an unclear risk of bias [18, 20, 23–26, 35–37, 40–42, 45, 47, 48, 50–54, 58–62, 70, 71, 73–75, 77–79, 81, 85, 87]. However, four studies [17, 19, 43, 49] that provided no information on financial support were considered to have a low risk of bias because they compared two provider-administered treatments.

## Results of Meta-analyses

Our main results on AGW clearance are reported in Fig. 2, with the numerator representing the effect of treatment A. Placebo was systematically found to have fewer side effects than comparators. Patient satisfaction, QOL during treatment, and cost/efficacy ratio were not examined in the included RCTs. Detailed results on podophyllin, which is no longer in use, are not reported.

### 5-FU Cream

A meta-analysis of data from three RCTs ($n$ = 299) [60, 65, 76] comparing 5-FU to a placebo estimated the pooled RR at 2.80 (95% CI 1.68–4.67; $\chi^2$ = 1.57; df = 2; $P$ = 0.46; $I^2$ = 0%) in favor of 5-FU. Nevertheless, recurrence at 3 months could not be estimated for two of these three studies [65, 76]. In one RCT ($n$ = 289) [71], a statistically significant difference in clearance slightly favored 5-FU over $CO_2$ laser (RR 1.37; 95% CI 1.11–1.70), with 5-FU causing less erosion. However, no differences in recurrence were found between the two treatments. Lastly, no differences were found between 5-FU and KOH (one RCT; $n$ = 60) [34] or between 5-FU and podophyllin 20–25% (one RCT; $n$ = 42) [59], except for the fact that podophyllin 20–25% caused less erosion than 5-FU.

### $CO_2$ Laser

One RCT ($n$ = 50) found no differences in clearance between $CO_2$ laser and ablative procedures [26]. In another RCT ($n$ = 289) [71], 5-FU was associated with higher clearance and with less erosion than $CO_2$ laser, but no differences in recurrence were found. In a third RCT ($n$ = 160) [19], $CO_2$ laser was associated with higher clearance (RR 2.05; 95% CI 1.61–2.62) and lower recurrence at 3 months (RR 0.28; 95% CI 0.09–0.89) than cryotherapy, but was found to cause more erosion. Studies comparing $CO_2$ laser to $CO_2$ laser + 5-FU (two RCTs; $n$ = 186; RR 0.82; 95% CI 0.34–1.98) [24, 71], photodynamic therapy (PDT) (one RCT; $n$ = 86) [25], or $CO_2$ laser + PDT (one RCT; $n$ = 211) [54] found no differences in clearance.

### Electrosurgery

In one RCT ($n$ = 99) [20], electrosurgery was associated with significantly higher clearance than placebo (RR 59.37; 95% CI 3.73–943.92), but recurrence at 6 months was not estimated. Another RCT ($n$ = 296) [74] compared electrosurgery to podophyllin 20–25%. A meta-analysis of data from two RCTs ($n$ = 348) [49, 74] comparing electrosurgery to cryotherapy estimated the pooled RR at 1.25 (95% CI 1.01–1.55) in favor of electrosurgery with no heterogeneity ($\chi^2$ = 0.05; df = 1, $P$ = 0.83, $I^2$ = 0%). This same meta-analysis found no differences in side effects or recurrence at 3 months.

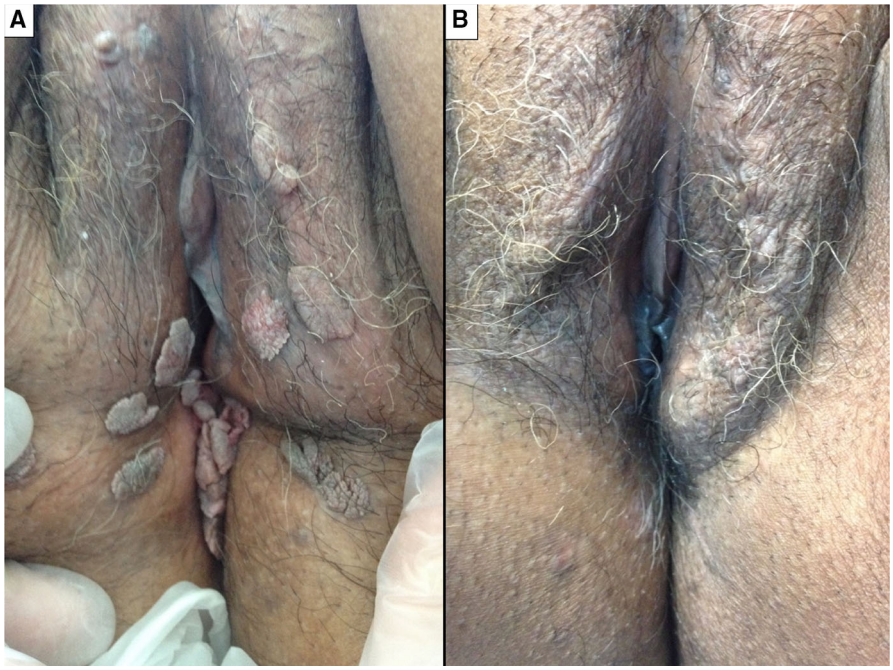



**Fig. 3** Efficacy of cryotherapy in one patient before (**a**) and after (**b**) four sessions at 1-month intervals

### Cryotherapy (Fig. 3)

No differences were found between cryotherapy and imiquimod (two RCTs; $n = 204$) [51, 62], TCA (four RCTs; $n = 453$) [17, 31, 43, 85], KOH (one RCT; $n = 48$) [23], or podophyllin (three RCTs; $n = 542$) [62, 74, 85]; however, KOH was associated with less erythema and pain. $CO_2$ laser (one RCT; $n = 160$) [19] and electrosurgery (two RCTs; $n = 348$) [49, 74] were associated with higher clearance and lower recurrence at 3 months than cryotherapy, but $CO_2$ laser was shown to cause more erosion. No clinical improvement was obtained by combining cryotherapy with polyphenon (one RCT; $n = 42$) [46] (RR 1.50; 95% CI 0.49–4.56) or with podophyllotoxin 0.15% (one RCT; $n = 140$) [30] (RR 1.31; 95% CI 0.95–1.80).

### Imiquimod 5% (Fig. 4)

One RCT ($n = 255$) [72] comparing imiquimod 5% to ablative procedures favored the latter, with significant differences in clearance (RR 1.43; 95% CI 1.25–1.62) and recurrence at 3 months (RR 0.39; 95% CI 0.16–0.98). A meta-analysis of data from four RCTs ($n = 465$) [18, 56, 64, 67] comparing imiquimod 5% to a placebo estimated the pooled RR at 5.84 (95% CI 2.36–14.41; $\chi^2 = 6.58$; df = 3; $P = 0.09$; $I^2 = 54\%$) in favor of imiquimod 5%. A subgroup analysis (without the study by Beutner et al. [64] on daily imiquimod application) estimated the pooled RR at 4.48 (95% CI 2.61–7.68; $\chi^2 = 1.61$; df = 2; $P = 0.45$; $I^2 = 0\%$). A meta-analysis of data from three RCTs ($n = 130$) [18, 64, 67] comparing recurrence at 3–6 months between imiquimod 5% and a placebo estimated the pooled RR at 1.15 (95% CI 0.41–3.27; $\chi^2 = 3.11$; df = 2; $P = 0.21$; $I^2 = 36\%$) in favor of imiquimod 5%. No differences in clearance, recurrence, and side effects were found between imiquimod 5% and cryotherapy (two RCTs; $n = 204$) [51, 62] or between imiquimod 5% and podophyllotoxin 0.50% solution (one RCT; $n = 51$) [40]. No differences in clearance were found between imiquimod and intralesional Bacillus Calmette–Guerin (one RCT; $n = 90$) [41] or between imiquimod and podophyllin 20–25% gel (two RCTs; $n = 144$) [47, 62]; however, imiquimod 5% was found to cause less erosion and ulceration than both treatments.

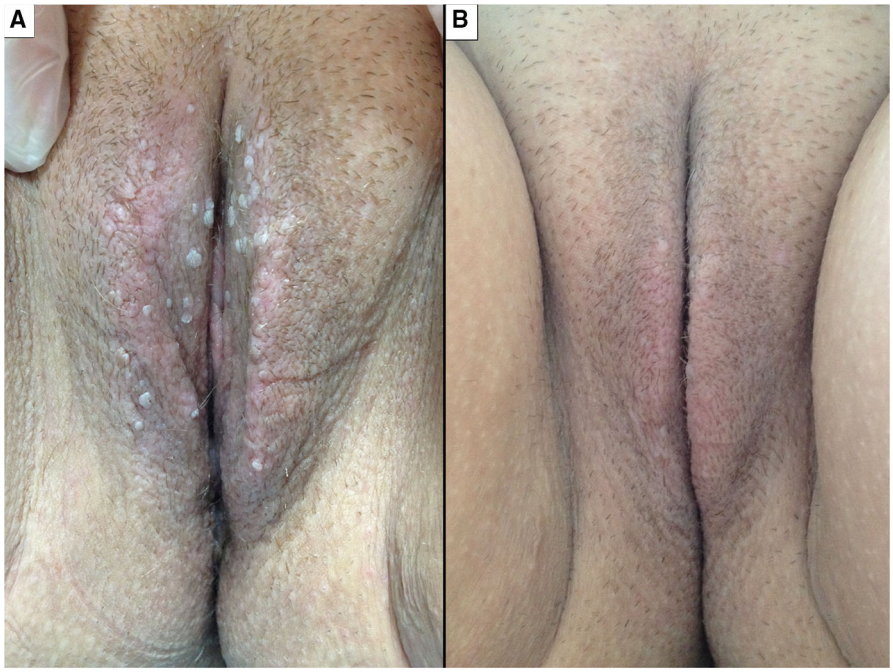



**Fig. 4** Efficacy of imiquimod in one patient before (**a**) and after (**b**) 6 weeks of use three times a week

### Podophyllotoxin 0.50% Solution

A meta-analysis of data from three RCTs ($n$ = 185) [21, 39, 81] comparing podophyllotoxin 0.50% solution to a placebo favored podophyllotoxin 0.50% solution, with an estimated pooled RR at 32.72 (95% CI 6.65–161.04; $\chi^2$ = 0.63; df = 3; $P$ = 0.089; $I^2$=0%). A meta-analysis of data from two RCTs ($n$ = 74) [48, 70] comparing podophyllotoxin 0.50% solution to podophyllotoxin 0.50% cream estimated the pooled RR at 1.58 in favor of the solution (95% CI 1.14–2.19; $\chi^2$ = 0.06; df = 1; $P$ = 0.81; $I^2$ = 0%); this same meta-analysis found similar side effects for both treatments. One RCT ($n$ = 28) [48] found no differences in recurrence at 1.5 month between podophyllotoxin 0.50% solution and podophyllotoxin 0.50% cream. A meta-analysis of data from three RCTs ($n$ = 417) [66, 69, 75] comparing podophyllotoxin 0.50% solution to podophyllotoxin 0.15% cream favored the solution, with an estimated pooled RR at 1.14 (95% CI 1.02–1.29; $\chi^2$ = 1.03; df = 2; $P$ = 0.60; $I^2$ = 0%). A significant difference in clearance favored podophyllotoxin 0.50% solution over podophyllin 20–25% (five RCTs; $n$ = 671) [28, 38, 42, 69, 70]. However, no significant differences in clearance were found between podophyllotoxin 0.50% solution and podophyllotoxin 0.30% cream (two RCTs; $n$ = 180) [66, 75] or between podophyllotoxin 0.50% solution and imiquimod 5% (one RCT; $n$ = 51) [40].

### Podophyllotoxin 0.50% Cream

A meta-analysis of data from four RCTs ($n$ = 190) [58, 77–79] comparing podophyllotoxin 0.50% cream to a placebo estimated the pooled RR at 5.11 (95% CI 1.97–13.23; $\chi^2$ = 5.18; df = 3; $P$ = 0.16; $I^2$ = 42%) in favor of podophyllotoxin 0.50% cream; it also found recurrence to be similar between the two treatments (two RCTs; $n$ = 80) [58, 78]. In two RCTs ($n$ = 74) [48, 70], podophyllotoxin 0.50% solution was associated with higher clearance than podophyllotoxin 0.50% cream, but no differences in recurrence or side effects were found. Two RCTs ($n$ = 98) [33, 70] found no differences in clearance between podophyllotoxin 0.50% cream and podophyllin 20–25%.

### Polyphenon 15%

A meta-analysis of data from three RCTs ($n$ = 767) [68, 73, 80] comparing polyphenon 15% to a placebo estimated the pooled RR at 1.52 (95% CI 1.28–1.82; $\chi^2$ = 0.92; df = 2; $P$ = 0.63; $I^2$ = 0%) in favor of polyphenon 15%. However, no differences in recurrence at 3 months were found, and polyphenon 15% was shown to cause more ulcerations.

### Surgery

No differences in clearance or side effects were found between surgery and podophyllin 20–25% (two RCTs; $n$ = 82) [35, 37], but surgery was associated with lower recurrence.

### TCA

Four RCTs ($n$ = 453) [17, 31, 43, 85] comparing TCA to cryotherapy and three RCTs ($n$ = 387) [45, 55, 85] comparing TCA to podophyllin 20–25% found no differences in clearance, recurrence, or side effects.

### KOH

While no differences in clearance were found between KOH and cryotherapy (one RCT; $n$ = 27) [24] or between KOH and 5-FU (one RCT; $n$ = 44) [34], KOH was shown to cause less erythema and pain than cryotherapy.

### Grade

The level of evidence was found to be very low for all outcome measures and treatments studied. The only exception was the study comparing high-grade local side effects between polyphenon 15% and a placebo, which was classified as having a low level of evidence. No high level of evidence was reported (Appendices S4–S9 in the supplementary material).

## DISCUSSION

Despite a low level of evidence, our systematic review with meta-analyses found that electrosurgery and $CO_2$ laser are slightly more efficacious than cryotherapy, but that $CO_2$ laser causes more erosion. No differences in efficacy and side effects were found between cryotherapy and imiquimod or between cryotherapy and TCA. Podophyllotoxin gel was shown to be slightly more efficacious than podophyllotoxin cream. Imiquimod 5% was found to be more efficacious than a placebo, which is in line with a Cochrane review from 2014 [10]. The slight quantitative differences with our results may be explained by the fact that the Cochrane review examined all imiquimod concentrations (1%, 5%) and that it likely considered overlapping studies as different studies [63, 64]. In addition, imiquimod was associated with higher recurrence in our review, likely because the Cochrane review included an intention-to-treat (ITT) analysis that identified patients lost to follow-up as presenting no recurrence. Our findings for patient-administered treatments were similar to those of a recent systematic review by Werner et al. [88]. However, that review included only 18 RCTs (from Europe and North America) and was restricted to patient-administered treatments. Moreover, it did not evaluate 5-FU and, most importantly, podophyllin, despite the fact that the latter remains the older standard to which most other therapeutic strategies are compared. Lastly, our results are globally consistent with those of Thurgar et al. [7]; in our review, however, 5-FU was associated with higher clearance and lower recurrence than $CO_2$ laser, and the two treatments induced the same local mild-grade side effects. Note, however, that we considered only immunocompetent adults, whereas Thurgar et al. indiscriminately included immunocompetent and human immunodeficiency virus-positive patients. Moreover, unlike these authors, we examined polyphenon and KOH, even though the paucity of RCTs and the high risk of bias prevented us from determining their respective efficacies.

Given the low-level evidence of the RCTs examined in our review, we wish to make the

following recommendations for future studies of AGW treatments. First, recurrence at 3, 6, and 12 months, patient satisfaction, and QOL should be properly addressed in future RCTs, as they constitute important clinical outcomes. Second, side effects that induce treatment interruption should be better characterized, with data on post-intervention intensity and duration, impact on QOL, and impact on compliance (in the case of patient-administered treatments). Third, efficacy analyses should be conducted not on AGWs but on patients themselves [89–93] for two reasons: on the one hand, the primary goal of therapy is complete healing of the patient; on the other, the observed heterogeneity of outcome measures statistically impedes direct and indirect comparisons and, therefore, the development of general recommendations based on available RCTs. Fourth, split studies should not be used to design new AGW treatments, both for statistical reasons and because of the biases induced by the lack of participant blinding [94]. Indeed, given the prevalence of performance biases identified in our review, future RCTs should ensure that outcome evaluation is systematically blinded via different approaches [95, 96] and that outcomes are assessed by an independent committee unaware of treatment group assignment. Fifth, treatments with clearly demonstrated lower efficacy (e.g., podophyllin 20–25%) should be definitively excluded from future RCTs. Lastly, medical-economic evaluation of AGW treatments should be systematically performed.

### Limitations

The main limitation of this systematic review is the high risk of bias of the overwhelming majority (66/70, 94%) of included RCTs [14], which prevented us from developing a clinically meaningful hierarchy of first-line treatments. Note, however, that ITT analysis was performed whenever possible as it comes closest to real-life practices. The lack of information on older therapies or AGW location and characteristics (flat, keratinized, etc.) made it impossible to analyze efficacy based on these criteria. Similarly, sensitivity analyses and assessments of publication bias [97] were not attempted because of the paucity of RCTs. As was the case in other systematic reviews, authors and pharmaceutical companies could not be contacted to obtain unpublished information [98, 99]. Another important limitation was restricted access to Chinese databases. While direct comparisons are statistically more robust than pooled analyses, the paucity of RCTs comparing several therapies also prevented the establishment of a hierarchy of treatments. In spite of these limitations, our pooled study found lower recurrence at 12 months for patient-administered treatments, suggesting that these are more relevant than provider-administered treatments as a global therapeutic response [8].

## CONCLUSION

The vast majority of included RCTs had a low level of evidence, preventing the establishment of a clinically meaningful hierarchy of treatments. Nevertheless, our systematic review provides an overview of the main AGW treatments available to general practitioners and specialists. While provider-administered treatments (e.g., surgery, $CO_2$ laser) are superior, patient-administered treatments (e.g., imiquimod, podophyllotoxin) are useful solutions for compliant patients.

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***Authors' Contributions.*** Christian Derancourt, Brigitte Milpied, and Nicolas Dupin conceptualized and designed the study. Antoine Bertolotti, Christian Derancourt, and Brigitte Milpied participated in the acquisition, analysis, and interpretation of data. Antoine Bertolotti and Christian Derancourt drafted the initial manuscript. André Cabié, Sébastien Fouéré, Nicolas Dupin, and Brigitte Milpied critically reviewed the manuscript. All authors read and approved the final manuscript.

***Disclosures.*** Antoine Bertolotti, André Cabié, Sébastien Fouéré, Nicolas Dupin, Brigitte Milpied, and Christian Derancourt have nothing to disclose.

***Compliance with Ethics Guidelines.*** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

***Data Availability.*** The datasets analyzed during the current study are available from the corresponding author on reasonable request.



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# To Supporting Information: Local management of anogenital warts in nonimmunocompromised adults: a systematic review and meta-analyses of randomized-controlled trial data

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**Supplement content**

**Appendix S1:** Search terms used to screen all databases

**MEDLINE and Web of Science**
1 hpv.all
2 papillomavirus.all.
3 acuminat*.all.
4 condyloma*.all.
5 wart*.all.
6 genital wart*.all.
7 or/1-6
8 randomized controlled trial.all.
9 controlled clinical trial.all.
10 random*.all.
11 placebo.all.
12 clinical trial*.all.
13 trial.all.
14 or/8-13
15 7 AND 14
16 hand.all.
17 foot.all.
18 feet.all.
19 animal*.all.
20 nonhuman*.all.
21 child*.all.
22 cancer*.all.
23 neoplasi*.all.
24 cervical.all.
25 laryn*.all.
26 vacci*.all.
27 tumor.all.
28 verruc*.all.
29 or/ 16-28
30 15 NOT 29

**SCOPUS.com**
#1.1 wart*:ab,ti
#1.2 condylom*:ab,ti
#1.3 acuminat*:ab,ti
#1.4 verruc*:ab,ti
#1.5 hpv:ab,ti
#1.6 papillomavirus*:ab,ti
#1.7 genital wart* :ab.ti
#1.8 condylomata acuminata : ab.ti
#1.9 wart virus:ab.ti
#1.10 #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9
#1.11 clinical trial:ab,ti
#1.12 random*:ab,ti
#1.13 randomized controlled trial;ab,ti
#1.14 controlled clinical:ab,ti
#1.15 placebo*:ab,ti

#1.16 trial:ab,ti
#1.17 #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR #1.16
#1.18 #1.10 AND #1.17
#1.19 hand:ab,ti
#1.20 foot:ab,ti
#1.21 feet:ab,ti
#1.22 animal*:ab,ti
#1.23 nonhuman*:ab,ti
#1.24 child*:ab,ti
#1.25 cancer*:ab,ti
#1.26 neoplasi*:ab,ti
#1.27 cervical:ab,ti
#1.28 laryn*:ab,ti
#1.29 vacci*:ab,ti
#1.30 tumor:ab,ti
#1.31 verruc*:ab,ti
#1.32 #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25 OR #1.26 OR #1.27 OR #1.28 OR #1.29 OR #1.30 OR #1.31
#1.33 #1.18 AND NOT #1.32

**LILACS**
(tw:(condylom*)) AND (tw:(Randomi*))

**Ovid Platform**
(condyloma OR acuminat OR wart) AND (clinical trial OR trial OR randomized trial OR randomized controlled trial OR controlled clinical OR placebo OR Randomized OR randomly)

**Cochrane Library**
(condyloma OR acuminata OR wart ) and (randomized controlled trial OR controlled clinical trial OR random OR placebo OR clinical trial) not (hand OR foot OR feet OR animal OR nonhuman OR child OR cancer OR neoplasia OR cervical OR laryn OR vacci OR tumor OR verruc) in Trials

**Cochrane Register and International Clinical Trials Registry Platform (ICTRP):**
Using the terms: warts, condylomas, condyloma, genital warts in title, abstract and keywords.

**Clinical Trials**
Wart OR condylomas OR condyloma OR genital warts OR acuminata

**EM-PREMIUM bibliography from 2010 in title and abstract:**
English and french request: condylo*
English request: anogenital wart*
French request: verrue anogénitale*

**Open Grey, SUDOC (title) and BABORD + bibliography (in French):**
Condylome
Verrue

**Appendix S2:** Characteristics of RCTs included in the meta-analyses

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Abdullah 1993[1] | UK | Cryo | 53 (43) | 1×/wk, maximum 6 wk | Applied with a cotton Q-tip until wart is frozen with 1-mm margin, 2× | 3 | Clearance after 6 wk, side effects | 1st treatment |
| | | TCA | 33 (30) | Same | A pointed plastic probe | | | |
| Akhavan 2014[2] | Iran | Podophyllin 20% | 42 (38) | 1×/wk, maximum 8 wk | NR | 8 | Clearance after 8 wk, recurrence after 3 mo, recurrence after 6 mo | 1st treatment, only women |
| | | Imiquimod | 42 (37) | 3×/wk, maximum 8 wk | Same | | | |
| | | Cryo | 42 (36) | 1×; no other information given | Same | | | |
| Arican 2004[3] | Turkey | Imiquimod 5% | 34 (33) | 3×/wk, maximum 12 wk | Applied with the tip of the stick and then cleaned with abundant amounts of water | 9 | Clearance after 3 mo, recurrence after 6 mo, side effects | ITT modified |
| | | Placebo | 11 (10) | Same | Same | | | |
| Azizjalali 2012[4] | Iran | $CO_2$ laser | 80 (80) | 1× every 2 wk, maximum 6 wk | Local anesthesia, 30 W, 10,600 nm, 4.5 J/cm$^2$ | 3 | Clearance after 6 wk, recurrence after 3 mo, side effects | ITT |
| | | Cryo | 80 (80) | Same | 2 freezing cycles | | | |
| Baker 2011[5] | USA | Imiquimod 2.5% | 202 (139) | 1×/d for 8 wk | Wash after 8 hr | 4 | Clearance after 4 mo, side effects | ITT, only women |
| | | Imiquimod 3.75% | 204 (149) | Same | Same | | | |
| | | Placebo | 105 (77) | Same | Same | | | |
| Benedetti Panici 1989[6] | Italy | Electro | 51 (51) | Until apparent elimination of the genital wart, interval: 3 wk | Local anesthesia, diathermocoagulation with bipolar electrodes | 12 | Clearance after 1 mo, recurrence after 2.6 mo, side effects | ITT, only women, some patients with AGWs on cervix; IFN arm (data not shown) |
| | | Placebo | 48 (48) | NR | NR | | | |
| Beutner 1989[7] | USA | Podophyllotoxin 0.5% gel | 56 (56) | 2×/d, 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 6 wk, recurrence after 10 wk, side effects, new warts | ITT, only men |
| | | Placebo | 53 (53) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Beutner 1998[8] | USA | Imiquimod 5% | 94 (69) | 1×/d, maximum 16 wk | Wash after 8 hr with soap and water | 7 | Clearance after 8, 12, 16 wk, recurrence after 3 mo, side effects, partial clearance, time for complete clearance, new warts | ITT |
| | | Imiquimod 1% | 90 (71) | Same | Same | | | |
| | | Placebo | 95 (67) | Same | Same | | | |
| Bilensoy 2011[9] | Turkey | Placebo | 6 (6) | 3×/wk, 1 wk/2, maximum 12 wk | Applied with a cotton-tipped swab | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance | ITT, only women; both 5-FU arms used with cyclodextrin thermosensitive gel |
| | | 5-FU cream | 14 (14) | Same | Same | | | |
| | | Placebo intra-lesional | 6 (6) | Same | NR | | | |
| | | 5-FU intra-lesional | 18 (18) | Same | Same | | | |
| Bornstein 1997[10] | Israel | IFNβ-1a intra-lesional 1 MIU | 30 (30) | 3×/wk, maximum 3 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance, time to complete clearance | ITT |
| | | Placebo intra-lesional | 30 (30) | Same | Same | | | |
| Camargo 2014[11] | Brazil | KOH | 24 (20) | 1×/d, maximum 12 wk | Applied with a cotton wrapped toothpick | 3 | Clearance after 12 wk, recurrence after 1 mo, side effects, time to complete clearance | 1st treatment, only men |
| | | Cryo | 24 (22) | Every 2 wk, maximum 12 wk | Freezing 1× 5-20 s | | | |
| Carpiniello 1988[12] | NR | $CO_2$ laser | 41 (NR) | NR | | 4 | Clearance after treatment, recurrence after 4 mo | Only men |
| | | $CO_2$ laser + 5-FU | 27 (NR) | 5-FU every night maximum 30 d | 5-FU initiated 1 wk after $CO_2$ laser | | | |
| Chen 2007[13] | China | $CO_2$ laser | 21 (21) | 1×/wk for 3 wk if not removed | topical anesthesia with 2% lidocaine | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | ITT, no quantification for side effects |
| | | PDT | 65 (65) | Same | ALA dissolved in sterile 0.9% NaCl just before application, 3 hr before light illumination (632 nm) | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Claesson 1996[14] | Sweden, Finland, France | Podophyllotoxin 0.15% cream | 60 (60) | 2×/d for 3 consecutive d, maximum 4 wk | | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT |
| | | Podophyllotoxin 0.3% cream | 60 (60) | Same | | | | |
| | | Podophyllotoxin 0.5% sol | 60 (60) | Same | | | | |
| Duus 1985[15] | Denmark | $CO_2$ laser | 25 (21) | 1×, maximum 2× | Continuous wave (5-20 W), spot diameter of 0-7 mm | 6 | Clearance after treatment, recurrence after 3 mo, side effects | |
| | | Ablative treatment (surgery, Electro) | 25 (23) | 1×, maximum 2× | NR | | | |
| Edwards 1998[16] | Multicentric: Hawaii, New York, Pennsylvania & Canada | Imiquimod 5% | 109 (90) | 3×/wk for 16 wk | Wash after 6-10 hr with soap and water | 7 | Clearance after 4 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Imiquimod 1% | 102 (71) | Same | Same | | | |
| | | Placebo | 100 (73) | Same | Same | | | |
| Edwards 1988[17] | UK | Podophyllotoxin 0.5% sol | 32 (32) | 2×/d for 3 consecutive d, maximum 6 wk | Self-applied | 6 | Clearance after 6 wk, side effects | ITT, only men |
| | | Podophyllin 20% | 19 (19) | 1×/wk, maximum 6 wk | Provider-applied | | | |
| Eron 1986[18] | USA | IFNα-2b (1 MIU) intra-lesional | 147 (125) | NR | NR | 7 | Clearance after 4,16 wk; recurrence after 3 mo, side effects | |
| | | Placebo intra-lesional | 149 (132) | Same | Same | | | |
| Gabriel 1983[19] | UK | Podophyllin 25% | 38 (29) | 1×/wk, maximum 6 wk | Applied with the tip of the stick | 3 | Clearance after 6 wk, recurrence after 6 wk, side effect, time to complete clearance | Only men |
| | | Podophyllin 25% + TCA 50% | 35 (31) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Gilson 2009[20] | UK | Cryo + placebo | 75 (40) | Cream 2×/d for 3 consecutive d, maximum 4 wk, Cryo: 45-s freezing/wk, maximum 12 wk | NR | 9 | Clearance after 3 mo, recurrence after 3 mo, side effects | ITT modified |
| | | Cryo + podophyllotoxin 0.15% cream | 74 (31) | Same | Same | | | |
| Godley 1987[21] | UK | TCA | 69 (57) | 1×/wk maximum 10 wk | Applied with an orange stick | 4,5 | Clearance after 10 wk; recurrence after 2 mo, side effects, time to complete clearance | Only men |
| | | Cryo | 61 (49) | Same | Freeze for 15 sec twice | | | |
| Greenberg 1991[22] | USA | Podophyllotoxin 0.5% sol & cream | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with a cotton tip | | Clearance after 4 wk; recurrence after 2 mo, distinctive side effects for gel & cream, new warts | ITT modified, only women |
| | | Placebo | 24 (21) | Same | Same | | | |
| Gross 2007[23] | Germany & Russia | Polyphenon 15% | 80 (46) | 3×/d, maximum 16 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, side effects | |
| | | Polyphenon 10% | 79 (36) | Same | Same | | | |
| | | Placebo | 83 (31) | Same | Same | | | |
| Hellberg 1995[24] | Sweden | Podophyllotoxin 0.5% cream | 30 (28) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | Only women |
| | | Podophyllin 20% | 30 (27) | 1×/wk, maximum 4 wk | Wash 4 hr after application | | | |
| Isik 2014[25] | Turkey | KOH | 30 (30) | 1×/d for 12 wk | Perilesional application of Vaseline | 6 | Clearance after 3 mo, recurrence after 3 mo, partial clearance | ITT |
| | | 5-FU + salicylic acid | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Jensen 1985[26] | Denmark | Podophyllin 25% | 30 (30) | 1×/wk, maximum 6 wk | Wash after 6 hr | 12 | Clearance after 4 wk; recurrence after 1.5, 4.5, 10.5 mo; side effects, time to complete clearance | ITT |
| | | Surgery | 30 (30) | Same | Local anesthesia with lignocaine | | | |
| Keay 1988[27] | USA | IFNα cream | 32 (31) | 3×/d, maximum 4 wk | Applied topically by gentle 30-s rubbing | 4 | Clearance after 4, 16 wk, side effects | ITT modified, only women |
| | | Placebo | 33 (30) | Same | Same | | | |
| Khawaja 1989[28] | UK | Podophyllin 25% | 19 (19) | 1×/wk, maximum 6 wk | Wash after 6 hr | 10.5 | Clearance after 6 wk, recurrence after 3, 9 mo; side effect, time to complete clearance | ITT, 1st treatment |
| | | Surgery | 18 (18) | 1× | Local anesthesia with lignocaine | | | |
| Kinghorn 1993[29] | UK | Podophyllotoxin 0.5% sol | 168 (138) | 2×/d for 3 consecutive d, maximum 5 wk | | 3 | Clearance after 54 wk; recurrence after 2 mo, side effects | |
| | | Podophyllin 25% | 84 (62) | 2×/wk, maximum 5 wk | Wash off after 4 hr | | | |
| Kirby 1990[30] | USA | Podophyllotoxin 0.5% sol | 19 (19) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT |
| | | Placebo | 19 (19) | Same | Same | | | |
| Komericki 2011[31] | Austria | Podophyllotoxin 0.5% sol | 26 (25) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk for podophyllotoxin and 16 wk for imiquimod, side effects | 1st treatment |
| | | Imiquimod 5% | 25 (20) | 3×/wk maximum 16 wk | Same | | | |
| Kumar 2014[32] | India | Imiquimod 5% | 44 (41) | 3×/wk, maximum 16 wk | Intradermal injections of the Mw vaccine and vehicle on both shoulders at baseline to sensitize and improve local immune response to intralesional therapy | 8 | Clearance after 20 wk; recurrence after 3 mo, side effects, time to complete clearance, partial clearance | ITT |
| | | *Mycobacterium* intra-lesional | 45 (39) | Every 2 wk, maximum 16 wk | – | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Lacey 2003[33] | UK | Podophyllin 25% | 116 (96) | 2×/wk, maximum 4 wk | In the clinic | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects, cost/efficacy ratio | |
| | | Podophyllotoxin 0.15% cream | 118 (82) | 2×/d for 3 consecutive d, maximum 4 wk | NR | | | |
| | | Podophyllotoxin 0.5% sol | 120 (98) | Same | Same | | | |
| Lassus 1987[34] | Finland | Podophyllotoxin 0.5% sol | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | At home | 3 | Clearance after 4 wk; recurrence after 2 mo | ITT, only men |
| | | Podophyllin 20% | 52 (52) | 1×/wk, maximum 4 wk | In the clinic | | | |
| Lotfabadi 2015[35] | Iran | Cryo | 34 (34) | Every 2 wk, maximum 12 wk | Freeze with 1-mm margin, 10-15 s | 6 | Clearance 1 mo after 12 wk of treatment; recurrence after 2 mo; side effects | |
| | | TCA | 34 (34) | Same | Applied by an applicator then washed | | | |
| Mahajan 2014[36] | India | Cryo + podophyllin 20% | 30 (24) | Cryo once & podo every 2 wk | Cryo: freezing with a 5-mm margin from a distance of 2-mm<br>Podo: Wash 3 hr after therapy | 6 | Clearance after 8,12, 24 wk; recurrence after 1 mo; side effects; time to complete clearance | |
| | | Bleomycin + placentrex intra-lesional | 30 (25) | Bleomycin every 2 wk, maximum 10 wk; placentrex every night | After bleomycin, ice water soaks twice daily for 4 d | | | |
| Mazurkiewicz 1990[37] | Poland | Podophyllin 20% | 16 (13) | Once/wk, maximum 6 wk | Doctor-applied | 1,5 | Clearance after 6 wk, side effects | |
| | | Podophyllotoxin 0.5% sol | 16 (14) | 2×/d for 3 consecutive d, maximum 6 wk | Patient-applied | | | |
| | | Podophyllotoxin 0.5% cream | 22 (16) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Nath 1990[38] | India | Podophyllin 25% | 50 (47) | 1×/wk, maximum 12 wk | Wash after 2 hr | 6 | Clearance after 3 mo, recurrence after 3 mo, time to complete clearance | Incompletely randomization (pregnant women got TCA) |
| | | TCA 50% | 50 (48) | Same | Applied with a swab stick | | | |
| On 2014[39] | USA | Polyphenon 15% + cryo | 21 (NR) | Polyphenon: 2×/d, maximum 16 wk; Cryo: 1× | Cryo: 2 5-s cycles/5-s interval rest | 16 | Clearance after 9 & 17 wk, side effects, partial clearance | ITT |
| | | Cryo | 21 (NR) | 1× | Same | | | |
| Ormerod 2015[40] | Germany, UK, Holland, Switzerland, Poland: 40 centers | Placebo | 75 (74) | 2×/d for 12 wk | Sodium nitrite was applied first, then citric acid, & the 2 creams were mixed. | 6 | Clearance after 3 mo, recurrence after 3 mo, side effects, time to complete clearance | |
| | | Sodium nitrite 3% + citric acid 4.5% | 74 (72) | 2×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 77 74) | 1×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 73 (70) | 2×/d for 12 wk | Same | | | |
| Padhiar 2006[41] | India | Imiquimod 5% | 30 (30) | 3×/wk, maximum 16 wk | Wash after 6-10 hr | 10 | Clearance after 4 mo, recurrence after 3 & 6 mo, side effects, partial clearance, time to complete clearance | ITT |
| | | Podophyllin 20% | 30 (30) | 1×/wk, maximum 6 wk | Applied with a swab stick, wash after 4-6 hr | | | |
| Petersen 1995[42] | Denmark | Podophyllotoxin 0.5% sol | 18 (18) | 2×/d for 3 consecutive d, maximum 4 wk | Fingertip application | 3 | Clearance after 6 wk, recurrence after 6 wk, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 18 (18) | Same | Same | | | |
| Reichman 1988[43] | USA | IFNα-n1 intra-lesional | 17 (15) | 3×/wk, maximum 4 wk | NR | 12 | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | IFNβ (1 MIU) intra-lesional | 20 (20) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Reichman 1988[43](continued) | | IFNα-2b intra-lesional | 23 (23) | Same | Same | | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | Placebo intra-lesional | 19 (18) | Same | Same | | | |
| Relakis 1996[44] | Brazil & Greece | $CO_2$ laser | 71 (71) | 1× | Applied Vaseline & $ZnO_2$ 10% cream | 12 | Clearance after 3 mo, recurrence after 3, 6 & 9 mo, side effects | ITT, only men |
| | | 5-FU | 218 (218) | 5×/wk, maximum 4 wk | Applied Vaseline 5% $ZnO_2$, before 5-FU | | | |
| | | $CO_2$ laser + 5-FU | 47 (47) | Both | Both | | | |
| Schofer 2006[45] | Germany | Ablative procedure (Electro, Cryo, laser, surgery) | 100 (100) | 1×/wk, maximum 4 wk | NR | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | ITT |
| | | Imiquimod 5% | 155 (155) | 3×/d, maximum 16 wk | Same | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | |
| | | Ablative procedure + imiquimod | 103 (103) | Both | Same | | | |
| Sherrard 2007[46] | UK | Podophyllin 25% | 79 (56) | Times/wk NR, but maximum 8 wk | NR | 2 | Clearance after 8 wk, side effects | |
| | | TCA | 88 (58) | Same | Same | | | |
| | | Cryo | 81 (66) | Same | Same | | | |
| | | TCA + Podophyllin | 85 (65) | Same | Same | | | |
| | | Cryo + Podophyllin | 76 (59) | Same | Same | | | |
| Simmons 1981[47] | UK | Cryo | 24 (16) | 1× every 2 wk, maximum 12 wk | Produced 2-mm ice-balls larger than wart | 3 | Clearance after 12 wk | |
| | | Electro | 18 (11) | 1× every 2 wk, maximum 12 wk | 2% lignocaine anesthesia | | | |
| Snoeck 2001[48] | Belgium | Cidofovir | 19 (19) | 1×/d, 5 d/wk, 1 wk/2 for 12 wk | Applied with a cotton tipped swab or a rubber glove | | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Placebo | 11 (11) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Stefanaki 2008[49] | Greece | Imiquimod | 60 (35) | 3×/wk, maximum 12 wk | NR | 12 | Clearance after 4, 8,12 & 24 wk, recurrence after 9 mo, side effects | 1st treatment |
| | | Cryo | 60 (45) | 1× every 3 wk, maximum 12 wk | Frozen 1× for 10-20 s | | | |
| Stockfelth 2008[50] | Multicentric (Europe, South Africa) | Polyphenon 15% | 201 (161) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | ITT modified |
| | | Polyphenon 10% | 199 (170) | Same | Same | | | |
| | | Placebo | 103 (80) | Same | Same | | | |
| Stone 1990[51] | USA | Podophyllin (dose NR) | 144 (53) | Times/week NR, but maximum 6 wk | NR | 5 | Clearance after 6 wk, recurrence after 3 mo, side effects | |
| | | Cryo | 154 (60) | 1×/wk, maximum 6 wk | Each AGW was frozen 1× | | | |
| | | Electro | 152 (51) | Same | 1% lidocaine anesthesia | | | |
| Strand 1995[52] | Sweden | Podophyllotoxin 0.15% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with an applicator | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT, only men |
| | | Podophyllotoxin 0.3% cream | 31 (31) | Same | Same | | | |
| | | Podophyllotoxin 0.5% sol | 29 (29) | Same | NR | | | |
| Swinehart 1997[53] | USA | 5-FU injection intra-lesional | 80 (78) | 1×/wk, maximum 6× over 8 wk | NR | 5 | Clearance after 8 wk, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | Individual lesion analysis |
| | | 5-FU | 80 (76) | NR | Same | | | |
| | | Placebo | 40 (33) | Same | Same | | | |
| Syed 1998[54] | Pakistan | Imiquimod 2% | 30 (30) | 2×/d for 5 consecutive d, maximum 6 wk | Wash & dry warts before each application and apply | 4 | Clearance after 6 wk, recurrence after 2.5 mo, side effects | ITT, only women, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Syed 1995 (a)[55] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, recurrence after 9 mo, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1995 (b)[56] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1994[57] | Pakistan | Podophyllotoxin 0.3% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Let dry for at least 1 min without washing | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 30 (30) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 2000[58] | Pakistan | Imiquimod 2% | 30 (30) | 3 consecutive d, maximum 4 wk | Applied with a finger cot | 18 | Clearance after 16 wk, recurrence after 18 mo, side effects | ITT, only men, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |
| Szeimies 2009[59] | Germany | PDT + $CO_2$ laser | 84 (84) | 1× | PDT: 100 J/cm$^2$, 100 mW/cm$^2$ (640-740 nm) occlusion for 4-6 hr | 12 | Clearance after treatment, recurrence after 1, 2, 3, 6 & 12 mo, side effects, satisfaction | ITT |
| | | $CO_2$ laser | 91 (91) | Same | Continuous wave, defocused beam (2-mm diameter), 10-20 W, general or local anesthesia | | | |
| Tabari 2010[60] | Iran | Podophyllin 20% | 60 (60) | 2×/wk | Wash after 20 min | 6 | Clearance after 4 or 8 wk, recurrence after 3 mo, side effects | ITT |
| | | TCA 30% | 60 (60) | NR | With a topical cotton soap and washed after 1 min | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Tatti 2008[61] | USA, Europe, S Africa multicenter | Polyphenon 15% | 196 (159) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 16 wk, recurrence after 3 mo, side effects, partial clearance | ITT modified |
| | | Polyphenon 10% | 202 (162) | Same | Same | | | |
| | | Placebo | 104 (83) | Same | Same | | | |
| Tyring 1998 (a)[62] | USA | Imiquimod 5% | 18 (16) | 3×/wk, maximum 16 wk | Applied with cotton swab tip | 4 | Clearance after 16 wk, side effects, partial clearance | |
| | | Placebo | 4 (3) | Same | Same | | | |
| Tyring 1998 (b)[63] | USA | Placebo | 107 (95) | 2×/d for 3 consecutive d, maximum 8 wk | NR | 4 | Clearance after 4 & 8 wk, recurrence after 3 mo, side effects | |
| | | Podophyllotoxin 0.5% gel | 219 (197) | Same | Same | | | |
| Vance 1986[64] | USA | IFNα-2b (1 MIU) intra-lesional | 37 (30) | 3×/wk, maximum 3 wk | NR | 3 | Clearance after 4, 5, 7 & 12 wk, side effects, partial clearance | ITT |
| | | IFNα-2b (0.1 MIU) intra-lesional | 38 (32) | Same | Same | | | |
| | | Placebo intra-lesional | 39 (29) | Same | Same | | | |
| von Krogh 1992[65] | Sweden | Placebo | 12 (11) | 2×/d, 3 d/wk for 2 wk | NR | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | |
| | | Podophyllotoxin 0.5% cream | 48 (44) | Same | Same | | | |
| von Krogh 1994[66] | Sweden | Podophyllotoxin 0.25% sol | 19 (18) | 2×/d, 3 d/wk for 2 wk | Applied with wool swabs | 6 | Clearance after 3 wk, recurrence after 2 & 6 mo, side effects | 1st treatment |
| | | Podophyllotoxin 0.5% sol | 19 (16) | Same | Same | | | |
| | | Placebo | 19 (17) | Same | Same | | | |
| Wallin 1977[67] | Sweden | 5-FU | 21 (18) | 1×/d for 2 wk | Applied with cotton swab tip | 9 | Clearance after 4 wk, recurrence after 6 mo, side effects | Only men |
| | | Podophyllin 25% sol | 21 (19) | 1×/wk for 4 wk | Provider-applied, wash 4-6 hr later | | | |

Appendix S2: Characteristics of RCTs included in the meta-analyses (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Weismann 1982[68] | Denmark | 5-FU | 30 (30) | 2×/wk for women, once/d for men | NR | 2 | Clearance after 8 wk, side effects, partial clearance, time to complete clearance | ITT |
| | | Placebo | 29 (29) | Same | Same | | | |
| Welander 1990[69] | USA | IFNα-2b (1 MIU) intra-lesional | 20 (16) | 3×/wk, maximum 3 wk | NR | NR | Clearance after 4 or 15 wk, side effects | |
| | | Placebo intra-lesional | 22 (21) | Same | Same | | | |
| White 1997[70] | UK | Podophyllotoxin 0.5% sol | 106 (77) | 2×/d for 3 consecutive d, maximum 12 wk | NR | 3 | Clearance after 5 wk, side effects | ITT, only men, 1st treatment |
| | | Podophyllin 0.5% | 103 (86) | Same | Same | | | |
| | | Podophyllin 2% | 106 (81) | Same | Same | | | |

Abbreviations: ITT, intention-to-treat; NR, not reported; KOH, potassium hydroxide; ALA, 5-aminolaevulinic acid; Mw, *Mycobacterium* w; Sol, solution; PDT, photodynamic therapy; Electro, electrosurgery; Cryo, cryotherapy; IFN, interferon.

**Appendix S3:** Exclusion criteria

| 1st Author | Year | Exclusion Criteria |
|---|---|---|
| Alfonso-Trujillo[71] | 2008 | not RCT |
| Alfonso-Trujillo[72] | 2008 | not RCT |
| Alfonso-Trujillo[73] | 2009 | not RCT |
| Alfonso-Trujillo[74] | 2009 | not RCT |
| Arany[75] | 1999 | duplicate of Tyring[62] |
| Armstrong[76] | 1996 | another treatment not considered herein |
| Bar-Am[77] | 1993 | dose escalation |
| Bashi[78] | 1985 | not RCT |
| Beutner[79] | 1998 | duplicate of Beutner[8] |
| Beutner[80] | 1995 | duplicate of Beutner[8] |
| Botacini[81] | 1993 | other localization |
| Buck[82] | 2002 | not RCT |
| Chen[83] | 2009 | missing data (no English translation of Chinese) |
| Chopra[84] | 1997 | duplicate of Tyring[62] |
| Collaborative Study Group[85] | 1991 | another treatment not considered herein |
| Collaborative Study Group[86] | 1993 | another treatment not considered herein |
| Damstra[87] | 1991 | missing data |
| Davidson-Parker[88] | 1988 | another treatment not considered herein |
| Dinsmore[89] | 1997 | not RCT |
| Douglas[90] | 1990 | HIV |
| Edwards[91] | 1998 | duplicate of Edwards[17] |
| Edwards[92] | 1995 | duplicate of Edwards[17] |
| Eron[93] | 1993 | another treatment not considered herein |
| Ferenczy[94] | 1998 | duplicate of Edwards[17] |
| Ferenczy[95] | 1995 | HIV |
| Fife[96] | 2001 | dose escalation |
| Fleshner[97] | 1994 | another treatment not considered herein |
| Fouere[98] | 2014 | missing data |
| Garland[99] | 2006 | dose escalation |
| Garland[100] | 2001 | not RCT |
| Goh[101] | 1998 | dose escalation |
| Gollnick[102] | 2001 | dose escalation |
| Gross[103] | 1996 | another treatment not considered herein |
| Gross[104] | 1998 | another treatment not considered herein |
| Handley[105] | 1991 | another treatment not considered herein |
| Handley[106] | 1992 | missing data (randomization unclear) |
| Hohenleutner[107] | 1990 | another treatment not considered herein |
| Hoy[108] | 2012 | not RCT |
| IRCT2017011531949N1[109] | 2017 | missing data (recruiting) |
| IRCT2015090514386N1[110] | 2015 | missing data (not recruiting) |
| IRCT2013111015364N1[111] | 2014 | missing data (not recruiting) |
| IRC 201202138992N1[112] | 2012 | not RCT |
| IRCT201412207848N1[113] | 2014 | not RCT |
| Jardine[114] | 2012 | another treatment not considered herein |
| Klutke[115] | 1995 | another treatment not considered herein |
| Lafuma[116] | 2003 | duplicate of Tyring[62] and Edwards[17] |
| Landthaler[117] | 1987 | HIV |
| Langley[118] | 2010 | not RCT |
| Lassus[119] | 1984 | duplicate of Lassus[34] |
| Li[120] | 2011 | dose escalation |
| Liang[121] | 2009 | missing data (condyloma analysis) |

**Appendix S3:** Continued

| | | |
|---|---|---|
| Liu[122] | 2012 | missing data (condyloma analysis) |
| Maiti[123] | 1985 | dose escalation |
| Maw[124] | 2002 | not RCT |
| Mazurkiewicz[125] | 1990 | missing data (not accessible) |
| Meltzer[126] | 2009 | not RCT and duplicate of Stockfleth[49] |
| Metawea[127] | 2005 | not RCT |
| Mi[128] | 2011 | missing data (condyloma analysis) |
| Mistrangelo[129] | 2010 | another treatment not considered herein |
| Monsonego[130] | 1996 | missing data (condyloma analysis) |
| NCT00674739[131] | 2011 | duplicate of Baker[5] |
| NCT00735462[132] | 2011 | duplicate of Baker[5] |
| NCT02520986[133] | 2016 | missing data (not recruiting) |
| NCT02724254[134] | 2016 | missing data (recruiting) |
| NCT01796821[135] | 2017 | missing data (recruiting) |
| NCT03153566[136] | 2017 | missing data (recruiting) |
| NCT01943630[137] | 2017 | missing data (recruiting) |
| NCT02849262[138] | 2016 | missing data (recruiting) |
| NCT02462187[139] | 2015 | missing data (not recruiting) |
| NCT02482428[140] | 2015 | missing data (not recruiting) |
| NCT02147353[141] | 2014 | missing data (not recruiting) |
| NCT02015260[142] | 2013 | missing data (not recruiting) |
| Nieminen[143] | 1994 | another treatment not considered herein |
| Owens[144] | 1999 | duplicate of Edwards[17] |
| Potocnik[145] | 1997 | missing data (not accessible) |
| Rosen[146] | 2015 | missing data (no placebo data) |
| Sauder[147] | 2003 | duplicate from of Edwards[17] |
| Sharma[148] | 2017 | missing data (condyloma analysis) |
| Shi[149] | 2013 | not RCT |
| Stefanaki[150] | 2014 | missing data |
| Stellato[151] | 1997 | another treatment not considered herein |
| Swinehart[152] | 1997 | duplicate from Swinehart[53] |
| Syed[153] | 2002 | missing data (not accessible) |
| Syed[154] | 1994 | other localization |
| Syed[155] | 1993 | dose escalation |
| Trofatter[156] | 2002 | dose escalation |
| Tuncel[157] | 2005 | missing data |
| Urban[158] | 2006 | missing data (not accessible) |
| Vesterinen[159] | 1984 | other localization |
| Viazis[160] | 2007 | HIV and other localization |
| von Krogh[161] | 1981 | not RCT |
| Xu[162] | 2009 | missing data (no English translation of Chinese) |
| Yaghoobi[163] | 2014 | not RCT |
| Yin[164] | 1998 | another treatment not considered herein |
| Yu[165] | 2004 | another treatment not considered herein |
| Zarcone[166] | 1996 | not RCT |
| Zervoudis[167] | 2010 | another treatment not considered herein |

Abbreviations: RCT: randomized-controlled trial; HIV: human immunodeficiency virus

**Appendix S4:** Imiquimod 5% vs placebo for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: imiquimod 5% arm + placebo arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence [c] |
| Complete clearance | 255 + 210 = 465 (4) | High | High | None serious | Imprecision | Detected | 5.84 (2.36–14.41) | +– – – Very low (1, 2, 5, 6, 8, 10, 11) |
| Complete clearance[d] | 161 + 115 = 276 (3) | High | Low | None serious | Imprecision | Detected | 4.27 (2.50–7.29) | +– – – Very low (1, 2, 3, 6, 8, 10, 11) |
| Recurrence (3-6 mo) | 116 + 14 = 130 (3) | High | Mild | None serious | Serious | Detected | 0.87 (0.31–2.45) | +– – – Very low (1, 2, 4, 6, 9, 10) |
| Low-grade local side effects | 255 + 210 = 465 (4) | High | Mild | None serious | Imprecision | Detected | 1.97 (1.19–3.26) | +– – – Very low (1, 2, 4, 6, 8, 10) |
| Mild-grade local side effects | 237 + 226 = 463 (3) | High | Low | None serious | Imprecision | Detected | 5.74 (2.91–11.31) | +– – – Very low (1, 2, 3, 6, 8, 10, 11) |
| High-grade local side effects | 203 + 195 = 398 (2) | High | Low | None serious | Imprecision | Detected | 9.40 (0.97–91.24) | +– – – Very low (1, 2, 3, 6, 9, 10) |
| Low-grade general side effects | 94 + 95 = 189 (1) | High | NA, only 1 study | None serious | Imprecision | Detected | 16.17 (3.99–65.56) | +– – – Very low (1, 2, 6, 8, 10, 11) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30=0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.
Indirectness of evidence: (6) direct comparison=0.
Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of imiquimod clearance: 0.515 (Lacey et al.[168]) and efficacy/side effect difference: 25% N=622): (7) Moderate imprecision: N > 622 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<622 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N*<622=–2.
Publication bias: (10) too few studies: publication bias detected=–1.
Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1.
[d]Subgroup analysis (without Beutner et al.[9]: because treatment was given every day).

**Appendix S5:** Polyphenon 15% vs placebo for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: Polyphenon15% arm + placebo arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence[c] |
| Complete clearance | 477 + 290 = 757 (3) | High | Low | None serious | Not detected | Detected | 1.52 (1.28–1.82) | +– – – Very low (1, 2, 3, 6, 10) |
| Recurrence (3 mo) | 259 + 104 = 363 (3) | High | Low | None serious | Serious | Detected | 1.11 (0.48–2.58) | +– – – Very low (1, 2, 3, 6, 9, 10) |
| Low-grade local side effects | 397 + 207 = 604 (2) | High | High | None serious | Moderate | Detected | 1.23 (0.68–2·.22) | +– – – Very low (1, 2, 5, 6, 7, 10) |
| Mild-grade local side effects | 397 + 207 = 604 (2) | High | High | None serious | Moderate | Detected | 2.54 (0.26–25.12) | +– – – Very low (1, 2, 5, 6, 7, 10) |
| High-grade local side effects | 477 + 290 = 757 (3) | High | Low | None serious | Not detected | Detected | 6.69 (2.09–21.44) | ++– – Low (1, 2, 3, 6, 10, 11) |
| Low-grade general side effects | 397 + 207 = 604 (2) | High | Low | None serious | Moderate | Detected | 2.89 (0.11–76.54) | +– – – Very low (1, 2, 3, 7, 10) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30% = 0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.

Indirectness of evidence: (6) direct comparison=0.
Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of polyphenon clearance: 0.53 (Lacey *et al.*[168]) and efficacy/side effect difference: 25% N=588): (7) Moderate imprecision: N>588 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<588 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N*<588=–2.
Publication bias: (10) too few studies: publication bias detected=–1.
Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1

**Appendix S6:** 5-FU vs placebo for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: 5-FU arm + placebo arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence[c] |
| Complete clearance | 124 + 75 = 199 (3) | High | Low | None serious | Imprecision | Detected | 3.09 (1.82–5.25) | +– – – Very low (1, 2, 3, 6, 8, 10, 11) |
| Recurrence (3 mo) | 45 + 0 = 45 (2) | High | Not Applicable | None serious | Not Applicable | Detected | Not Applicable | +– – – Very low (1, 2, 6, 10) |
| Low-grade local side effects | 30 + 29 = 59 (1) | High | Not Applicable | None serious | Imprecision | Detected | 59.03 (3.78–922.48) | +– – – Very low (1, 2, 6, 8, 10, 11) |
| High-grade local side effects | 30 + 29 = 59 (1) | High | Not Applicable | None serious | Serious | Detected | 2.90 (0.12–68.50) | +– – – Very low (1, 2, 3, 6, 9, 10) |
| Low-grade general side effects | 30 + 29 = 59 (1) | High | Not applicable | None serious | Serious | Detected | 0.97 (0.50–1.87) | +– – – Very low (1, 2, 6, 9, 10) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30%=0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.

Indirectness of evidence: (6) direct comparison=0.

Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of 5-FU clearance: 0.70 (Batista *et al.*[169]) and efficacy/side effect difference: 25% N=322): (7) Moderate imprecision: N > 322 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<322 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N*<322=–2.

Publication bias: (10) too few studies: publication bias detected=–1. Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1

**Appendix S7:** Podophyllotoxin cream 0.5% vs placebo for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: Podophyllotoxin cream 0.5% arm + placebo arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence[c] |
| Complete clearance | 118 + 72 = 190 (4) | High | Mild | None serious | Imprecision | Detected | 6.48 (3.22–13.03) | +– – – Very low (1, 2, 4, 6, 8, 10, 11) |
| Recurrence (2-3 mo) | 76 + 4 = 80 (3) | High | Low | None serious | Serious | Detected | 3.27 (0.33–32.00) | +– – – Very low (1, 2, 3, 6, 9, 10) |
| Low-grade local side effects | 142 + 96 = 238 (5) | High | Low | None serious | Imprecision | Detected | 1.5 (1.08–2.54) | +– – – Very low (1, 2, 3, 6, 8, 10) |
| Mild-grade local side effects | 72 + 36 = 108 (2) | High | Low | None serious | Imprecision | Detected | 2.58 (1.43–4.67) | +– – – Very low (1, 2, 3, 6, 8, 10, 11) |
| High-grade local side effects | 48 + 12 = 60 (1) | High | Not applicable | None serious | Serious | Detected | 1.33 (0.07–25.96) | +– – – Very low (1, 2, 6, 9, 10) |
| Low-grade general side effects | 72 + 36 = 108 (2) | High | Mild | None serious | Serious | Detected | 3.94 (0.77–20.06) | +– – – Very low (1, 2, 4, 6, 9, 10) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30%=0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.

Indirectness of evidence: (6) direct comparison=0.
Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of Podophyllotoxin cream 0.5% clearance: 0.565 (Lacey *et al.*[168]) and efficacy/side effect difference: 25% N=524): (7) Moderate imprecision: N>524 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<524 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N* < 524=–2.
Publication bias: (10) too few studies: publication bias detected=–1.
Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1.

**Appendix S8:** Podophyllotoxin solution 0.5% vs placebo for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: Podophyllotoxin gel 0.5% arm + placebo arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence[c] |
| Complete clearance | 94 + 91 = 511 (3) | High | Low | None serious | Low | Detected | 32.72 (6.65–161.02) | ++– – Low (1, 2, 3, 6, 10, 11) |
| Recurrence (3 mo) | 52 + 0 = 52 (3) | High | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable |
| Low-grade local side effects | 75 + 72 = 147 (2) | High | High | None serious | Low | Detected | 5.95 (1.48–23.93) | +– – – Very low (1, 2, 5, 6, 10, 11) |
| Mild-grade local side effects | 94 + 91 = 185 (2) | High | High | None serious | Low | Detected | 3.74 (0.42–32.94) | +– – – Very low (1, 2, 5, 6, 10, 11) |
| High-grade local side effects | 19 + 19 = 38 (1) | High | Not applicable | None serious | Serious | Detected | 7.00 (0.39–126.92) | +– – – Very low (1, 2, 6, 9, 10) |
| Low-grade general side effects | 75 + 72 = 147 (2) | High | High | None serious | Low | Detected | 4.38 (1.77–10.79) | +– – – Very low (1, 2, 5, 6, 10) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30%=0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.

Indirectness of evidence: (6) direct comparison=0.
Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of Podophyllotoxin gel 0.5% clearance: 0.64 (Lacey *et al.*[168]) and efficacy/side effect difference: 25% N=400): (7) Moderate imprecision: N>400 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<400 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N*<400=–2.
Publication bias: (10) too few studies: publication bias detected=–1.
Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1.

**Appendix S9:** Cryotherapy vs TCA for anogenital warts in non-immunocompromised adults: summary of findings

| | Quality assessment of RCTs[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome[a] | *N* subjects: cryotherapy arm + TCA arm (*n* trials) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Relative effect (95% CI) | Quality of evidence[c] |
| Complete clearance | 229 + 224 = 453 (4) | High | High | None serious | Serious | Detected | 1.09 (0.91–1.32) | +– – – Very low (1, 2, 5, 6, 9, 10) |
| Recurrence (2 mo) | 69 + 71 = 140 (2) | High | Low | None serious | Serious | Detected | 1.17 (0.70–1.98) | +– – – Very low (1, 2, 3, 6, 9, 10) |
| Low-grade local side effects | 61 + 69 = 130 (1) | High | Not applicable | None serious | Serious | Detected | 3.39 (0.96–11.97) | +– – – Very low (1, 2, 6, 9, 10) |
| Mild-grade local side effects | 150 + 157 = 307 (2) | High | Not applicable | None serious | Imprecision | Detected | 0.44 (0.23–0.83) | +– – – Very low (1, 2, 6, 8, 10, 11) |
| High-grade local side effects | 114 + 102 = 216 (2) | High | High | None serious | Serious | Detected | 0.32 (0.00–31.80) | +– – – Very low (1, 2, 5, 6, 9, 10) |
| Low-grade general side effects | 123 + 122 = 245 (2) | High | Not applicable | None serious | Serious | Detected | 1.33 (1.00–1.76) | +– – – Very low (1, 2, 6, 9, 10) |

[a]Low-grade local side effects: erythema, stinging or irritation; mild-grade local side effects: skin burn, soiling, minor bleeding, erosion, and infection; high-grade side effects: blisters and ulceration; low-grade general side effect: pain.

[b]RCT: randomized–controlled trial.

[c]GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group grades of evidence: ++++ High quality: further research is very unlikely to change our confidence in the estimate of effect. +++– Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. ++– – Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. +– – – Very low quality: we are very uncertain about the estimate.

Study design: (1) RCT=+4.

Study limitations (risk of bias): (2) high risk of bias=–2.

Inconsistency: (3) $I^2$<30% = 0; (4) heterogeneity $I^2$>30%=–1; (5) heterogeneity $I^2$>50%=–2.

Indirectness of evidence: (6) direct comparison=0.

Imprecision: sample sizes and numbers of events fewer than the number of patients generated by a conventional sample-size calculation for a single adequately powered trial (percentages of TCA clearance: 0.685 (Lacey *et al.*[168]) and cryotherapy clearance: 0.595 (Lacey *et al.*[71]); N=1192): (7) Moderate imprecision: N>1192 and the 95% CI overlaps no effect=–1; (8) Imprecision: N<1192 and the 95% CI does not overlap 1=–1; (9) Serious imprecision: *N*<1192=–2.
Publication bias: (10) too few studies: publication bias detected=–1.
Factors that can increase the quality of the evidence: (11) RR>2 or RR<0.5=+1.

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Enfin, de nombreux essais cliniques randomisés n'ayant pas eu lieu entre les diverses thérapeutiques explorées, il était primordial de pouvoir comparer statistiquement de manière indirecte ces données. Une méta-analyse en réseau a donc été réalisée avec pour critère de jugement l'association de : l'efficacité thérapeutique et de l'absence de récurrence. Les comparaisons indirectes concernant les effets secondaires n'ont pu être réalisées pour le moment. Ces résultats ont fait l'objet d'un refus du *Journal American Academy of Dermatology* puis du *British Journal of Dermatology*. Il est actuellement en cours d'évaluation au près de *Journal of European Academy of Dermatology and Venereology*.

# Local management of anogenital warts in non-immunocompromised adults: a network meta-analysis of randomized controlled trials


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# Local management of anogenital warts in non-immunocompromised adults: a network meta-analysis of randomized controlled trials

**Running title (70 characters): Local treatment for anogenital warts**

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**Keywords:** Anogenital warts; Condyloma; Systematic review; Network meta-analysis; Frequentist approach; Sexually transmitted disease.

## ABSTRACT

***Background:*** No hierarchy of first-line treatments for anogenital warts (AGWs) is provided in international guidelines.

***Objectives:*** To compare the efficacy of topical treatments and ablative procedures for the management of AGWs.

***Methods:*** Twelve electronic databases were systematically searched. All randomized controlled trials (RCTs) comparing immunocompetent adults with AGWs who received at least 1 provider-administered or patient-administered treatment in at least 1 parallel group were included. Risk of bias assessment followed the Cochrane Handbook. The study endpoint was complete lesion response after clearance and recurrence assessment. A network meta-analysis was performed.

***Results:*** A network geometry was constructed based on 49 of the 70 RCTs included in our systematic review. All but 4 RCTs had a high risk of bias. The most efficacious treatments compared to placebo were surgery (RR 10.54; CI95% 4.53-24.52), ablative therapy + imiquimod (RR 7.52; CI95% 4.53-24.52), and electrosurgery (RR 7.10; CI95% 3.47-14.53). SUCRA values confirmed the superiority of surgery (90.9%), ablative therapy + imiquimod (79.8%), and electrosurgery (77.1%). The most efficacious patient-administered treatments were podophyllotoxin 0.5% solution (63.5%) and podophyllotoxin 0.5% cream (62.2%).

***Conclusions:*** With low-level evidence of most included RCTs, surgery and electrosurgery were superior to other treatments after clearance and recurrence assessment. Podophyllotoxin 0.5% was the most efficacious patient-administered treatment.

Anogenital warts (AGWs) are benign epithelial skin lesions that are predominantly caused by the human papillomavirus (HPV types 6 and 11), but are sometimes associated with other types of oncogenic HPV.[1] With an overall prevalence rate of around 1-5%, they are one of the most common sexually transmitted infections.[2] AGWs are usually asymptomatic, but they can be painful or pruritic and can cause significant psychosocial distress depending on size and location.[3,4] Numerous HPV vaccination campaigns have been conducted, but few studies have demonstrated their efficacy in reducing the number of AGWs.[5] Moreover, in most countries, vaccination coverage is partial and has yet to be extended to men.[6,7]

Many treatments are available to treat AGWs. These can be divided into provider-administered treatments (ProTs) (trichloroacetic acid (TCA), podophyllin resin, $CO_2$ laser surgery, cryotherapy, surgical excision, electrosurgery, intralesional therapy, etc.) and patient-administered treatments (PaTs) (podophyllotoxin, imiquimod, sinecatechins, 5-fluorouracil (5-FU) cream, etc.). The latest guidelines[8-11] recommend that treatment of AGWs be adapted to: size, number, and anatomic site of AGWs; patient preference; convenience; adverse effects; cost of treatment; and physician experience. These recommendations, however, are based on head-to-head randomized trials or on expert advice. Furthermore, RCTs comparing several major treatments for AGWs (cryotherapy[12] vs. podophyllotoxin cream or gel, imiquimod vs. TCA, $CO_2$ laser vs. surgery or electrosurgery, etc.) are lacking[10,13-15] and may never be performed (because they are costly, time-consuming, less attractive than new treatments, etc.). Reliable evidence on the comparative efficacy of these treatments is nevertheless needed to make informed clinical decisions.

In this context, network meta-analyses (NMAs) can help compare the relative benefits associated with different types of intervention for the same disease.[16,17] The

only NMA on AGWs, which was conducted by Thurgar et al[13] based on a systematic review up to September 2014, concluded to the superiority of ablative techniques; it also found podophyllotoxin 0.5% gel to be the most cost-effective topical treatment. However, this NMA did not examine sinecatechins and 5-FU cream, and several RCTs on new treatments (citric acid, intralesional bleomycin, potassium hydroxide (KOH), photodynamic therapy (PDT), etc.) have since been published.

Our NMA aims to establish a clinically meaningful hierarchy of PaTs and ProTs for the management of AGWs.

## METHODS

The study protocol is registered with PROSPERO (no. CRD42015025827). The systematic review, which has been published earlier,[14] adheres to the PRISMA Statement.[18] The present study adheres to the PRISMA extension for NMA.[19]

### Systematic review

Twelve electronic databases were systematically searched from inception to August 2018 by 2 independent reviewers (A.B. and C.D.). Search terms included 2 synonym groups, AGW and RCT, with adjustments for each database (see online supplement Appendix S1). The reference lists of all published studies and all recent reviews and meta-analyses were also searched.[8-10,13-15,20-22] No language restriction was imposed. To be included in the NMA, RCTs had to: 1) have at least 1 treatment group composed of immunocompetent adults clinically diagnosed with AGWs and treated with a ProT (TCA, podophyllin, $CO_2$ laser, cryotherapy, surgical excision, electrosurgery, all intralesional treatments, KOH, PDT, citric acid) or a PaT (podophyllotoxin, imiquimod, sinecatechins, 5-FU, cidofovir, interferon (INF) cream); and 2) provide original estimates with risk ratios and confidence intervals (CIs) or

present sufficient data to allow calculation of these estimates. Complete lesion response (CLR) at the end of follow-up was assessed based on 2 outcomes measures: clearance at 3 months and recurrence 3 months later.

An extraction grid was developed after collegial discussion. For all selected studies, variables of interest were extracted independently by 2 independent reviewers (A.B. and C.D.). These reviewers assessed the risk of bias in the selected RCTs using the Cochrane Collaboration Risk of Bias tool.[23] When different RCTs involved the same patient cohort, the RCT with the longest follow-up period was considered.

**Data synthesis**

An NMA was performed that combined the results of all selected comparisons of AGW treatments. This statistical technique is used to account for direct comparisons performed in single trials and to make indirect comparisons across trials based on a common comparator intervention.[24] In our NMA, placebo and podophyllin served as comparators for indirect comparisons even though they are not used in clinical practice. For RCTs comparing treatments at lower or higher dosages than recommended in published guidelines, only recommended dosages were considered. All analyses were performed with a frequentist approach using a random effects model, with an equal heterogeneity variance assumed for all comparisons.

The network geometry was assessed by graphically examining the connections between interventions.[25] Each node represented an intervention. The thickness of nodes was proportional to the number of allocated patients. The thickness of connecting lines was inversely proportional to the variance between 2 interventions.

Netmeta R package version 8.0 (available at: http://CRAN.R-project.org/package=netmeta) was used to perform head-to-head comparisons of

different treatments to a placebo.[26] Specifically, 2 forest plots using random effects models were generated by calculating point estimates of relative risk (RR) with a CI95%. A heat mapping function (which is a type of matrix visualization) was created with the Netmeta R package to evaluate heterogeneity and inconsistency.[27] Warmer or cooler colors indicated significant inconsistency.

The patient was the unit of analysis for all RCTs. The endpoint—CLR after clearance and recurrence assessment—was evaluated using per protocol analysis (cured patients / follow-up patients). Sensitivity analyses of 2 scenarios were performed: 1) a worst-case (intention to treat) scenario, in which patients lost to follow-up were considered to be failing treatment (cured patients / all included patients); and 2) a best-case scenario, in which patients lost to follow-up were considered cured ((cured patients + lost to follow-up patients) / all included patients).

The probability that each intervention achieved CLR was estimated based on the relative effect sizes estimated with the NMA. A hierarchy of compared interventions was performed using the Surface Under the Cumulative RAnking curve (SUCRA). SUCRA values are expressed as percentages and show the relative probability of an intervention being among the best options.

## RESULTS

### Characteristics of selected trials

Seventy RCTs involving 9,931 patients with a mean of 142 participants per study fulfilled the inclusion criteria[14] (Appendix S2-S3). The overwhelming majority of included RCTs (66/70) were found to be of poor quality (Appendix S4).[14] Twenty-one RCTs were excluded from the NMA: 6 because they compared dosages that were lower than recommended,[28-33] 14 because they did not evaluate recurrence,[34-47] and

1 because it was disconnected from the network (intralesional bleomycin vs. podophyllin + cryotherapy).[48]

Nine studies comparing a recommended dosage with a lower dosage were included, but without the treatment arm that received the lower dosage.[49-57] Ultimately, 29 treatments or combination therapies were included. One RCT compared 4 arms,[58] 5 RCTs compared 3 arms,[59-63] and 43 compared 2 arms.[49-57,64-97] Following these inclusion criteria, only two of 4 low risk of bias RCT were included.[28,46] The median follow-up for the 6,006 covered patients was 6 months (3-12 month range).

**Network geometry**

The complex network generated from the 49 included RCTs is shown in Fig. 1. Compared treatments were connected either directly or indirectly through 1 or more "comparators." The level of evidence informing each comparison was evaluated. Treatment comparisons involving the largest number of patients were polyphenon vs. placebo (3 trials; 767 patients receiving treatment) and podophyllin vs. podophyllotoxin gel (6 trials; 1,005 patients receiving treatment). Only 12 RCTs[51,58,59,63,78,79,82,84,85,88,91,97] directly compared a ProT to a PaT; of these, 9 examined treatments that are not used in clinical practice (6 on podophyllin and 3 on intralesional therapies). The most commonly studied agents were placebo (18 trials; 939 patients receiving treatment) and podophyllin (13 trials; 716 patients receiving treatment).

**Complete lesion response**

Fig. 2 presents the CLR of all treatments and placebos compared using a random effects model. Most CIs were wide, but rarely included value 1. Cidofovir, citric acid

9%, intralesional INF, intralesional placebo, and polyphenon 15% achieved a CLR not significantly different from placebo. Surgery (RR 10.54; CI95% 4.53-24.52), ablative therapy + imiquimod (RR 7.52; CI95% 4.53-24.52), and electrosurgery (RR 7.10; CI95% 3.47-14.53) achieved the best CLR compared to placebo. Other comparisons to placebo had RRs that ranged from 3.84 to 6.75.

Head-to-head comparisons using NMA are shown in the online supplement (Appendix S4). Surgery was more efficacious than imiquimod (RR 2.22; CI95% 1.04-4.76), TCA (RR 2.28; CI95% 1.09-4.75), KOH (RR 2.48; CI95% 1.02-6.01), cryotherapy (RR: 2.43; CI95% 1.17-5.03), 5-FU (RR 2.44; CI95% 1.07-5.56), and polyphenon (RR 7.07, CI95% 2.82-17.72). No significant differences were found between surgery and other ablative therapies (electrosurgery, $CO_2$ laser), or between surgery and podophyllotoxin 0.5% solution or 0.5% cream. As regards direct comparisons (except for those involving a placebo or podophyllin), the only significant result was the superiority of $CO_2$ laser over cryotherapy (RR 2.40; CI95% 1.29-4.46).

Examined RCTs presented both heterogeneity and inconsistency. The Netmeta R package provided an $I^2$ value of 60% from a Q statistic for the overall network of 70.7, which had a chi-square distribution with 28 degrees of freedom and yielded a p-value of 0.0001.[26] The Q statistic was further decomposed into heterogeneity and inconsistency components, valued at 14.7 and 56.0, respectively.

As shown in the net heat plot in Fig. 3, a high inconsistency among mapping functions was found for RCTs comparing the following treatments: cryotherapy vs. podophyllin 20-25% vs. electrosurgery; 5-FU vs. podophyllin; 5-FU vs. $CO_2$ laser vs. 5-FU + $CO_2$ laser; and $CO_2$ laser vs. cryotherapy. Treatments examined in a single study were not evaluated.

Table presents the SUCRA results that emerged from these data. These results confirm that ablative therapy, surgery (90.9%), and electrosurgery (77.1%) are the most efficacious treatments for AGWs. The SUCRA value of combination therapies was also good (PDT + $CO_2$ laser: 68.0%; $CO_2$ laser + 5-FU: 67.4%; Cryotherapy + podophyllotoxin 0.5% cream: 59.5%). Podophyllotoxin 0.5% solution (63.5%) and podophyllotoxin 0.5% cream (62.2%) had the highest SUCRA values of all PaTs. The SUCRA values of imiquimod, TCA, KOH, cryotherapy, and 5-FU ranged from 40% to 50%. The SUCRA value of polyphenon 15% was low at 13.1%.

**Sensitivity analyses**

Only polyphenon and podophyllin + TCA had a CI that included value 1 (Appendix S5).

Worst-case (intention to treat) scenario sensitivity analyses showed a superiority of surgery over podophyllotoxin 0.5% solution (RR 1.94; CI95% 1.00-3.76), $CO_2$ laser (RR 2.20; CI95% 1.05-4.60), electrosurgery (RR 2.28; CI95% 1.10-4.74), and cryotherapy + podophyllotoxin 0.5% cream (RR 2.68; CI95% 1.18-6.07). Ablative therapy + imiquimod was superior to imiquimod alone (RR 1.57; CI95% 1.01-2.44) and to cryotherapy (RR 1.74; CI95% 1.05-2.89). A superiority of podophyllotoxin 0.5% cream and podophyllotoxin 0.5% solution over cryotherapy was also found (RR 1.66; CI95% 1.04-2.66 and RR 1.52; CI95% 1.06-2.18, respectively) (Appendix S6).

Sensitivity analyses of SUCRA values confirmed the superiority of surgery and combination therapies. Worst-case scenario sensitivity analyses showed an increase in the efficacy of podophyllotoxin 0.5% cream and 0.5% solution (72.2% and 77.7%, respectively), as well as a decrease in the efficacy of electrosurgery due to the high number of patients lost to follow-up in the study by Stone et al.[62] (Appendix S7).

## DISCUSSION

In our NMA, ProTs—mainly surgery and electrosurgery—achieved the best CLR, with a median follow-up of 6 months. These results differ from our pooled analysis, which found higher clearance for ProTs but lower recurrence at 12 months for PaTs.[98] Few RCTs have used CLR as a study endpoint. This is unfortunate given that CLR, which assesses clearance until no recurrence, is more meaningful for patients undergoing treatment for AGWs. Combined with the more robust statistical methods of NMA, this endpoint yields more accurate results than pooled analyses. Cidofovir was ranked 4$^{th}$ in our SUCRA analysis. Yet, it is difficult to conclude on the efficacy of this treatment, as the only RCT on the topic found no significant difference with placebo use.

Our results are in line with the NMA of Thurgar et al,[13] which concluded to the superiority of ablative techniques. However, unlike us, Thurgar et al recommended $CO_2$ laser as first-line treatment. This difference may be explained by the fact that their NMA was restricted to 39 RCTs and included immunocompromised patients, whereas our NMA compared 49 RCTs and focused on non-immunocompromised adults. Moreover, Thurgar et al found that podophyllotoxin 0.5% solution was the most cost-effective therapeutic solution, followed by $CO_2$ laser. In our NMA, podophyllotoxin 0.5% solution achieved the best CLR among all PaTs.

Unlike systematic reviews on AGW management,[10,13,98] our NMA examined the efficacy of combination therapies, including ablative therapy + imiquimod, cryotherapy + podophyllotoxin 0.5% cream, and $CO_2$ laser + 5-FU. However, many combination therapies are missing from our NMA, including those most commonly recommended and used in practice: cryotherapy + imiquimod and cryotherapy +

podophyllotoxin 0.5% solution. Combination therapies should be given greater consideration and should be adapted as best as possible to individual patients.

Our search was limited by restrictions on access to Chinese databases, especially regarding treatments like PDT. While our NMA results suggest that this treatment is highly efficacious, they are based on only 1 RCT (note that numerous non-randomized studies on MEDLINE have yielded the same finding[99,100]). Other RCTs on PDT have likely been performed, but they remain inaccessible to the scientific community.

The management of AGWs is heterogeneous in terms of: the type of treatment used; the level of physician experience (for ProTs); the level of patient compliance (for PaTs); the clinical type of AGWs (papillary, flat, or pedunculated); the location of AGWs; and the sex of the patient.[101,102] Such heterogeneity renders more difficult the establishment of a clinically meaningful hierarchy of treatments. In our systematic review, more than 90% of RCTs were found to have a high risk of bias,[14] thus casting doubt on the validity of published recommendations. NMAs do not increase the level of evidence of risks of bias, as they remain dependent on the methodology of each RCT. But they do increase statistical power because they encompass all patients included in examined RCTs. Moreover, NMAs can be used to compare treatments that have never been compared before, to identify gaps in knowledge, and to help develop clinically meaningful hierarchies of treatments.[24]

Only 2 RCTs in our NMA compared a recommended ProT to a recommended PaT (imiquimod and cryotherapy in both cases).[59,91] Future RCTs should compare recommended ProTs and PaTs—for instance, cryotherapy vs. podophyllotoxin cream or solution; surgery vs. imiquimod; surgery vs. podophyllotoxin cream or solution;

$CO_2$ laser vs. imiquimod; and $CO_2$ laser vs. podophyllotoxin cream or solution. Moreover, combination therapies should be more thoroughly assessed to help increase the efficacy of AGW management, and to make it better adapted to the number, type, and location of AGWs. New treatments (KOH, PDT alone or as an adjuvant) should also be evaluated further. Although 5-FU was not mentioned in guidelines until 2019,[10] it could be proposed as a second-line treatment in the future.

Our systematic review and our NMA should be updated regularly. Side effects should be assessed to help physicians personalize treatments for their individual patients. Lastly, study endpoints and ProT use practices (e.g., standardization of freezing or surgical procedures) should be homogenized to allow better comparison of RCTs.

To conclude, in our NMA, surgery and electrosurgery achieved the best CLR, and podophyllotoxin 0.5% was the most efficacious patient-administered treatment.

## Abbreviations and acronyms

5-FU: 5-fluorouracil

AGW: Anogenital wart

CI: Confidence interval

CLR: Complete lesion response

INF: Interferon

KOH: Potassium hydroxide

NMA: Network meta-analysis

PDT: Photodynamic therapy

ProT: Provider-administered treatment

PaT: Patient-administered treatment

RCT: Randomized controlled trial

RR: Relative risk

SUCRA: Surface Under the Cumulative RAnking curve

TCA: Trichloroacetic acid



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## Authors' contributions

CD, BM, and ND conceptualized and designed the study. AB, CD, and CF

participated in the acquisition, analysis, and interpretation of data. AB and CD drafted the initial manuscript. LH, ND, and BM critically reviewed the manuscript. All authors read and approved the final manuscript.

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## Figure legends

**Fig. 1 Evidence network of eligible comparisons for complete lesion response in network meta-analysis.** The thickness of connecting lines represents the cumulative number of trials for each comparison, and the thickness of nodes is proportional to the number of enrolled participants. Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Fig. 2 Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response.**

Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Fig. 3 Net heat plot. Assessment of consistency between direct and indirect evidence.**

Horizontal: detached comparisons; vertical: comparisons observed in the network; warm color in the net heat plot indicates that significant inconsistency may arise from a specific comparison and this trend is illustrated by the intensity of the color; grey color: contribution of each direct comparison to the network estimates.

**Table Probabilities of treatment ranking.**

SUCRA: surface under the cumulative ranking curve; ablative treatment: surgery or electrosurgery or CO2 laser or cryotherapy; 5-FU: 5 fluorouracil; TCA: trichloroacetic acid; PDT: photodynamic therapy; KOH: potassium hydroxide; INF-1a: interferon-1α; INF-2b: interferon-2β.

## Supplement content

**Appendix S1.** Keywords used to search databases

**Appendix S2.** Characteristics of RCTs included

**Appendix S3**. Reason for exclusion

**Appendix S4**. Risk of bias assessment

**Appendix S5. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies.**

Treatments are reported in order of relative ranking for efficacy. Comparisons between treatments should be read from left to right. The relative risk of each comparison is in the cell in common between the column-defining treatment and the row-defining treatment. A relative risk (RR) above 1 favors the column-defining treatment for the network estimates and the row-defining treatment for the direct estimates. IFN = interferon. Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium

hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S6. Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response. Sensitivity analyses: (A) Worst-case scenario, (B) Best-case scenario.**

Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S7. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies. Sensitivity analyses: Intention to treat.**

Treatments are reported in order of relative ranking for efficacy. Comparisons between treatments should be read from left to right. The relative risk of each comparison is in the cell in common between the column-defining treatment and the row-defining treatment. A relative risk (RR) above 1 favors the column-defining

treatment for the network estimates and the row-defining treatment for the direct estimates. IFN = interferon. Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S8. Probabilities of treatment ranking. Sensitivity analyses: (A) Worst-case scenario, (B) Best-case scenario.**

SUCRA: surface under the cumulative ranking curve**.** Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

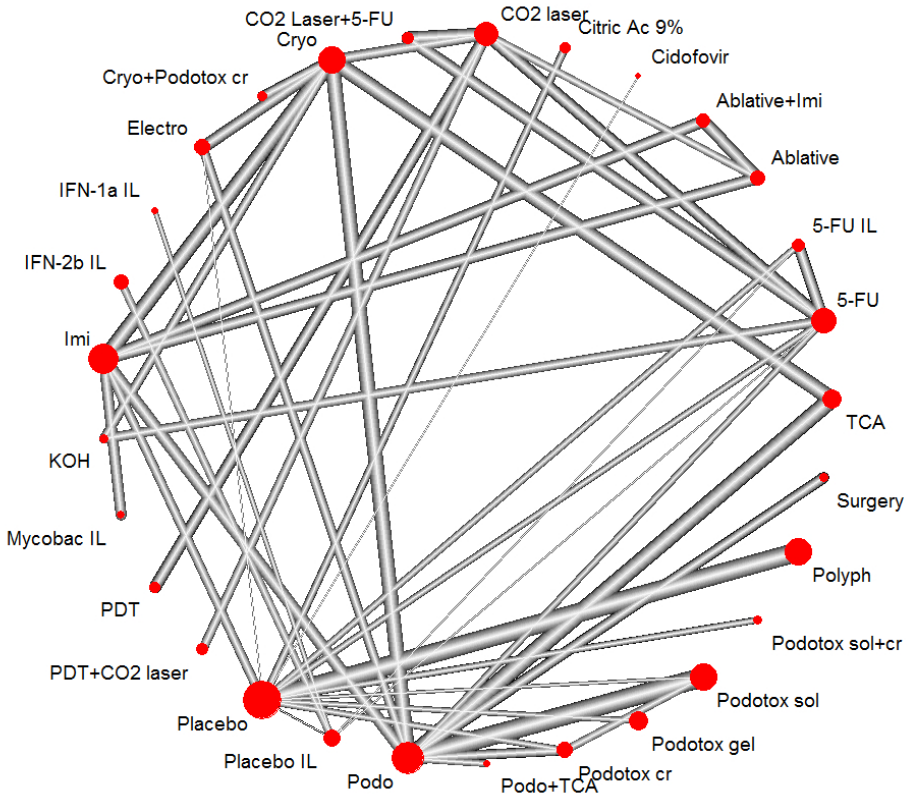


Fig. 1 Evidence network of eligible comparisons for complete lesion response in network meta-analysis. The thickness of connecting lines represents the cumulative number of trials for each comparison, and the thickness of nodes is proportional to the number of enrolled participants. Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

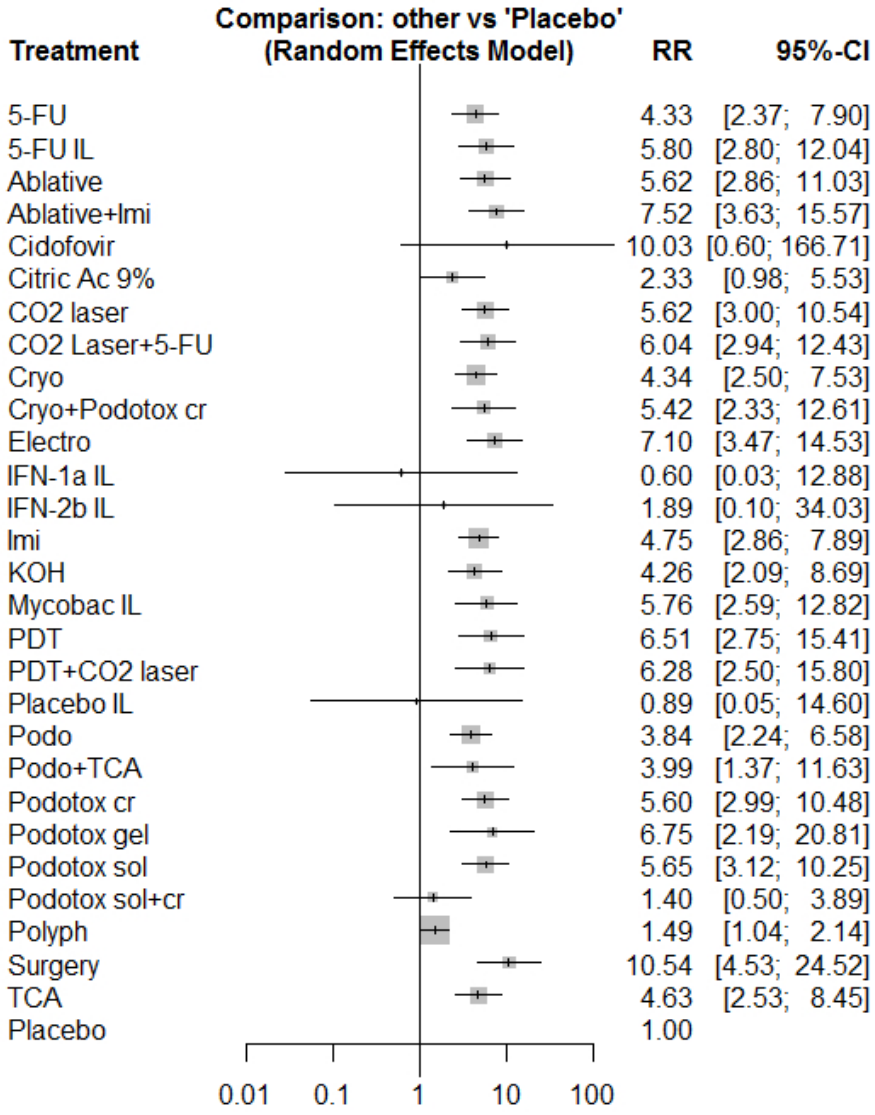


Fig. 2 Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response.
Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.


Fig. 3 Net heat plot. Assessment of consistency between direct and indirect evidence. Horizontal: detached comparisons; vertical: comparisons observed in the network; warm color in the net heat plot indicates that significant inconsistency may arise from a specific comparison and this trend is illustrated by the intensity of the color; grey color: contribution of each direct comparison to the network estimates.

**Table** Probabilities of treatment ranking

| | SUCRA | | SUCRA |
|---|---|---|---|
| Surgery | 0.909 | Imiquimod | 0.494 |
| Ablative therapy + Imiquimod | 0.798 | TCA | 0.480 |
| Electrosurgery | 0.771 | Podophyllin + TCA | 0.432 |
| Cidofovir | 0.710 | KOH | 0.430 |
| PDT | 0.707 | 5-FU | 0.426 |
| Podophyllotoxin 0.5% gel | 0.686 | Cryotherapy | 0.421 |
| PDT+$CO_2$ laser | 0.680 | Podophyllin 20-25% | 0.334 |
| $CO_2$ Laser+5-FU | 0.674 | Intralesional IFN-2b | 0.334 |
| Intralesional 5-FU | 0.642 | Citric Acid 9% | 0.232 |
| Podophyllotoxin 0.5% solution | 0.635 | Intralesional placebo | 0.163 |
| Intralesional mycobacterium | 0.632 | Podophyllotoxin 0.5% gel+cream | 0.132 |
| $CO_2$ laser | 0.626 | Polyphenon 15% | 0.131 |
| Podophyllotoxin 0.5% cream | 0.622 | Intralesional IFN-1a | 0.117 |
| Ablative therapy | 0.621 | Placebo | 0.066 |
| Cryotherapy + Podophyllotoxin 0.5% cream | 0.595 | | |

SUCRA: surface under the cumulative ranking curve; ablative treatment: surgery or electrosurgery or $CO_2$ laser or cryotherapy; 5-FU: 5 fluorouracil; TCA: trichloroacetic acid; PDT: photodynamic therapy; KOH: potassium hydroxide; INF-1a: interferon-1α; INF-2b: interferon-2β.

# To Supporting Information: Local management of anogenital warts in non-immunocompromised adults: a network meta-analysis of randomized controlled trials

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**Supplement content**

**Appendix S1.** Keywords used to search databases

**Appendix S2.** Characteristics of RCTs included

**Appendix S3**. Reason for exclusion

**Appendix S4**. Risk of bias assessment

**Appendix S5. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies.**

Treatments are reported in order of relative ranking for efficacy. Comparisons between treatments should be read from left to right. The relative risk of each comparison is in the cell in common between the column-defining treatment and the row-defining treatment. A relative risk (RR) above 1 favors the column-defining treatment for the network estimates and the row-defining treatment for the direct estimates. IFN = interferon. Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium

hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S6. Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response. Sensitivity analyses: (A) Worst-case scenario, (B) Best-case scenario.**

Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S7. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies. Sensitivity analyses: Intention to treat.**

Treatments are reported in order of relative ranking for efficacy. Comparisons between treatments should be read from left to right. The relative risk of each comparison is in the cell in common between the column-defining treatment and the row-defining treatment. A relative risk (RR) above 1 favors the column-defining

treatment for the network estimates and the row-defining treatment for the direct estimates. IFN = interferon. Data presented as RR (95% CI). Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S8. Probabilities of treatment ranking. Sensitivity analyses: (A) Worst-case scenario, (B) Best-case scenario.**

SUCRA: surface under the cumulative ranking curve**.** Cryo: cryotherapy; ablative: ablative treatment (surgery or electrosurgery or CO2 laser or cryotherapy); imi: imiquimod 5%; 5-FU: 5 fluorouracil; 5-FU intra: intralesional 5 fluorouracil; TCA: trichloroacetic acid; podo: podophyllin 20-25%; citric ac: citric acid 9%; polyph: polyphenon 15%; podotox cr: podophyllotoxin 0.5% cream; podotox cr/gel: podophyllotoxin 0.5% gel + cream: podotox gel: podophyllotoxin 0.5% gel; PDT: photodynamic therapy; mycobac intra: intralesional mycobacterium; KOH: potassium hydroxide; electro: electrosurgery; INF-1a intra: intralesional interferon-1α; INF-2b intra: intralesional interferon-2β.

**Appendix S1:** Search terms used to screen all databases

**MEDLINE and Web of Science**

1 hpv.all
2 papillomavirus.all.
3 acuminat*.all.
4 condyloma*.all.
5 wart*.all.
6 genital wart*.all.
7 or/1-6
8 randomized controlled trial.all.
9 controlled clinical trial.all.
10 random*.all.
11 placebo.all.
12 clinical trial*.all.
13 trial.all.
14 or/8-13
15 7 AND 14
16 hand.all.
17 foot.all.
18 feet.all.
19 animal*.all.
20 nonhuman*.all.
21 child*.all.
22 cancer*.all.
23 neoplasi*.all.
24 cervical.all.
25 laryn*.all.
26 vacci*.all.
27 tumor.all.
28 verruc*.all.
29 or/ 16-28
30 15 NOT 29

**SCOPUS.com**

#1.1 wart*:ab,ti
#1.2 condylom*:ab,ti
#1.3 acuminat*:ab,ti
#1.4 verruc*:ab,ti
#1.5 hpv:ab,ti
#1.6 papillomavirus*:ab,ti
#1.7 genital wart* :ab.ti
#1.8 condylomata acuminata : ab.ti
#1.9 wart virus:ab.ti
#1.10 #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9
#1.11 clinical trial:ab,ti
#1.12 random*:ab,ti
#1.13 randomized controlled trial;ab,ti
#1.14 controlled clinical:ab,ti
#1.15 placebo*:ab,ti

#1.16 trial:ab,ti
#1.17 #1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR #1.16
#1.18 #1.10 AND #1.17
#1.19 hand:ab,ti
#1.20 foot:ab,ti
#1.21 feet:ab,ti
#1.22 animal*:ab,ti
#1.23 nonhuman*:ab,ti
#1.24 child*:ab,ti
#1.25 cancer*:ab,ti
#1.26 neoplasi*:ab,ti
#1.27 cervical:ab,ti
#1.28 laryn*:ab,ti
#1.29 vacci*:ab,ti
#1.30 tumor:ab,ti
#1.31 verruc*:ab,ti
#1.32 #1.19 OR #1.20 OR #1.21 OR #1.22 OR #1.23 OR #1.24 OR #1.25 OR #1.26 OR #1.27 OR #1.28 OR #1.29 OR #1.30 OR #1.31
#1.33 #1.18 AND NOT #1.32

**LILACS**
(tw:(condylom*)) AND (tw:(Randomi*))

**Ovid Platform**
(condyloma OR acuminat OR wart) AND (clinical trial OR trial OR randomized trial OR randomized controlled trial OR controlled clinical OR placebo OR Randomized OR randomly)

**Cochrane Library**
(condyloma OR acuminata OR wart ) and (randomized controlled trial OR controlled clinical trial OR random OR placebo OR clinical trial) not (hand OR foot OR feet OR animal OR nonhuman OR child OR cancer OR neoplasia OR cervical OR laryn OR vacci OR tumor OR verruc) in Trials

**Cochrane Register and International Clinical Trials Registry Platform (ICTRP):**
Using the terms: warts, condylomas, condyloma, genital warts in title, abstract and keywords.

**Clinical Trials**
Wart OR condylomas OR condyloma OR genital warts OR acuminata

**EM-PREMIUM bibliography from 2010 in title and abstract:**
English and french request: condylo*
English request: anogenital wart*
French request: verrue anogénitale*

**Open Grey, SUDOC (title) and BABORD + bibliography (in French):**
Condylome
Verrue

**Appendix S2:** Characteristics of RCTs included

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Abdullah 1993[1] | UK | Cryo | 53 (43) | 1×/wk, maximum 6 wk | Applied with a cotton Q-tip until wart is frozen with 1-mm margin, 2× | 3 | Clearance after 6 wk, side effects | 1st treatment |
| | | TCA | 33 (30) | Same | A pointed plastic probe | | | |
| Akhavan 2014[2] | Iran | Podophyllin 20% | 42 (38) | 1×/wk, maximum 8 wk | NR | 8 | Clearance after 8 wk, recurrence after 3 mo, recurrence after 6 mo | 1st treatment, only women |
| | | Imiquimod | 42 (37) | 3×/wk, maximum 8 wk | Same | | | |
| | | Cryo | 42 (36) | 1×; no other information given | Same | | | |
| Arican 2004[3] | Turkey | Imiquimod 5% | 34 (33) | 3×/wk, maximum 12 wk | Applied with the tip of the stick and then cleaned with abundant amounts of water | 9 | Clearance after 3 mo, recurrence after 6 mo, side effects | ITT modified |
| | | Placebo | 11 (10) | Same | Same | | | |
| Azizjalali 2012[4] | Iran | $CO_2$ laser | 80 (80) | 1× every 2 wk, maximum 6 wk | Local anesthesia, 30 W, 10,600 nm, 4.5 J/cm$^2$ | 3 | Clearance after 6 wk, recurrence after 3 mo, side effects | ITT |
| | | Cryo | 80 (80) | Same | 2 freezing cycles | | | |
| Baker 2011[5] | USA | Imiquimod 2.5% | 202 (139) | 1×/d for 8 wk | Wash after 8 hr | 4 | Clearance after 4 mo, side effects | ITT, only women |
| | | Imiquimod 3.75% | 204 (149) | Same | Same | | | |
| | | Placebo | 105 (77) | Same | Same | | | |
| Benedetti Panici 1989[6] | Italy | Electro | 51 (51) | Until apparent elimination of the genital wart, interval: 3 wk | Local anesthesia, diathermocoagulation with bipolar electrodes | 12 | Clearance after 1 mo, recurrence after 2.6 mo, side effects | ITT, only women, some patients with AGWs on cervix; IFN arm (data not shown) |
| | | Placebo | 48 (48) | NR | NR | | | |
| Beutner 1989[7] | USA | Podophyllotoxin 0.5% gel | 56 (56) | 2×/d, 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 6 wk, recurrence after 10 wk, side effects, new warts | ITT, only men |
| | | Placebo | 53 (53) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Beutner 1998[8] | USA | Imiquimod 5% | 94 (69) | 1×/d, maximum 16 wk | Wash after 8 hr with soap and water | 7 | Clearance after 8, 12, 16 wk, recurrence after 3 mo, side effects, partial clearance, time for complete clearance, new warts | ITT |
| | | Imiquimod 1% | 90 (71) | Same | Same | | | |
| | | Placebo | 95 (67) | Same | Same | | | |
| Bilensoy 2011[9] | Turkey | Placebo | 6 (6) | 3×/wk, 1 wk/2, maximum 12 wk | Applied with a cotton-tipped swab | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance | ITT, only women; both 5-FU arms used with cyclodextrin thermosensitive gel |
| | | 5-FU cream | 14 (14) | Same | Same | | | |
| | | Placebo intra-lesional | 6 (6) | Same | NR | | | |
| | | 5-FU intra-lesional | 18 (18) | Same | Same | | | |
| Bornstein 1997[10] | Israel | IFNβ-1a intra-lesional 1 MIU | 30 (30) | 3×/wk, maximum 3 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, partial clearance, time to complete clearance | ITT |
| | | Placebo intra-lesional | 30 (30) | Same | Same | | | |
| Camargo 2014[11] | Brazil | KOH | 24 (20) | 1×/d, maximum 12 wk | Applied with a cotton wrapped toothpick | 3 | Clearance after 12 wk, recurrence after 1 mo, side effects, time to complete clearance | 1st treatment, only men |
| | | Cryo | 24 (22) | Every 2 wk, maximum 12 wk | Freezing 1× 5-20 s | | | |
| Carpiniello 1988[12] | NR | $CO_2$ laser | 41 (NR) | NR | | 4 | Clearance after treatment, recurrence after 4 mo | Only men |
| | | $CO_2$ laser + 5-FU | 27 (NR) | 5-FU every night maximum 30 d | 5-FU initiated 1 wk after $CO_2$ laser | | | |
| Chen 2007[13] | China | $CO_2$ laser | 21 (21) | 1×/wk for 3 wk if not removed | topical anesthesia with 2% lidocaine | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | ITT, no quantification for side effects |
| | | PDT | 65 (65) | Same | ALA dissolved in sterile 0.9% NaCl just before application, 3 hr before light illumination (632 nm) | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Claesson 1996[14] | Sweden, Finland, France | Podophyllotoxin 0.15% cream | 60 (60) | 2×/d for 3 consecutive d, maximum 4 wk | | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT |
| | | Podophyllotoxin 0.3% cream | 60 (60) | Same | | | | |
| | | Podophyllotoxin 0.5% sol | 60 (60) | Same | | | | |
| Duus 1985[15] | Denmark | $CO_2$ laser | 25 (21) | 1×, maximum 2× | Continuous wave (5-20 W), spot diameter of 0-7 mm | 6 | Clearance after treatment, recurrence after 3 mo, side effects | |
| | | Ablative treatment (surgery, Electro) | 25 (23) | 1×, maximum 2× | NR | | | |
| Edwards 1998[16] | Multicentric: Hawaii, New York, Pennsylvania & Canada | Imiquimod 5% | 109 (90) | 3×/wk for 16 wk | Wash after 6-10 hr with soap and water | 7 | Clearance after 4 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Imiquimod 1% | 102 (71) | Same | Same | | | |
| | | Placebo | 100 (73) | Same | Same | | | |
| Edwards 1988[17] | UK | Podophyllotoxin 0.5% sol | 32 (32) | 2×/d for 3 consecutive d, maximum 6 wk | Self-applied | 6 | Clearance after 6 wk, side effects | ITT, only men |
| | | Podophyllin 20% | 19 (19) | 1×/wk, maximum 6 wk | Provider-applied | | | |
| Eron 1986[18] | USA | IFNα-2b (1 MIU) intra-lesional | 147 (125) | NR | NR | 7 | Clearance after 4,16 wk; recurrence after 3 mo, side effects | |
| | | Placebo intra-lesional | 149 (132) | Same | Same | | | |
| Gabriel 1983[19] | UK | Podophyllin 25% | 38 (29) | 1×/wk, maximum 6 wk | Applied with the tip of the stick | 3 | Clearance after 6 wk, recurrence after 6 wk, side effect, time to complete clearance | Only men |
| | | Podophyllin 25% + TCA 50% | 35 (31) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Gilson 2009[20] | UK | Cryo + placebo | 75 (40) | Cream 2×/d for 3 consecutive d, maximum 4 wk, Cryo: 45-s freezing/wk, maximum 12 wk | NR | 9 | Clearance after 3 mo, recurrence after 3 mo, side effects | ITT modified |
| | | Cryo + podophyllotoxin 0.15% cream | 74 (31) | Same | Same | | | |
| Godley 1987[21] | UK | TCA | 69 (57) | 1×/wk maximum 10 wk | Applied with an orange stick | 4,5 | Clearance after 10 wk; recurrence after 2 mo, side effects, time to complete clearance | Only men |
| | | Cryo | 61 (49) | Same | Freeze for 15 sec twice | | | |
| Greenberg 1991[22] | USA | Podophyllotoxin 0.5% sol & cream | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with a cotton tip | | Clearance after 4 wk; recurrence after 2 mo, distinctive side effects for gel & cream, new warts | ITT modified, only women |
| | | Placebo | 24 (21) | Same | Same | | | |
| Gross 2007[23] | Germany & Russia | Polyphenon 15% | 80 (46) | 3×/d, maximum 16 wk | NR | 6 | Clearance after 12 wk, recurrence after 3 mo, side effects | |
| | | Polyphenon 10% | 79 (36) | Same | Same | | | |
| | | Placebo | 83 (31) | Same | Same | | | |
| Hellberg 1995[24] | Sweden | Podophyllotoxin 0.5% cream | 30 (28) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | Only women |
| | | Podophyllin 20% | 30 (27) | 1×/wk, maximum 4 wk | Wash 4 hr after application | | | |
| Isik 2014[25] | Turkey | KOH | 30 (30) | 1×/d for 12 wk | Perilesional application of Vaseline | 6 | Clearance after 3 mo, recurrence after 3 mo, partial clearance | ITT |
| | | 5-FU + salicylic acid | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Jensen 1985[26] | Denmark | Podophyllin 25% | 30 (30) | 1×/wk, maximum 6 wk | Wash after 6 hr | 12 | Clearance after 4 wk; recurrence after 1.5, 4.5, 10.5 mo; side effects, time to complete clearance | ITT |
| | | Surgery | 30 (30) | Same | Local anesthesia with lignocaine | | | |
| Keay 1988[27] | USA | IFNα cream | 32 (31) | 3×/d, maximum 4 wk | Applied topically by gentle 30-s rubbing | 4 | Clearance after 4, 16 wk, side effects | ITT modified, only women |
| | | Placebo | 33 (30) | Same | Same | | | |
| Khawaja 1989[28] | UK | Podophyllin 25% | 19 (19) | 1×/wk, maximum 6 wk | Wash after 6 hr | 10.5 | Clearance after 6 wk, recurrence after 3, 9 mo; side effect, time to complete clearance | ITT, 1st treatment |
| | | Surgery | 18 (18) | 1× | Local anesthesia with lignocaine | | | |
| Kinghorn 1993[29] | UK | Podophyllotoxin 0.5% sol | 168 (138) | 2×/d for 3 consecutive d, maximum 5 wk | | 3 | Clearance after 54 wk; recurrence after 2 mo, side effects | |
| | | Podophyllin 25% | 84 (62) | 2×/wk, maximum 5 wk | Wash off after 4 hr | | | |
| Kirby 1990[30] | USA | Podophyllotoxin 0.5% sol | 19 (19) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT |
| | | Placebo | 19 (19) | Same | Same | | | |
| Komericki 2011[31] | Austria | Podophyllotoxin 0.5% sol | 26 (25) | 2×/d for 3 consecutive d, maximum 4 wk | NR | 4 | Clearance after 4 wk for podophyllotoxin and 16 wk for imiquimod, side effects | 1st treatment |
| | | Imiquimod 5% | 25 (20) | 3×/wk maximum 16 wk | Same | | | |
| Kumar 2014[32] | India | Imiquimod 5% | 44 (41) | 3×/wk, maximum 16 wk | Intradermal injections of the Mw vaccine and vehicle on both shoulders at baseline to sensitize and improve local immune response to intralesional therapy | 8 | Clearance after 20 wk; recurrence after 3 mo, side effects, time to complete clearance, partial clearance | ITT |
| | | *Mycobacterium* intra-lesional | 45 (39) | Every 2 wk, maximum 16 wk | – | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Lacey 2003[33] | UK | Podophyllin 25% | 116 (96) | 2×/wk, maximum 4 wk | In the clinic | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects, cost/efficacy ratio | |
| | | Podophyllotoxin 0.15% cream | 118 (82) | 2×/d for 3 consecutive d, maximum 4 wk | NR | | | |
| | | Podophyllotoxin 0.5% sol | 120 (98) | Same | Same | | | |
| Lassus 1987[34] | Finland | Podophyllotoxin 0.5% sol | 48 (48) | 2×/d for 3 consecutive d, maximum 4 wk | At home | 3 | Clearance after 4 wk; recurrence after 2 mo | ITT, only men |
| | | Podophyllin 20% | 52 (52) | 1×/wk, maximum 4 wk | In the clinic | | | |
| Lotfabadi 2015[35] | Iran | Cryo | 34 (34) | Every 2 wk, maximum 12 wk | Freeze with 1-mm margin, 10-15 s | 6 | Clearance 1 mo after 12 wk of treatment; recurrence after 2 mo; side effects | |
| | | TCA | 34 (34) | Same | Applied by an applicator then washed | | | |
| Mahajan 2014[36] | India | Cryo + podophyllin 20% | 30 (24) | Cryo once & podo every 2 wk | Cryo: freezing with a 5-mm margin from a distance of 2-mm<br>Podo: Wash 3 hr after therapy | 6 | Clearance after 8,12, 24 wk; recurrence after 1 mo; side effects; time to complete clearance | |
| | | Bleomycin + placentrex intra-lesional | 30 (25) | Bleomycin every 2 wk, maximum 10 wk; placentrex every night | After bleomycin, ice water soaks twice daily for 4 d | | | |
| Mazurkiewicz 1990[37] | Poland | Podophyllin 20% | 16 (13) | Once/wk, maximum 6 wk | Doctor-applied | 1,5 | Clearance after 6 wk, side effects | |
| | | Podophyllotoxin 0.5% sol | 16 (14) | 2×/d for 3 consecutive d, maximum 6 wk | Patient-applied | | | |
| | | Podophyllotoxin 0.5% cream | 22 (16) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Nath 1990[38] | India | Podophyllin 25% | 50 (47) | 1×/wk, maximum 12 wk | Wash after 2 hr | 6 | Clearance after 3 mo, recurrence after 3 mo, time to complete clearance | Incompletely randomization (pregnant women got TCA) |
| | | TCA 50% | 50 (48) | Same | Applied with a swab stick | | | |
| On 2014[39] | USA | Polyphenon 15% + cryo | 21 (NR) | Polyphenon: 2×/d, maximum 16 wk; Cryo: 1× | Cryo: 2 5-s cycles/5-s interval rest | 16 | Clearance after 9 & 17 wk, side effects, partial clearance | ITT |
| | | Cryo | 21 (NR) | 1× | Same | | | |
| Ormerod 2015[40] | Germany, UK, Holland, Switzerland, Poland: 40 centers | Placebo | 75 (74) | 2×/d for 12 wk | Sodium nitrite was applied first, then citric acid, & the 2 creams were mixed. | 6 | Clearance after 3 mo, recurrence after 3 mo, side effects, time to complete clearance | |
| | | Sodium nitrite 3% + citric acid 4.5% | 74 (72) | 2×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 77 74) | 1×/d for 12 wk | Same | | | |
| | | Sodium nitrite 6% + citric acid 9% | 73 (70) | 2×/d for 12 wk | Same | | | |
| Padhiar 2006[41] | India | Imiquimod 5% | 30 (30) | 3×/wk, maximum 16 wk | Wash after 6-10 hr | 10 | Clearance after 4 mo, recurrence after 3 & 6 mo, side effects, partial clearance, time to complete clearance | ITT |
| | | Podophyllin 20% | 30 (30) | 1×/wk, maximum 6 wk | Applied with a swab stick, wash after 4-6 hr | | | |
| Petersen 1995[42] | Denmark | Podophyllotoxin 0.5% sol | 18 (18) | 2×/d for 3 consecutive d, maximum 4 wk | Fingertip application | 3 | Clearance after 6 wk, recurrence after 6 wk, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 18 (18) | Same | Same | | | |
| Reichman 1988[43] | USA | IFNα-n1 intra-lesional | 17 (15) | 3×/wk, maximum 4 wk | NR | 12 | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | IFNβ (1 MIU) intra-lesional | 20 (20) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Reichman 1988[43](continued) | | IFNα-2b intra-lesional | 23 (23) | Same | Same | | Clearance after 5, 10 & 15 wk, side effects; time to complete clearance | |
| | | Placebo intra-lesional | 19 (18) | Same | Same | | | |
| Relakis 1996[44] | Brazil & Greece | $CO_2$ laser | 71 (71) | 1× | Applied Vaseline & $ZnO_2$ 10% cream | 12 | Clearance after 3 mo, recurrence after 3, 6 & 9 mo, side effects | ITT, only men |
| | | 5-FU | 218 (218) | 5×/wk, maximum 4 wk | Applied Vaseline 5% $ZnO_2$, before 5-FU | | | |
| | | $CO_2$ laser + 5-FU | 47 (47) | Both | Both | | | |
| Schofer 2006[45] | Germany | Ablative procedure (Electro, Cryo, laser, surgery) | 100 (100) | 1×/wk, maximum 4 wk | NR | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | ITT |
| | | Imiquimod 5% | 155 (155) | 3×/d, maximum 16 wk | Same | 6 | Clearance after 4 wk, recurrence after 3 & 6 mo, side effects | |
| | | Ablative procedure + imiquimod | 103 (103) | Both | Same | | | |
| Sherrard 2007[46] | UK | Podophyllin 25% | 79 (56) | Times/wk NR, but maximum 8 wk | NR | 2 | Clearance after 8 wk, side effects | |
| | | TCA | 88 (58) | Same | Same | | | |
| | | Cryo | 81 (66) | Same | Same | | | |
| | | TCA + Podophyllin | 85 (65) | Same | Same | | | |
| | | Cryo + Podophyllin | 76 (59) | Same | Same | | | |
| Simmons 1981[47] | UK | Cryo | 24 (16) | 1× every 2 wk, maximum 12 wk | Produced 2-mm ice-balls larger than wart | 3 | Clearance after 12 wk | |
| | | Electro | 18 (11) | 1× every 2 wk, maximum 12 wk | 2% lignocaine anesthesia | | | |
| Snoeck 2001[48] | Belgium | Cidofovir | 19 (19) | 1×/d, 5 d/wk, 1 wk/2 for 12 wk | Applied with a cotton tipped swab or a rubber glove | | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance | ITT |
| | | Placebo | 11 (11) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Stefanaki 2008[49] | Greece | Imiquimod | 60 (35) | 3×/wk, maximum 12 wk | NR | 12 | Clearance after 4, 8,12 & 24 wk, recurrence after 9 mo, side effects | 1st treatment |
| | | Cryo | 60 (45) | 1× every 3 wk, maximum 12 wk | Frozen 1× for 10-20 s | | | |
| Stockfelth 2008[50] | Multicentric (Europe, South Africa) | Polyphenon 15% | 201 (161) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 3 mo, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | ITT modified |
| | | Polyphenon 10% | 199 (170) | Same | Same | | | |
| | | Placebo | 103 (80) | Same | Same | | | |
| Stone 1990[51] | USA | Podophyllin (dose NR) | 144 (53) | Times/week NR, but maximum 6 wk | NR | 5 | Clearance after 6 wk, recurrence after 3 mo, side effects | |
| | | Cryo | 154 (60) | 1×/wk, maximum 6 wk | Each AGW was frozen 1× | | | |
| | | Electro | 152 (51) | Same | 1% lidocaine anesthesia | | | |
| Strand 1995[52] | Sweden | Podophyllotoxin 0.15% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Applied with an applicator | 4 | Clearance after 4 wk; recurrence after 3 mo, side effects | ITT, only men |
| | | Podophyllotoxin 0.3% cream | 31 (31) | Same | Same | | | |
| | | Podophyllotoxin 0.5% sol | 29 (29) | Same | NR | | | |
| Swinehart 1997[53] | USA | 5-FU injection intra-lesional | 80 (78) | 1×/wk, maximum 6× over 8 wk | NR | 5 | Clearance after 8 wk, recurrence after 3 mo, side effects, partial clearance, time to complete clearance | Individual lesion analysis |
| | | 5-FU | 80 (76) | NR | Same | | | |
| | | Placebo | 40 (33) | Same | Same | | | |
| Syed 1998[54] | Pakistan | Imiquimod 2% | 30 (30) | 2×/d for 5 consecutive d, maximum 6 wk | Wash & dry warts before each application and apply | 4 | Clearance after 6 wk, recurrence after 2.5 mo, side effects | ITT, only women, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Syed 1995 (a)[55] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, recurrence after 9 mo, side effects | ITT, only men, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1995 (b)[56] | Pakistan | IFNα cream | 20 (20) | 3×/d for 3 consecutive d, maximum 4 wk | Applied with a finger cot | 4 | Clearance after 4 wk, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 20 (20) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 1994[57] | Pakistan | Podophyllotoxin 0.3% cream | 30 (30) | 2×/d for 3 consecutive d, maximum 4 wk | Let dry for at least 1 min without washing | 4 | Clearance after 4 wk, recurrence after 3 mo, side effects | ITT, only women, individual lesion analysis |
| | | Podophyllotoxin 0.5% cream | 30 (30) | Same | Same | | | |
| | | Placebo | 20 (20) | Same | Same | | | |
| Syed 2000[58] | Pakistan | Imiquimod 2% | 30 (30) | 3 consecutive d, maximum 4 wk | Applied with a finger cot | 18 | Clearance after 16 wk, recurrence after 18 mo, side effects | ITT, only men, individual lesion analysis |
| | | Placebo | 30 (30) | Same | Same | | | |
| Szeimies 2009[59] | Germany | PDT + $CO_2$ laser | 84 (84) | 1× | PDT: 100 J/cm$^2$, 100 mW/cm$^2$ (640-740 nm) occlusion for 4-6 hr | 12 | Clearance after treatment, recurrence after 1, 2, 3, 6 & 12 mo, side effects, satisfaction | ITT |
| | | $CO_2$ laser | 91 (91) | Same | Continuous wave, defocused beam (2-mm diameter), 10-20 W, general or local anesthesia | | | |
| Tabari 2010[60] | Iran | Podophyllin 20% | 60 (60) | 2×/wk | Wash after 20 min | 6 | Clearance after 4 or 8 wk, recurrence after 3 mo, side effects | ITT |
| | | TCA 30% | 60 (60) | NR | With a topical cotton soap and washed after 1 min | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Tatti 2008[61] | USA, Europe, S Africa multicenter | Polyphenon 15% | 196 (159) | 3×/d, maximum 16 wk | NR | 7 | Clearance after 16 wk, recurrence after 3 mo, side effects, partial clearance | ITT modified |
| | | Polyphenon 10% | 202 (162) | Same | Same | | | |
| | | Placebo | 104 (83) | Same | Same | | | |
| Tyring 1998 (a)[62] | USA | Imiquimod 5% | 18 (16) | 3×/wk, maximum 16 wk | Applied with cotton swab tip | 4 | Clearance after 16 wk, side effects, partial clearance | |
| | | Placebo | 4 (3) | Same | Same | | | |
| Tyring 1998 (b)[63] | USA | Placebo | 107 (95) | 2×/d for 3 consecutive d, maximum 8 wk | NR | 4 | Clearance after 4 & 8 wk, recurrence after 3 mo, side effects | |
| | | Podophyllotoxin 0.5% gel | 219 (197) | Same | Same | | | |
| Vance 1986[64] | USA | IFNα-2b (1 MIU) intra-lesional | 37 (30) | 3×/wk, maximum 3 wk | NR | 3 | Clearance after 4, 5, 7 & 12 wk, side effects, partial clearance | ITT |
| | | IFNα-2b (0.1 MIU) intra-lesional | 38 (32) | Same | Same | | | |
| | | Placebo intra-lesional | 39 (29) | Same | Same | | | |
| von Krogh 1992[65] | Sweden | Placebo | 12 (11) | 2×/d, 3 d/wk for 2 wk | NR | 3 | Clearance after 3 wk, recurrence after 2 mo, side effects | |
| | | Podophyllotoxin 0.5% cream | 48 (44) | Same | Same | | | |
| von Krogh 1994[66] | Sweden | Podophyllotoxin 0.25% sol | 19 (18) | 2×/d, 3 d/wk for 2 wk | Applied with wool swabs | 6 | Clearance after 3 wk, recurrence after 2 & 6 mo, side effects | 1st treatment |
| | | Podophyllotoxin 0.5% sol | 19 (16) | Same | Same | | | |
| | | Placebo | 19 (17) | Same | Same | | | |
| Wallin 1977[67] | Sweden | 5-FU | 21 (18) | 1×/d for 2 wk | Applied with cotton swab tip | 9 | Clearance after 4 wk, recurrence after 6 mo, side effects | Only men |
| | | Podophyllin 25% sol | 21 (19) | 1×/wk for 4 wk | Provider-applied, wash 4-6 hr later | | | |

Appendix S2: Characteristics of RCTs included (continued)

| Reference | Country | Intervention | No. of Patients randomized (analyzed) | Frequency | Modalities | Follow-Up (mo) | Outcomes | Comments |
|---|---|---|---|---|---|---|---|---|
| Weismann 1982[68] | Denmark | 5-FU | 30 (30) | 2×/wk for women, once/d for men | NR | 2 | Clearance after 8 wk, side effects, partial clearance, time to complete clearance | ITT |
| | | Placebo | 29 (29) | Same | Same | | | |
| Welander 1990[69] | USA | IFNα-2b (1 MIU) intra-lesional | 20 (16) | 3×/wk, maximum 3 wk | NR | NR | Clearance after 4 or 15 wk, side effects | |
| | | Placebo intra-lesional | 22 (21) | Same | Same | | | |
| White 1997[70] | UK | Podophyllotoxin 0.5% sol | 106 (77) | 2×/d for 3 consecutive d, maximum 12 wk | NR | 3 | Clearance after 5 wk, side effects | ITT, only men, 1st treatment |
| | | Podophyllin 0.5% | 103 (86) | Same | Same | | | |
| | | Podophyllin 2% | 106 (81) | Same | Same | | | |

Abbreviations: ITT, intention-to-treat; NR, not reported; KOH, potassium hydroxide; ALA, 5-aminolaevulinic acid; Mw, *Mycobacterium* w; Sol, solution; PDT, photodynamic therapy; Electro, electrosurgery; Cryo, cryotherapy; IFN, interferon.

**Appendix S3:** Reason for exclusion

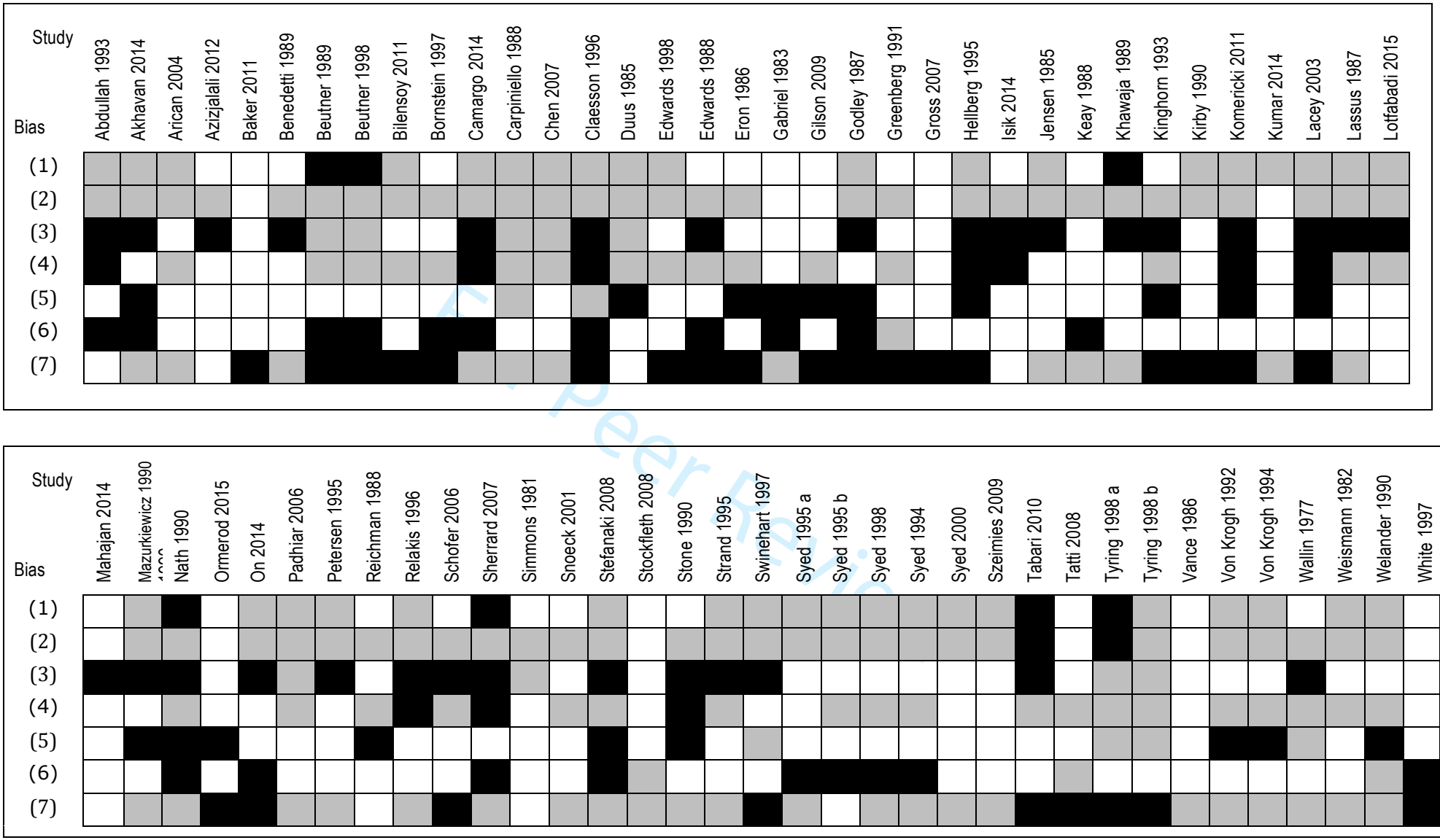
| 1st Author | Year | Exclusion Criteria |
|---|---|---|
| Alfonso-Trujillo[71] | 2008 | not RCT |
| Alfonso-Trujillo[72] | 2008 | not RCT |
| Alfonso-Trujillo[73] | 2009 | not RCT |
| Alfonso-Trujillo[74] | 2009 | not RCT |
| Arany[75] | 1999 | duplicate of Tyring[62] |
| Armstrong[76] | 1996 | another treatment not considered herein |
| Bar-Am[77] | 1993 | dose escalation |
| Bashi[78] | 1985 | not RCT |
| Beutner[79] | 1998 | duplicate of Beutner[8] |
| Beutner[80] | 1995 | duplicate of Beutner[8] |
| Botacini[81] | 1993 | other localization |
| Buck[82] | 2002 | not RCT |
| Chen[83] | 2009 | missing data (no English translation of Chinese) |
| Chopra[84] | 1997 | duplicate of Tyring[62] |
| Collaborative Study Group[85] | 1991 | another treatment not considered herein |
| Collaborative Study Group[86] | 1993 | another treatment not considered herein |
| Damstra[87] | 1991 | missing data |
| Davidson-Parker[88] | 1988 | another treatment not considered herein |
| Dinsmore[89] | 1997 | not RCT |
| Douglas[90] | 1990 | HIV |
| Edwards[91] | 1998 | duplicate of Edwards[17] |
| Edwards[92] | 1995 | duplicate of Edwards[17] |
| Eron[93] | 1993 | another treatment not considered herein |
| Ferenczy[94] | 1998 | duplicate of Edwards[17] |
| Ferenczy[95] | 1995 | HIV |
| Fife[96] | 2001 | dose escalation |
| Fleshner[97] | 1994 | another treatment not considered herein |
| Fouere[98] | 2014 | missing data |
| Garland[99] | 2006 | dose escalation |
| Garland[100] | 2001 | not RCT |
| Goh[101] | 1998 | dose escalation |
| Gollnick[102] | 2001 | dose escalation |
| Gross[103] | 1996 | another treatment not considered herein |
| Gross[104] | 1998 | another treatment not considered herein |
| Handley[105] | 1991 | another treatment not considered herein |
| Handley[106] | 1992 | missing data (randomization unclear) |
| Hohenleutner[107] | 1990 | another treatment not considered herein |
| Hoy[108] | 2012 | not RCT |
| IRCT2017011531949N1[109] | 2017 | missing data (recruiting) |
| IRCT2015090514386N1[110] | 2015 | missing data (not recruiting) |
| IRCT2013111015364N1[111] | 2014 | missing data (not recruiting) |
| IRC 201202138992N1[112] | 2012 | not RCT |
| IRCT201412207848N1[113] | 2014 | not RCT |
| Jardine[114] | 2012 | another treatment not considered herein |
| Klutke[115] | 1995 | another treatment not considered herein |
| Lafuma[116] | 2003 | duplicate of Tyring[62] and Edwards[17] |
| Landthaler[117] | 1987 | HIV |
| Langley[118] | 2010 | not RCT |
| Lassus[119] | 1984 | duplicate of Lassus[34] |
| Li[120] | 2011 | dose escalation |
| Liang[121] | 2009 | missing data (condyloma analysis) |

**Appendix S3:** Continued

| | | |
|---|---|---|
| Liu[122] | 2012 | missing data (condyloma analysis) |
| Maiti[123] | 1985 | dose escalation |
| Maw[124] | 2002 | not RCT |
| Mazurkiewicz[125] | 1990 | missing data (not accessible) |
| Meltzer[126] | 2009 | not RCT and duplicate of Stockfleth[49] |
| Metawea[127] | 2005 | not RCT |
| Mi[128] | 2011 | missing data (condyloma analysis) |
| Mistrangelo[129] | 2010 | another treatment not considered herein |
| Monsonego[130] | 1996 | missing data (condyloma analysis) |
| NCT00674739[131] | 2011 | duplicate of Baker[5] |
| NCT00735462[132] | 2011 | duplicate of Baker[5] |
| NCT02520986[133] | 2016 | missing data (not recruiting) |
| NCT02724254[134] | 2016 | missing data (recruiting) |
| NCT01796821[135] | 2017 | missing data (recruiting) |
| NCT03153566[136] | 2017 | missing data (recruiting) |
| NCT01943630[137] | 2017 | missing data (recruiting) |
| NCT02849262[138] | 2016 | missing data (recruiting) |
| NCT02462187[139] | 2015 | missing data (not recruiting) |
| NCT02482428[140] | 2015 | missing data (not recruiting) |
| NCT02147353[141] | 2014 | missing data (not recruiting) |
| NCT02015260[142] | 2013 | missing data (not recruiting) |
| Nieminen[143] | 1994 | another treatment not considered herein |
| Owens[144] | 1999 | duplicate of Edwards[17] |
| Potocnik[145] | 1997 | missing data (not accessible) |
| Rosen[146] | 2015 | missing data (no placebo data) |
| Sauder[147] | 2003 | duplicate from of Edwards[17] |
| Sharma[148] | 2017 | missing data (condyloma analysis) |
| Shi[149] | 2013 | not RCT |
| Stefanaki[150] | 2014 | missing data |
| Stellato[151] | 1997 | another treatment not considered herein |
| Swinehart[152] | 1997 | duplicate from Swinehart[53] |
| Syed[153] | 2002 | missing data (not accessible) |
| Syed[154] | 1994 | other localization |
| Syed[155] | 1993 | dose escalation |
| Trofatter[156] | 2002 | dose escalation |
| Tuncel[157] | 2005 | missing data |
| Urban[158] | 2006 | missing data (not accessible) |
| Vesterinen[159] | 1984 | other localization |
| Viazis[160] | 2007 | HIV and other localization |
| von Krogh[161] | 1981 | not RCT |
| Xu[162] | 2009 | missing data (no English translation of Chinese) |
| Yaghoobi[163] | 2014 | not RCT |
| Yin[164] | 1998 | another treatment not considered herein |
| Yu[165] | 2004 | another treatment not considered herein |
| Zarcone[166] | 1996 | not RCT |
| Zervoudis[167] | 2010 | another treatment not considered herein |

Abbreviations: RCT: randomized-controlled trial; HIV: human immunodeficiency virus

**Appendix S4.** Risk of bias assessment (Bertolotti et al. *J Am Acad Dermatol* 2019.pii:S0190-9622(19)30525-0)



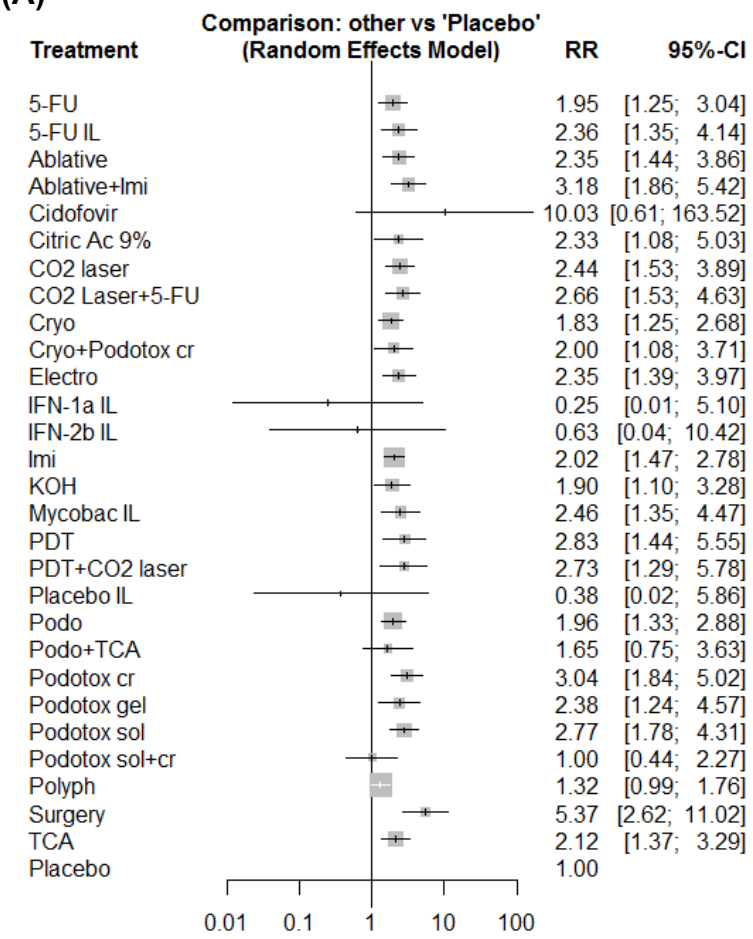

White square: low; grey square: uncertain; black square: high; (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); (7) Other bias.

## Appendix S5. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies.

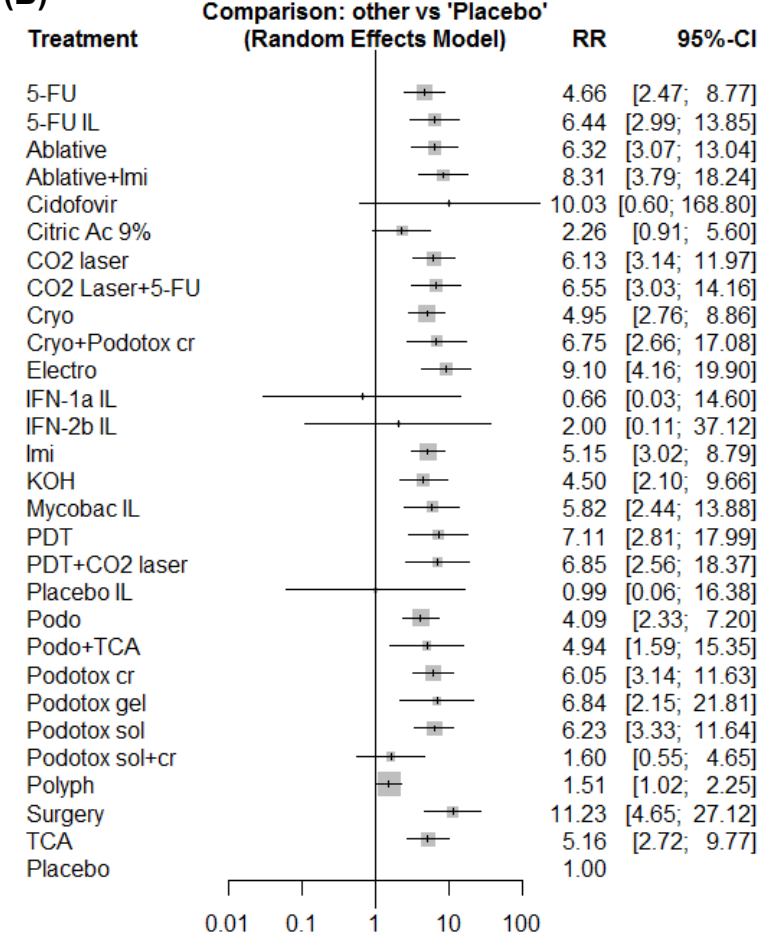
| | Surgery | Ablative+Imi | Electro | Cidofovir | PDT | Podotox gel | PDT+CO2 lase | CO2 Laser+5-F | Podotox sol | Mycobac IL | CO2 laser | Podotox cr | Ablative | ryo+Podotox | Imi | TCA | KOH | 5-FU | Cryo | Polyph |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Surgery** | | | | | | | | | | | | | | | | | | | | |
| **Ablative+Imi** | 1.40 [0.56; 3.52] | | | | | | | | | | | | 1.36 [0.78; 2.40] | | 1.55 [0.88; 2.73] | | | | | |
| **Electro** | 1.48 [0.63; 3.47] | 1.06 [0.48; 2.35] | | | | | | | | | | | | | | | | | 1.21 [0.68; 2.14] | |
| **Cidofovir** | 1.05 [0.06; 19.79] | 0.75 [0.04; 13.68] | 0.71 [0.04; 12.88] | | | | | | | | | | | | | | | | | |
| **PDT** | 1.62 [0.59; 4.46] | 1.15 [0.47; 2.83] | 1.09 [0.45; 2.67] | 1.54 [0.08; 29.12] | | | | | | | 1.16 [0.64; 2.09] | | | | | | | | | |
| **Podotox gel** | 1.56 [0.38; 6.38] | 1.11 [0.29; 4.25] | 1.05 [0.28; 3.99] | 1.49 [0.07; 30.68] | 0.96 [0.23; 3.98] | | | | | | | | | | | | | | | |
| **PDT+CO2 laser** | 1.68 [0.58; 4.87] | 1.20 [0.46; 3.11] | 1.13 [0.44; 2.93] | 1.60 [0.08; 30.75] | 1.04 [0.42; 2.54] | 1.07 [0.25; 4.61] | | | | | 1.12 [0.57; 2.19] | | | | | | | | | |
| **CO2 Laser+5-FU** | 1.74 [0.71; 4.32] | 1.24 [0.57; 2.74] | 1.18 [0.54; 2.55] | 1.66 [0.09; 30.23] | 1.08 [0.51; 2.30] | 1.12 [0.29; 4.26] | 1.04 [0.46; 2.38] | | | | 1.31 [0.80; 2.16] | | | | | | | 1.14 [0.65; 2.00] | | |
| **Podotox sol** | 1.86 [0.90; 3.87] | 1.33 [0.65; 2.73] | 1.26 [0.67; 2.37] | 1.77 [0.10; 31.38] | 1.15 [0.50; 2.66] | 1.19 [0.33; 4.27] | 1.11 [0.45; 2.73] | 1.07 [0.53; 2.16] | | | | 1.00 [0.47; 2.13] | | | | | | | | |
| **Mycobac IL** | 1.83 [0.69; 4.88] | 1.31 [0.57; 2.97] | 1.23 [0.52; 2.95] | 1.74 [0.09; 32.37] | 1.13 [0.42; 3.06] | 1.17 [0.29; 4.67] | 1.09 [0.38; 3.11] | 1.05 [0.43; 2.56] | 0.98 [0.44; 2.18] | | | | | | 1.21 [0.65; 2.25] | | | | | |
| **CO2 laser** | 1.88 [0.82; 4.28] | 1.34 [0.68; 2.63] | 1.26 [0.64; 2.48] | 1.78 [0.10; 31.81] | 1.16 [0.64; 2.09] | 1.20 [0.33; 4.36] | 1.12 [0.57; 2.19] | 1.08 [0.67; 1.73] | 1.01 [0.55; 1.83] | 1.02 [0.46; 2.28] | | | 0.94 [0.45; 1.96] | | | | | 0.75 [0.42; 1.35] | **2.40 [1.29; 4.46]** | |
| **Podotox cr** | 1.88 [0.83; 4.25] | 1.34 [0.61; 2.95] | 1.27 [0.61; 2.61] | 1.79 [0.10; 31.88] | 1.16 [0.47; 2.86] | 1.21 [0.33; 4.37] | 1.12 [0.43; 2.93] | 1.08 [0.50; 2.34] | 1.01 [0.60; 1.68] | 1.03 [0.44; 2.42] | 1.00 [0.51; 1.98] | | | | | | | | | |
| **Ablative** | 1.88 [0.78; 4.50] | 1.34 [0.78; 2.31] | 1.26 [0.60; 2.66] | 1.79 [0.10; 32.16] | 1.16 [0.52; 2.60] | 1.20 [0.32; 4.47] | 1.12 [0.47; 2.68] | 1.08 [0.54; 2.16] | 1.01 [0.52; 1.95] | 1.03 [0.46; 2.26] | 1.00 [0.58; 1.74] | 1.00 [0.48; 2.08] | | | 1.14 [0.64; 2.02] | | | | | |
| **Cryo+Podotox cr** | 1.95 [0.74; 5.14] | 1.39 [0.56; 3.42] | 1.31 [0.57; 3.00] | 1.85 [0.10; 34.86] | 1.20 [0.45; 3.21] | 1.25 [0.30; 5.10] | 1.16 [0.41; 3.26] | 1.12 [0.46; 2.68] | 1.04 [0.47; 2.30] | 1.06 [0.40; 2.80] | 1.04 [0.47; 2.27] | 1.03 [0.44; 2.44] | 1.04 [0.44; 2.43] | | | | | | 1.25 [0.66; 2.37] | |
| **Imi** | **2.22 [1.04; 4.76]** | 1.58 [0.92; 2.73] | 1.50 [0.81; 2.76] | 2.11 [0.12; 36.76] | 1.37 [0.63; 2.99] | 1.42 [0.41; 4.89] | 1.32 [0.57; 3.08] | 1.27 [0.67; 2.42] | 1.19 [0.72; 1.97] | 1.21 [0.65; 2.25] | 1.18 [0.71; 1.97] | 1.18 [0.65; 2.14] | 1.18 [0.72; 1.94] | 1.14 [0.54; 2.41] | | | | | 0.95 [0.59; 1.53] | |
| **TCA** | **2.28 [1.09; 4.75]** | 1.62 [0.81; 3.25] | 1.53 [0.85; 2.78] | 2.17 [0.12; 38.41] | 1.41 [0.63; 3.14] | 1.46 [0.41; 5.23] | 1.36 [0.57; 3.24] | 1.31 [0.67; 2.54] | 1.22 [0.76; 1.96] | 1.24 [0.57; 2.70] | 1.21 [0.70; 2.10] | 1.21 [0.67; 2.19] | 1.21 [0.65; 2.27] | 1.17 [0.56; 2.43] | 1.03 [0.64; 1.64] | | | | 1.10 [0.71; 1.71] | |
| **KOH** | **2.48 [1.02; 6.01]** | 1.77 [0.79; 3.93] | 1.67 [0.79; 3.51] | 2.35 [0.13; 42.81] | 1.53 [0.65; 3.59] | 1.59 [0.42; 6.01] | 1.48 [0.59; 3.68] | 1.42 [0.71; 2.84] | 1.33 [0.67; 2.62] | 1.35 [0.56; 3.27] | 1.32 [0.71; 2.45] | 1.32 [0.62; 2.80] | 1.32 [0.63; 2.74] | 1.27 [0.55; 2.96] | 1.11 [0.59; 2.09] | 1.09 [0.58; 2.05] | | 0.95 [0.49; 1.84] | 1.02 [0.50; 2.07] | |
| **5-FU** | **2.44 [1.07; 5.56]** | 1.74 [0.85; 3.57] | 1.64 [0.83; 3.26] | 2.32 [0.13; 41.05] | 1.50 [0.71; 3.17] | 1.56 [0.44; 5.59] | 1.45 [0.64; 3.28] | 1.40 [0.84; 2.32] | 1.31 [0.72; 2.37] | 1.33 [0.59; 3.02] | 1.30 [0.82; 2.05] | 1.29 [0.66; 2.54] | 1.30 [0.69; 2.45] | 1.25 [0.56; 2.80] | 1.10 [0.64; 1.88] | 1.07 [0.61; 1.87] | 0.98 [0.58; 1.68] | | | |
| **Cryo** | **2.43 [1.17; 5.03]** | 1.73 [0.92; 3.27] | 1.64 [0.97; 2.76] | 2.31 [0.13; 40.54] | 1.50 [0.71; 3.15] | 1.56 [0.44; 5.45] | 1.45 [0.64; 3.26] | 1.39 [0.77; 2.53] | 1.30 [0.82; 2.06] | 1.33 [0.64; 2.74] | 1.29 [0.82; 2.04] | 1.29 [0.73; 2.29] | 1.29 [0.74; 2.26] | 1.25 [0.66; 2.37] | 1.09 [0.75; 1.60] | 1.07 [0.75; 1.51] | 0.98 [0.57; 1.70] | 1.00 [0.61; 1.62] | | |
| **Polyph** | **7.07 [2.82; 17.72]** | **5.04 [2.24; 11.37]** | **4.76 [2.13; 10.63]** | 6.73 [0.40; 114.51] | **4.37 [1.72; 11.12]** | **4.53 [1.39; 14.78]** | **4.22 [1.57; 11.35]** | **4.05 [1.81; 9.09]** | **3.79 [1.89; 7.61]** | **3.86 [1.61; 9.30]** | **3.77 [1.82; 7.79]** | **3.76 [1.82; 7.75]** | **3.77 [1.75; 8.10]** | **3.63 [1.45; 9.12]** | **3.19 [1.71; 5.94]** | **3.11 [1.54; 6.27]** | **2.86 [1.28; 6.36]** | **2.90 [1.44; 5.86]** | **2.91 [1.51; 5.63]** | |

**Appendix S6. Forest plot of the estimates of relative risk between each treatment and the reference placebo for complete lesion response. Sensitivity analyses: (A) Worst case scenario, (B) Best case scenario.**

**(A)**




**(B)**



**Appendix S7. Network meta-analysis estimates (lower triangle) and direct estimates (upper triangle) of complete lesion response for all therapies. Sensitivity analyses, worst-case scenari**

| | Surgery | Cidofovir | Ablative+Imi | Podotox cr | Podotox sol | PDT | CO2 Laser+5-F | PDT+CO2 lase | CO2 laser | Mycobac IL | Electro | Podotox gel | Ablative | TCA | Cryo+Podotox | Imi | 5-FU | KOH | Cryo | Polyph |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Surgery** | | | | | | | | | | | | | | | | | | | | |
| **Cidofovir** | 0.54 [0.03; 9.57] | | | | | | | | | | | | | | | | | | | |
| **Ablative+Imi** | 1.69 [0.76; 3.77] | 3.15 [0.18; 54.11] | | | | | | | | | | | 1.36 [0.86; 2.16] | | | 1.55 [0.98; 2.45] | | | | |
| **Podotox cr** | 1.77 [0.85; 3.69] | 3.30 [0.19; 56.24] | 1.05 [0.55; 1.99] | | 1.00 [0.51; 1.97] | | | | | | | | | | | | | | | |
| **Podotox sol** | **1.94 [1.00; 3.76]** | 3.62 [0.21; 61.05] | 1.15 [0.64; 2.04] | 1.10 [0.71; 1.70] | | | | | | | | | | | | | | | | |
| **PDT** | 1.90 [0.78; 4.60] | 3.54 [0.20; 62.60] | 1.12 [0.54; 2.33] | 1.07 [0.51; 2.27] | 0.98 [0.49; 1.95] | | | | 1.16 [0.71; 1.89] | | | | | | | | | | | |
| **CO2 Laser+5-F** | 2.02 [0.90; 4.50] | 3.76 [0.22; 64.81] | 1.19 [0.63; 2.27] | 1.14 [0.60; 2.18] | 1.04 [0.58; 1.86] | 1.06 [0.56; 2.00] | | | 1.34 [0.88; 2.05] | | | | | | | | 1.14 [0.72; 1.80] | | | |
| **PDT+CO2 lase** | 1.97 [0.77; 5.06] | 3.67 [0.20; 66.14] | 1.16 [0.52; 2.60] | 1.11 [0.49; 2.53] | 1.02 [0.47; 2.18] | 1.04 [0.48; 2.22] | 0.98 [0.48; 2.00] | | 1.12 [0.62; 2.01] | | | | | | | | | | | |
| **CO2 laser** | **2.20 [1.05; 4.60]** | 4.11 [0.24; 69.62] | 1.30 [0.75; 2.25] | 1.25 [0.71; 2.20] | 1.14 [0.70; 1.85] | 1.16 [0.71; 1.89] | 1.09 [0.73; 1.64] | 1.12 [0.62; 2.01] | | | | | 1.00 [0.55; 1.83] | | | | 0.75 [0.46; 1.22] | | **2.40 [1.42; 4.06]** | |
| **Mycobac IL** | 2.19 [0.93; 5.11] | 4.08 [0.23; 70.90] | 1.29 [0.66; 2.53] | 1.24 [0.61; 2.50] | 1.13 [0.59; 2.15] | 1.15 [0.51; 2.60] | 1.08 [0.52; 2.24] | 1.11 [0.46; 2.67] | 0.99 [0.52; 1.91] | | | | | | | 1.21 [0.73; 2.01] | | | | |
| **Electro** | **2.28 [1.10; 4.74]** | 4.26 [0.25; 72.98] | 1.35 [0.72; 2.53] | 1.29 [0.73; 2.29] | 1.18 [0.73; 1.91] | 1.20 [0.58; 2.48] | 1.13 [0.61; 2.12] | 1.16 [0.52; 2.57] | 1.04 [0.61; 1.78] | 1.04 [0.52; 2.08] | | | | | | | | | 1.09 [0.70; 1.71] | |
| **Podotox gel** | 2.25 [0.85; 5.96] | 4.21 [0.24; 74.02] | 1.33 [0.57; 3.10] | 1.28 [0.56; 2.91] | 1.16 [0.53; 2.56] | 1.19 [0.47; 3.03] | 1.12 [0.48; 2.63] | 1.15 [0.42; 3.10] | 1.02 [0.46; 2.28] | 1.03 [0.43; 2.50] | 0.99 [0.43; 2.28] | | | | | | | | | |
| **Ablative** | **2.28 [1.05; 4.93]** | 4.26 [0.25; 72.51] | 1.35 [0.87; 2.10] | 1.29 [0.70; 2.37] | 1.18 [0.69; 2.01] | 1.20 [0.62; 2.33] | 1.13 [0.64; 2.01] | 1.16 [0.55; 2.43] | 1.04 [0.66; 1.63] | 1.04 [0.55; 1.99] | 1.00 [0.56; 1.80] | 1.01 [0.45; 2.29] | | | | 1.14 [0.71; 1.83] | | | | |
| **TCA** | **2.53 [1.30; 4.94]** | 4.73 [0.28; 79.81] | 1.50 [0.86; 2.62] | 1.43 [0.88; 2.35] | 1.31 [0.89; 1.92] | 1.33 [0.69; 2.60] | 1.26 [0.72; 2.19] | 1.29 [0.61; 2.71] | 1.15 [0.73; 1.81] | 1.16 [0.62; 2.17] | 1.11 [0.70; 1.75] | 1.12 [0.51; 2.47] | 1.11 [0.67; 1.85] | | | | | | 1.08 [0.76; 1.56] | |
| **Cryo+Podotox** | **2.68 [1.18; 6.07]** | 5.01 [0.29; 87.35] | 1.59 [0.79; 3.20] | 1.52 [0.77; 2.98] | 1.38 [0.76; 2.53] | 1.41 [0.65; 3.09] | 1.33 [0.66; 2.67] | 1.36 [0.58; 3.19] | 1.22 [0.66; 2.25] | 1.23 [0.57; 2.62] | 1.17 [0.63; 2.21] | 1.19 [0.48; 2.92] | 1.18 [0.61; 2.28] | 1.06 [0.60; 1.86] | | | | | 1.09 [0.67; 1.78] | |
| **Imi** | **2.65 [1.34; 5.25]** | 4.95 [0.30; 82.24] | **1.57 [1.01; 2.44]** | 1.50 [0.92; 2.44] | 1.37 [0.92; 2.04] | 1.40 [0.74; 2.64] | 1.32 [0.78; 2.22] | 1.35 [0.66; 2.76] | 1.21 [0.80; 1.82] | 1.21 [0.73; 2.01] | 1.16 [0.73; 1.86] | 1.18 [0.57; 2.43] | 1.16 [0.78; 1.74] | 1.05 [0.72; 1.52] | 0.99 [0.56; 1.74] | | | | 1.04 [0.73; 1.49] | |
| **5-FU** | **2.75 [1.32; 5.76]** | 5.14 [0.30; 86.80] | 1.63 [0.91; 2.90] | 1.56 [0.89; 2.74] | 1.42 [0.87; 2.31] | 1.45 [0.78; 2.69] | 1.37 [0.90; 2.07] | 1.40 [0.70; 2.81] | 1.25 [0.86; 1.82] | 1.26 [0.65; 2.44] | 1.21 [0.70; 2.08] | 1.22 [0.55; 2.69] | 1.21 [0.72; 2.02] | 1.09 [0.68; 1.73] | 1.03 [0.55; 1.92] | 1.04 [0.68; 1.58] | | 1.05 [0.59; 1.87] | | |
| **KOH** | **2.83 [1.29; 6.20]** | 5.28 [0.31; 90.85] | 1.67 [0.87; 3.21] | 1.60 [0.85; 3.01] | 1.46 [0.84; 2.55] | 1.49 [0.73; 3.04] | 1.40 [0.79; 2.51] | 1.44 [0.66; 3.15] | 1.29 [0.77; 2.16] | 1.29 [0.63; 2.65] | 1.24 [0.68; 2.25] | 1.26 [0.54; 2.94] | 1.24 [0.68; 2.26] | 1.12 [0.66; 1.89] | 1.06 [0.54; 2.05] | 1.07 [0.64; 1.77] | 1.03 [0.65; 1.62] | | 1.06 [0.60; 1.90] | |
| **Cryo** | **2.94 [1.52; 5.67]** | 5.48 [0.33; 91.73] | **1.74 [1.05; 2.89]** | **1.66 [1.04; 2.66]** | **1.52 [1.06; 2.18]** | 1.55 [0.84; 2.86] | 1.46 [0.88; 2.40] | 1.49 [0.74; 3.00] | 1.33 [0.92; 1.94] | 1.34 [0.75; 2.41] | 1.29 [0.86; 1.92] | 1.30 [0.61; 2.77] | 1.29 [0.82; 2.02] | 1.16 [0.87; 1.54] | 1.09 [0.67; 1.78] | 1.11 [0.83; 1.48] | 1.07 [0.72; 1.59] | 1.04 [0.66; 1.63] | | |
| **Polyph** | **4.07 [1.88; 8.83]** | 7.60 [0.46; 125.86] | **2.41 [1.32; 4.42]** | **2.31 [1.30; 4.11]** | **2.10 [1.24; 3.56]** | **2.15 [1.03; 4.46]** | **2.02 [1.08; 3.77]** | 2.07 [0.93; 4.62] | **1.85 [1.07; 3.20]** | 1.86 [0.96; 3.62] | 1.78 [0.98; 3.24] | 1.81 [0.89; 3.68] | **1.79 [1.01; 3.16]** | 1.61 [0.95; 2.72] | 1.52 [0.77; 3.00] | **1.54 [1.00; 2.36]** | 1.48 [0.87; 2.51] | 1.44 [0.78; 2.67] | 1.39 [0.86; 2.24] | |

**Appendix S8. Probabilities of treatment ranking. Sensitivity analyses: (A) Worst case scenario, (B) Best case scenario.**

**(A)**

| | SUCRA |
|---|---|
| Surgery | 0.949 |
| Cidofovir | 0.856 |
| Ablative+Imi | 0.802 |
| Podotox cr | 0.777 |
| Podotox sol | 0.727 |
| PDT | 0.712 |
| CO2 Laser+5-FU | 0.685 |
| PDT+CO2 laser | 0.677 |
| CO2 laser | 0.617 |
| Mycobac IL | 0.612 |
| Electro | 0.585 |
| 5-FU IL | 0.583 |
| Podotox gel | 0.582 |
| Ablative | 0.581 |
| Citric Ac 9% | 0.566 |
| TCA | 0.492 |
| Cryo+Podotox cr | 0.450 |
| Imi | 0.440 |
| 5-FU | 0.408 |
| Podo | 0.407 |
| KOH | 0.399 |
| Cryo | 0.339 |
| Podo+TCA | 0.338 |
| IFN-2b IL | 0.250 |
| Polyph | 0.190 |
| Podotox sol+cr | 0.150 |
| Placebo IL | 0.131 |
| Placebo | 0.105 |
| IFN-1a IL | 0.091 |

**(B)**

| | SUCRA |
|---|---|
| Surgery | 0.890 |
| Electro | 0.829 |
| Ablative+Imi | 0.787 |
| PDT | 0.693 |
| Cidofovir | 0.689 |
| PDT+CO2 laser | 0.668 |
| Cryo+Podotox cr | 0.663 |
| CO2 Laser+5-FU | 0.658 |
| Podotox gel | 0.647 |
| 5-FU IL | 0.643 |
| Ablative | 0.633 |
| Podotox sol | 0.631 |
| CO2 laser | 0.616 |
| Podotox cr | 0.606 |
| Mycobac IL | 0.578 |
| TCA | 0.495 |
| Podo+TCA | 0.495 |
| Imi | 0.489 |
| Cryo | 0.457 |
| 5-FU | 0.421 |
| KOH | 0.415 |
| IFN-2b IL | 0.330 |
| Podo | 0.329 |
| Citric Ac 9% | 0.211 |
| Placebo IL | 0.167 |
| Podotox sol+cr | 0.148 |
| Polyph | 0.127 |
| IFN-1a IL | 0.122 |
| Placebo | 0.062 |

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## IV CONCLUSION :

Ce travail apporte des éléments objectifs, établis à l'aide de méthodes scientifiques, à partir d'essais cliniques randomisés existants pour éclairer le choix des rédacteurs de futures recommandations française, européenne et internationale.

La prise en charge des condylomes ano-génitaux externes repose sur de très nombreuses possibilités thérapeutiques pour laquelle une hiérarchie précise est délicate. Le haut risque de biais de la grande majorité des essais, limite très largement une prise de position claire et précise dans une hiérarchisation. Ce haut risque de biais concerne de multiples essais cliniques récents alors que les premières recommandations méthodologiques de type CONSORT datent de 1996(33).

Avec ces réserves, ce travail met en valeur la supériorité des thérapeutiques destructrices telles que la chirurgie ou l'éléctrochirurgie, mais qui nécessitent une anesthésie. Le laser $CO_2$, apparaît dans certaines analyses, supérieur à plusieurs autres traitements, mais l'analyse médico-économique devant le coût de son acte, reste à évaluer. Dans les traitements auto-administrés par les patients eux-mêmes, la podophyllotoxine 0.5%, de préférence en solution, semble la plus efficace. Cependant, tout comme l'imiquimod, le risque d'inobservance dans les suites d'effets secondaires induits par ces thérapeutiques est élevé. La cryothérapie reste un pivot dans la prise en charge de cette pathologie, mais l'évaluation de sa reproductibilité d'un praticien à un autre est difficile. Ce travail, comparé aux précédents, met au jour, de nouvelles thérapeutiques qui n'apparaissaient pas jusqu'à 2019 dans les recommandations (KOH, 5-FU). La place de la photothérapie dynamique reste aussi à définir.

Ce travail se poursuivra par la réalisation de méta-analyses en réseau sur les effets secondaires afin d'essayer de hiérarchiser les thérapeutiques selon ce critère de jugement. La réalisation de telles analyses sur des sous populations (sexe, type de condylomes et localisations) permettraient également de mieux adapter le type de thérapeutique. Une analyse médico-économique selon le point de vue de l'assurance maladie française pourrait,

mieux orienter les cliniciens d'un point de vue santé publique. Enfin la réalisation de nouveaux essais cliniques randomisés à la lumière des traitements combinés, pourrait permettre de mieux les appréhender dans la prise en charge de cette pathologie en attendant que la vaccination vienne profiler la diminution nette de cette infection sexuellement transmissible.

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