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Topical Polyphenon® E in the treatment of external genital and perianal warts: a randomized controlled trial

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Conflicts of interest
A.M., H.T. and C.T. are employees of the sponsor, MediGene AG, Munich, Germany, and hold MediGene AG stocks; E.S. is a consultant for MediGene AG; and E.S., H.B., R.O. and F.G. have a contractual involvement as study investigators.

Summary

Background Benign external genital and perianal warts (condylomata acuminata) are disfiguring, displeasing skin tumours caused by human papillomavirus that may vitally burden affected patients and their partners. Current treatment options are still unsatisfactory due to low efficacy, high recurrence rates or an unfavourable side-effect profile. Although most recently prophylactic vaccines have been recommended for adolescent women, appropriate treatment modalities for anogenital warts are still needed. Green tea catechins exert antiviral, antioxidative, antiproliferative and immunostimulatory activity. Polyphenon® E (MediGene AG, Munich, Germany), a proprietary extract of green tea leaves, was therefore investigated for the topical treatment of this frequent viral disease.

Objectives To investigate Polyphenon® E 15% and 10% ointment for efficacy and safety in the treatment of anogenital warts in immunocompetent men and women.

Methods Five hundred and three patients were randomized to receive either Polyphenon® E 15% or 10% ointment or matching vehicle. The topical treatment was self-applied by the patients three times daily to all warts. Assessment of response and of adverse events was performed biweekly until complete clearance of all (baseline and new) anogenital warts or for up to 16 weeks. Recurrence was evaluated during a 12-week treatment-free follow-up period for patients with complete clearance.

Results About 53% of patients treated with Polyphenon® E 15% ointment showed complete clearance of all baseline and new anogenital warts, 51% for Polyphenon® E 10% ointment, and 37% for vehicle ($P = 0{\cdot}01$ and $P = 0{\cdot}03$, respectively; two-sided Fisher's exact test; intent-to-treat population, last observation carried forward analysis). Women responded better than men, with about 60% of women and 45% of men in both active groups achieving complete clearance of all warts. Time to complete clearance was comparable for both strengths of Polyphenon® E ointment. About 78% of all patients treated with either Polyphenon® E 15% or 10% ointment showed wart clearance rates of 50% or better. Less than 6% and 4% of patients in the Polyphenon® E 15% and 10% ointment groups experienced wart recurrence during follow-up. Polyphenon® E ointments demonstrated a good safety profile with the majority of all adverse events being local application site reactions assessed as mild or moderate. Local reactions declined during continued treatment.

Conclusions The results indicate that Polyphenon® E ointment is an efficacious and safe patient-applied topical treatment for external genital and perianal warts. Its use in intra-anal, intravaginal and cervical condylomas and other intraepithelial lesions warrants further clinical investigation.

External genital and perianal warts (EGWs, condylomata acuminata) are benign skin tumours caused by infection with human papillomavirus (HPV) types 6 and 11. They are one of the fastest growing sexually transmitted diseases worldwide. Current estimates quote more than 20 million potential patients with EGWs or subclinical disease in the U.S.A. and Europe. The incidence of EGWs in the Western world is about 1% of the sexually active population (15–49 years), with about 3·5 million new cases of genital warts in the seven major marketplaces worldwide every year.[1,2] After 1–8 months of incubation,[3] the infection causes disfiguring, displeasing, and even painful skin lesions that can coalesce into large plaques of up to several square centimetres in size. Distinct stages of the disease have not been classified; progression is rather defined by the increase in the number and/or size of the warts. As HPV 6 and 11 are not high-risk virus strains, progression of EGWs into a malignant stage is very unusual. These virus types are rarely associated with invasive squamous cell carcinoma. A rare exacerbated manifestation of HPV 6 and 11 infection is the Buschke–Loewenstein tumour (giant condylomata).

The type, appearance and prevalence of warts are generally determined by their anatomical location, gender, and type of skin, including degree of skin keratinization.[4,5] Warts in moist areas generally respond better to topical treatment than those located on dry surfaces.[6] Treatment success is influenced by the number and size of warts, location of warts, gender, and degree of skin keratinization.[7,8]

Currently available treatment options for EGWs improve the patient's condition, but a satisfactory balance of clearance rates, recurrence of warts after successful clearance, and the accompanying adverse reaction profile is rarely achieved. Current treatment modalities do not eliminate subclinical lesions or the virus, leading to new EGWs and considerable recurrence rates of up to 90%.[9] Chemical and destructive treatment options are painful and can be associated with tissue destruction and scarring. Recently, a quadrivalent HPV vaccine, including HPV strains 6 and 11, which cause EGWs, was approved and recommended for HPV vaccination of adolescent and young women (ages 11–26 years). Vaccination of older women and of men is not recommended.[10,11]

Polyphenon® E (MediGene AG, Munich, Germany) is a quantified extract from green tea leaves of the species *Camellia sinensis*, containing mainly tea polyphenols, including a group of related flavonoids, particularly catechins (> 80%). The lead catechin, (–)-epigallocatechin gallate (EGCG), comprises 50–72% of the catechin fraction. Although the exact pharmacological mechanism of action is still under investigation, specific properties may contribute to the antiwart efficacy of Polyphenon® E ointment. Tea catechins are very powerful antioxidants,[12–14] and Rösl *et al.*[15] demonstrated the inhibition of transcription of HPV viral proteins by antioxidants. In addition, inhibition of viral binding to receptors,[16] signal transduction and cell cycle modification, antiproliferative effects as well as induction of apoptosis[17–19] by tea catechins may add to the pharmacological effect of Polyphenon® E ointment.

The efficacy and safety of two strengths of patient-applied Polyphenon® E ointments, 15% and 10%, compared with vehicle, were investigated in men and women in two identical pivotal phase III clinical trials. In this article, we summarize the key results of the first pivotal study, conducted in Europe and South Africa. Study CT 1017 demonstrated efficacy and safety of Polyphenon® E ointment in the treatment of EGWs, with remarkably low recurrence rates.

Materials and methods

Study design

The study was a randomized, double-blind, three-arm parallel-group, vehicle-controlled, multicentre phase III trial to investigate the clinical efficacy and safety of Polyphenon® E 15% and 10% ointments as compared with vehicle in the topical treatment of EGWs, and to determine the most effective and safe dose. The maximum duration of treatment was 16 weeks or until complete clearance of all warts (baseline and newly appearing during treatment), whichever came first. For complete responders, a 12-week treatment-free follow-up phase directly followed to assess wart recurrence. Patient enrolment started on 30 September 2002 and ended on 20 May 2003. The last patient completed the study on 2 December 2003.

Data were collected at 46 dermatological, gynaecological and urological centres throughout Europe and South Africa, including university hospitals, hospitals and clinical practices. The study protocol and any other relevant study documentation were approved by the relevant authorities and the responsible local and/or national independent ethics committees prior to patient enrolment. The study was performed according to the Declaration of Helsinki and the International Conference on Harmonisation – Good Clinical Practice guideline as well as the demands of national drug and data protection laws and other applicable regulatory requirements. It was fully monitored and audited. All patients gave informed consent before participation.

Women and men, 18 years of age or older, with two to 30 clinically diagnosed EGWs with a total wart area of 12–600 mm^2, were enrolled. Locations of warts were glans penis, penile shaft, scrotum and foreskin for men, vulva for women, and the inguinal, perineal and perianal skin areas for both genders. Female patients and partners of male patients with childbearing potential had negative pregnancy tests and were to use effective contraception during the treatment period. Patients were not enrolled if they had a current episode of herpes genitalis or any other current and/or recurrent genital or uncontrolled infection, including known human immunodeficiency virus infection. Patients who had participated in an investigational trial, had treatment of anogenital warts or had systemic intake of virostatics or immunosuppressive medication within 30 days prior to enrolment were excluded. Patients with organ allograft, with skin conditions that may interfere with the study drug, with internal (vaginal or rectal)

warts that required treatment, or who were lactating, were also excluded.

Treatment

Patients were randomly assigned to Polyphenon® E 15% ointment, Polyphenon® E 10% ointment or vehicle in a 2 : 2 : 1 allocation ratio (Fig. 1). Centres were provided with medication kits that had a pre-assigned patient number, with each patient allocated the lowest available number. The randomization sequence was generated by Almedica HPS AG (Reinach/Basel, Switzerland). Throughout the study, the randomization list was neither available at the study centres nor to the project teams. Patients were instructed to apply the ointment three times daily, each application about 8 h apart, to all EGWs. If treatment of local skin reactions was needed, paracetamol could be given orally. No additional topical treatment was allowed.

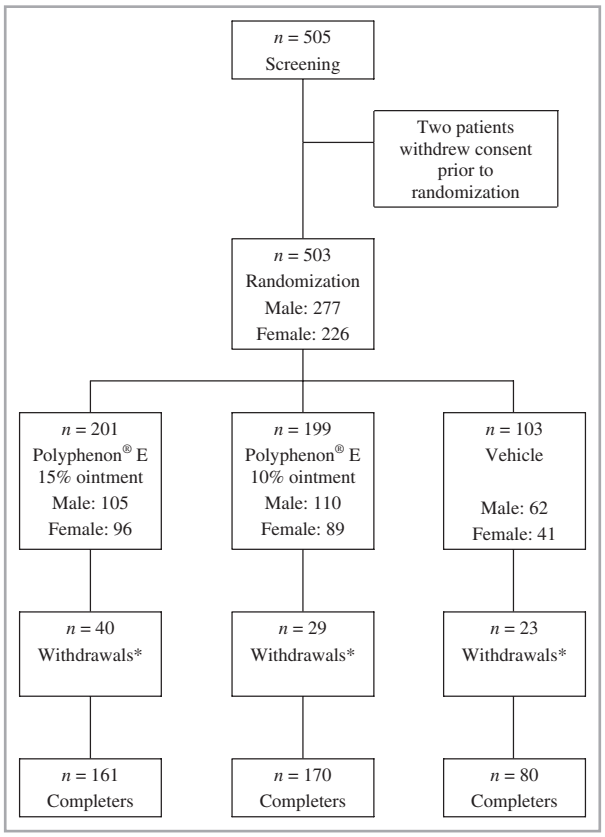

Fig 1. Patient disposition: flow diagram of patient progress through the three treatment groups and the study phases. *Withdrawals: The most frequently reported primary reasons for premature discontinuation were 'patient withdrew consent' in 16 (8·0%) patients, 10 (5·0%) patients and nine (8·7%) patients in the Polyphenon® E 15% and 10% ointment and vehicle groups, respectively, and 'noncompliance with study procedures' in six (3·0%) patients, seven (3·5%) patients and two (1·9%) patients, respectively. An adverse event was documented as the primary reason for premature study termination by eight (1·6%) patients: six (3·0%) patients, one (0·5%) patient and one (1·0%) patient in the Polyphenon® E 15% and 10% ointment and vehicle groups, respectively.

Study assessments

During screening and baseline visits, disease and medical history, demographic data, adverse events (AEs) and concomitant medications were recorded, laboratory assessments and a pregnancy test (women only), wart measurement, physical examination, assessment of vital signs and local tolerability parameters were performed as well as inclusion and exclusion criteria reviewed. In South Africa, women underwent a Pap smear test. Patient randomization and initial dispensing of study medication were done at baseline followed by treatment initiation. During the treatment period, wart measurements and local tolerability parameters, AEs, concomitant medication and drug compliance were checked every other week. At the last (end of treatment) visit, screening and baseline examinations were repeated. Patients with complete clearance of all warts stopped treatment and went into the treatment-free follow-up phase with visits after 4 and 12 weeks to assess recurrence rates. At these visits, local tolerability was evaluated and previously reported AEs and concomitant medications were updated. Photodocumentation was optional throughout the study.

Local reactions at the application site are important for the use of topical treatments. Therefore, they were evaluated and described separately from the other AEs. The investigator assessed local skin signs, including erythema, oedema, induration, vesicles, erosion/ulceration, other skin signs and overall skin signs, and the patient was questioned about local skin symptoms, including burning, itching, pain, other skin symptoms and overall skin symptoms. Intensity of all skin reactions at the site of application was graded as: none, mild (local skin reaction which can be easily tolerated), moderate (local skin reaction which is associated with considerable discomfort, but does not prevent usual activity), or severe (local skin reaction which substantially interferes with the patient's usual activity).

Statistical methods

The primary efficacy analysis was a comparison of the proportion of patients with complete clearance of all warts within the 16-week treatment period between the active treatment groups and vehicle. Sample size calculations were based on the hypotheses that complete clearance rates were 65% and 55% for the Polyphenon® E 15% and 10% ointments, respectively, and 35% for the vehicle group [based on the results of the previous 12-week study (CT 1005), implying an extrapolation of the treatment period from 12 to 16 weeks in the current study, and findings in the literature]. Using two-sided Fisher's exact tests with a target significance level of 5%, 400 patients (160 patients for both active treatment groups and 80 patients for the vehicle

group) were required to detect a significant difference for the comparison of each active treatment with placebo. With respect to multiple comparisons, the Hochberg procedure was applied to test the above hypotheses. To compensate for nonevaluable patients, we initially planned to enrol 480 patients in total.

The primary efficacy analysis was performed on the intent-to-treat (ITT) population. The confirmatory analysis was done by the last observation carried forward (LOCF) method, involving all efficacy-evaluable patients, i.e. patients who had the baseline and at least one postbaseline efficacy assessment. A second analysis, the observed-case (OC) analysis, included all patients who either achieved complete clearance within the treatment phase or completed the full 16 weeks of treatment without complete clearance. In addition, an exploratory analysis on the per-protocol (PP) population was performed.

Secondary efficacy endpoints, including complete clearance of baseline warts, total wart number, total wart area, partial clearance, and recurrent and new warts, were also analysed for the ITT population. For categorical data, differences among the different treatment groups with respect to demographic and clinical variables as well as for secondary endpoints were analysed by means of Fisher's exact test. For normally distributed data an analysis of variance was performed; for nonnormally distributed data the Wilcoxon two-sample test was used. All statistical tests applied were two sided. A 5% significance level without any adjustments for multiple comparisons was used in the analyses of demographic and clinical variables as well as for the secondary efficacy endpoints.

Safety assessments included biweekly AE reporting and evaluation of laboratory variables, vital signs, and physical examination performed before and after the treatment period. Safety/tolerability endpoints were analysed descriptively.

Statistical analysis was performed using SAS software, version 8.02 (SAS Institute, Cary, NC, U.S.A.).

Results

Demographic data

The three treatment groups were comparable with respect to their baseline characteristics, and statistical analysis did not reveal any significant differences (Table 1). There were slightly more men (55·1%) than women (44·9%), represented in all three treatment groups. Most patients were caucasian (477; 94·8%). The mean age was 30·7 years. Most men (251; 90·6%) were not circumcised; most women were of childbearing potential (201; 88·9%). Most patients (303; 60·2%) were nonsmokers.

All patients had previous episodes of EGWs. The majority of patients (462; 91·8%) had one episode, 19 (3·8%) patients had two, and 22 (4·4%) patients had three or more previous episodes. The mean lengths of time between first diagnosis of anogenital warts, current episode, and study baseline visit were comparable between the active treatment groups. The mean time between the start of the current episode and start of study treatment was similar between the active treatment groups and vehicle (31·5 weeks). Although all patients had at least one previous episode of EGWs, only 180 (35·8%) patients, similarly in all three treatment groups, had received treatment for previous episodes. Podofilox followed by curettage and electrodesiccation, laser surgery, and cryotherapy were the predominantly used previous treatment modalities.

The most affected areas were located at the penis shaft (65·0%) and the glans penis (24·2%) in men, and the vulva (84·1%) and perianal area (21·7%) in women. At baseline, a median of 6·0 warts was identical in the three treatment groups. The median baseline wart area was comparable in the three groups (50·5, 51·0 and 51·5 mm^2 for the Polyphenon® E 15% and 10% ointment and vehicle groups, respectively). Only in the Polyphenon® E 15% ointment group did the median baseline wart area of women (63·0 mm^2) differ markedly from that of men (35·0 mm^2).

Efficacy results

Complete clearance of all warts: primary endpoint

In the Polyphenon® E 15% and 10% ointment groups, complete clearance of all warts was established in 102 of 194 (52·6%) and 99 of 195 (50·8%) patients as compared with 38 of 102 (37·3%) patients in the vehicle group (ITT population, LOCF analysis) (Figs 2, 3). The comparison between both active treatment groups and vehicle showed statistical significance. Patients who completed the 16-week treatment period (OC analysis) showed complete clearance of all warts in 62·6%, 57·2% and 46·3% of patients (Polyphenon® E 15% and 10% ointment and vehicle, respectively). Only Polyphenon® E 15% ointment was statistically significantly superior to vehicle ($P = 0·0199$, Fisher's exact test). In general, complete clearance rates in women were higher than in men (Table 2). Analyses for the PP population strongly supported the results achieved in the ITT population.

The complete clearance rates of baseline warts were higher than the results obtained for the clearance rates of all warts. Statistically significant treatment effects were observed in the comparison of both Polyphenon® E 15% ointment (54·6%; $P = 0·0143$, Fisher's exact test) and Polyphenon® E 10% ointment with vehicle (52·3%; $P = 0·0376$, Fisher's exact test) for the LOCF analysis. Considering the OC analysis, only Polyphenon® E 15% ointment achieved a statistically significantly higher complete clearance of all baseline warts when compared with vehicle (65·0%; $P = 0·0188$, Fisher's exact test. Polyphenon® E 10% ointment: 59·5%; $P = 0·1371$, Fisher's exact test. Vehicle: 48·8%).

Total wart number and total wart area

Analogous to the complete clearance of all warts, median total wart number and median total wart area went to zero

Table 1 Baseline characteristics (intent-to-treat population)

	Polyphenon® E 15% ointment	Polyphenon® E 10% ointment	Vehicle	Total	P-value
Gender					
Male, n (%)	105 (52·2)	110 (55·3)	62 (60·2)	277 (55·1)	
Female, n (%)	96 (47·8)	89 (44·7)	41 (39·8)	226 (44·9)	
Total, n (%)	201 (100)	199 (100)	103 (100)	503 (100)	0·4174[a]
Ethnic group					
African, n (%)	6 (3·0)	6 (3·0)	4 (3·9)	16 (3·2)	
Asian, n (%)	1 (0·5)	1 (0·5)	1 (1·0)	3 (0·6)	
Caucasian, n (%)	191 (95·0)	189 (95·0)	97 (94·2)	477 (94·8)	
Hispanic, n (%)	1 (0·5)	0	0	1 (0·2)	
Other, n (%)	2 (1·0)	3 (1·5)	1 (1·0)	6 (1·2)	
Total, n (%)	201 (100)	199 (100)	103 (100)	503 (100)	0·9709[a]
Age (years)					
Mean	30·8	30·6	30·4	30·7	0·9070[b]
SD	11·1	10·8	10·9	10·9	
Range	17[c]–69	16[c]–98	18–60	16[c]–98	
Height (cm)					
Mean	173·0	173·7	173·9	173·5	0·7476[b]
SD	8·5	9·1	9·3	8·9	
Range	154–197	150–198	154–203	150–203	
Body weight (kg)					
Mean	70·4	71·7	71·2	71·1	0·6151[b]
SD	14·2	13·8	15·0	14·2	
Range	46–115	47–133	44–105	44–133	
Body mass index (kg m^{-2})					
Mean	23·4	23·7	23·4	23·5	0·7103[b]
SD	3·8	3·7	3·9	3·8	
Range	16·1–38·7	17·3–43·9	16·9–36·7	16·1–43·9	
Circumcision (men only)					
No, n (%)	98 (93·3)	97 (88·2)	56 (90·3)	251 (90·6)	
Yes, n (%)	7 (6·7)	13 (11·8)	6 (9·7)	26 (9·4)	0·45[a]
Childbearing potential (women only)					
No, n (%)	11 (11·5)	10 (11·2)	4 (9·8)	25 (11·1)	
Yes, n (%)	85 (88·5)	79 (88·8)	37 (90·2)	201 (88·9)	0·99[a]
Smoking history					
Current, n (%)	64 (31·8)	75 (37·7)	29 (28·2)	168 (33·4)	0·51[a]
Nonsmoker, n (%)	123 (61·2)	113 (56·8)	67 (65·0)	303 (60·2)	
Previous, n (%)	14 (7·0)	11 (5·5)	7 (6·8)	32 (6·4)	

[a]Fisher's exact test. [b]Analysis of variance model. [c]Including protocol violators.

in both Polyphenon® E 15% and 10% ointment groups by the end of treatment. For both parameters, a statistically significant difference when compared with vehicle was determined (Table 3).

Time to complete clearance, time to partial clearance

The median time to complete clearance of all warts was 16·3 weeks for Polyphenon® E 15% ointment and was close to statistical significance ($P = 0·0595$, log rank test), and 16·4 weeks for Polyphenon® E 10% ointment, which was not statistically different from 16·7 weeks for vehicle. The earliest and latest time points of complete clearance of all warts with Polyphenon® E 15% ointment were 2·0 weeks and 18·9 weeks after treatment start, and with Polyphenon® E 10% ointment at 4·0 weeks and 18·1 weeks after treatment start, respectively.

The median times to partial clearance of all warts, i.e. to 50%, 70%, 80% and 90% clearance, were all statistically significantly shorter for the treatment with both Polyphenon® E ointments than with vehicle.

Partial clearance

Partial clearance rates of at least 50% based on all patients' last visit during the 16-week treatment period were reported for 77·3% and 78·0% of patients of the Polyphenon® E 15% and 10% ointment groups, respectively, yielding statistically significant better results when compared with vehicle (52·9%; $P < 0·001$ each; Fisher's exact test).

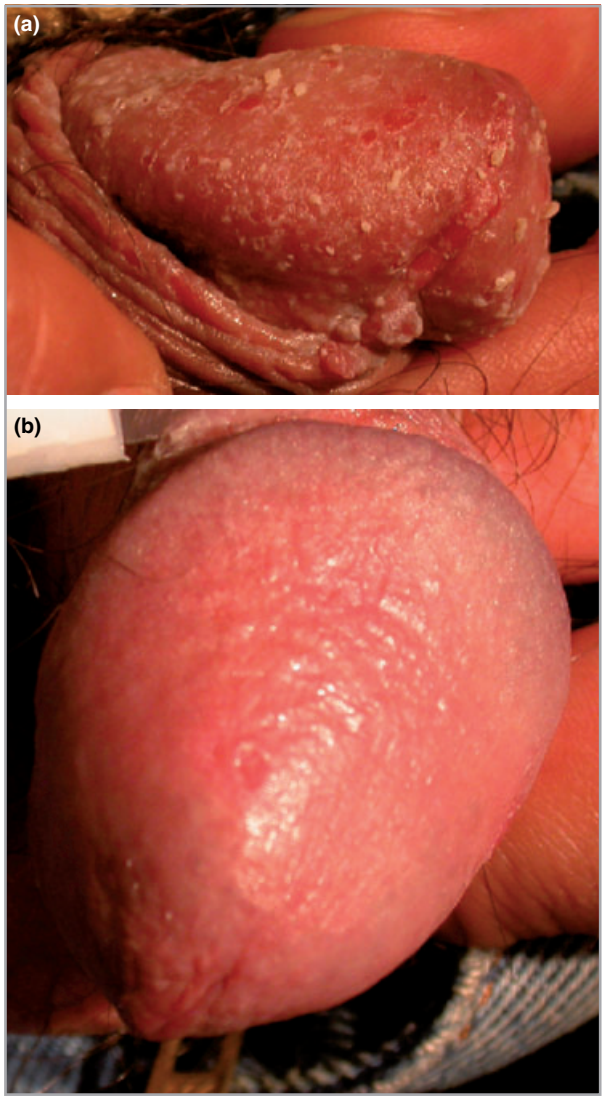

Fig 2. Patient with external genital warts on glans penis, frenulum and foreskin, treated with Polyphenon® E 10% ointment for 12 weeks when complete clearance of all warts was achieved. The clinical appearance is shown (a) before and (b) after treatment.

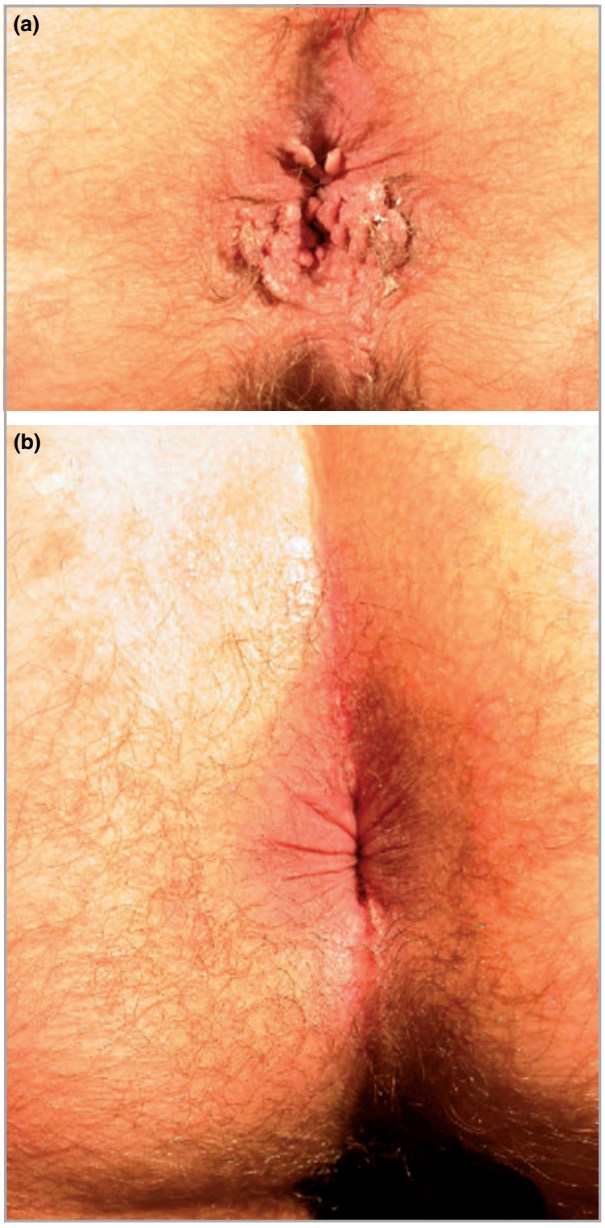

Fig 3. Complete clearance of all external anogenital warts on the anus treated with Polyphenon® E 15% ointment for 16 weeks. The clinical appearance is shown (a) before and (b) after treatment.

Recurrence and new warts

During the 12-week treatment-free follow-up period, six (5·9%) and four (4·1%) patients in the Polyphenon® E 15% and 10% ointment groups had a recurrence of anogenital warts compared with one (2·6%) patient in the vehicle group.

Seven patients developed new warts during the 12 weeks of follow-up: one (1·0%) in the Polyphenon® E 15% ointment group, five (5·1%) in the Polyphenon® E 10% ointment group and one (2·6%) in the vehicle group.

Safety results

The safety population consisted of 502 patients who were randomized and who received at least one application of the study medication. The mean duration of treatment in the safety population was 98·7 days in the Polyphenon® E 10% ointment group, 92·9 days in the Polyphenon® E 15% ointment group and 95·8 days in the vehicle group.

Local reactions

Prior to study treatment at baseline (visit 1), 64 (12·7%) patients presented with local skin signs and 93 (18·5%) patients with local skin symptoms, with 1·5–2 times higher patient percentages showing local skin signs in the active treatment groups than in the vehicle group.

Table 2 Complete clearance of all warts (baseline and new) and complete clearance of baseline warts: intent-to-treat population, last observation carried forward (LOCF) and observed case (OC) analyses

	Polyphenon® E 15% ointment (n = 201)			Polyphenon® E 10% ointment (n = 199)			Vehicle (n = 103)		
	n	%, LOCF (n = 194)	%, OC (n = 163)	n	%, LOCF (n = 195)	%, OC (n = 173)	n	%, LOCF (n = 102)	%, OC (n = 82)
Complete clearance of all warts									
All patients	102	52·6	62·6	99	50·8	57·2	38	37·3	46·3
P-value		0·0143[a]	0·0199[a]		0·0280[a]	0·1089[a]			
Men	48	47·5	59·3	47	43·1	51·1	21	34·4	43·8
Women	54	58·1	65·9	52	60·5	64·2	17	41·5	50·0
Complete clearance of baseline warts									
All patients	106	54·6	65·0	102	52·3	59·5	40	39·2	48·8
P-value		0·0143[a]	0·0188[a]		0·0376[a]	0·1371[a]			
Men	49	48·5	60·5	49	45·0	53·3	22	36·1	45·8
Women	57	61·3	69·5	53	61·6	66·7	18	43·9	52·9

[a]Two-sided Fisher's exact test.

Table 3 Total wart number and total wart area (mm^2) at start and end of treatment: intent-to-treat population, last observation carried forward analysis

	Polyphenon® E 15% ointment (n = 201)	Polyphenon® E 10% ointment (n = 199)	Vehicle (n = 103)
Total wart number			
Visit 1/baseline			
Mean ± SD	8·2 ± 6·3	8·3 ± 5·8	7·2 ± 4·6
Median	6·0	6·0	6·0
Range	2·0–29·0	2·0–28·0	2·0–25·0
P-value	0·5147[a]	0·1804[a]	
Visit 9/end of treatment			
Mean ± SD	2·7 ± 4·5	3·1 ± 5·6	4·5 ± 5·1
Median	0·0	0·0	3·0
Range	0·0–25·0	0·0–40·0	0·0–20·0
P-value	0·0007[a]	0·0025[a]	
Total wart area			
Visit 1/baseline			
Mean ± SD (mm^2)	94·2 ± 116·5	99·5 ± 117·1	75·6 ± 79·2
Median	50·5	51·0	51·5
Range (mm^2)	12·0–591·0	13·0–572·0	12·0–490·0
P-value	0·9152[a]	0·3882[a]	
Visit 9/end of treatment			
Mean ± SD (mm^2)	27·1 ± 63·8	28·7 ± 86·7	41·3 ± 66·0
Median	0·0	0·0	15·0
Range (mm^2)	0·0–424·0	0·0–728·0	0·0–401·0
P-value	0·0011[a]	0·0010[a]	

Median total wart number and median total wart area were similar between both Polyphenon® E ointment groups and vehicle at treatment start (visit 1/baseline), but were zero in both active treatment groups compared with 3·0 and 15·0 mm^2, respectively, in the vehicle group at the end of treatment. This constitutes a statistically significant difference between both Polyphenon® E ointment groups and vehicle for both parameters. [a]Two-sided Wilcoxon test: active treatment group compared with vehicle.

Local skin reactions, i.e. local skin signs and local skin symptoms, were reported during the treatment phase in 169 (86·2%) patients of the Polyphenon® E 15% ointment group, 159 (81·5%) patients of the Polyphenon® E 10% ointment group and 63 (61·8%) patients of the vehicle group.

During the treatment period, 352 (70·1%) patients presented with local skin signs (investigator assessment): 152 (75·6%) patients in the Polyphenon® E 15% ointment group, 153 (77·3%) patients in the Polyphenon® E 10% ointment group and 47 (45·6%) patients in the vehicle group. The local skin signs increased in all three treatment groups and in both

genders until week 2 (Polyphenon® E ointment groups) or week 4 (vehicle) and decreased thereafter gradually with continued treatment, resulting, by the end of treatment, in slightly elevated levels compared with baseline. Overall, the most frequently observed local skin signs were erythema, oedema and erosion. Severe local skin signs were noted for 35 (7·0%) patients during the treatment period [Polyphenon® E 15% ointment: 25 (12·4%) patients; Polyphenon® E 10% ointment: eight (4·0%) patients; vehicle: two (1·9%) patients].

Most local skin reactions were of mild intensity in all three treatment groups. The time courses of local skin reactions of moderate and severe intensity paralleled the overall occurrence of local skin reactions in the Polyphenon® E ointment groups: a peak at visit 2 followed by a gradual decrease by the end of treatment.

Adverse events

During the treatment period, 113 (22·5%) patients in the safety population had 180 AEs other than local reactions: 70 events occurred in 44 (21·9%) patients in the Polyphenon® E 15% ointment group, 84 events occurred in 47 (23·7%) patients in the Polyphenon® E 10% ointment group, and 26 events occurred in 22 (21·4%) patients in the vehicle group, indicating no significant difference between active treatments and vehicle ($P = 0·89$, Fisher's exact test). The most frequently reported AEs, headaches (19 patients; 3·8%), respiratory tract infections (eight patients; 1·6%) and influenza (seven patients, 1·4%), were evenly distributed in the three treatment groups and were not related to the study medication.

AEs other than local reactions that were probably related to study medication were reported by four (0·8%) patients, including moderate balanitis, severe herpes simplex, mild lymphadenitis and severe phimosis, all in the Polyphenon® E 15% ointment group. Six (1·2%) patients had AEs other than local reactions that were considered to be possibly related to the study medication: one patient treated with Polyphenon® E 15% ointment (mild urethritis), three patients treated with Polyphenon® E 10% ointment (moderate lymphadenitis, moderate rash, moderate phimosis) and two patients treated with vehicle (mild dysuria, moderate eczema).

Most of the AEs reported were of mild intensity. AEs assessed as mild were reported by 28 (13·9%) patients in the Polyphenon® E 15% ointment group, 24 (12·1%) patients in the Polyphenon® E 10% ointment group and 17 (16·5%) patients in the vehicle group. Moderate AEs were documented for 17 (8·5%) patients in the Polyphenon® E 15% ointment group, for 30 (15·2%) patients in the Polyphenon® E 10% ointment group and for six (5·8%) patients in the vehicle group. Severe AEs were noted in 10 (2·0%) patients: seven (3·5%) patients in the Polyphenon® E 15% ointment group, two (1·0%) patients in the Polyphenon® E 10% ointment group and one (1·0%) patient in the vehicle group.

Serious AEs occurred in two patients only, one patient in each of the active treatment groups. The patient in the Polyphenon® E 15% ointment group had an application site reaction with severe local symptoms (redness, oedema, burning and pain). The patient sought surgical wart removal at a hospital, and recovered without sequelae. The second patient (Polyphenon® E 10% ointment) had an unrelated limb injury.

Compliance with the treatment was good and only a few patients reported treatment reductions (with a maximum of 6·1%, 5·4% and 5·0% for Polyphenon® E 15% and 10% ointment and vehicle, respectively) or interruptions (with maximum of 10·3%, 5·9% and 4·8% for Polyphenon® E 15% and 10% ointment and vehicle, respectively) per visit. Only eight (1·6%) patients from all three treatment groups withdrew from the study due to AEs.

Other safety parameters

The three treatment groups were comparable with regards to all baseline haematological, biochemical and urinalysis variables as well as to all mean values of systolic and diastolic blood pressure, body weight and body mass index. The mean values measured for each laboratory parameter were mainly within the reference range and no clinically significant changes were noted during the treatment period.

Discussion

Green tea, green tea extracts, or their components, polyphenols or catechins, showed compelling effects in preclinical *in vitro* and *in vivo* studies suggesting multifaceted properties, including antioxidant, antiviral, antiproliferative and anticancer/cancer chemopreventive activity. However, human clinical studies, particularly with topical administration, have so far been investigated only to a limited extent. A couple of clinical studies exploring ultraviolet protection[20–22] showed effectiveness for green tea extracts or EGCG, the most abundant green tea catechin. Recently, tumour-related clinical studies also demonstrated the clinical efficacy of green tea extracts. Bettuzzi *et al.*[23] showed that in patients with high-grade prostate intraepithelial neoplasia, daily oral administration of a green tea catechin preparation (600 mg total) resulted in only 3% of patients who developed prostate cancer while 30% of vehicle-treated patients developed prostate cancer. Based on *in vitro* results with EGCG indicating inhibition of HPV-induced cervical cancer cell growth through apoptosis, cell cycle arrest, and the regulation of gene expression,[24] Ahn *et al.*[25] investigated the clinical efficacy of green tea extracts, Polyphenon® E and EGCG, on human cervical lesions. Overall, topical application of Polyphenon® E ointment showed clinical efficacy in 74% of patients, and in combination with oral administration of Polyphenon® E capsules 75% of patients showed a positive response. Polyphenon® E or EGCG capsules alone achieved 50% and 60% positive clinical response.

Although a prophylactic quadrivalent HPV vaccine, covering HPV 6 and 11, was approved recently, topical treatment

modalities remain of considerable relevance as only adolescent and young women are recommended for vaccination.[10,11] Thus, the affected population not vaccinated, particularly adult women of sexually active age and the entire male population, continuously needs efficacious, available and affordable medical treatment.

It is in this context that clinical studies investigating the clinical efficacy of a topically applied defined green tea extract, Polyphenon® E, in HPV-induced benign skin tumours, were set up. The clinical study presented here was designed as a randomized, double-blind, three-arm parallel-group, vehicle-controlled phase III study with the objectives of investigating the clinical efficacy and safety of Polyphenon® E 15% and 10% ointments in the topical treatment of EGWs in immunocompetent men and women, and to determine the most efficacious and safe dose over a maximum treatment period of 16 weeks.

Complete clearance of all warts, i.e. all warts present at baseline and before first study medication application, and all new warts occurring during the 16-week treatment period, represents a unique study endpoint to be reached for the first time by a treatment for genital and perianal warts. So far, for the other approved treatment options, only the baseline warts had to be cleared. Complete clearance of all warts was shown in 52·6% of the patients treated with Polyphenon® E 15% ointment and in 50·8% of the patients treated with Polyphenon® E 10% ointment (ITT population, LOCF). When all patients were considered who achieved complete clearance of all warts within the 16-week treatment period or who completed the full 16 weeks of treatment (OC analysis) according to protocol, the clearance rates are considerably higher: 62·6% and 57·2% for the Polyphenon® E 15% and 10% ointments, indicating higher complete clearance rates when patients continue wart treatment. This is supported by the results of the PP population, patients who fully adhered to the protocol stipulations, with almost identical complete clearance rates. In comparison, recommended regimens for EGWs[26] showed clearance rates for baseline warts of 60–90% (cryotherapy), 30–80% (imiquimod), 45–80% (podofilox), 30–80% (podophyllin resin), 35–70% (surgical excision) and 50–80% (trichloroacetic acid).[9,27] Thus, Polyphenon® E ointment was found to be competitive with these regimens when considering complete clearance of all warts and particularly when considering the even higher efficacy rates for complete clearance of baseline warts. Moreover, Polyphenon® E ointment offered additional benefit by clearing warts by 50% and more in almost 80% of patients.

The use of Polyphenon® E 15% and 10% ointment led to recurrence rates of 5·9% and 4·1%, respectively. Other treatment modalities gave recurrence rates ranging between 5% and 65%. Cryotherapy, for instance, showed a convincing clearance rate but risk of recurrence is about 20–40%. Likewise, imiquimod 5% cream and podofilox demonstrated comparable efficacy rates but recurrence rates ranged from 13% to 19% and up to 91%, respectively.[9,27] Similarly, occurrence of new warts after complete clearance was low (1·0% and 5·1% for Polyphenon® E 15% and 10% ointment), suggesting that topical Polyphenon® E might have also an effect on adjoining subclinical lesions as well.

Median time to clearance was 16 weeks, a surprisingly long time period. This may partly be due to a considerable number of patients who achieved complete clearance but delayed attendance at the regular final wart assessment at the clinical centre. However, analyses of onset of clearance revealed that in week 2 of treatment the first effects and even the first complete clearances were observed. In addition, local inflammatory reactions at the application site typically occurred with highest intensity between weeks 2 and 4. In accordance with preclinical findings, it is assumed that Polyphenon® E ointments stimulate the immune system locally releasing pro-inflammatory cytokines (e.g. interleukin-1, interferon-γ, tumour necrosis factor-α), which, in turn, elicit the observed local skin reactions such as erythema, oedema and itching. This suggests that local reactions at the application site are indicative and essential for achieving clinical response. And, indeed, a correlation analysis of previous clinical data confirmed this hypothesis (own unpublished data). Although postulated to be needed for wart clearance, local skin reactions were predominantly mild or moderate and only up to 2·2% of patients reported severe local reactions at any given visit.

Compliance with the treatment was good and only a few patients reduced, interrupted or were withdrawn from study treatment. Almost all of these patients were diagnosed with local skin reactions with single cases of hypersensitivity, allergy or drug toxicity, presumably wrongly classified as severe without correct understanding the interrelation of AEs with the active principle.

AEs other than local reactions that were related to study medication were infrequent. This result, in combination with the pharmacokinetic finding of a negligible systemic availability of Polyphenon® E catechins (own unpublished results), underscores that the vast majority of side-effects are local skin reactions at the application site and that systemic effects seem to be minor and very rare.

In conclusion, the efficacy results of this first pivotal phase III study indicated superiority of topical Polyphenon® E 15% and 10% ointments over vehicle. Both ointment strengths had comparable good safety profiles taking into consideration the generally very low number of treatment-related AEs (other than local reactions), serious and severe AEs. The vast majority of AEs were local skin reactions at the application site, deemed necessary for clinical response according to the active principle. Most of the AEs were of mild or moderate intensity and declined during continued treatment by the end of the treatment period.

Thus, the data suggest that Polyphenon® E 15% and 10% ointments may prove to be a promising, self-applied, topical treatment option for EGWs, with a favourable safety profile. For the first time, excellent complete clearance rates of all (baseline and new) anogenital warts were achieved. Very low rates of wart recurrence and occurrence of new warts after the end of treatment underpin the competitive profile of this novel and unique green tea extract. On this basis, treatment of

other skin diseases is conceivable in the further drug development of this unique natural herbal product.

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