



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.

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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. CO₂ 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 CO₂ 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.

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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, CO₂ 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

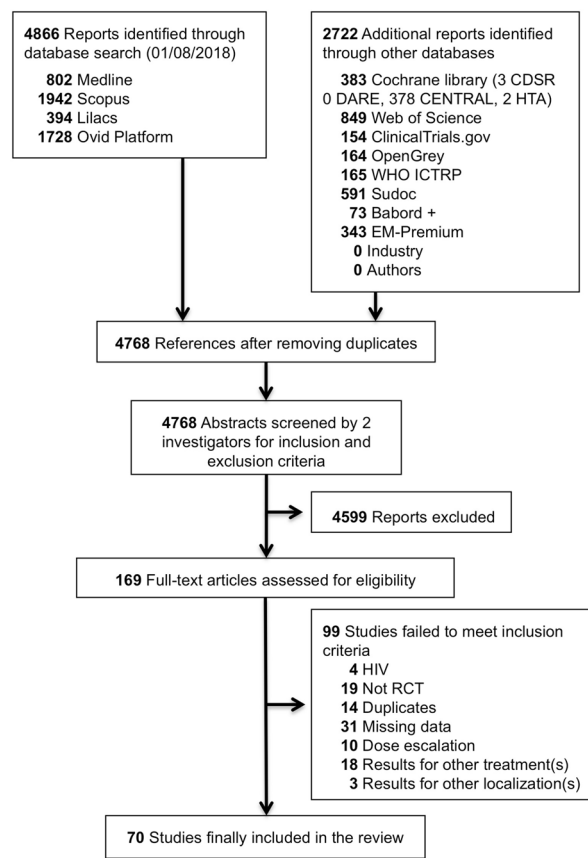
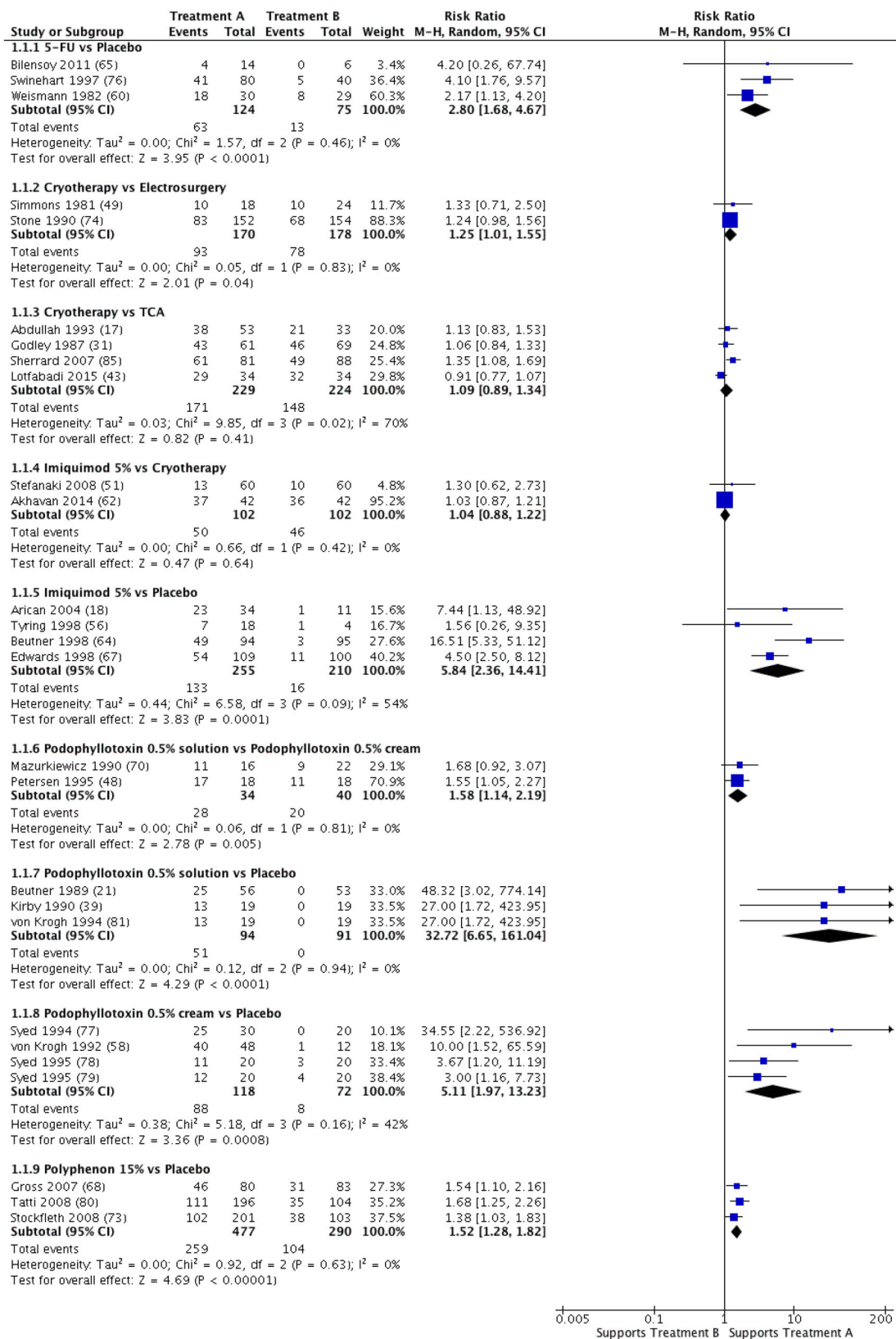


Fig. 1 Flow diagram of randomized controlled trials (RCTs) selected for treatment of anogenital warts. *CDSR* Cochrane Database of Systematic Reviews, *DARE* Database of Abstract of Reviews of Effects, *HTA* Health Technology Assessment, *WHO ICTRP* World Health Organization International Clinical Trials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

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).

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



◀**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 CO₂ 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.

CO₂ Laser

One RCT ($n = 50$) found no differences in clearance between CO₂ laser and ablative procedures [26]. In another RCT ($n = 289$) [71], 5-FU was associated with higher clearance and with less erosion than CO₂ laser, but no differences in recurrence were found. In a third RCT ($n = 160$) [19], CO₂ 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 CO₂ laser to CO₂ 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 CO₂ 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.

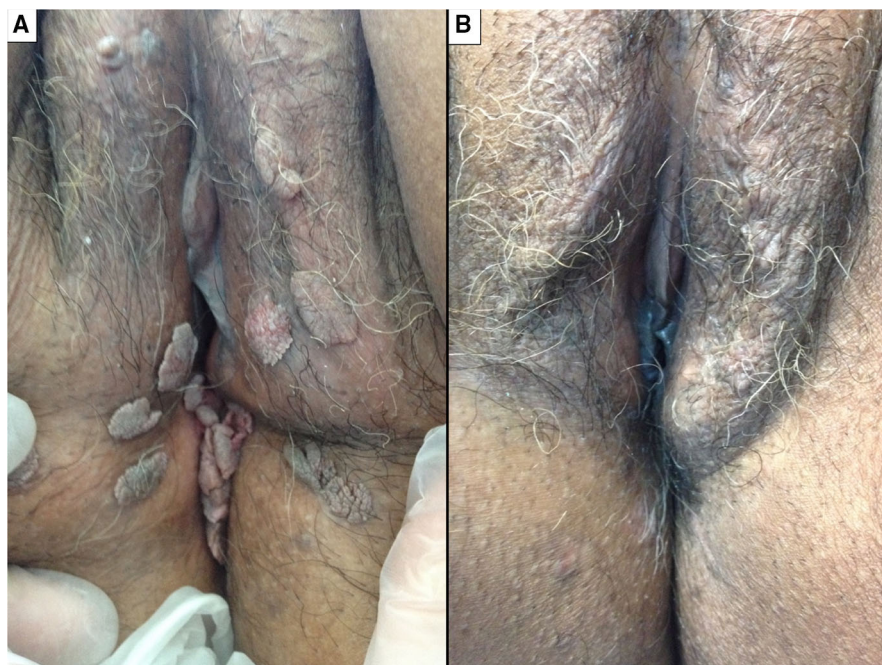


Fig. 3 Efficacy of cryotherapy in one patient before (a) and after (b) four sessions at 1-month intervals

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. CO₂ 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 CO₂ 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 electro-surgery and CO₂ laser are slightly more efficacious than cryotherapy, but that CO₂ 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 CO₂ 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, CO₂ 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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