Brief Report

A short, 8-week course of imiquimod 5% cream versus podophyllotoxin in the treatment of anogenital warts: A retrospective comparative cohort study

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Abstract

Background: Studies comparing head-to-head treatment modalities for anogenital warts are lacking.

Aim: We sought to compare a short, 8-week course of imiquimod 5% cream to versus the standard 4 week course of podophyllotoxin in the treatment of anogenital warts and to assess factors that may affect response to treatment.

Methods: This was a retrospective cohort study. We reviewed medical files of otherwise healthy patients with a first episode of anogenital warts who were treated with either a short, 8-week course of imiquimod or the standard 4-week course of podophyllotoxin. Inverse probability of treatment weighted (IPTW). Logistic regression was employed to evaluate factors that may affect response to therapy.

Results: The study included 347 patients. In patients with lesions on dry, keratinized anatomical sites, the complete clearance rates were 7.6% for imiquimod and 27.9% for podophyllotoxin ($P < 0.001$). In patients with lesions on moist, partially keratinized sites, no difference between the treatments was revealed. Significant predictors of > 50% reduction in wart area were location of lesions [odds ratio (OR) (95% confidence interval (CI)): 3.6 (1.84–7.08), $P = 0.0002$] for "partially keratinized" versus "keratinized" sites and treatment used [OR (95% CI): 1.79 (1.08–2.97), $P = 0.024$] for podophyllotoxin versus imiquimod.

Limitations: The retrospective design of the study was a limitation that we mitigated against with the use of IPTW logistic regression.

Conclusion: A standard 4 week course of Podophyllotoxin was more effective than an 8-week course of imiquimod only for lesions on keratinized sites. Treatment with podophyllotoxin and location of lesions on partially keratinized sites were independent predictors of >50% reduction in wart area.

Key words: Anogenital warts, comparison, human papillomavirus, imiquimod, podophyllotoxin

Introduction

Anogenital warts rank among the most frequent sexually transmitted infections.[1] Treatment modalities for the management of anogenital warts are divided into provider-administered (such as cryotherapy) and patient-applied (imiquimod, podophyllotoxin, and sinecatechins).[2,3]

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Imiquimod and podophyllotoxin are the most commonly used patient-applied treatments for anogenital warts. To our knowledge, there are only two studies comparing imiquimod and podophyllotoxin in the treatment of anogenital warts which concluded that both treatments were equally effective.[4,5] Reports on the cost-effectiveness of anogenital wart treatments favor podophyllotoxin over imiquimod, because imiquimod is more expensive and the duration of treatment with imiquimod is longer.[6,7] On the other hand, because imiquimod enhances the immune responses against human papillomavirus, recurrence rates following treatment with imiquimod are lower, compared with podophyllotoxin.[7] Thus, the choice between the two agents is not clear cut.

Imiquimod can be used for up to 16 weeks.[2,3] Shorter courses (4-week, 8-week, and 12-week) have been evaluated and produced results comparable to the 16-week course.[8,9]

In this study, we compared response rates between a short, 8-week course of imiquimod 5% cream and podophyllotoxin in patients with anogenital warts. Apart from general response rates, we also assessed factors that may affect response to treatment. We decided to evaluate an 8-week course of imiquimod instead of the licensed 16-week course, because we need more data on this more practical and less expensive imiquimod regime.

Methods

In this retrospective cohort study, we reviewed the database of all patients with anogenital warts who presented to the sexually transmitted infections unit of "Andreas Sygros" hospital for skin and venereal diseases, between January 2012 and December 2016. The study was approved by the institutional review board.

The inclusion criteria were the following: (a) otherwise healthy males and females age 18 years and older with a clinically diagnosed first episode of anogenital warts lasting no more than 3 months and (b) monotherapy with either an 8-week course of imiquimod 5% cream or a 4-week course of podophyllotoxin. Exclusion criteria included (a) receiving any treatment for anogenital warts before presentation to our department, (b) presence of either intra-anal/intravaginal warts or warts of the urethral meatus, (c) presence of giant condylomata (Buschke–Lowenstein tumors), (d) presence of only one wart or wart area larger than 6 cm^2, and (e) pregnancy.

Anatomical sites of anogenital warts were divided into two groups. The first group included sites covered by dry, keratinized skin, such as pubic area, penile shaft, scrotum, groin, and the outer surface of labia majora of the vulva ("keratinized" sites). The second group included sites covered by moist, partially keratinized skin, such as perianal area, perineum, preputial cavity, inner surface of labia majora, and labia minora of the vulva ("partially keratinized" sites). Disease extent was defined as *small*, if the number of lesions was between 2 and 4 or affected area was <1 cm^2; *medium*, if lesions were between 5 and 10 or area between 1 and 4 cm^2, and *large*, if lesions were more than 10 or area affected was 4–6 cm^2.

Imiquimod was applied three times weekly. Podophyllotoxin was applied each week twice daily for 3 consecutive days, followed by 4 days of rest. Podophyllotoxin 0.5% solution was prescribed for lesions on "keratinized" sites and podophyllotoxin 0.15% cream was prescribed for lesions on "partially keratinized" sites, in agreement with the recent European guidelines.[2]

For the comparison of the response rates between the different treatment groups, Chi-square test was used. We also performed a stratified analysis using Chi-square test for the comparison of response rates among the categories of location ("keratinized" sites vs. "partially keratinized" sites). For the comparison of medians between independent groups of patients, we used Mann–Whitney *U*-test.

Estimated odds ratios (OR) and 95% confidence intervals (CIs) were determined using a logistic regression model. To account for the observational nature of the study and possible confounding, inverse probability of treatment weighted logistic regression was also applied, with weights stabilized by the marginal probabilities of receiving each treatment. Analyses were conducted in R, version 3.5.1, and IPT weights were estimated using package "ipw."

Results

In total, 347 patients were included in the study. Demographic and baseline characteristics of the treatment groups are shown in Table 1.

Complete clearance rates and more than 50% reduction in wart area for the groups as a whole and separately for lesions on "keratinized" and "partially keratinized" sites are shown in Tables 2 and 3. For lesions on "keratinized" sites, the difference between imiquimod and podophyllotoxin both in clearance rates (7.6% and 27.9%, respectively) and in >50% reduction in wart area (54.3% and 76.0%, respectively) was statistically significant.

The results of the univariate logistic regression for patients with >50% reduction in wart area versus <50% reduction in wart area are presented in Table 4.

Multivariate analysis revealed that only type of treatment and location of lesions were independent predictors of response to treatment [Table 5]. More specifically, treatment with podophyllotoxin [OR (95% CI): 1.9 (1.11–3.23), $P = 0.018$] and location on "partially keratinized" sites [OR (95% CI): 3.75 (1.88–7.49), $P = 0.0001$] were statistically significantly associated with > 50% reduction in wart area.

Table 1: Overview of demographic and baseline characteristics of the two groups

Treatment	Imiquimod (*n*=202), *n* (%)	Podophyllotoxin (*n*=145), *n* (%)	*P*
Gender			
Men	148 (73.3)	129 (89.0)	<0.001*
Women	54 (26.7)	16 (11.0)	
Age (median)	34	33	0.509
Location of AGW			
"Keratinized" sites	92 (45.5)	104 (71.7)	<0.0001*
"Partially keratinized" sites	76 (37.6)	23 (15.9)	
Both	34 (16.8)	18 (12.4)	
Extent of AGW			
Small	62 (30.7)	56 (38.6)	0.282
Medium	70 (34.7)	47 (32.4)	
Large	70 (34.7)	42 (29.0)	

AGW: anogenital wart. "Keratinized" sites: pubic area, penile shaft, scrotum, groin, and outer surface of labia majora of the vulva. "Partially keratinized" sites: perianal area, perineum, preputial cavity, inner surface of labia majora, and labia minora of the vulva. *Statistically significant

Table 2: Complete clearance rates of anogenital wart for both groups

	Complete clearance rates of AGW		
Patients	Imiquimod, *n*/*n* treated (%)	Podophyllotoxin, *n*/*n* treated (%)	*P*
All	51/202 (25.2)	46/145 (31.7)	0.185
With lesions on "keratinized" sites	7/92 (7.6)	29/104 (27.9)	<0.001*
With lesions on "partially keratinized" sites	38/76 (50.0)	12/23 (52.2)	0.855
Both	6/34 (17.6)	5/18 (27.8)	0.621

AGW: anogenital wart. Keratinized" sites: pubic area, penile shaft, scrotum, groin, outer surface of labia majora of the vulva. "Partially keratinized" sites: perianal area, perineum, preputial cavity, inner surface of labia majora, labia minora of the vulva. *Statistically significant

Due to the observational nature of the study and nonrandom assignment of treatments, an inverse probability of treatment weighted logistic regression model was estimated. Stabilized inverse probability of treatment weights were calculated with marginal treatment probabilities as stabilizing factors and age, gender, extent of lesions, and location of lesions as probability of treatment factors. inverse probability of treatment weighted diagnostics demonstrated that weighting resulted in a balanced sample between treatment groups in important predictors for treatment and response [Table 6]. The inverse probability of treatment weighted model estimated a slightly smaller treatment effect of podophyllotoxin [OR (95% CI): 1.79 (1.08–2.97), $P = 0.024$], while the rest of the variables were found to have similar effects compared with the unweighted analysis [Table 5].

Discussion

In everyday clinical practice, imiquimod and podophyllotoxin are often considered first-line treatments for anogenital warts.

Table 3: >50% reduction in wart area for both groups

	>50% reduction in wart area		
Patients	Imiquimod, *n*/*n* treated (%)	Podophyllotoxin, *n*/*n* treated (%)	*P*
All	142/202 (70.3)	111/145 (76.6)	0.196
With lesions on "keratinized" sites	50/92 (54.3)	79/104 (76.0)	0.001*
With lesions on "partially keratinized" sites	66/76 (86.8)	20/23 (87.0)	0.989
Both	26/34 (76.5)	12/18 (66.7)	0.667

"Keratinized" sites: pubic area, penile shaft, scrotum, groin, outer surface of labia majora of the vulva. "Partially keratinized" sites: perianal area, perineum, preputial cavity, inner surface of labia majora, labia minora of the vulva. *Statistically significant

Table 4: Univariate logistic regression model for >50% reduction in wart area

	OR (95% CI)	*P*
Treatment		
Podophyllotoxin vs. Imiquimod	1.38 (0.85-2.25)	0.197
Gender		
Women vs. men	2.03 (1.04-3.98)	0.0389*
Location of AGW		
"Partially keratinized" vs. "keratinized" sites	3.44 (1.79-6.61)	0.0002*
"Both" vs. "keratinized" sites	1.41 (0.71-2.78)	0.32
Extent of AGW		
Medium vs. small	0.95 (0.53-1.69)	0.851
Large vs. small	0.82 (0.46-1.46)	0.493
Age	0.98 (0.95-1.006)	0.12

OR: odds ratio, CI: confidence interval, AGW: anogenital wart. "Keratinized" sites: pubic area, penile shaft, scrotum, groin, outer surface of labia majora of the vulva. "Partially keratinized" sites: perianal area, perineum, preputial cavity, inner surface of labia majora, labia minora of the vulva. *Statistically significant

Imiquimod is shown to have a clearance rate ranging widely between 35% and 75% for treatment periods up to 16 weeks.[5,8-14] In our study, the imiquimod clearance rate after 8 weeks of treatment was 25.2%. However, the clearance rate was 50%, for lesions on "partially keratinized" sites, and 7.6%, for lesions on "keratinized" sites. So, if imiquimod is prescribed for patients with warts on "partially keratinized" sites, our study showed that even an 8-week course can lead to a clearance rate comparable to the clearance rates mentioned in the literature for treatment up to 16 weeks.

Podophyllotoxin 0.5% solution has been shown to have a clearance rate between 54% and 85% after use for 4 weeks.[5,15-18] For podophyllotoxin 0.15% cream, clearance rates of 63%[19] and 75%[18] have been reported. In this study, the clearance rate was 27.9% for podophyllotoxin solution (for lesions on "keratinized" sites) and 52.2% for podophyllotoxin cream (for lesions on "partially keratinized" sites). The low clearance rate that we observed for podophyllotoxin 0.5% solution can be attributed to the fact that we used it only for lesions on "keratinized" sites, which, according to the results of our study, are more resistant to treatment.

Table 5: Multivariate logistic regression model for >50% reduction in wart area, with and without inverse probability of treatment weighted

	OR (95% CI)	*P*	OR (95% CI) IPTW	*P* (IPTW)
Treatment				
Podophyllotoxin vs. imiquimod	1.9 (1.11-3.23)	0.018*	1.79 (1.08-2.97)	0.024*
Gender				
Women vs. men	1.74 (0.83-3.66)	0.14	1.87 (0.89-3.92)	0.10
Location of AGW				
"Partially keratinized" vs. "keratinized" sites	3.75 (1.88-7.49)	0.0001*	3.6 (1.84-7.08	0.0002*
"Both" vs. "keratinized" sites	1.26 (0.6-2.63)	0.54	1.15 (0.55-2.39)	0.72
Extent of AGW				
Medium vs. small	1.03 (0.56-1.89)	0.93	0.98 (0.54-1.78)	0.95
Large vs. small	0.95 (0.51-1.76)	0.87	0.93 (0.51-1.69)	0.80
Age	0.98 (0.96-1.01)	0.15	0.99 (0.97-1.01)	0.39

OR: odds ratio, CI: confidence interval, AGW: anogenital wart, IPT: inverse probability of treatment, IPTW: inverse probability of treatment weighted. IPT weights were calculated using marginal treatment probability as stabilizing factors and age, gender, extent of AGW, and location of AGW as probability of treatment factors. "Keratinized" sites: pubic area, penile shaft, scrotum, groin, outer surface of labia majora of the vulva. "Partially keratinized" sites: perianal area, perineum, preputial cavity, inner surface of labia majora, labia minora of the vulva. *Statistically significant

Table 6: Chi-square statistics for the association between treatment received and patients' gender as well as location of anogenital wart in the unweighted sample and after weighting by inverse probability of treatment weighted

Variable	Chi-square statistic (df) unweighted sample	Chi-square statistic (df) IPT weighted sample	*P* (unweighted sample)	*P* (IPT weighted sample)
Gender	12.5 (2)	0.08 (2)	0.0001*	0.78
Location of AGW	25.3 (2)	0.1 (2)	<0.0001*	0.95

AGW: anogenital wart, IPT: inverse probability of treatment. Marginal probabilities of treatment were used as stabilizing factors and gender, location of AGW, extent of AGW, and age as IPT factors. Results are presented for gender and location of AGW, which were unbalanced in the unweighted sample. *Statistically significant

Previous studies comparing imiquimod and podophyllotoxin in the treatment of anogenital warts include a meta-analysis[4] (that evaluated three placebo-controlled trials of imiquimod and nine placebo-controlled trials of podophyllotoxin) and a head-to-head comparison in a randomized, open-label trial that included 45 patients.[5] Both studies concluded that imiquimod and podophyllotoxin were equally effective. In this study, we compared podophyllotoxin with a shorter, 8-week imiquimod course. For lesions on "keratinized" skin, the difference between imiquimod and podophyllotoxin both in clearance rates and in >50% reduction in wart area was statistically significant. For lesions on "partially keratinized" skin, no difference was detected between the two treatments.

In univariate analysis, lesions on "partially keratinized" sites and female patients were statistically significantly associated with a >50% reduction in wart area. In the multivariate analysis, however, gender of patients was no longer associated with response to treatment and only location of lesions on "partially keratinized" sites and treatment with podophyllotoxin were independent predicting factors of >50% reduction in wart area. These findings reflect the fact that patients with lesions on "keratinized" sites, that is, with "difficult-to-treat" lesions, were mostly men and had been treated more frequently with podophyllotoxin, compared with imiquimod. Men more often have lesions on "keratinized" sites, such as the penile shaft and the pubic area, while women usually have lesions on "partially keratinized" sites, such as the perineum, inner surface of labia majora, and labia minora of the vulva. In the multivariate model that took into account the location of lesions, gender was no longer a predictor of response to treatment and, on the contrary, type of treatment was. So, our study showed that location of lesions and not patients' gender predicts response to treatment.

The main limitation of our study is its retrospective design. We mitigated this shortcoming by basing the main results of our study on an inverse probability of treatment weighted analysis, creating a sample in which treatment assignment was independent of (measured) baseline covariates.

Conclusion

Our study showed that lesions' location plays a central role on response to patient-applied treatments for anogenital warts. For lesions on "partially keratinized" sites, an 8-week course of imiquimod was equally effective to the standard 4-week course of podophyllotoxin. For lesions on "keratinized" sites, the 8-week course of imiquimod was less effective, compared with podophyllotoxin, so either podophyllotoxin or the standard "up to 16 weeks" imiquimod regime should be preferred. Lesions on "partially keratinized" sites responded more favorably to both treatments.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given

their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
EN has received honoraria from Meda Pharmaceuticals and Glaxosmithkline.

AK and GB have received honoraria from Meda Pharmaceuticals.

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