ORIGINAL ARTICLE

Efficacy, safety and tolerability of green tea catechins in the treatment of external anogenital warts: a systematic review and meta-analysis

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Abstract

Background External anogenital warts (EGWs) are non-malignant skin tumours caused by human papillomavirus. They are one of the fastest growing sexually transmitted diseases. Current treatments are unsatisfactory. Green tea sinecatechin Polyphenon E ointment is a botanical extract from green tea leaves exhibiting anti-oxidant, anti-viral and anti-tumour properties.

Objective The aim of this study was to integrate valid information and provide basis for rational decision making regarding efficacy and safety of green tea extracts in the treatment of EGWs.

Methods A systematic search in electronic databases was conducted using specific key terms. Main search was performed independently by two reviewers. The accumulated relevant literature was subsequently systematically reviewed and a meta-analysis was conducted.

Results Three randomized, double-blind, placebo-controlled studies evaluating efficacy and safety of Polyphenon E 15% and 10% in the treatment of warts were included in the systematic review and meta-analysis. A total of 660 men and 587 women were enrolled. Regarding primary outcome, both Polyphenon E 15% and 10% demonstrated significantly higher likelihood of complete clearance of baseline and baseline and new warts compared with controls. No significant heterogeneity was detected. Recurrence rates were very low. Commonest local skin sign was erythema and local skin symptom was itching.

Conclusions Efficacy of Polyphenon 15% and 10%, at least for the primary endpoint, is clearly indicated. Polyphenon E treatment exhibits very low recurrence rates and appears to have a rather favourable safety and tolerability profile. Recommendations for future studies should include evaluation of the efficacy of green tea catechins in the treatment of internal anogenital warts and direct comparison with its principal comparator, imiquimod.

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Keywords

catechins, condylomata acuminata, genital warts, green tea, polyphenon E

Conflict of interest

None.

Introduction

External anogenital warts (EGWs) or condylomata acuminata are non-malignant skin tumours.[1] They are caused by human papillomavirus (HPV) infection, mainly types 6 and 11.[1] The disease is one of the fastest growing sexually transmitted diseases.[2] Data suggest that 0.5–1% of the general population is infected with HPV.[3] It is estimated that each year approximately 30 million cases of genital warts and more than 1 million new cases of EGWs are diagnosed.[2–5] Furthermore, about 20 million potential patients with EGWs or with subclinical disease are estimated to exist in USA and Europe.[6]

External anogenital warts are disfiguring and painful skin lesions, which cause significant physical and psychological problems.[7] Despite that, current treatment options are often unsatisfactory.[8] Treatments for EGWs include patient-administered topical treatments[9,10] and physician-administered treatments. Most modalities are associated with adverse events (AEs) like erythema, tissue destruction, pain, burning, itching, scarring and ulceration.[11]

Furthermore, they do not address the source of EGWs or subclinical lesions, resulting in high recurrence rates.[12,13] Recently, prophylactic vaccines were approved and proven to offer immunity against HPV. However, they are not a therapeutic option and protect only against a limited number of strains.[14]

Food and Drug Administration has recently approved Polyphenon E ointment for treatment of EGWs.[15] Polyphenon E is a botanical quantified extract from green tea leaves consisting of more than 85% catechins. Green tea catechins exhibit specific anti-oxidant, anti-viral, anti-tumour and immunostimulatory properties, which highly contribute to Polyphenon E efficacy in the treatment of EGWs.[16–18]

Although reviews exist suggestive of green tea catechins efficacy in the treatment of EGWs, most of them are narrative. One recently published systematic review did not include one randomized controlled trial.[19] To efficiently integrate valid information and provide a basis for rational decision making, relevant literature was systematically reviewed and a meta-analysis of all available randomized controlled trials was conducted to determine the efficacy, safety and tolerability of green tea extracts in the treatment of EGWs.

Methods

Search strategy

To identify eligible studies, the main search was conducted in the electronic databases MEDLINE, EMBASE, PubMed, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through February 2010, using the terms ('warts' [MeSH] OR 'condylomata acuminata' [MeSH]) AND ('polyphenon E' [MeSH] OR 'catechin' [MeSH]), without language restrictions. Finally, perusal of the reference sections of all relevant trials or reviews, contact with experts on the subject and manual search of key journals and abstracts from the major annual meetings in the fields of Clinical Pharmacology and Dermatology were conducted, to identify related unpublished data. The main search was conducted independently by two reviewers (TT, CS), with expertise in conducting systematic reviews. Any disagreement was resolved by a third reviewer, not involved in the initial procedure (DK).

Eligibility of relevant studies

Eligible studies were randomized controlled trials, which compared the efficacy of green tea catechins to placebo in the treatment of anogenital warts in women and men ≥18 years old, regardless of dosage or duration of treatment. Trials were excluded if uncontrolled and/or open-label. Reviews, case series, letters to the editor, observational studies and experimental preclinical studies were excluded. Each article was reviewed independently by two reviewers before final inclusion.

Data extraction

Information from each study was extracted independently by two reviewers (TT, CS), using a standardized data extraction form. General study characteristics (author group, journal, year of publication, design, study size, intervention and control group sample size), methodology (inclusion criteria, duration of treatment, dosage, study quality and limitations) and outcomes for both intervention and control groups were recorded, where available, and double-checked. Where necessary, data set was completed through communication with the authors. Study quality was assessed using the six-item instrument developed by Jadad *et al.*[20] independently by two reviewers. Any disagreement was resolved by consensus.

Outcomes

The primary outcome was response to treatment with either Polyphenon E 15% ointment or 10% ointment/cream compared with placebo, expressed as risk ratios (RR). Response to treatment was defined as (i) the complete clearance of baseline warts and (ii) the complete clearance of baseline and new warts.

Statistical analysis

Risk ratios with 95% confidence interval (CI) in each study were combined using a fixed effects model and the Mantel-Haensel method as weighing scheme. Although clinically relevant, a separate analysis on sex was not feasible because of missing data. Heterogeneity between results of different studies was examined using the I^2 test ($I^2 > 50\%$: significant heterogeneity, $I^2 = 50–25\%$: moderate heterogeneity, $I^2 < 25\%$: insignificant heterogeneity), which can be interpreted as the percentage of total variation across several studies because of heterogeneity. Assessment of publication bias was not undertaken because of the small number of included studies. Meta-analysis was conducted using Review Manager (RevMan Version 5.0.; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results

Search results

Search results are depicted as a flow diagram in Fig. 1. The search identified 12 publications. Five narrative reviews and three duplicate publications were excluded. From the four remaining articles, one was also excluded because it was a cost-effectiveness analysis of sinecatechins in the treatment of external genital warts.[21] Finally, three randomized, double-blinded, placebo-controlled studies comparing green tea catechins to placebo met the inclusion criteria and were included in the systematic review and meta-analysis.[22–24]

Systematic review

Characteristics of the included studies are described in Table 1. All studies were of high quality (quality score = 8), multicentre double-blinded, placebo-controlled, with parallel design, evaluating efficacy, safety and tolerability of Polyphenon E in the treatment of EGWs. Inclusion criteria were well described and highly consistent in all three studies.

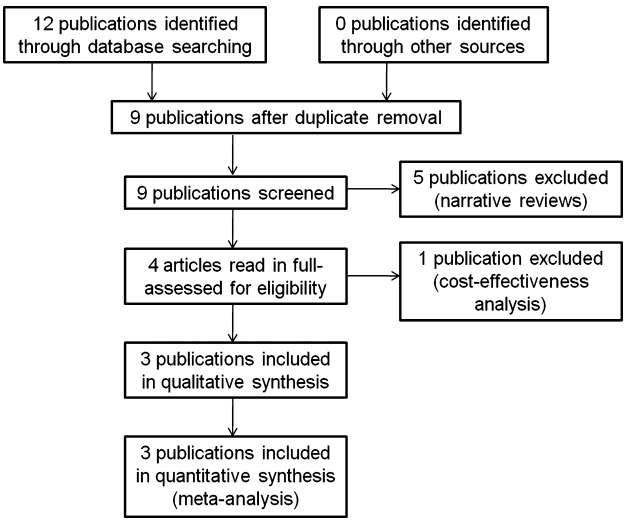

Figure 1 Flow diagram describing search results of the systematic review (identification, screening eligibility, inclusion).

Gross *et al.*[22] evaluated the efficacy of Polyphenon E 15% ointment and Polyphenon E 10% cream use for 12 weeks with a treatment-free follow-up period of 12 weeks for complete responders (complete clearance of baseline EGWs), whereas the other two studies[23,24] evaluated the efficacy of Polyphenon E 15% and 10% ointment use for 16 weeks with a follow-up period of 12 weeks for complete responders (complete clearance of baseline + new EGWs).

Overall, 660 men and 587 women were enrolled in all three studies. An intention-to-treat analysis was performed in all studies and baseline characteristics did not differ significantly between treatment groups, although Gross *et al.*[22] did not perform a thorough statistical comparison for all baseline characteristics. In all three studies men were mostly uncircumcised and women were of childbearing age. The most common sites of EGWs for men was the penis shaft and glans penis and for women vulva and perianal area. Stockfleth *et al.*[23] reported that all patients had previous episodes of EGWs, whereas the other two studies mostly enrolled patients with no previous history of warts.

Efficacy

Outcome assessment of studies is presented in Table 2.

Primary endpoint: complete clearance of baseline and complete clearance of baseline + new EGWs

Stockfleth *et al.* and Tatti *et al.* both report higher complete clearance rates in women than men. Both also report statistically significant complete clearance of baseline and baseline + new warts for Polyphenon E 15% ointment compared with placebo at the end of treatment period. Regarding complete clearance of baseline + new warts Stockfleth *et al.* report a percentage of 52.6% for both genders and Tatti *et al.* 50% and 64.6% for male and female patients, respectively. Almost identical were the rates regarding complete clearance of baseline warts.

For polyphenon E 10% ointment use, Tatti *et al.* also report statistically significant difference both for complete clearance of baseline + new warts (48% males, 64.9% females) and baseline warts (52% males, 70.1% females). Stockfleth *et al.* also come to the same conclusion both for baseline + new warts (50.8%) and baseline warts (52.3%) complete clearance. Interestingly, rates for Polyphenon E 15% and 10% ointment are quite identical. In fact, Tatti *et al.* suggest that women 'performed' slightly better with 10% rather than 15% Polyphenon E ointment. Furthermore, one must highlight the high clearance rate for placebo groups. Stockfleth *et al.* report a placebo clearance rate of 38% and Tatti *et al.* an 'unexpected' 45.8% for women.

On the other hand, Gross *et al.* present statistically different outcomes, while reporting almost identical numerical rates for Polyphenon E 15% ointment. For complete clearance of baseline + new warts no treatment reached statistical significance, although percentages for 15% ointment (56.4%) and placebo (37.5%) are more 'favourable' than the ones reported by Stockfleth *et al.* For complete clearance of baseline warts statistical significance for Polyphenon E 15% ointment was reached only when data for both genders were pooled. Gross *et al.* suggest that the short treatment period (12 weeks) affected the outcome. In addition, placebo clearance rates were high and identical with the two previously mentioned studies.

Recurrence at the end of follow-up period

In all studies, recurrence rates for complete responders were low. Gross *et al.* report a 10.6%, 11.8% and 10.3% recurrence rate of baseline warts for Polyphenon 15% ointment, 10% cream and placebo, respectively, with no recurrences for female patients. The two other studies report even lower recurrence rates of EGWs.

Safety and tolerability

Data regarding safety, tolerability and compliance are presented in Tables 1 and 2.

Regarding safety and tolerability, all studies failed to thoroughly analyse AEs per treatment group. Local skin signs (LSS) and local skin symptoms (LSM) are generally poorly presented. Gross *et al.* do not clearly report dropouts.

Local skin reactions (LSR)

Treatment with Polyphenon E was well tolerated. Stockfleth *et al.* report that at baseline LSR incidence was higher in treatment groups compared with placebo, whereas the other two studies clearly report that it was identical.

Local skin signs and LSM in all studies were mostly mild. Although no statistical analysis is clearly performed in any study, data suggest that LSR were consistently higher in treatment groups throughout study periods. In all studies, the commonest

Table 1 Characteristics of the three trials included in the meta-analysis

Author, year, study area	Design	Inclusion criteria	Intervention/control, sample size	Quality score	Tolerability/safety, dropouts	Limitations
Gross *et al.*, 2007[22] Germany, Russia	Multicentre, phase II/III, randomized, double-blind, placebo-controlled, four arm parallel group	M + F, >18 years old, with 2–30 external anogenital warts,with total wart area 12–600 mm^2, no other active genital infection, no internal warts, no treatment of anogenital warts or acyclovir/imunosuppressives 30 days prior to enrolment	125 M, 117 F 42 M/38 F PE 15% ointment 41 M/38 F PE 10% cream 42 M/41 F PL topically three times/day, for 12 weeks or until complete clearance of baseline warts + 12 week treatment-free follow-up period for complete responders 38 M/35 F PE 15% ointment 37 M/35 F PE 10% cream 39 M/37 F PL completed	8	21 discontinued: six lost to follow-up, three because of AE, nine dropouts LSS and LSM most frequent in PE 15% LSS: mostly of mild intensity, most frequent: erythema (78 patients) LSM: most frequent: burning (60 patients) itching (65 patients) most AE (other that local) were of mild and moderate intensity 4 PE 15% ointment 2 PE 10% cream, 0 PL	No clear report for dropouts and AE per treatment group, no thorough statistical analysis of AE per treatment group, no thorough statistical comparison for baseline characteristics between groups, poor data report
Stockfleth *et al.*, 2007[23] Germany, Romania, Russia, South Africa	Multicentre, phase III, randomized, double-blind, placebo-controlled, three-arm parallel-group	M + F, >18 years old, with 2–30 external anogenital warts, with total wart area 12–600 mm^2, no other genital infection, no internal warts, no treatment of anogenital warts or acyclovir/ imunosuppressives 30 days prior to enrolment, no HIV infection	277 M, 226 F 105 M/96 F PE 15% ointment 110 M/89 F PE 10% ointment 62 M/41 F PL for 16 weeks or until complete clearance of baseline + new warts + 12 week treatment free follow-up period for complete responders completed: 161 PE 15% ointment 170 PE 10% ointment 80 PL	8	92 discontinued, 'patient withdrew consent' as the most frequent reason, 8 for AE (6 PE 15%, 1 PE 10%, 1 PL) LSS: most frequent: erythema, oedema, erosion, 152 PE 15%, 153 PE 10%, 47 PL LSR: 169 PE 15%, 159 PE 10%, 63 PL most AE (other than local) were of mild intensity, severe AE: 7 PE 15%. 2 PE 10%, 1 PL	Oral use of paracetamol if treatment of local skin reactions was needed, no thorough statisticalanalysis for AE per treatment group, no clear report of LSM
Tatti *et al.*, 2008[24] USA, Latin America, Romania	Multicentre, phase III, randomized, double-blind, placebo-controlled, three-arm parallel-group	M + F, >18 years old, with 2–30 external anogenital warts, with total wart area 12–600 mm^2, no other genital infection, no internal warts, no treatment of anogenital warts or acyclovir/ imunosuppressives 30 days prior to enrolment, no HIV infection	258 M, 244 F 100 M/96 F PE 15% ointment 102 M/100 F PE 10% ointment 56 M/48 F PL for 16 weeks or until complete clearance of baseline + new warts + 12 week treatment free follow-up period for complete responders 74 M/85 F PE 15% ointment 79 M/83 F PE 10% ointment 41 M/42 F PL completed	8	98 discontinued, 'patient withdrew consent' and 'lack of efficacy/ treatment failure' as the most frequent reasons LSR: 171 PE 15%, 172 PE 10%, 75 PL, most mild or moderate, itching as the predominant severe LSR most AE (other that local) were ofmild and moderate intensity, severe AE: 5 PE 15%. 2 PE 10%, 0 PL	Oral use of paracetamol or acetaminophen if treatment of local skin reactions was needed, no thorough statistical analysis for AE per treatment group, no clear report of LSM and LSS

AE, adverse events; F, female; LSR, local skin reactions; LSS, local skin signs; LSM, local skin symptoms; M, male; PE, Polyphenon® E; PL, placebo.

Table 2 Outcome assessment of the three trials included in this meta-analysis

Author, year	Complete clearance of baseline + new warts	Complete clearance of baseline warts	Partial clearance	Recurrence (at the end of follow-up period)	Compliance	Other outcomes
Gross *et al.* (2007)[22]	PE 15% ointment: 56.4% PL ointment: 37.5% (NSD) PE 10% cream: 45.5% PL cream: 37.2% (NSD)	PE 15% ointment: M 61% F 56.8% ($P = 0.006$)* NSD when data for M and F examined separately PE 10% cream: M 53.8% F 39.5% (NSD) PL (pooled): M 40.5% F 34.1%	Treatment success (75–100% clearance of baseline warts): PE 15% ointment: M 80.5%, F 81.1% SD when data for M and F examined separately and combined PE 10% cream: M 61.5%, F 47.4% (NSD) PL (pooled): M 52.4%, F 51.2%	Recurrence of baseline warts: no recurrence in female patients PE 15% ointment: 10.6% (five males) PE 10% cream: 11.8% (four males) PL (pooled): 10.3% (three males)	Comparable for both genders 94.5% of patients adequate compliance (>75%) at each visit 5.5% poor compliance (<75%) in at least one visit (1 PE 10% cream, 4 PE 15% ointment, 8 PL)	Mean time to complete clearance of all baseline warts: 10.6 ± 2.6 weeks (comparable between gender and active treatment groups) recurring baseline warts during the treatment period: 4.2% (10 patients), highest in PE 15% ointment group for both genders (four males, two females)
Stockfleth *et al.* (2007)[23]	Higher complete clearance rates in women than men PE 15% ointment: 102 patients (52.6%), SD† PE 10% ointment: 99 patients (50.8%), SD PL ointment: 38 patients (37.3%)	PE 15% ointment: 106 patients (54.6%), SD† PE 10% ointment: 102 patients (52.3%), SD PL ointment: 40 patients (39.2%)	Partial clearance of all warts >50%: PE 15% ointment: 77.3% PE 10% ointment: 78% PL ointment: 52.9%	Recurrence of any warts: PE 15% ointment: 6 (5.9%) PE 10% ointment: 4 (4.1%) PL: 1 (2.6%) appearance of new warts: PE 15% ointment: 1 (1%) PE 10% ointment: 5 (5.1%) PL: 1 (2.6%)	Reported treatment reductions PE 15% ointment: (6.1%) PE 10% ointment: (5.4%) PL: (5%) reported treatment interruption PE 15% ointment: (10.3%) PE 10% ointment: (5.9%) PL: (4.8%)	Median time to complete clearance of all warts: PE 15% ointment: 16.3 weeks, NSD PE 10% ointment: 16.4 weeks, NSD PL ointment: 16.7 median total wart number (last visit) PE 15% ointment: 0, SD PE 10% ointment: 0, SD PL: 3 median total wart area (last visit) PE 15% ointment: 0 mm^2, SD PE 10% ointment: 0 mm^2, SD PL: 15 mm^2
Tatti *et al.* (2008)[24]	PE 15% ointment: 49 M (50%) ($P = 0.001$) 62 F (64.6%) ($P = 0.048$) PE 10% ointment: 48 M (48%) ($P = 0.003$) 63 F (64.9%) ($P = 0.003$) PL ointment: 13 M (23.2%) 22 F (45.8%)	PE 15% ointment: 51 M (52%) ($P < 0.001$) 63 F (65.6%) ($P < 0.001$) PE 10% ointment: 52 M (52%) ($P < 0.001$) 68 F (70.1%) ($P < 0.001$) PL ointment: 13 M (23.2%) 22 F (45.8%)	Partial clearance of all warts >50%: PE 15% ointment: 41 (21.1%) PE 10% ointment: 34 (17.3%) PL ointment: 18 (17.5%) partial clearance of all warts 0–50%: PE 15% ointment: 32 (16.5%) PE 10% ointment: 32 (16.3%) PL ointment: 31 (30.1%)	Recurrence of any warts: PE 15% ointment: 7 (6.5%) PE 10% ointment: 11 (10.7%) PL: 3 (8.8%) appearance of new warts: PE 15% ointment: 4 (3.7%) PE 10% ointment: 9 (8.3%) PL: none	Compliance >90% at any visit PE 15% ointment: 81.6% PE 10% ointment: 84.1% PL: 95.2% compliance >65% PE 15% ointment: 96.7% PE 10% ointment: 96.6% PL: 99.1%	Median total wart number PE 15% ointment: 100% decrease, SD PE 10% ointment: 100% decrease, SD PL: 64% decrease median total wart area PE 15% ointment: 100% decrease, SD PE 10% ointment: 100% decrease, SD PL: 69% decrease <0% clearance (increase) PE 15% ointment: 10 (5.2%) PE 10% ointment: 19 (9.7%) PL: 19 (18.4%)

*When data for both gender were pooled.

†LOCF (last observation carried forward) method.

F, female; M, male; NSD, no significant difference; PE, Polyphenon® E; PL, placebo; SD, significant difference.

LSS was erythema (mostly mild), followed by oedema and erosion, whereas the commonest LSM was itching, followed by burning.

Interestingly, in all groups LSR' incidence peaked between the second and fourth week of use, followed by a rapid decline in the subsequent period. Strangely, Stockfleth *et al.* report that LSR' incidence was slightly elevated in all groups after treatment cessation, compared with baseline, whereas in the other studies LSR' incidence at the end of treatment was well below that at baseline.

Furthermore, LSR' incidence of Polyphenon E 15% and 10% groups was largely identical. Stockfleth *et al.*, for example, report that LSR affected 86.2% and 81.5% of Polyphenon E 15% and 10% users, respectively. They also report that LSS affected 75.6% and 77.3% of Polyphenon E 15% and 10% users respectively. This could be an indication of the fact that LSR are primarily active substance related and not dose-related. Finally, a well-performed statistical analysis by Gross *et al.* clearly showed that complete responders had a statistically significant increase in LSR' incidence, compared with non-responders.

AEs other than LSR

Adverse events other than LSR were mostly mild. Gross *et al.* and Tatti *et al.* report a low AEs' incidence in the safety population, ranging from 19 to 30 patients. Tatti *et al.* report no AEs in the placebo group whereas Gross *et al.* report AEs in three placebo users. Both studies indicate that AEs related, or probably related to treatment, were recorded only in active treatment groups and that the main AEs recorded were the clustering of symptoms 'infections and infestations'. AEs were evenly distributed in Polyphenon E 15% and 10% groups in both studies.

Stockfleth *et al.* describe a different safety profile. They report an AEs incidence of approximately 22% in all groups, with no statistical difference between groups. They also report that AEs probably related to treatment were recorded in all groups, including placebo one. As in the other two studies, the most frequent was the cluster of 'infections and infestations'.

Withdrawls-dropouts-compliance

Two-hundred and eleven patients dropped out in total. All studies report 'patient withdrew consent' and 'lack of efficacy/treatment failure' as reasons for dropping out. Gross *et al.* and Stockfleth *et al.* report that only 3/242 and 8/303 patients respectively withdrew because of 'AE related to treatment'. Compliance was very high in all studies.

Meta-analysis

15% ointment vs. placebo. Patients using the 15% ointment demonstrated significantly higher likelihood of complete clearance of baseline warts (three studies – fixed effects RR: 1.53, 95% CI: 1.29–1.82, $P < 0.001$; Fig. 2) and of baseline and new warts (three studies – fixed effects RR: 1.45, 95% CI: 1.21–1.74, $P < 0.001$; Fig. 3) compared with controls at endpoint. No sign of heterogeneity among studies was detected ($I^2 = 0\%$ and 0%, respectively).

10% ointment/cream vs. placebo. Patients using the 10% ointment/cream had significantly higher likelihood of complete clearance of baseline warts (three studies – RR: 1.46, 95% CI: 1.23–1.75, $P < 0.001$; Fig. 4) and of baseline and new warts (three studies – fixed effects RR: 1.42, 95% CI: 1.19–1.70, $P < 0.001$; Fig. 5) compared with controls at endpoint. No sign of significant heterogeneity among studies was detected ($I^2 = 29\%$ and 0%, respectively).

Discussion

This systematic review and meta-analysis clearly demonstrates that both Polyphenon E formulations (15–10%) are efficacious for the treatment of EGWs, at least for the primary endpoint (complete clearance). Furthermore, a remarkably low rate of recurrence for both formulations is reported.

All studies report a remarkably low rate of recurrence for both 15% and 10% Polyphenon E. Although no direct comparison with other treatments can be performed, data from studies suggest superiority of Polyphenon E. Cryotherapy showed a risk of recurrence about 20–40%.[12] Imiquimod 5% cream and podofilox studies indicated recurrence rates ranging from 13% to 19%.[12,25] This data taken into account with preclinical data about green tea extracts, could be an indication that Polyphenon E may also have an effect on subclinical lesions.

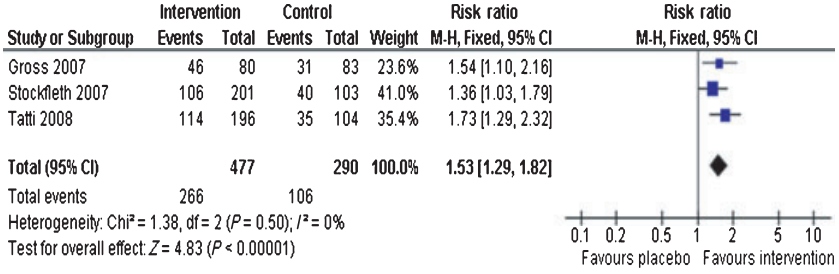

Figure 2 Complete clearance of baseline warts – 15% ointment vs. placebo.

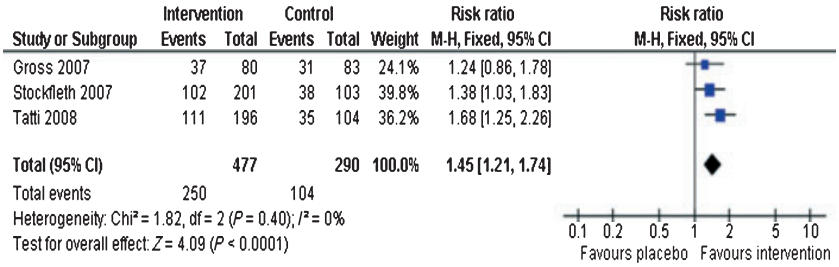

Figure 3 Complete clearance of baseline and new warts – 15% ointment vs. placebo.

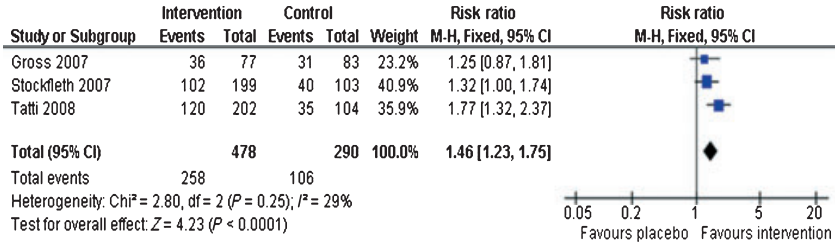

Figure 4 Complete clearance of baseline warts – 10% ointment/cream vs. placebo.

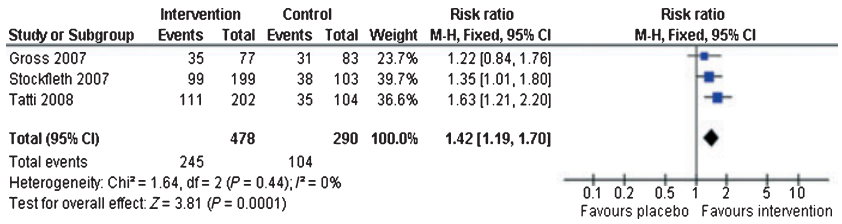

Figure 5 Complete clearance of baseline and new warts – 10% ointment/cream vs. placebo.

Gross *et al.* point out that a 12-week treatment period is perhaps short, as more than two-thirds of patients first have complete clearance between week 8 and 12 of treatment. However, the efficacy data presented for Polyphenon E 15% ointment are numerically identical to the other studies. Furthermore, Tatti *et al.* report that superiority of both 15% and 10% formulations compared with placebo is first observed at week 4 and 6 respectively and then at all subsequent visits. Stockfleth *et al.* report the same. All authors propose that onset of clearance starts at week 2 and that local reactions (peaking at week 2–4) at the application site are indicative and essential for achieving clinical response. One must keep in mind that time to clearance can be up to 16 weeks for Polyphenon E, compared with up to 8 weeks for imiquimod and 12 weeks for podophyllotoxin.

Polyphenon E use appears to be safe and well tolerated. All reported LSR and AEs are mostly mild, peaking between week 2 and 4 of treatment. The commonest LSS is erythema and the commonest LSM is itching. Compliance is very high and withdrawal attributed to is AEs minimum. The commonest AEs, other than local reactions, are 'infections and infestations'. Authors suggest that itching and erythema are signs of local stimulation of the immune system releasing pro-inflammatory cytokines. Based on unpublished data, it is suggested that onset of clearance starts at week 2 and that local reactions are indicative and essential for achieving clinical response.[22–24] This is partially supported by Gross *et al.*, whose well-performed statistical analysis clearly shows that complete responders had a significantly increased LSR' incidence compared with non-responders.

A clear comparison with other treatment modalities cannot be attempted, as there is no head-to-head studies available directly comparing Polyphenon E with other treatments. Treatments like cryotherapy, laser treatment, curettage and trichloroacetic acid application are often painful, tissue destructive and cause considerable problems like scarring, erosions, ulcers and infections.[9–11] Studies regarding imiquimod use report itching and burning as the main AE,[10,25] along with a 10% of fungal infections.[25]

An added benefit of Polyphenon E ointment use is that it is self-administered, resulting in a decreased number of required visits. It has been reported that, for privately insured patients, each case of genital warts results in an average of more than three physician visits at a cost of $436.[26] The proposed dosage schedule for Polyphenon E is three times daily, compared with three times/week for imiquimod.[10] This more complicated dosage schedule might decrease long-term compliance.

Some concern about the generalization of these results exists. Two of the included studies[23,24] excluded HIV-positive patients. It is well known that HIV-positive patients exhibit a higher EGWs prevalence rate and that the two conditions usually co-exist.[27] This exclusion criterion certainly limits the applicability of these results to immunocompetent EGWs patients. No data exist on efficacy of the treatment on internal warts.

Two studies allowed the concomitant oral usage of paracetamol or acetaminophen, if treatment of LSRs was needed.[23,24] Although this practice is not unusual, authors did not report frequency and size of this usage. This fact may have led to overestimation of tolerability. It is also important to highlight that all three studies state conflict of interest (mostly industry funding).

As EGWs is a chronic disease recurring frequently, cost-effectiveness is of great importance. A recent cost-effectiveness study evaluated cost-effectiveness and treatment-cost impact of sinecatechins use against imiquimod use, as first-line treatment of EGWs.[21] It concluded that sinecatechins yields a lower treatment cost, offering cost savings to healthcare systems, compared with imiquimod. However, this study fails to include in its decision analysis model the study by Gross *et al.*[22] As Gross *et al.* study indicated a slightly less efficacious profile than the other two studies,[23,24] this could be a great selection bias.

Overall, this meta-analysis clearly indicates efficacy of Polyphenon 15% and 10%, at least for the primary endpoint. Furthermore, Polyphenon E treatment shows very low recurrence rates, although follow-up periods are relatively short, and seems to have a rather favourable safety and tolerability profile. Recommendations for future studies should include longer follow-up periods, evaluation of the efficacy of green tea catechins in the treatment of internal anogenital warts and, most importantly, direct comparison of green tea catechins with its principal comparator, imiquimod.

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