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A Randomized, Double-blind, Placebo-Controlled Proof of Concept Trial of Topical Cidofovir, 1% and 3%, for the Prevention of Beard Hair Growth in Men

Unwanted facial hair, hirsutism, and pseudofolliculitis barbae occur commonly, and billions of dollars are spent annually on hair removal products.^{1,2} Eflornithine, the only prescription topical agent approved in the United States for female facial hirsutism, has only a 32% success rate and has not been evaluated in men.¹ Therefore, additional topical treatments effective in preventing hair growth are needed. The antiviral agent cidofovir has been reported to induce local alopecia when applied topically.³ In this study, we evaluate the efficacy and safety of topical cidofovir in preventing beard hair growth in healthy men.

Methods. Eligible participants were men who shaved daily and had beards scoring 4 (dense) or 5 (very dense) on the physician global assessment (PGA) of hair density.⁴ Subjects were excluded if they used any medication affecting hair growth or had a history of alopecia areata. The study was approved by the institutional review board and registered at ClinicalTrials.gov (NCT00948506).

Subjects were randomized as to which side of the face received cidofovir or placebo and to either the 1% or 3% concentration. Cidofovir and placebo were applied once daily after shaving to a circular area (2.5-cm diameter) within the beard in a split-face design. Templates delineating the treatment area were used in drug application and evaluation.⁴ Treatment duration was increased from 6 to 8 weeks following an interim analysis of the first 5 subjects. Subjects were evaluated every 2 weeks during treatment; those receiving 6-week treatment were evaluated post treatment at weeks 8 and 10, while those receiving 8-week treatment were seen at weeks 10 and 12 only if they had a PGA change or unresolved adverse event at week 8. Subjects did not shave for 48 hours before visits to grow visible hair for assessment.

At each visit, the investigator performed a PGA and photographed the treatment areas. The number of hairs within the treatment area in each photograph were counted as previously described.⁴ Laboratory test results, including for renal and liver function, were assessed at baseline and every 2 to 4 weeks.

The primary outcome was response to treatment, which was defined as a PGA score of 2 (sparse) or lower at the end of treatment. We compared response rates and hair count changes between cidofovir and placebo sites in both intention-to-treat and as-treated populations. Data were analyzed using Stata IC, version 10 (StataCorp LP).

Results. Of 39 subjects screened, 20 were enrolled. Seventy percent of subjects were white (n=14), 15% black (n=3), and 15% Asian (n=3). The median age of subjects was 32 years (interquartile range, 26-42 years). Four subjects withdrew during treatment owing to scheduling conflicts and health problems unrelated to the study. Sixteen subjects (8 each in the 1% and 3% groups) completed treatment, and 11 subjects followed up post treatment. Baseline PGA scores and hair counts did not differ significantly between the active and placebo groups or between the 1% and 3% groups (**Table**). All subjects had normal baseline blood urea nitrogen and creatinine levels.

We observed a 5% (95% confidence interval 0.1%-24.9%) response rate in the cidofovir and placebo groups (**Table**). Hair count changes did not differ significantly between the cidofovir and placebo sites. However, we observed a negative trend in hair counts within the 3% group compared with placebo (median difference in hair count changes [$\Delta\Delta$] -73) ($P=.08$).

Twelve subjects experienced 24 adverse events, the most common being upper respiratory infection (20%; [n=4]), headache (15%; [n=3]), and erythema and/or hyperpigmentation (15%; [n=3]), or pruritus of the treatment area (10%; [n=2]). However, all local skin reactions were mild and dose independent, did not require stopping application of the drug, and resolved with little or no intervention by 8 weeks after treatment cessation. No significant changes in laboratory values were observed.

Comment. The negative trend in hair count with use of cidofovir, 3%, suggests a dose-response relationship and that the 3% concentration may be promising for preventing hair growth. We did not observe induction of total alopecia as was previously reported when topical cidofovir was applied to virally infected skin of immunocompromised patients.³ Treatment dose and duration may have been insufficient to trigger cidofovir's effect in normal skin. Nevertheless, topical cidofovir was well tolerated and showed an incidence of local skin reactions similar to that of eflornithine.¹

Limitations of this trial include the low statistical power of a small study. The use of templates to localize the treatment area may have introduced variability in drug application or evaluation. Finally, preventing facial hair growth in men may be a high-efficacy bar relative to preventing facial hair growth in women; cidofovir likely needs to reach the rapidly proliferating bulb matrix cells in the deepest portion of the follicle,

Table. Intention-to-Treat Analysis^a of Hair Density Measurements

Test Group	Baseline PGA	End-of- Treatment ^b PGA	Response Rate, % (95% CI)	P Value ^c	Baseline Hair Count	End-of- Treatment ^b Hair Count	Δ Hair Count ^d	ΔΔ ^e	P Value ^f
Overall (1% and 3% Concentrations Combined) (n = 20)									
Cidofovir	4 (4 to 4)	4 (3 to 4)	5.0 (0.1 to 24.9)	>.99	238 (185 to 306)	231 (192 to 289)	0 (-40 to 15)	0 (-65 to 31)	.65
Placebo	4 (4 to 4)	4 (4 to 4)	5.0 (0.1 to 24.9)		242 (214 to 274)	240 (193 to 298)	0 (-35 to 34)		
Stratified by Cidofovir Concentration									
1% Only (n = 11)									
Cidofovir	4 (4 to 5)	4 (3 to 4)	9.1 (0.2 to 41.3) ^g	>.99	235 (166 to 294)	232 (188 to 291)	0 (-39 to 39)	7 (-1 to 34)	.26
Placebo	4 (4 to 5)	4 (4 to 4)	0 (0 to 28.5)		248 (222 to 270)	237 (214 to 303)	0 (-40 to 5)		
3% Only (n = 9)									
Cidofovir	4 (4 to 4)	4 (3 to 4)	0 (0 to 33.6)	>.99	240 (204 to 318)	230 (207 to 271)	0 (-66 to 3)	-73 (-92 to 0)	.08
Placebo	4 (4 to 4)	4 (3 to 4)	11.1 (0.3 to 48.2) ^h		230 (200 to 277)	256 (172 to 293)	26 (-26 to 90)		

Abbreviation: PGA, physician global assessment of hair density.⁴

^aAll enrolled subjects who received treatment were included in the intention-to-treat analysis; for subjects who withdrew during the treatment period, data from their last visit were carried forward. As-treated analysis including only subjects who completed treatment yielded similar results (not shown). Unless otherwise indicated, data are median (interquartile range) values.

^bDuration of active treatment was 6 weeks for the first 5 subjects and 8 weeks for the subsequent 15 subjects.

^cMcNemar exact test.

^dEnd-of-treatment hair count minus baseline hair count.

^eDifference in Δ hair counts between cidofovir minus placebo groups.

^fWilcoxon matched pairs signed-rank test comparing Δ hair counts between the cidofovir and placebo groups.

^gSubject's PGA score remained 2 for 4 weeks after treatment cessation but increased to 3 by 8 weeks posttreatment.

^hSubject withdrew from the study during posttreatment follow-up owing to scheduling conflict.

which reside deeper in male beard follicles than female facial follicles.⁵

In conclusion, topical cidofovir was safe and well tolerated, and the 3% concentration may be promising for further studies of hair growth prevention. Future trials evaluating higher concentrations, longer treatment durations, and use in women are warranted.

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Clinical Decision Making Based on Histopathologic Grading and Margin Status of Dysplastic Nevi

The purpose of the present study was to determine how clinicians elect to treat a histologic dysplastic nevus (DN) given a reported grade of the dysplasia and margin involvement on a biopsy report.

Methods. An anonymous survey was distributed to the members of the Chicago Dermatologic Society during the annual meeting in March of 2009. Respondents were asked what clinical decisions they would make based on hypothetical pathology reports of varying histopathologic grades of DN with and without margin involvement. For survey purposes, we characterized DN as histopathologically displaying mild, moderate, or severe atypia. We did not specify if the nevi were primarily graded on the architectural or cytologic features. A total of 6 case scenarios were presented to the respondents. The survey questions were presented as follows:

Biopsy report states the patient has a mildly (or moderately/severely) dysplastic nevus with positive (or clear) margins. Elect to: Observe, Re-excise or Other.

A freehand response was allowed for the "Other" option. Institutional review board approval was waived for this anonymous survey.

Results. Of the 158 surveys distributed, 101 were returned for a 58% response rate. There was no significant difference in the probability of electing to reexcise nevi with mild vs moderate dysplasia in patients with clear margins reported on pathologic evaluation (Figure, A). If the margins were positive, there was a significantly greater probability of electing to reexcise the DN for all grades of dysplasia (Figure, B). The greatest quantitative shift in decision making (from observe to reexcise) as a function of involved margins was seen for DN with moderate dysplasia. Specifically, the decision to reexcise DN with moderate dysplasia inverted from 9% to 81% of respondents.

Comment. This study finds that both grade and margin status are important variables in determining surgical decisions; margin status is most influential when applied to DN of moderate grade. Margin status does not appear to be as critical for clinical decision making of DN with mild or severe dysplasia.

Previous studies,^{1,2} also using surveys, have attempted to elicit the reexcision rate of DN histologically confirmed, but those studies did not directly address the histologic grade of the lesion or the margin status of the biopsy specimen. The responses from both of those studies indicated that both the margin status and the degree

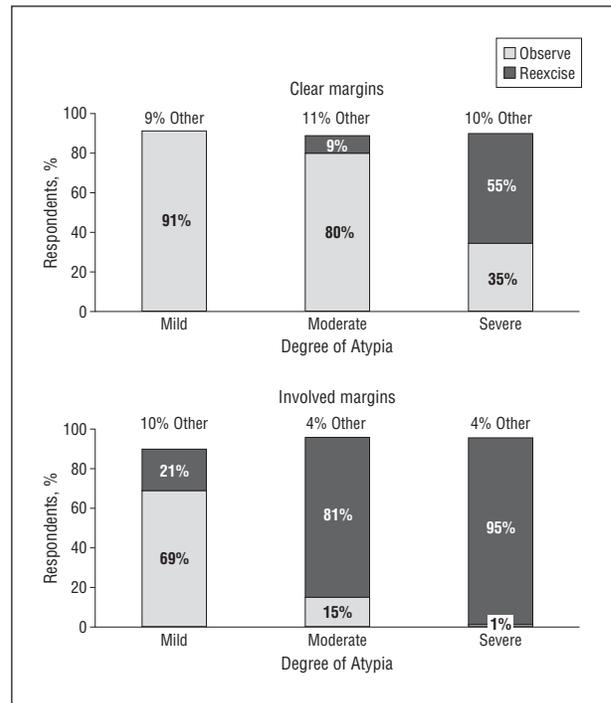


Figure. Degree of atypia with clear margins (A) and involved margins (B).

of dysplasia had some role in the decision to reexcise. The present study addresses the effect of both degree of atypia and margin status reported on the clinician's decision to observe or reexcise a DN.

The DN is a controversial subject in dermatology, and although there are no universally accepted criteria for grading DN (or the biologic consequence of these lesions), it remains common clinical practice. In our small sample, 83% of respondents indicated that the dermatopathology reports they receive comment on the grade of a dysplastic nevus.

Our findings are relevant because there is mounting evidence that reexcision of lesions with low-grade atypia (mild and moderate DN) may not be necessary, even when positive margins are found^{3,4}; the recurrence rates of these nevi are low, and there are no reports of subsequent development of melanoma in these lesions. Larger prospective trials are still needed to help define a standard of care with respect to histopathologically proven DN.

Our survey demonstrates the likely clinical decisions given a pathology report defining the degree of histopathologic atypia and margin involvement. It is helpful for dermatopathologists to know the clinical consequences of their pathology report and for other clinicians to see how their colleagues approach these controversial lesions.

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