Self-administered interventions for anogenital warts in immunocompetent patients: A systematic review and meta-analysis

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Online Supplement

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Abbreviations

AE – adverse events

GRADE – Grading of Recommendations Assessment, Development and Evaluation

MID – minimal important difference

SIGN – Scottish Intercollegiate Guidelines Network

1. Methods

1.1. Search strategy

A comprehensive literature search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and MEDLINE on March 3rd, 2016, from inception of the databases through the date of the search. The search included terms for disease specification combined with terms for the interventions of interest to be searched in the titles and abstracts. Additionally, MeSH-terms were used in MEDLINE and CENTRAL, and Emtree terms in Embase. In Embase and MEDLINE, the Scottish Intercollegiate Guidelines Network (SIGN) filters for RCTs[1] were used.

Detailed search strategy as used in Medline:

1. Randomized Controlled Trials as Topic/
2. randomized controlled trial/
3. Random Allocation/
4. Double Blind Method/
5. Single Blind Method/
6. clinical trial/
7. clinical trial, phase i.pt.
8. clinical trial, phase ii.pt.
9. clinical trial, phase iii.pt.
10. clinical trial, phase iv.pt.
11. controlled clinical trial.pt.
12. randomized controlled trial.pt.
13. multicenter study.pt.
14. clinical trial.pt.
15. exp Clinical Trials as topic/
16. or/1-15
17. (clinical adj trial$).tw.
18. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
19. PLACEBOS/
20. placebo$.tw.
21. randomly allocated.tw.
22. (allocated adj2 random$).tw.
23. or/17-22
24. 16 or 23
25. case report.tw.
26. letter/
27. historical article/
28. or/25-27
29. 24 not 28
30. exp Papillomavirus infection/
31. HPV.ab,ti.
32. (papillomavirus or "papilloma virus").ab,ti.
33. wart$.ab,ti.
34. or/30-33
35. anogenital.ab,ti.
36. anal.ab,ti.
37. genital.ab,ti.
38. genitoanal.ab,ti.
39. vulva$.ab,ti.
40. perianal.ab,ti.
41. vagina$.ab,ti.
42. (penis or penile).ab,ti.
43. scrotal.ab,ti.
44. mucocutaneous.ab,ti.
45. venereal.ab,ti.
46. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 34 and 46
48. Condylomata Acuminata/
49. "condyloma$ acuminat$".ab,ti.

50. "condyloma$ accuminat$".ab,ti.
51. condyloma$.ab,ti.
52. or/48-51
53. 47 or 52
54. imiquimod.ab,ti,nm.
55. sinecatechins.ab,ti.
56. "green tea catechins".ab,ti.
57. "green tea extract".ab,ti.
58. polyphenon.ab,ti.
59. polyphenon E.nm.
60. Podophyllotoxin/
61. podophyllotoxin.ab,ti.
62. or/54-61
63. 29 and 53 and 62

1.2. Data items

The data items included data on the study population (inclusion / exclusion criteria, number of participants randomized, localization and extent of the lesions, gender, age, previous treatments, smoking, sexual behaviour: orientation, promiscuity), length of follow-up, outcomes assessed, and results (according to the predefined primary and secondary outcomes).

1.3. GRADE evaluations: downgrading the quality of the evidence

According to the GRADE approach, we evaluated the quality of the evidence on the outcome level for each comparison that was available for this systematic review.[2] The quality of the evidence started with “high” for each available comparison and outcome, due to the restriction of the included studies to randomized trials. In the presence of risk of bias,[3, 4] inconsistency,[5] indirectness,[6] imprecision,[7] and publication bias,[8] the quality of the evidence for each outcome within the available comparisons could be downgraded.

1.3.1. Downgrading due to risk of bias

For the evaluations of the risk of bias on the outcome level, we considered the overall risk of bias in the contributing studies as based upon the prior determination of the risk of bias at the study level (“Cochrane Collaboration’s tool for assessing risk of bias in randomized trials” [4]). Since specific aspects are of more importance to specific outcomes, this evaluation could differ from outcome to outcome although the contributing studies were the same: For patient-reported outcomes and outcomes based on patient decisions such as pain or withdrawal due to adverse events (AE), the category of blinding of participants and personnel (performance bias) was emphasized. For investigator-reported outcomes such as complete clearance, recurrence, or local AE, the categories of sequence generation, allocation concealment and blinding of outcome assessment were considered more relevant.

1.3.2. Downgrading due to inconsistency

The evaluation of consistency of the results for an outcome were based both on the visual inspection of the forest plots and on the evaluation of the I^2 test which quantifies the proportion of the variation in the point estimates due to among-study-differences.[5] According to the GRADE guidelines, we considered grading the quality of the evidence down due to inconsistency in the presence of widely varying point estimates, minimal or no overlap of confidence intervals or $I^2 > 50\%$.[5] In the case of only one contributing study, consistency could not be evaluated and no downgrading due to inconsistency was performed.

1.3.3. Downgrading due to indirectness

The assessment of indirectness was based upon the evaluation of participants, interventions and outcomes of the included studies[6]. Since these parameters had been precisely defined and considered during the inclusion or exclusion of studies, we solely evaluated the localization

of anogenital warts (external vs. internal) as a criterion for indirectness. Studies with participants who had external warts were separately assessed from studies whose participants had internal warts. In the case that an outcome included data from studies with a significant amount of participants who had both external and internal warts, the quality of the evidence was downgraded due to indirectness.

1.3.4. Downgrading due to imprecision

In order to evaluate the precision of the results, we considered two criteria: 1) the evaluation of the clinical importance of differences as based upon a predefined threshold of a minimal important difference (MID threshold) as previously reported,[9] and 2) the size of the confidence interval.[7]

For binary outcomes, we defined the MID threshold as the line of no effect +/- 0.25 (i.e. 0.75 and 1.25). For continuous outcomes, the MID threshold was defined as the line of no effect +/- 0.5 x the standard deviation of the control group outcome. A statistically significant effect of an intervention was considered imprecise, if the confidence interval crossed the MID threshold (i.e., the effect was statistically significant but of questionable clinical significance). If the effect was statistically significant but did not cross the MID threshold (i.e., statistically significant and supposedly clinically significant) or if the effect was statistically insignificant and did not cross the MID threshold (i.e., no statistically or clinically significant difference between the interventions), no downgrading due to imprecision was performed.

A confidence interval was evaluated as being very large and therefore displaying an imprecise effect estimate, if the magnitude of 0.01 or 100 was exceeded.

1.3.5. Downgrading due to publication bias

Since we did not perform searches in trial registers, our evaluation of publication bias was solely based upon the visual evaluation of funnel plots. This was only considered possible in the case of more than ten trials contributing data for a comparison. Where evaluation of funnel plots was not possible due to the small number of contributing trials, we rated publication bias as ‘undetected’.

2. Results

2.1. Reasons for the exclusion of studies during the full text evaluation

The following table (Table 1) gives an overview of the reasons for the exclusion of studies during the full text evaluations:

Table 1: Reasons for exclusion of studies during the fulltext evaluation

Study	Reason for exclusion
Akhavan et al. 2014[10]	comparators not relevant
Baker et al. 2010[11]	only abstract available, data reported here might at least partially be included in Baker 2011[12]
Beutner 1995[13]	data reported elsewhere (Beutner et al. 1998a[14], Beutner et al. 1998b[15], only abstract available
Beutner et al. 1998[16]	data reported elsewhere (Beutner et al. 1998a[14], Beutner et al. 1998b[15], only abstract available
Bonnez et al. 1994[17]	prophylactic treatment in the RCT stage of the trial
Buck et al. 2002[18]	uncontrolled cohort study
Ferenczy 1998[19]	no original data, data reported elsewhere (Edwards et al. 1998[20])
Fife et al. 2001[21]	comparators not relevant (imiquimod dosing study)
Garland et al. 2001[22]	uncontrolled cohort study
Goldenberg et al. 2014[23]	only abstract available, no data of the total number of participants reported (evaluation the reported rates of AE not possible)
Gollnick et al. 2001[24]	not randomized (sequential allocation)
Greenberg et al. 1991[25]	podophyllotoxin 0.5% solution not reported separately from cream
Gross 2008[26]	no original data, data reported here might at least partially be included in Gross et al. 2007[27]
Haidopoulos et al. 2004[28]	uncontrolled cohort study
Hoy 2012[29]	no original data, data reported elsewhere (Stockfleth et al. 2008[30], Tatti et al. 2008[31])
Krogh et al. 1992[32]	Intervention: podophyllotoxin 0.5% cream (not solution / gel)
Lafuma et al. 2003[33]	no original data, language: French
Nelson et al. 2014[34]	only abstract available; evaluation of complete clearance rates not possible due to missing information
Petersen et al. 1995[35]	Intervention: podophyllotoxin 0.5% cream (not solution / gel)
Puri et al. 2009[36]	uncontrolled cohort study
Rosen et al. 2014a[37]	only abstract available; evaluation of data not possible due to missing information
Rosen et al. 2014b[38]	only abstract available; evaluation of data not possible due to missing information
Sauder et al. 2003[39]	no original data, data reported elsewhere (Edwards et al. 1998[20])
Tatti et al. 2010[40]	no original data, data reported elsewhere (Stockfleth et al. 2008[30], Tatti et al. 2008[31])
Trofatter et al. 2002[41]	comparators not relevant (imiquimod dosing study)

2.2. Risk of bias

Eight trials (44%) reported sufficient information regarding sequence generation and were judged at low risk of bias. In the other ten trials the method of the sequence generation was not stated and the risk of bias rated as unclear. With respect to allocation concealment, five trials (28%) were rated at low risk of bias while two trials (11%) were judged to be at high risk. Regarding the blinding of participants, a high percentage of low-risk-ratings were seen in 55% (ten) of the studies while five trials (28%) were rated to be at high risk of bias. The risk of bias in blinding of outcome assessment was evaluated to be at low risk in five trials (28%), and at high risk in another five trials (28%). The highest percentage of high-risk ratings was noted regarding attrition bias (incomplete outcome data) with eight studies (44%), while only three studies (17%) were rated to be at low risk of bias. Selective reporting was judged to be at high risk in two trials (11%) and at low risk in four trials (22%). Regarding the item 'other sources of bias', four trials (22%) were rated of high risk for reporting insufficient data on the baseline characteristics of the studied sample.

The following figure (Figure 1) gives an overview of the risk of bias evaluations for the included studies. A detailed presentation of the risk of bias evaluations for each study is given within the original publication.

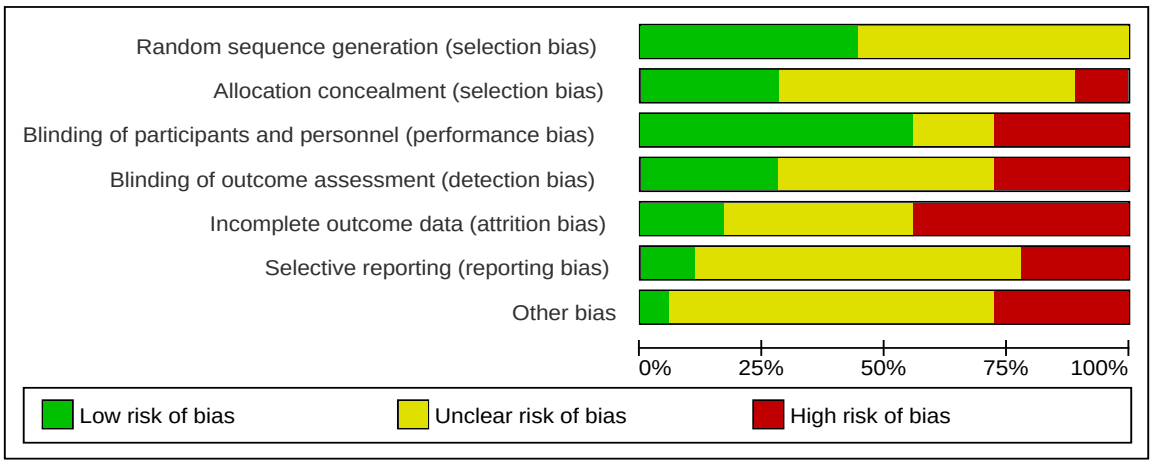

Figure 1: Risk of Bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

2.3. Imiquimod 3.75% cream vs. placebo

Table 2: Summary of findings: imiquimod3.75% cream vs. placebo

Summary of findings:

Imiquimod 3.75% cream compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 3.75% cream

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Imiquimod 3.75% cream				
Complete clearence at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		
Complete clearence at 16w (+/- 8w) after EOT	Study population		RR 2.88 (1.84 to 4.51)	601 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	94 per 1000	271 per 1000 (173 to 424)				
Drop outs due to adverse events	Study population		RR 2.14 (0.36 to 12.59)	602 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	5 per 1000	11 per 1000 (2 to 62)				
Pain during treatment and 0-4 weeks after EOT	Study population		RR 17.18 (1.04 to 282.95)	323 (1 RCT)	⊕⊕◯◯ LOW [2,3,4]	
	5 per 1000[5]	81 per 1000 (5 to 1000)				
Erythema/inflammation/skin irritation	Study population		RR 21.30 (1.30 to 348.79)	308 (1 RCT)	⊕⊕⊕◯ MODERATE [2,4]	
	5 per 1000[5]	101 per 1000 (6 to 1000)				
Erosion/excoriation/ulceration	Study population		RR 13.45 (1.85 to 97.73)	308 (1 RCT)	⊕⊕⊕⊕ HIGH [2]	
	10 per 1000	128 per 1000 (18 to 931)				
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Imiquimod 3.75% cream compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 3.75% cream

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Imiquimod 3.75% cream				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Confidence interval crosses the MID threshold of 0.75 and 1.25
2. (evaluation based on one study)
3. Confidence interval crosses the MID threshold of 1.25
4. Very large confidence interval
5. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo group. The calculation of the risk in the intervention group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.4. Imiquimod 5% cream vs. placebo

Table 3: Summary of findings: imiquimod 5% cream vs. placebo

Summary of findings:

Imiquimod 5% cream compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 5% cream

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Imiquimod 5% cream				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 9.16 (3.39 to 24.71)	551 (4 RCTs)	⨁⨁◯◯ LOW [1,2,3]	
	57 per 1000	522 per 1000 (193 to 1000)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		RR 4.30 (0.48 to 38.34)	298 (3 RCTs)	⨁⨁⨁◯ MODERATE [4]	
	4 per 1000[7]	15 per 1000 (2 to 134)				
Pain during treatment and 0-4 weeks after EOT	Study population		RR 16.00 (3.95 to 64.82)	184 (1 RCT)	⨁⨁⨁⨁ HIGH [5]	
	22 per 1000	348 per 1000 (86 to 1000)				
Erythema/inflammation/skin irritation	Study population		RR 2.36 (1.87 to 2.98)	428 (3 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	299 per 1000	707 per 1000 (560 to 892)				
Erosion/excoriation/ulceration	Study population		RR 6.80 (4.16 to 11.12)	428 (3 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	76 per 1000	518 per 1000 (317 to 847)				
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Imiquimod 5% cream compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 5% cream

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Imiquimod 5% cream				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		RR 1.41 (0.28 to 6.97)	122 (3 RCTs)	⨁⨁◯◯ LOW [4,6]	
	77 per 1000	108 per 1000 (22 to 536)				
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. sequence generation, allocation concealment and blinding of outcome assessment unclear in all of the studies
2. I^2 = 55%, point estimates vary widley across studies
3. Beutner 1998b contained a minority of participants with internal warts, but the number is not relevant to the overall number of participants
4. Confidence interval crosses the MID threshold of 0.75 and 1.25
5. (evaluation based on one study)
6. blinding of outcome assessment unclear in all studies; data solely refer to baseline lesions
7. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo groups. The calculation of the risk in the intervention group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.5. Podophyllotoxin 0.5% solution vs. placebo

Table 4: Summary of findings: podophyllotoxin 0.5% solution vs. placebo

Summary of findings:

Podophyllotoxin 0.5% solution compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% solution

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Podophyllotoxin 0.5% solution				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 19.86 (3.88 to 101.65)	185 (3 RCTs)	⨁⨁◯◯ LOW [1,2]	
	6 per 1000 [5]	109 per 1000 (21 to 559)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		no data available	(0 studies)		
Pain during treatment and 0-4 weeks after EOT	Study population		RR 5.86 (1.01 to 33.85)	147 (2 RCTs)	⨁⨁◯◯ LOW [3,4]	
	97 per 1000	570 per 1000 (98 to 1000)				
Erythema/inflammation/skin irritation	Study population		RR 12.67 (4.50 to 35.64)	147 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	42 per 1000	528 per 1000 (188 to 1000)				
Erosion/excoriation/ulceration	Study population		RR 17.68 (5.16 to 60.52)	147 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	28 per 1000	491 per 1000 (143 to 1000)				
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Podophyllotoxin 0.5% solution compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% solution

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Podophyllotoxin 0.5% solution				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		not calculated	27 (2 RCTs)	no participants in placebo group	
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. sequence generation unclear in 2 of 3 studies, allocation concealment at high risk in 1 study and at unclear risk in 2 studies
2. confidence interval very large
3. I^2 = 47%; point estimates vary widely
4. Confidence interval crosses MID threshold of 1.25
5. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo groups. The calculation of the risk in the intervention group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.6. Podophyllotoxin 0.5% gel vs. placebo

Table 5: Summary of findings: podophyllotoxin 0.5% gel vs. placebo

Summary of findings:

Podophyllotoxin 0.5% gel compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% gel

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Podophyllotoxin 0.5% gel				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 9.89 (3.72 to 26.28)	326 (1 RCT)	⨁⨁⨁◯ MODERATE [1,2]	
	37 per 1000	370 per 1000 (139 to 982)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		RR 7.36 (0.42 to 127.74)	326 (1 RCT)	⨁◯◯◯ VERY LOW [2,3,4]	
	5 per 1000[5]	34 per 1000 (2 to 597)				
Pain during treatment and 0-4 weeks after EOT	Study population		RR 9.27 (4.22 to 20.35)	316 (1 RCT)	⨁⨁⨁◯ MODERATE [2,3]	
	58 per 1000	540 per 1000 (246 to 1000)				
Erythema/inflammation/skin irritation	Study population		RR 6.13 (3.57 to 10.50)	316 (1 RCT)	⨁⨁⨁◯ MODERATE [1,2]	
	117 per 1000	714 per 1000 (416 to 1000)				
Erosion/excoriation/ulceration	Study population		RR 18.54 (6.04 to 56.92)	316 (1 RCT)	⨁⨁⨁◯ MODERATE [1,2]	
	29 per 1000	540 per 1000 (176 to 1000)				
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Podophyllotoxin 0.5% gel compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% gel

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Podophyllotoxin 0.5% gel				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. unclear risk of selection bias, performance bias and detection bias
2. (evaluation based on one study)
3. unclear risk of bias concerning blinding of the participants
4. Confidence interval crosses the MID threshold of 0.75 and 1.25; very large confidence interval
5. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo group. The calculation of the risk in the intervention group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.7. Polyphenon E (sinecatechins) 10% ointment vs. placebo

Table 6: Summary of findings: polyphenon E 10% ointment vs. placebo

Summary of findings:

Polyphenon E 10% ointment compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 10% ointment

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Sinecatechins 10% ointment				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 1.48 (1.20 to 1.82)	608 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	353 per 1000	522 per 1000 (423 to 642)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		RR 0.52 (0.03 to 8.19)	608 (2 RCTs)	⊕⊕⊕◯ MODERATE [2,3]	
	5 per 1000	3 per 1000 (0 to 40)				
Pain during treatment and 0-4 weeks after EOT	Study population		no data available	(0 studies)		
Erythema/inflammation/skin irritation	Study population		no data available	(0 studies)		
Erosion/excoriation/ulceration	Study population		no data available	(0 studies)		
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Polyphenon E 10% ointment compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 10% ointment

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Sinecatechins 10% ointment				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		RR 1.54 (0.18 to 13.30)	137 (1 RCT)	⊕⊕⊕◯ MODERATE [2,3]	
	26 per 1000	41 per 1000 (5 to 350)				
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Confidence interval crosses MID threshold of 1.25
2. (evaluation based on one study)
3. Confidence interval crosses MID threshold of 0.75 and 1.25

2.8. Polyphenon E (sinecatechins) 15% ointment vs. placebo

Table 7: Summary of findings: polyphenon E 15% ointment vs. placebo

Summary of findings:

Polyphenon E 15% ointment compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 15% ointment

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Sinecatechins 15% ointment				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 1.50 (1.26 to 1.80)	767 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	359 per 1000	538 per 1000 (452 to 646)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		RR 3.33 (0.74 to 15.05)	767 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	3 per 1000	11 per 1000 (3 to 52)				
Pain during treatment and 0-4 weeks after EOT	Study population		no data available	(0 studies)		
Erythema/inflammation/skin irritation	Study population		no data available	(0 studies)		
Erosion/excoriation/ulceration	Study population		no data available	(0 studies)		
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Polyphenon E 15% ointment compared to placebo for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 15% ointment

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Sinecatechins 15% ointment				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		RR 1.38 (0.44 to 4.30)	217 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	58 per 1000	80 per 1000 (26 to 249)				
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Confidence interval crosses the MID threshold of 0.75 and 1.25

2.9. Podophyllotoxin 0.5% solution vs. podophyllotoxin 0.15% cream

Table 8: Summary of findings: podophyllotoxin 0.5% solution vs. podophyllotoxin 0.15% cream

Summary of findings:

Podophyllotoxin 0.5% solution compared to podophyllotoxin 0.15% cream for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% solution

Comparison: podophyllotoxin 0.15% cream

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with podophyllotoxin 0.15% cream	Risk with Podophyllotoxin 0.5% solution				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 1.26 (1.07 to 1.48)	417 (3 RCTs)	⨁⨁◯◯ LOW [1,2]	
	500 per 1000	630 per 1000 (535 to 740)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		RR 1.22 (0.82 to 1.81)	59 (1 RCT)	⨁⨁◯◯ LOW [2,3,4]	
	567 per 1000	691 per 1000 (465 to 1000)				
Drop outs due to adverse events	Study population		no data available	(0 studies)		
Pain during treatment and 0-4 weeks after EOT	Study population		no data available	(0 studies)		
Erythema/inflammation/skin irritation	Study population		RR 1.00 (0.70 to 1.43)	120 (1 RCT)	⨁⨁◯◯ LOW [3,4,5]	
	500 per 1000	500 per 1000 (350 to 715)				
Erosion/excoriation/ulceration	Study population		not pooled	358 (2 RCTs)	⨁◯◯◯ VERY LOW [6,7,8]	
	not pooled	not pooled				
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Podophyllotoxin 0.5% solution compared to podophyllotoxin 0.15% cream for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Podophyllotoxin 0.5% solution

Comparison: podophyllotoxin 0.15% cream

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with podophyllotoxin 0.15% cream	Risk with Podophyllotoxin 0.5% solution				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		RR 0.91 (0.57 to 1.45)	175 (3 RCTs)	⨁⨁◯◯ LOW [5,9]	
	240 per 1000	218 per 1000 (137 to 348)				
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Unclear sequence generation in 2 of 3 studies, unclear allocation concealment in all studies, high risk of detection bias in all studies.
2. Confidence interval crosses the MID threshold of 1.25
3. Unclear sequence generation, unclear allocation concealment, high risk of detection bias
4. (evaluation based on one study)
5. Confidence interval crosses the MID threshold of 0.75 and 1.25
6. high risk of detection bias in both studies
7. I^2 =75%, point estimates favour different interventions; not pooled
8. Both confidence intervals cross the line of no effect and MID threshold
9. high risk of detection bias in all studies; incomplete outcome data with respect to recurrence in Lacey et al.

2.10. Imiquimod 5% cream vs. podophyllotoxin 0.5% solution

Table 9: Summary of findings: imiquimod 5% cream vs. podophyllotoxin 0.5% solution

Summary of findings:

Imiquimod 5% cream compared to podophyllotoxin 0.5% solution for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 5% cream

Comparison: podophyllotoxin 0.5% solution

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with podophyllotoxin 0.5% solution	Risk with Imiquimod 5% cream				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 0.87 (0.58 to 1.31)	51 (1 RCT)	⨁⨁◯◯ LOW [1,2,3]	
	692 per 1000	602 per 1000 (402 to 907)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		no data available	(0 studies)		
Pain during treatment and 0-4 weeks after EOT	Study population		no data available	(0 studies)		
Erythema/inflammation/skin irritation	Study population		RR 1.17 (0.80 to 1.73)	45 (1 RCT)	⨁⨁◯◯ LOW [1,2,4]	
	640 per 1000	749 per 1000 (512 to 1000)				
Erosion/excoriation/ulceration	Study population		RR 1.48 (0.86 to 2.55)	45 (1 RCT)	⨁⨁◯◯ LOW [1,2,4]	
	440 per 1000	651 per 1000 (378 to 1000)				

Summary of findings:

Imiquimod 5% cream compared to podophyllotoxin 0.5% solution for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Imiquimod 5% cream

Comparison: podophyllotoxin 0.5% solution

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with podophyllotoxin 0.5% solution	Risk with Imiquimod 5% cream				
Quality of life	Study population		no data available	(0 studies)		
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. high risk of selection bias, performance bias and detection bias
2. (evaluation based on one study)
3. Confidence interval crosses the MID threshold of 0.75 and 1.25
4. Confidence interval crosses the MID threshold of 1.25

2.11. Polyphenon E (sinecatechins) 10% vs. 15% ointment

Table 10: Summary of findings: polyphenon E 10% vs. 15% ointment

Summary of findings:

Polyphenon E 15% ointment compared to polyphenon E 10% ointment for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 15% ointment

Comparison: Polyphenon E 10% ointment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with sinecatechins 10% ointment	Risk with Sinecatechins 15% ointment				
Complete clearence at 2w (+/- 2w) after EOT	Study population		RR 1.03 (0.90 to 1.17)	798 (2 RCTs)	⨁⨁⨁⨁ HIGH	
	524 per 1000	539 per 1000 (471 to 613)				
Complete clearence at 16w (+/- 8w) after EOT	Study population		no data available	(0 studies)		
Drop outs due to adverse events	Study population		RR 4.87 (0.84 to 28.31)	798 (2 RCTs)	⨁⨁⨁◯ MODERATE [1]	
	2 per 1000	12 per 1000 (2 to 71)				
Pain during treatment and 0-4 weeks after EOT	Study population		no data available	(0 studies)		
Erythema/inflammation/skin irritation	Study population		no data available	(0 studies)		
Erosion/excoriation/ulceration	Study population		no data available	(0 studies)		
Quality of life	Study population		no data available	(0 studies)		

Summary of findings:

Polyphenon E 15% ointment compared to polyphenon E 10% ointment for anogenital warts in immunocompetent adults

Patient or population: anogenital warts in immunocompetent adults

Setting:

Intervention: Polyphenon E 15% ointment

Comparison: Polyphenon E 10% ointment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with sinecatechins 10% ointment	Risk with Sinecatechins 15% ointment				
Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		RR 1.46 (0.42 to 5.00)	201 (1 RCT)	⊕⊕◯◯ LOW [2,3,4]	
	40 per 1000	59 per 1000 (17 to 202)				
Complete clearence at 12m (+/- 2m) after EOT	Study population		no data available	(0 studies)		
Recurrence of lesions at 12m (+/- 2w) after EOT in pts. who had CC at 2w (+/- 2w) after EOT	Study population		no data available	(0 studies)		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Confidence interval crosses the MID threshold of 1.25
2. data solely refer to baseline lesions
3. (evaluations based on one study)
4. Confidence interval crosses the MID threshold of 0.75 and 1.25

3. Discussion

3.1. Limitations to the systematic review not discussed in the main document

We meta-analysed data from trials that reported the CC of all lesions as well as CC solely of the baseline lesions, for pragmatic reasons with regards to the overall aim of the review. Reporting of AE was particularly heterogeneous in the included trials. In order to generate comparable data of local AE, we combined data of related outcomes and generated two separate outcomes (erythema/inflammation/skin irritation; erosion/excoriation/ulceration). Therefore, no conclusions concerning the single local AEs can be drawn.

4. References

1. SIGN. SEARCH FILTERS: Scottish Intercollegiate Guidelines Network; Last modified 27/08/15 [Available from: http://www.sign.ac.uk/methodology/filters.html#random.
2. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-6. DOI 10.1016/j.jclinepi.2010.07.015.
3. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-15. DOI 10.1016/j.jclinepi.2010.07.017.
4. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343. DOI 10.1136/bmj.d5928.
5. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *J Clin Epidemiol*. 2014;64(12):1294-302. DOI 10.1016/j.jclinepi.2011.03.017.
6. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *J Clin Epidemiol*. 2011;64(12):1303-10. DOI 10.1016/j.jclinepi.2011.04.014.
7. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *J Clin Epidemiol*. 2014;64(12):1283-93. DOI 10.1016/j.jclinepi.2011.01.012.
8. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin Epidemiol*. 2011;64(12):1277-82. DOI 10.1016/j.jclinepi.2011.01.011.
9. National Clinical Guideline Centre. Psoriasis: Assessment and management of psoriasis - Clinical Guideline. Methods, evidence and recommendations The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT 2012.
10. Akhavan S, Mohammadi SR, Modarres Gillani M, et al. Efficacy of combination therapy of oral zinc sulfate with imiquimod, podophyllin or cryotherapy in the treatment of vulvar warts. *J Obstet Gynaecol Res*. 2014;40(10):2110-3. DOI 10.1111/jog.12457.
11. Baker D, Ferris D, Tyring S, et al. Imiquimod 2.5% and 3.75% applied daily for up to 8 weeks to treat external genital warts. *Contraception*. 2010;82 (2):211.
12. Baker DA, Ferris DG, Martens MG, et al. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. *Infect Dis Obstet Gynecol*. 2011;2011:806105.
13. Beutner K. Comparison of the results from two well controlled trials of topical imiquimod for the treatment of genital / perianal warts Abstract 52. *J Invest Dermatol*. 1995;104:563.
14. Beutner KR, Spruance SL, Hougham AJ, et al. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol*. 1998;38(2 Pt 1):230-9.
15. Beutner KR, Tyring SK, Trofatter Jr KF, et al. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. *Antimicrob Agents Chemother*. 1998;42(4):789-94.
16. Beutner K, Edwards L, Owens M, et al. Comparison of two vehicle-controlled trials of imiquimod 5% cream for the treatment of external genital warts.(Abstract 1259). *J Invest Dermatol*. 1998;110(4):682.
17. Bonnez W, Elswick Jr RK, Bailey-Farchione A, et al. Efficacy and safety of 0.5% podofilox solution in the treatment and suppression of anogenital warts. *Am J Med*. 1994;96(5):420-5.
18. Buck HW, Fortier M, Knudsen J, et al. Imiquimod 5% cream in the treatment of anogenital warts in female patients. *International Journal of Gynecology and Obstetrics*. 2002;77(3):231-8.
19. Ferenczy A. Immune response modifiers: Imiquimod. *J Obstet Gynaecol*. 1998;18(SUPPL. 2):S76-S8.
20. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol*. 1998;134(1):25-30.
21. Fife KH, Ferenczy A, Douglas JM, et al. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. *Sex Transm Dis*. 2001;28(4):226-31.

22. Garland SM, Sellors JW, Wikstrom A, et al. Imiquimod 5% cream is a safe and effective self-applied treatment for anogenital warts - Results of an open-label, multicentre Phase IIIB trial. *Int J STD AIDS*. 2001;12(11):722-9.
23. Goldenberg G, Nelson A, Smith CC, et al. Imiquimod 2.5% and 3.75% for the treatment of external genital warts: Assessment of safety in 981 randomized patients. *J Am Acad Dermatol*. 2014;1):AB46.
24. Gollnick H, Barasso R, Jappe U, et al. Safety and efficacy of imiquimod 5% cream in the treatment of penile genital warts in uncircumcised men when applied three times weekly or once per day. *Int J STD AIDS*. 2001;12(1):22-8.
25. Greenberg MD, Rutledge LH, Reid R, et al. A double-blind, randomized trial of 0.5% podofilox and placebo for the treatment of genital warts in women. *Obstet Gynecol*. 1991;77(5):735-9.
26. Gross G. Polyphenon E: A new topical therapy for condylomata acuminata. [German]. *Hautarzt*. 2008;59(1):31-5.
27. Gross G, Meyer KG, Pres H, et al. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol*. 2007;21(10):1404-12.
28. Haidopoulos D, Diakomanolis E, Rodolakis A, et al. Safety and efficacy of locally applied imiquimod cream 5% for the treatment of condylomata acuminata of the vulva. *Arch Gynecol Obstet*. 2004;270(4):240-3.
29. Hoy SM. Polyphenon E 10% ointment: in immunocompetent adults with external genital and perianal warts. *Am J Clin Dermatol*. 2012;13(4):275-81.
30. Stockfleth E, Beti H, Orasan R, et al. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol*. 2008;158(6):1329-38.
31. Tatti S, Swinehart JM, Thielert C, et al. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol*. 2008;111(6):1371-9.
32. Krogh G, Hellberg D. Self-treatment using a 0.5% podophyllotoxin cream of external genital condylomata acuminata in women. A placebo-controlled, double-blind study. *Sex Transm Dis*. 1992;19(3):170-4.
33. Lafuma A, Monsonego J, Moyal-Barracco M, et al. [A model-based comparison of cost effectiveness of imiquimod versus podophyllotoxin for the treatment of external anogenital warts in France]. *Comparaison cout-efficacite par modelisation de l'imiquimod et de la podophyllotoxine dans le traitement du condylome acumine externe en France*. 2003;130(8-9 Pt 1):731-6.
34. Nelson A, Ault K, Kaur M, et al. Imiquimod 2.5% and 3.75% for the treatment of external genital warts: Assessment of efficacy in 981 randomized patients. *J Am Acad Dermatol*. 2014;1):AB46.
35. Petersen CS, Agner T, Ottevanger V, et al. A single-blind study of podophyllotoxin cream 0.5% and podophyllotoxin solution 0.5% in male patients with genital warts. *Genitourin Med*. 1995;71(6):391-2.
36. Puri M. A study on the use of imiquimod for the treatment of genital molluscum contagiosum and genital warts in female patients. *Indian Journal of Sexually Transmitted Diseases and AIDS*. 2009;30(2):84-8.
37. Rosen T, Smith CC, Kaur M, et al. Imiquimod 2.5% and 3.75% for the treatment of external genital warts: Additional insights into efficacy. *J Am Acad Dermatol*. 2014;1):AB46.
38. Rosen T, Goldenberg G, Ault K, et al. Imiquimod 2.5% and 3.75% for the treatment of external genital warts: Sex differences in a study of 981 randomized patients. *J Am Acad Dermatol*. 2014;1):AB46.
39. Sauder DN, Skinner RB, Fox TL, et al. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis*. 2003;30(2):124-8.
40. Tatti S, Stockfleth E, Beutner KR, et al. Polyphenon E: a new treatment for external anogenital warts. *Br J Dermatol*. 2010;162(1):176-84.

41. Trofatter Jr KF, Ferenczy A, Fife KH. Increased frequency of dosing of imiquimod 5% cream in the treatment of external genital warts in women. *International Journal of Gynecology and Obstetrics*. 2002;76(2):191-3.