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Is 5% Imiquimod Cream More Efficacious at Sustained Clearance of Genital Warts at 3 Months Compared to 1% Imiquimod, Ablation Therapy, and a Placebo Vehicle Cream?

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Is 5% Imiquimod cream more efficacious at sustained clearance of genital warts at 3 months compared to 1% Imiquimod, ablation therapy, and a placebo vehicle cream?

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not 5% Imiquimod is more efficacious at sustained treatment of genital warts at 3 months compared to 1% Imiquimod, ablation, and a placebo vehicle cream.

STUDY DESIGN: Primary literature published between 1996 and the present.

DATA SOURCES: RCT's were found using Ovid, PubMed, Medline, and Cochrane databases.

OUTCOMES MEASURED: The outcomes measured were a sustained clearance of genital warts at 3 months. The outcomes were measured by photographs, measurements, counts, locations, and mapping.

RESULTS: Three RCTs were included in this review. RCTs conducted by Beutner and Edwards (separate articles) showed that Imiquimod 5% is superior to most methods including different ablation therapies and Imiquimod 1%. One RCT by Schofer showed possibly Imiquimod used in combination with ablation may be superior to other treatments.

CONCLUSION: All three RCTs showed that Imiquimod 5% is more effective in clearing genital warts and sustaining clearance at 3 months as compared to Imiquimod 1%, ablation, and placebo.

KEYWORDS: Genital warts, HPV, Imiquimod, ablation, and placebo.

INTRODUCTION

Genital warts caused by HPV are one of the most common STDs in the world and encountered by the medical practitioner. Currently there are many different treatments for genital warts including lotions, creams, cryosurgery, ablation, and excision.

An estimated 30-50% of sexually active adults are infected with HPV. It is estimated that up to 1% actually have genital warts caused by strains 16 and 21. Genital warts that do appear will either progress or regress, although this process is not completely understood. Standard treatment regimens of excision, ablation, and cryosurgery are only directed at the lesion instead of the cause.

Regression on genital wart and HPV is thought to be due to an immune response, but is still widely unknown. Sustained clearance is still relatively random from patient to patient, however, it is thought to be improved with immune-response modifiers (Imiquimod).

There are no approved OTC therapies for the treatment of genital warts caused by HPV. Prescription drugs include Imiquimod (Aldara), Podophyllotoxin (Podofilox). Other methods include ablation, cryotherapy, excision, and podophyllin resin.

These prescription drugs are many times successful for the eradication of initial genital warts, however, sustained clearance is still difficult to predict.

OBJECTIVE

The objective of this systematic review is to determine whether or not 5% Imiquimod is more efficacious at sustained treatment of genital warts at 3 months compared to 1% Imiquimod, ablation, and a placebo vehicle cream.

METHODS

Criteria for the selection of studies included healthy men and women 18 years old and older. The intervention used was 5% Imiquimod cream with comparisons against 1% Imiquimod cream, ablation therapy, and placebo vehicle cream. The outcomes measured were the recurrence of genital warts after treatment with the above therapies at 3 months post-treatment. The method was to find RCTs with similar inclusion and exclusion criteria. For example all the three RCTs used for this systematic review required healthy man and women at least 18 years of age, and excluded patients who were imunnosupressed or recently treated for genital warts using the treatments in question. It is of note that each study had additional inclusion and exclusion criteria.

The types of studies used were RCTs comparing 5% Imiquimod to 1% Imiquimod and placebo, 5% Imiquimod and 1% Imiquimod to placebo, and 5% Imiquimod to ablation alone and combined.

The key words used in this review include genital warts, HPV, Imiquimod, ablation, and placebo. All articles were published in English and peer-reviewed. Searches were conducted David A Smith using PubMed, Ovid, and Medline. All articles were selected by Patient Oriented Evidence that Matters (POEM). All articles had to rely on primary literature published between 1996 to present, with at least 2 RCTs. All articles had to contain POEMs. Summary of statistics reported or used were p-values; RRR; ARR; and NNT.

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Beutner, USA, 1998	RCT; double-blind; parallel-group study	279	18+	Healthy men & women, >= 2 to <= 50 warts at least 10mm in area	HIV (+); Pregnant (+); Tx within 4 weeks of study; Pre-study pap smear = HSIL	72	5% Imiquimod; 1% Imiquimod; Placebo
Edwards, USA, 1998	RCT; double-blind; placebo controlled	311	18+	Healthy men & women, >= 2 to <= 50 warts at least 50mm in area	Immunosuppressed; HSIL; Pregnant or lactating; Drug/etoh dependency; other skin disease; Rx in the area within 2 weeks; wart Tx within 4 weeks	77	5% Imiquimod; 1% Imiquimod; Placebo
Schofer, Germany, 2006	RCT; 3-arm comparison	377	18+	Healthy men & women with external genital warts up to 2000mm area and up to 1 inch	Previous use of 5% Imiquimod within 6 months; any Tx with interferon, immunomodulators, oral antivirals; cytotoxic drugs; pregnant or lactating women; immunocompromised	91	5% Imiquimod; Ablation; 5% Imiquimod & Ablation

OUTCOMES MEASURED

The outcomes measured were a sustained clearance of genital warts at 3 months. The outcomes were measured by photographs, measurements, counts, locations, and mapping.

RESULTS

The primary efficacy parameter was based upon all individuals who were completely cleared of all genital warts at 12 or 16 weeks and successfully followed up for 3 months.

Schofer et al reported a sustained clearance of 83.9% for ablation therapy, 93.8% for 5% Imiquimod, and 91.7% for ablation and 5% Imiquimod. The difference between 5% Imiquimod treatment is statistically significant with p = 0.074. The ARR was calculated to be -0.099 and the RRR was -0.615. The NNT was 48.

Beutner et al sustained clearance 81% for 5% Imiquimod, 83% for 1% Imiquimod, and 100% for placebo. The ARR was calculated to be -0.38 and the RR was -0.44. The NNT was -5

Edwards et al reported a sustained clearance of 87% for Imiquimod 5%, 100% for Imiquimod 1%, and 90% placebo. The ARR was calculated to be 0.3 and the RRR was 0.3. The NNT was -8.

Table 2 - Efficacy of Imiquimod 5% in Sustained Clearance at 3 Months

Study	Imiquimod 5% (SCP)	Imiquimod 1% (SCP)	Ablation (SCP)	Placebo (SCP)	C.I.	RRR	ARR	NNT	p-value
Edwards et al	39/45 (87%)	18/18 (100%)	N/A	9/10 (90%)	NR	0.3	0.3	-8*	NR
Beutner et al	39/48 (81%)	10/12 (83%)	N/A	100%	NR	-0.44	-0.38	-5**	NR
Schofer et al	94/100 (93.8%)	N/A	77/92 (83.9%) & 69/75 (91.7%)*	N/A	NR	-0.615	-0.099	48***	0.074

*NNT compares Imiquimod 5% to Imiquimod
**NNT compares Imiquimod 5% to Placebo
***NNt compares Imiquimod 5% to Ablation & Imiquimod 5% combined treatment

SCP = Sustained Clearance Percentage, C.I. = Confidence Interval, RRR = Relative Risk Reduction, ARR = Absolute Risk Reduction, NNT = Numbers Needed to Treat
**91.7 % was recorded with a combination of Imiquimod 5%.*

Although all three studies measured total clearance of genital warts over a period of 12 to 16 weeks, this systematic review was concerned with the sustained clearance of at least 3 months of initial genital warts that were measured and removed by the above treatments. All three studies reported that 5% Imiquimod had the highest percentage of initial clearance; however, sustained clearance did not produce the same results.

In the studies conducted by Edwards and Beutner 1% Imiquimod and placebo both reported a higher percentage of sustained clearance. Schofer reported 5% Imiquimod with the highest percentage of sustained clearance.

Table 3 – Reported Adverse Reaction of *Moderate Erythema* at Application Site

Study	5% Imiquimod	1% Imiquimod	Vehicle or Ablation
Beutner et al	40 (43.5%)	N/A	8 (8.7%) Vehicle
Edwards et al	36/106 (34%)	4/106 (4.1%)	3/106 (3.2%) Vehicle
Schofer et al	56.7% 55% with ablation	N/A	N/A Ablation

**Beutner and Edwards reported at 16 weeks (total treatment phase); Schofer reported at 4 weeks.*

The most common side effect and complaint in all three studies was moderate erythema at the application site. It was reported that 40%, 56.7%, and 34% of the 5% Imiquimod group in the Beutner et al, Schofer et al, and Edwards et al studies respectively experienced these symptoms. The 1% Imiquimod group reported moderate erythema in only 4.1% in the Edwards et al study.

In all three studies patients were instructed on how to apply 1% Imiquimod, 5% Imiquimod, and place vehicle cream. Patients receiving cryotherapy/ablation were treated on an outpatient basis. No study had direct supervision of application, other than assessing wart clearance at different time intervals. Edwards et al saw patients weekly for the first 2 weeks and then biweekly for 16 weeks. Patients who had complete clearance were entered into a 12 week follow-up phase. Schofer et al conducted an initial 16 week treatment phase with a 1 month, 3 month, and 6 month follow-up for those who initially cleared during the treatment phase. In the Beutner et al study patients were evaluated weekly for the first 4 weeks and every 2 weeks for the 16 week treatment phase. A 12 week follow-up was performed for those patients who had initial clearance during the treatment phase.

DISCUSSION

Topical Imiquimod is an immune response modifier that has been shown to exhibit antitumor and antiviral properties. It is an imidazoquinolin heterocyclic amine that can increase interferon alpha production. Interferon alpha is still very expensive and has been shown to effectively treat anogenital warts.

Each study had a different modality that proved to be more effective on a percentage basis for sustained clearance at 3 months. In the Edwards et al study 5% Imiquimod had a higher recurrence rate than that of 1% Imiquimod and placebo cream, however, that may be due to the fact that total 5% Imiquimod had more patients in the follow-up phase with 45; while 1% Imiquimod had only 18 patients and place cream with 10.

The Beutner et al reported that placebo cream had the highest sustained clearance at 3 months but did not report how many patients were involved in the follow-up phase. In the same study 1% Imiquimod reported a higher percentage (83%) than 5% Imiquimod (81%) but again

the 5% Imiquimod group had more patients at 48 compared to 12 patients with the 1% Imiquimod group.

Finally, the Schofer et al study reported 5% Imiquimod with highest sustained clearance compared to ablation and 5% Imiquimod combined with ablation. In this study 5% Imiquimod had the highest total of follow-up patients with 100.

All three studies were utilized for this systematic review without any significant limitations to the studies themselves.

CONCLUSION

The studies reviewed demonstrated that 5% Imiquimod therapy alone is not the most effective treatment at sustaining genital wart clearance at 3 months when initially cleared with the same therapy. Each study produced a different answer to the proposed hypothesis. At this time there is not enough data to support that any one therapy is superior to another in sustaining clearance at 3 months. Although 5% Imiquimod is superior in establishing an initial baseline clearance of genital warts, an individual's immune response may play a more vital role in sustainment of clearance than supporting initial clearance. This is impossible to assess since the studies do not report the age of participants, only that they have to be at least 18 years old.

Ideally the best systematic review would have an equal number of patients in the follow-up phase with similar ages regardless of therapeutic intervention; however, this may not be possible to due to the fact that some treatments are more efficacious than others at establishing initial clearance, which mean inevitably the number of patients in follow-up will be skewed.

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