

An Open-Label Exploratory Study Evaluating the Efficacy and Safety of Ingenol Mebutate Gel 0.05% for the Treatment of Verruca Vulgaris

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INTRODUCTION

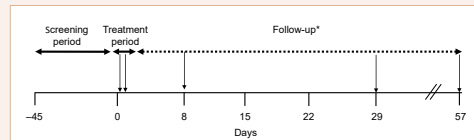
- Verruca vulgaris is caused by the human papillomavirus (HPV) and is most frequently associated with HPV types 1, 2, 4, 27, 29, and 57.^{1,2} It commonly occurs on the hands^{1,2}
- Current therapies are aimed at destroying tissue or influencing the body's inflammatory response against the virus.¹ There is no FDA-approved topical therapy for common warts²
- Ingenol mebutate gel 0.05% is FDA approved for the topical treatment of actinic keratosis (AK)^{3,4} and has a dual mechanism of action: (1) induction of rapid lesion necrosis followed by (2) an inflammatory reaction thought to be mediated by protein kinase C activation⁵
- HPV-infected keratinocytes behave similarly to keratinocytes damaged by UV in the pathogenesis of AK. These similarities include hyperproliferation and mutagenesis^{1,2,6}; therefore, cytotoxicity of target tissue using an AK topical treatment might be beneficial in wart destruction
- A recent case study showed the efficacy of ingenol mebutate against anogenital warts⁷
- The current study was an open-label, exploratory study using ingenol mebutate gel 0.05% for the treatment of verruca vulgaris on the hands

METHODS

Design

- Open-label, exploratory study (Figure 1)
- Conducted at a single site in the US in 2016-2017
- 16 eligible subjects were treated once daily for 2 consecutive days, on days 1 and 2 of the study, with ingenol mebutate gel 0.05%
- Warts were pared to allow for effective penetration without the callous
 - Additionally, one wart in each subject was occluded with a standard adhesive bandage for 24 hours after each application
- Follow-up visits occurred on days 8, 29, and 57 to assess application-site reactions (ASRs)
- At day 57 (study end), wart clearance was assessed

Figure 1. Study design



*Follow-up consisted of major safety assessments, including visual assessment of ASRs on a 5-point scale (0=clear to 4=severe) and the recording of adverse reactions. Photographs were taken at follow-up visits. At day 57 (study end), patient satisfaction was assessed with a 6-question survey.

Key inclusion criteria

- Eligible subjects were >18 years of age; nonpregnant
- Minimum of 2 and maximum of 5 verrucous papules diagnosed as common warts on the hands, excluding proximity to the nails

Key exclusion criteria

- Pregnancy
- Use of any investigational drug or device that could affect common wart treatment
 - Use of an investigational drug or investigational device treatment within 30 days prior to visit 1
 - Prior exposure to ingenol mebutate gel

Physician's assessments

- Pregnancy test (day 1)
- Lesion counts and measurement of wart size (day 1 and 57)
- Photography (days 1, 2, 8, 29, 57)

Safety

- Visual assessment of ASRs on a 5-point scale (0=clear to 4=severe) (days 1, 2, 8, 29, 57)
- Adverse events were recorded

Questionnaire

- 6-question survey on patient satisfaction (at study end, day 57)

Primary efficacy end point

- Complete clearance of all warts

RESULTS

- Baseline subject demographics and characteristics are described in Table 1

Table 1. Baseline subject demographics and characteristics

Characteristic	
Age, mean, years	41.17
Gender, female, n (%)	6 (37.5)
Race, n (%)	
White	14 (87.5)
Asian	1 (6)
Other*	1 (6)
Number of warts at baseline	
Mean	3.38
2	5 subjects
≥3 and ≤5	11 subjects
Size of warts, mm* (mean)	0.3

*Native Hawaiian/Pacific Islander.

Treatment regimen

- Subjects were treated from April 2016 to January 2017
- Treatment began after subjects met key inclusion criteria of confirmed common warts
- Of the identified 54 warts, 16 lesions were occluded and 38 lesions were not occluded
 - Ingenol mebutate gel 0.05% was applied to cover the lesion, plus a 0.5-cm margin
 - Duration of treatment: once daily for 2 consecutive days, on days 1 and 2 of the study
 - A maximum of one treatment kit (containing 2 tubes of medication) was used

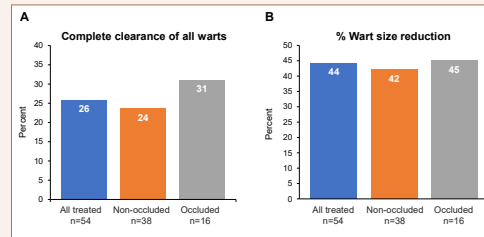
Primary efficacy end point

- The primary end point of complete clearance of all warts was not met in any of the 16 subjects
- However, overall wart count was reduced from 54 at baseline to 40 at study end, a 26% reduction in wart count (Figure 2A)

Warts reduced in size

- Of the non-occluded warts, 57% (22/38) showed a partial reduction in size; they were reduced by 42% in size (Figure 2B)
- Of the occluded warts, 50% (8/16) showed a partial reduction in size; they were reduced by 45% in size (Figure 2B)

Figure 2. Ingenol mebutate gel 0.05% efficacy for treatment of warts



Subject satisfaction

- 11 of the 16 subjects stated that the wart treatment was tolerable or very tolerable
- 6 of the 16 subjects noted that the use of the bandage was moderately to extremely difficult during the 2 days of treatment
- Satisfaction with treatment results
 - Neutral: 7 of 16 subjects
 - Moderately or very satisfied: 5 of 16 subjects
 - Disappointed: 4 of 16 subjects
- 7 of 16 subjects preferred this treatment over previous topical treatments or office procedures, with 5 strongly preferring and 2 slightly or moderately preferring this treatment

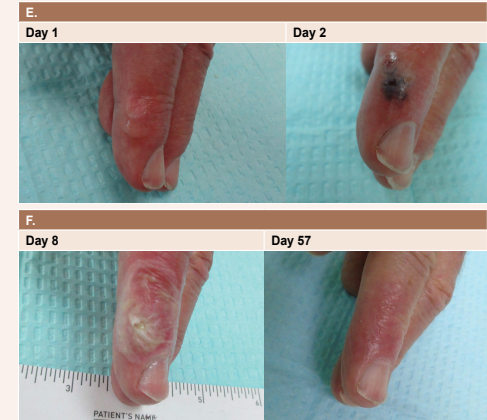
ASRs

- ASRs were defined as erythema, flaking/scaling, crusting, swelling, erosion/ulceration and vesiculation/pustulation
- All subjects experienced ASRs that began on day 2 of treatment
- ASRs peaked within 8 days (Figure 3) and resolved without relief treatment, with the exception of 2 subjects who required lysis of bullae
- ASRs most commonly reported as severe were swelling (3/16) and vesiculation/pustulation (3/16) on day 8

Follow-up

- All ASRs were clinically resolved at short-term follow-up at 3 to 4 weeks
- No adverse effects were reported

Figure 3. Photos of representative subjects treated for warts with ingenol mebutate gel 0.05% (A-F)



Courtesy of Neal Bhatia, MD.

DISCUSSION

- The mechanism of action of ingenol mebutate in AK is often referred to as dual action: rapid lesion necrosis and then activation of the innate immune system via a specific neutrophil-mediated antibody-dependent cellular cytotoxicity⁸
- Protein kinases play a fundamental role in the mechanism of action of ingenol mebutate treatment and the cell death of primary keratinocytes and patient-derived squamous cell carcinoma cells⁹
- HPV-infected keratinocytes behave similarly to UV-damaged keratinocytes in AK. Given their similarities in mutagenesis and hyperproliferation,^{1,2,6} the cytotoxicity of target tissue with ingenol mebutate was hypothesized to be beneficial in wart destruction
- The primary end point of complete clearance of all warts was not met in any of the 16 subjects in this study. However, overall wart count was reduced from 54 at baseline to 40
- Of the occluded warts, 81.25% (13/16) were reduced in size from baseline, with 31% showing complete clearance (5/16) (Figure 2) and 50% (8/16) showing a partial reduction in size. Among the 38 non-occluded warts, fewer lesions were cleared: complete clearance was observed in 9 of these warts (24%), and 22 warts (57%) were reduced in size

CONCLUSION

- Ingenol mebutate gel 0.05% was efficacious and well tolerated for reducing the overall size of warts
- The occluding treatment was associated with increased efficacy and anticipated ASRs
- The majority of subjects found the treatment to be tolerable or very tolerable

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