

ORIGINAL ARTICLE

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

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Summary: This dose-escalation study was performed to evaluate safety and efficacy of imiquimod 5% cream in the treatment of uncircumcised men with penile warts associated with the foreskin. The cream was applied 3 times/week ($n=34$) or once per day ($n=30$) over 8 ± 2 h. Imiquimod 5% cream was safe in both treatment groups. However, the 3 times/week regimen was better tolerated with a lower incidence of local skin reactions. In both groups, the 2 most frequently reported local skin reactions were erythema and erosion; they were more severe with the once-daily dosing. The most frequently reported application site reactions were burning, pruritus and irritation or pain (once-daily patients only). Total clearance was achieved in 62% of the patients in the 3 times/week group and by 57% in the once-daily group. Thus, imiquimod 5% cream administered 3 times/week was the optimal dosing regimen in the treatment of penile warts in uncircumcised men.

Keywords: External genital warts, imiquimod 5% cream, uncircumcised men, dose escalation, immune response modifier

INTRODUCTION

Genital infections with the human papillomavirus (HPV) are known to be the most frequent viral sexually transmitted disease (STD). In most cases the infection takes a latent course without clinical manifestations. Epidemiological data from the United States show that only about 1% of the sexually-active population present anogenital warts while as many as 5–20% are infected with HPV¹. Most genital warts are seen in young adults with the highest prevalence in women under 25 years of age. External anogenital warts in females are mostly in the vulva and the perianal area; in males they are mainly located on the penile shaft and the perianal area.

An effective treatment of the disease is of great importance from the medical, psychological and economic perspectives. This is especially true due to a strong correlation between HPV infections

caused by certain virus types and the development of dysplasia and intraepithelial neoplasia which may lead to the development of carcinomas.

To date, none of the common treatments have proven to be curative. Both ablative methods and drug treatments may remove HPV-induced warts in a high percentage of cases, but recurrences may be expected in about 1/4 to 2/3 of cases².

Imiquimod (1-(2-methylpropyl)-1*H*-imidazo-[4,5-*c*]quinolin-4 amine) is the first representative of a new class of *immune response modifiers*, demonstrating *in vivo* potent antiviral and antitumour activity^{3,4}. The biological activity of imiquimod is attributed to its ability to induce the production of interferon-alpha and other cytokines (including interleukin-1 (IL-1), IL-6, IL-8 and tumour necrosis factor-alpha [TNF- α]), thereby stimulating cellular immunity of the skin. It has been shown that the biological effects of imiquimod are similar to the immunological events occurring during the spontaneous regression of genital warts^{5,6}.

As a topically applied 5% cream, imiquimod showed good efficacy in treating external genital and perianal warts^{5,7–9}. In the pivotal phase III trial⁷ with 3 times/week dosing, total clearance was

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achieved in 50% of all patients receiving imiquimod 5% compared with 11% of those receiving placebo. The application of imiquimod 5% cream is often followed by a local inflammatory skin reaction which is believed to be related to the pharmacological properties of the drug. This reaction may present a particular risk when the drug is administered in occluded or potentially occluded areas such as under the foreskin.

Most of the male patients enrolled in the previous studies were circumcised, a common circumstance in the United States and Canada where the studies were conducted. This dose-escalation study was performed to evaluate the safety and efficacy of imiquimod 5% cream in the treatment of uncircumcised men with penile warts associated with the foreskin.

METHODS

Study design

This was a phase II, open-label, dose-escalation, multicentre study. Nine study sites were located in Germany and 4 in France. The primary objective was to evaluate the safety of imiquimod 5% cream in uncircumcised males. The safety population included all patients who received at least one dose of study drug. The approval of local ethical committees was obtained prior to the start of the study and each patient's written consent was obtained prior to enrolment. The study was performed according to Good Clinical Practice (GCP) and International Committee on Harmonization (ICH) Guidelines.

Patients

Uncircumcised male outpatients (aged ≥ 18 years) with external anogenital warts were enrolled. Patients were required to have at least 3 warts with a minimum wart area of 30 mm² and at least one target wart located in the foreskin area. Patients were required to be able to retract the foreskin and were instructed to practise daily hygiene by retracting and cleaning under the foreskin. HIV-positive patients who met the United States Centers for Disease Control classification of A1 could be enrolled into the study if they were asymptomatic or with peripheral generalized lymphadenopathy and CD4-positive T-cell counts greater than 500.

Patients were excluded if they had had any previous treatment with imiquimod, interferon, immunomodulators, oral or topical antiviral therapy (except for oral acyclovir for suppressive or acute therapy), cytotoxic drugs, other investigational drugs or drugs known to have major organ toxicity, or chemical and/or surgical wart therapy within 4 weeks of entering the study. Additionally, no oral or inhaled corticosteroids ($>1200 \mu\text{g}/\text{day}$) or any topical non-wart therapy to the wart sites were allowed within 2 weeks prior to initiating the

study. Other exclusion criteria included: frequent outbreaks ($>6/\text{year}$) of herpes genitalis at any wart site; known penile or anal intraepithelial neoplasia 2 or 3; evidence of clinically significant cardiovascular (New York Heart Association 3–4 Congestive Heart Failure), immunosuppressive, haematological, hepatic, neurological, renal, endocrine, collagen, vascular or gastrointestinal abnormalities or diseases; current chemical or alcohol dependency; psoriasis or any dermatological disease at the wart site which may have interfered with the study; any clinically significant laboratory abnormalities which would have interfered with the patient's participation in the study. If clinically indicated, screening for other STDs (including syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) was performed and patients with a positive screen were treated and cleared of the condition prior to enrolment in the study.

Treatment schedule and control visits

The planned treatment schedule included the application of imiquimod 5% cream 3 times/week, once daily or twice daily. Patients who fulfilled the inclusion and exclusion criteria were sequentially allocated to the different treatment groups starting with the 3 times/week application. The study only progressed to the next treatment group when the safety profile, established when the 30th patient in the ongoing treatment group had completed 8 weeks of imiquimod treatment, was considered acceptable. The safety and efficacy of a 3 times/week treatment has been well established in previous vehicle-controlled trials^{5,7,8}. Therefore this dosing group served as a control group to which results from the other 2 treatment groups could be compared. The twice-daily dosing regimen was included to better understand the safety profile of imiquimod in the event it was used at this dosing regimen post-licensure. However, when the safety data of the once-daily treatment group were evaluated, 3M Pharmaceuticals decided not to perform the twice-daily dosing schedule.

Imiquimod 5% cream was applied for 8 ± 2 h during normal sleeping hours in the 3 times/week and in the once-daily treatment group. Treatment was continued for a maximum of 16 weeks or until the baseline target warts cleared, whichever occurred first. Patients were allowed to take rest periods for a maximum of 42 days during the 16-week treatment period if the severity of local skin reactions warranted study drug interruption. Any single rest period was limited to 14 consecutive days.

During the screening visit, the inclusion and exclusion criteria were reviewed and anogenital wart and medical histories collected, including information on allergies, alcohol and tobacco use or substance abuse. Patients returned to the clinic after 1, 2, 4, 8, 12 and 16 weeks to evaluate changes in wart area, local skin reactions, adverse events

and vital signs. Blood and urine samples were collected at specified visits for routine laboratory tests.

Assessment of safety parameters

Criteria for evaluation were objective local skin reactions (erythema, oedema, induration, vesicles, erosion, ulceration, excoriation/flaking, scabbing) at the wart sites and at sites remote to the target wart sites; the severity of each reaction was rated by the study site staff and separately by the patients on a scale of 0 to 3 (0=none, 1=mild, 2=moderate and 3=severe). Photographs were taken to document the skin reactions. Patients were asked to assess the severity of subjective application site reactions like itching, burning, pain with a rating scale of 0 (no discomfort) to 4 (substantial discomfort interfering with the patient's daily activities). Further safety parameters were other adverse events, vital signs (sitting blood pressure, pulse rate, respiratory rate, temperature), physical examination, clinical laboratory tests and concomitant medication.

Assessment of efficacy

The criterion for evaluation of efficacy was wart clearance assessed by 2 dimensional measurements and photographs. The area of each target wart was calculated by measuring the 2 largest perpendicular dimensions (height, width or length) of each wart or cluster of warts, and taking the product of these 2 measurements. The locations of target warts were diagrammed and numbered at the initiation visit. Any new warts developing during the treatment were added to the diagram and clearly documented as new warts. Photographs served to document wart progression or regression.

Statistics

Local skin reaction scores at each week were compared across treatments using the Wilcoxon rank sum test. The proportion of patients reporting at least one adverse event was compared across treatments using the Fisher's exact test. The effect of treatment, for each treatment group, on the laboratory parameters was assessed using the McNemar's test. The Wilcoxon signed rank test and Student's two-sample *t*-test were used to test for differences within treatments for numerical laboratory values. The Wilcoxon rank sum test and Student's two-sample *t*-test were used to compare each laboratory parameter across treatments.

The proportion of patients experiencing total clearance of target warts by week 16 was compared across treatments by the Fisher's exact test. The generalized Wilcoxon test compared time to total clearance across treatments. Time to clearance was computed using Kaplan-Meier estimates.

RESULTS

Patient characteristics

A total of 64 male patients were included in the study, 34 were treated 3 times/week and 30 were treated once per day. Ages ranged from 19-69 years with a mean of 30.7 years. Thirty-eight patients (59.4%) were current tobacco smokers and 23 patients (35.9%) were alcohol drinkers. No patient had a history of substance abuse. Four patients (6.3%) reported allergies to medications, and 14 patients (21.9%) reported other allergies.

Characteristics of wart disease at baseline

The most common location of warts was in the subpreputial area (76.6%). The median total wart area at baseline was 65.5 mm². Time since initial outbreak of the disease ranged from 0.0-8.9 years (mean 1.4 years), and the mean duration of the current outbreak was 6.85 months. Overall, 62.5% of patients had undergone previous treatment, most often with podophyllotoxin (20.3%) or laser treatment (21.9%).

The treatment groups were comparable for all baseline characteristics, however, no formal testing was performed to assess the baseline comparability of these parameters across treatment groups, as recommended by Altman¹⁰ and Senn¹¹. Details on the characteristics of the target warts and the history of disease are given in Table 1.

Patient accountability and reasons for withdrawal

Seventy-two patients were screened, of whom 64 were eligible for the study. The 16-week treatment period was completed by 27/34 patients in the 3 times/week group and 24/30 patients in the once-daily group, respectively. Overall, 13 patients were withdrawn prior to completion of the study as shown in Table 2. No significant differences were seen between treatment groups. More than one reason could be recorded: 3 of the 6 patients with multiple reasons discontinued due to personal reasons in combination with lack of therapeutic effect (one in the 3 times/week group and 2 in the daily treatment group).

Those 5 patients who discontinued the study because of skin reactions reported the following application site reactions to the medication: burning, dryness, moderate erythema, severe irritation, moderate to severe erosion, mild vesicles and mild excoriation/flaking.

Safety evaluation

The mean total number of doses was 24.4 (range 3-50) in the 3 times/week group and 43.9 (range 2-112) in the once-daily group. No serious adverse events or deaths were reported during the study. No clinically meaningful, drug-related changes in clinical laboratory values or vital signs occurred during the study. Overall, the tolerability of

Table 1. Baseline characteristics of target warts and history of disease

	Treatment groups		
	3 times/week	Once daily	Overall
No. of patients	<i>n</i> =34 (%)	<i>n</i> =30 (%)	<i>n</i> =64 (%)
Localization of warts			
Subpreputial	27 (79.4)	22 (73.3)	49 (76.6)
Preputial	10 (29.4)	9 (30.0)	19 (29.7)
Penis shaft	6 (17.6)	9 (30.0)	15 (23.4)
Glans penis	6 (17.6)	6 (20.0)	12 (18.8)
Perianal	3 (8.8)	3 (10.0)	6 (9.4)
Urethral meatus	0	5 (16.7)	5 (7.8)
Scrotum	0	2 (6.7)	2 (3.1)
Wart area (mm ²)			
Mean (SD)	120.1 (±130.66)	415.4 (±1575.81)	258.5 (±1083.54)
Median (range)	63.5 (18–555)	74.0 (32–8716)	65.5 (18–8716)
Duration of disease			
Time since initial outbreak (years)			
Mean (SD)	1.42 (±1.953)	1.41 (±1.518)	1.41 (±1.746)
Median (range)	0.56 (0.1–8.9)	0.92 (±0.0–5.7)	0.74 (0.0–8.9)
Time since current outbreak (months)			
Mean (SD)	5.29 (±8.380)	8.57 (±14.983)	6.85 (±11.999)
Median (range)	3.25 (0.4–47.3)	3.33 (0.2–68.8)	3.25 (0.2–68.8)
Previous treatments			
No. (%) of patients previously treated	21 (61.8%)	19 (63.3%)	40 (62.5%)
Laser treatment	7 (20.6%)	7 (23.3%)	14 (21.9%)
Podophyllotoxin	5 (14.7%)	8 (26.7%)	13 (20.3%)
Podophyllin resin	5 (14.7%)	5 (16.7%)	10 (15.6%)
Cryotherapy/liquid nitrogen	5 (14.7%)	5 (16.7%)	10 (15.6%)
Electrocautery	4 (11.8%)	4 (13.3%)	8 (12.5%)
TCA	4 (11.8%)	1 (3.3%)	5 (7.8%)
Surgical excision	1 (2.9%)	2 (6.7%)	3 (4.7%)
Other	1 (2.9%)	1 (3.3%)	2 (3.1%)

SD=standard deviation; TCA=trichloroacetic acid

imiquimod 5% cream was similar in both treatment groups; 64.7% of patients in the 3 times/week group reported at least one adverse event compared with 66.7% in the once-daily group. There were no statistically significant differences regarding the incidence of adverse reactions probably related to study drug except for dysuria which was reported by 6 patients (4 of the 6 cases were considered to be drug related) in the once-daily group and none in the 3 times/week group. This difference is probably related to the fact that only patients in the once-daily treatment group had condylomata acuminata located at the meatus

urethrae. Significantly more patients in the once-daily group reported more severe adverse events (8.8% vs 30.0%, $P=0.052$). The percentage of patients requiring at least one rest period because of local skin reactions and adverse events increased with the frequency of dosing: during the 3 times/week treatment, 29% of patients took at least one rest period, while 70% had a treatment interruption in the once-daily group.

Application site reactions were the most commonly observed adverse events. The percentage of patients was similar in both treatment groups (50% and 56.7%, respectively in the 3 times/week and once-daily dosing groups). Patients most frequently reported burning ($n=8/n=10$), itching ($n=6/n=3$) or irritation ($n=4/n=4$). Pain at the application site was reported only by patients in the once-daily group ($n=0/n=5$). The predominant local skin reactions were erythema and erosion, which were usually mild to moderate with a tendency to more severe reactions in the once-daily group. Table 3 summarizes the local skin reactions with respect to frequency and severity in both treatment groups.

The most marked differences between the treatment groups (and the only differences which were statistically significant at the 5% level) occurred, both in physicians' and patients' assessments, for a group of 5 symptoms (Figure 1):

Table 2. Patient withdrawals prior to completion of the study

	3 times/week	Once daily
Total No. of patients withdrawn (%)	<i>n</i> =7/34 (20.6%)	<i>n</i> =6/30 (20%)
Reason for withdrawal	No. of reasons/Treatment group	
Personal/other	4	3
Lack of therapeutic effect	3	2
Skin reactions	2	3
Non-compliance	1	1
Diagnosis of molluscum contagiosum	1	0
Lost to follow-up	0	1

Table 3. Frequency and severity of local skin reactions

Reaction	3 times/week (n=33)/[n=x (%)]				Once daily (n=30)/[n=x (%)]			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Erythema	8 (24.2)	12 (36.4)	10 (30.3)	3 (9.1)	3 (10.0)	3 (10.0)	19 (63.3)	5 (16.7)
Erosion	19 (57.6)	8 (24.2)	4 (12.1)	2 (6.1)	11 (36.7)	7 (23.3)	10 (33.3)	2 (6.7)
Oedema	30 (90.9)	2 (6.1)	1 (3.0)	0	17 (56.7)	9 (30.0)	3 (10.0)	1 (3.3)
Ulceration	29 (87.9)	0	3 (9.1)	1 (3.0)	19 (63.3)	4 (13.3)	7 (23.3)	0
Vesicles	33 (100)	0	0	0	27 (90.0)	0	3 (10.0)	0
Induration	32 (97.0)	1 (3.0)	0	0	25 (83.3)	5 (16.7)	0	0
Excoriation/flaking	27 (81.8)	4 (12.1)	2 (6.1)	0	26 (86.7)	4 (13.3)	0	0
Scabbing	32 (97.0)	1 (3.0)	0	0	29 (96.7)	1 (3.3)	0	0

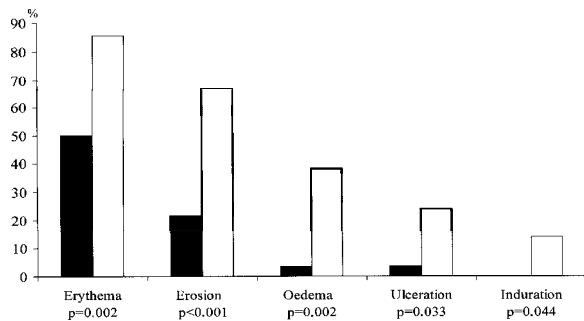


Figure 1. Significant differences between local skin reactions at wart site following 2 weeks of treatment (Wilcoxon rank sum test; p =differences between treatments). ■ 3 times/week; □ once daily

erythema, erosion, oedema, ulceration and induration. All of these symptoms occurred more severely at week 2 in the once-daily group. These differences became less marked towards the end of the study.

During the study, 6 patients in the 3 times/week dosing group and 4 patients in the once-daily group experienced adverse events associated with the foreskin. Less severe reactions or symptoms in both treatment groups were mild burning or moderate irritation (2 cases) of the foreskin, mild discomfort on retracting the foreskin without evidence of stricture and moderate frenulum tear. Similar to other application site reactions, more severe reactions were reported in the once-daily group. One

case of severe fissure occurred in the 3 times/week group. In the once-daily group patients reported the following: one case of severe pain when retracting the foreskin, 2 cases of severe balanitis and one moderate fissure which had to be circumcised post-study. Four patients, 2 in each treatment group, discontinued from the study specifically because of foreskin-associated adverse events or local skin reactions: burning of the balanic mucosa and moderate erythema (3 times/week dosing); moderate burning of the glans penis and subpreputial moderate erythema/moderate to severe erosion (daily dosing). All reactions had resolved or significantly improved within one month of stopping treatment with imiquimod 5% cream.

After completion of the once-daily treatment period and evaluation of the safety parameters, the decision was made to not proceed to the twice-daily dosing schedule.

Efficacy evaluation

By week 16, 21/34 patients (61.8%) in the 3 times/week group and 17/30 (56.7%) patients in the once-daily group experienced total clearance of their target warts. The differences between the groups were not statistically significant. The median time to clearance was 12.7 weeks and 10.3 weeks, respectively (95% confidence interval [CI] 9.4–17.0 and 5.4–not calculable [NC]). A detailed Kaplan–Meier plot shows the estimated proportion of patients on each treatment regimen experiencing total clearance against time (Figure 2). This analysis used the actual date of clearance at each timepoint and shows the more immediate effect of the once-daily treatment in the first 8 weeks, with the curves then approaching each other towards 16 weeks.

DISCUSSION

Imiquimod 5% cream has been available since 1997 for the treatment of external genital/perianal condylomata acuminata. The cream is well tolerated, with mild to moderate inflammatory skin reactions at the application site in about two-thirds of patients. The incidence of local side effects depends upon several factors, being more frequent

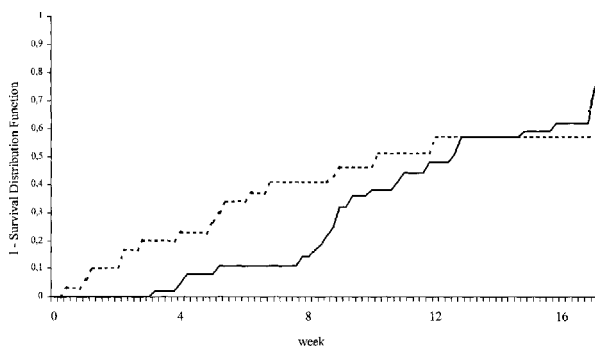


Figure 2. Wart clearance over time. — 3 times/week; - - - once daily

in women with vulvar warts compared with males with their warts most frequently located on the penile shaft and in the perianal area¹. The frequency and intensity of application site reactions seem to be related to the extent of keratinization of the skin, which is known to be increased in dry, hair-bearing regions compared with moist, non hair-bearing areas. Similar to the female vulva, the glans penis and the inner surface of the foreskin are only partially keratinized in uncircumcised males, and a higher frequency of inflammatory reactions can be expected when the cream is applied under the foreskin. Additionally, due to the semi-occlusive location, the absorption of imiquimod might be enhanced. During the previous clinical trials, in very rare cases, major complications have been reported in patients whose warts were located under the foreskin. In one case, an immunocompromised patient experienced a stricturing of the foreskin because of skin irritation attributed partly to the effect of imiquimod and partly to the location of the warts themselves; the patient underwent circumcision 9 months post-study. As previous studies were mainly performed in male circumcised patients, more information on the potential risks of imiquimod 5% cream in uncircumcised males is warranted.

Topical imiquimod is an immunomodulating agent which acts through the endogenous induction of a number of cytokines involved in a Th-1 type immunological response to viral infections in the skin¹²⁻¹⁶. Some of the cytokines produced by macrophages and lymphocytes, namely TNF- α and IL-8 are believed to be responsible for the frequently observed inflammatory skin reaction with mild to moderate erythema, erosion or excoriation/flaking which develop mainly during the first 2 weeks of treatment, peak at 4 weeks and usually resolve within 2 weeks of stopping treatment. More severe erythema occurred in 6% of patients, other severe reactions in less than 1% of patients⁷. Patients most frequently complained of itching (22%) and burning (13%), rarely of pain (6%) or tenderness (4%)¹⁷. Adverse effects at the application site were more severe and more frequent with a daily treatment regimen compared with 3 times weekly application¹⁷. Moreover, in women, severe erythema was more often reported than in males with a dosing regimen of 3 times/week (6.8% *vs* 4.8%) but not with a daily treatment (22.0% females *vs* 23.5% males) (data on file).

The present study was performed to evaluate the specific risk profile of imiquimod 5% cream in uncircumcised males with condylomata associated with the foreskin. Similar to previous studies, the 3 times/week dosing regimen was better tolerated than the daily treatment^{7,9}. The incidence of mild to moderate local skin reactions was comparable to other trials in predominantly circumcised men. Erythema was the most frequently reported side effect and occurred in about 76% of patients. As expected, due to the similar skin type and semi-

occluded location of the warts the local skin reactions observed in uncircumcised men with foreskin-associated warts were similar to those seen in female patients with vulvar warts. Severe erythema was reported in 9.1% of patients in the 3 times/week dosing group compared with 16.7% in the daily group. The increase in frequency and severity of symptoms with a daily treatment is reflected also by the number of rest periods taken by the patients. In the once-daily treatment group 70% of patients took at least one rest period compared with 29% of patients in the 3 times/week group. The increase in local adverse effects in the daily treatment group could be partly attributed to a subgroup of patients with warts located at the meatus urethrae, present only in this treatment group, who suffered from dysuria assessed to be related to the study drug in two-thirds of the cases.

Four patients, 2 in each treatment group, stopped treatment prematurely because of local skin reactions at the foreskin representing 5.9% and 6.7% of patients respectively. This percentage is somewhat higher compared with previous studies with a 3 times/week dosing schedule (1.8%⁷; 3.9%⁸) and daily application (1.1%⁹). This might reflect a slightly higher potential of more severe local skin reactions in uncircumcised men but does not seem to give major concern with respect to the safety of the drug because the symptoms usually resolved within 4 weeks after discontinuation. However, patients should be instructed that whenever subpreputial inflammatory reactions occur, in particular severe pain, erosions or difficulties in retracting the foreskin, they should interrupt the treatment until the reactions have resolved completely.

Most patients (62.5%) had undergone at least one other treatment before participating in the present study. Any of the presently available treatment options should be used with caution in the preputial area of uncircumcised males. Chemodestructive substances like podophyllin, podophyllo-toxin or trichloroacetic acid (TCA) are associated with a considerable risk of local inflammation with erythema, erosion or pain as they cause local tissue necrosis in the wart area. In most studies performed in males, patients with condylomata acuminata on the shaft of the penis were included and only a few publications mention specific safety results regarding the preputial area. Occasionally cases of balanoposthitis or difficulties in retracting the foreskin are reported. The incidence of more pronounced side effects seems to be lower with podophyllotoxin compared with podophyllin¹⁸⁻²⁰. TCA is associated with a rather high rate of ulceration²¹ and should be avoided in patients with condylomata acuminata associated with the foreskin. On the other hand, surgical manipulation, electrocautery, cryotherapy or laser ablation can lead to fibrosis, scarring and phimosis in patients who are treated for extensive condylomata acuminata on the inner surface of the foreskin²² and

should be administered only by experienced physicians.

A secondary objective of this study was the efficacy assessment of imiquimod 5% cream in uncircumcised males. Compared with previous studies in predominantly circumcised males (clearance rates 33% for 3 times/week⁷, 42% for daily application⁹) the clinical outcome in the present study is significantly better with a clearance rate of 62% in the 3 times weekly dosing group and 57% in the daily group. These results are similar to those achieved in females in the previous trials (72%⁷ and 64%⁹). The lower degree of skin keratinization and the semi-occlusive condition in uncircumcised males does not only seem to be responsible for more skin reactions through an enhanced absorption of the drug but also to result in a higher clearance rate.

In conclusion, the results of this study confirm that imiquimod 5% cream is safe and effective in uncircumcised males with foreskin-associated genital warts. The more frequent dosing schedule did not result in a higher rate of total clearance. Considering the incidence of more pronounced local side effects with the daily treatment, patients should be instructed to apply the drug no more often than 3 times/week and to practise thorough local hygiene to prevent more serious side effects.

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