Warts vs. Actinic Keratosis:
New Weapons in the Therapeutic Civil War

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Dr. Bhatia’s Disclosures:

- Affiliations with Abbvie, Almirall, Biofrontera, BiopharmX, Dermira, Dr. Reddy’s, Encore, EPI Health, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, Leo, Mayne, Menlo, Novartis, Ortho, Pfizer, Pierre-Fabre, Regeneron, Sanofi, SkinFix, Soligenix, SunPharma, Vidac, and Vyome

- Some slides from industry were borrowed for explanation of data and scientific background, not for promotion

- Off-label discussion is likely

- Copies of pdf or questions: bhatiaharbor@gmail.com

- Acknowledgments: Adam Friedman, MD; Ted Rosen, MD
Is there a civil war between AKs and Warts? Or is it sibling rivalry?

- They look alike, can linger for a long time untreated, share a similar trigger (HPV), and resist host apoptosis and defenses.
- Patients often overlook them until they either grow, bleed, change in size, or meet their deductibles.
- Dermatologists usually take the same approach with each disease: freeze and go.
- There are few prevention strategies that are either adhered to, are approved, or actually work.
- The topical management strategies for these are usually painful, expensive, or impossible to get covered by insurance.
HPV: The Double Agent

- HPV 21, 23, 38 linked to AKs and SCC
  - Induced anti-apoptotic effects in UV-damaged cells
- Multiple phenotypes of warts linked to HPV
- E6 and E7 proteins essential for accumulation of further mutation
  - E6 of the cutaneous HPV types 5, 8, 20, 22, 38, 76, 92, and 96 (betaPV types) degrade BAK
  - Binds and inactivates p53 and BAK—slows DNA repair
  - Anti-apoptotic effect of the E6 protein in HPV proposed as a tumor inducing factor

Transmission and Life Cycle of HPV

If there are “Subclinical AKs,” what about “Subclinical Warts?”

- **Evolving AKs are still AKs,** whether we see them with our eyes, dermatoscope, confocal microscopy, or fluorescence
- **Atypical keratinocytes not often correlated clinically except as photodamaged skin**
- **Subclinical or precursor warts more often over genitals or cervical disease**
- **Innocent lateral skin often without clinical change despite histological presence of HPV-infected keratinocytes**
- **Koilocytosis delayed after initial infection**

Malvehy, J, “A new vision of actinic keratosis beyond visible clinical lesions,” *JEADV*, 2015, 29 (supp) 1:3-8
Similar Weapons in the War

- Same destructive and immune-based therapies approved for AKs have been studied off-label for warts
  - Topical 5-FU, Tazarotene, Imiquimod, Ingenol Mebutate, Sinecatechins, ALA-PDT all for AK, also in combo with cryo
  - Imiquimod, IM gel, and Sinecatechins studied for genital warts
  - Impact on the “field” effects of warts still poorly understood
- Costs, tolerability, and compliance are all limiting factors
- Summaries of combination studies with cryo for warts are incomplete unless studied against topical therapies alone
Cryo-necrosis induces destruction

5 Seconds

10 seconds

Courtesy Adam Friedman, MD
What does Dr. Google prescribe?

- Banana Peels
- Duct Tape
- Vicks Vaporub/Robitussin
- Teatree oil—One study against HSV not HPV
- Apple Cider Vinegar

- Salicylic Acid-- 40% or bust
  - Mediplast, Occlusal HP
  - Solution of salicylic acid 17%
  - DuoFilm, Compound W, Occlusal HP

- Apply after wart has been wet (eg, in shower)
- Apply every other night.
- Pare or file (at home) twice monthly (after soaking)

Courtesy Adam Friedman, MD
Zinc for Warts

- Multiple trials (Korea and Brazil): 62.5-87.7% success
- MOA: increases APC activity
- Zinc sulfate 10mg/kg/day (max 600mg): Rx up to 3 mo
  - Failures: insufficient dose, too short treatment regimen
- Gastritis/Gastric perforation
- Use divided doses after meals, not to exceed 120-140mg elemental zinc per day

Courtesy Ted Rosen, MD
Cimetidine vs Zinc Sulphate

- Randomized, DB prospective study 18 pts 7-20 yo with multiple (11-120) warts (VV, flat, plantar)
- 9 / 9 completed 35 mg/kg/d cimetidine x 3 m
  - 0/9 Complete
  - 4/9 Partial
  - 5/9 No response
- 8 / 9 completed 10 mg/kg/d zinc sulphate x 3 m
  - 5/8 Complete
  - 2/8 Partial
  - 1/8 No response
Old and New

- **5-FU**: Study comparing 5% 5-FU cream plantar warts under tape occlusion vs. tape occlusion alone, n=40
  - 19/20 patients (95%) in active group 5% 5-FU with tape occlusion had complete eradication within 12 weeks
  - Average time to healing 9 weeks, 3 recurrences by 6 months

- **New Keratolytic**: 28.5% salicylic acid extended release antiviral film-forming solution is the only extended release salicylic acid available for wart removal

- **Thermal pad**: 2 hours exposure, raises local temperature to 42-43°C for with recalcitrant warts
  - Proof of concept study, n=3, all clear by 4-5 wks


Sinecatechins 15% ointment: Complete Clearance of Baseline and Newly Emerging Warts

ITT=intent-to-treat; LOCF=last observation carried forward.

ITT/LOCF analysis

*P=.01 vs vehicle

## PDT for Warts

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stender et al.</td>
<td>20% ALA, 4h incubation, Red light (590-700nm, 70 J/cm²) 3-6 tx, placebo control, n=45</td>
<td>At weeks 14 and 18, wart area decreased significantly in ALA-PDT arm compared to placebo PDT arm</td>
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</tbody>
</table>
| Fabbrocini et al. | 20% ALA, 5h incubation, 10% SA+10% urea cream, tungsten lamp (400-700nm, 50 J/cm²), 1-3 tx, vehicle control, n=67 | -ALA-PDT: 48 of 64 (75%) warts completely healed  
-VEH-PDT: 13 of 57 (22.8%) warts completely healed |
| Smucler & Jatsova | 20% ALA, 3h incubation, local anesthetic, PDL (595nm) or LED (635nm) light, up to 5 tx, controlled, n=274 warts | -PDL: 81% cure rate, mean of 3.34 tx  
-ALA+PDL: 100% cure rate, mean of 1.95 tx  
-ALA+LED: 96% cure rate, mean of 2.53 tx |


**Hall: Jeffrey A. Hall, MD; Pamela J. Keller, RN; Gregory S. Keller, MD.** Dose Response of Combination Photorejuvenation Using Intense Pulsed Light–Activated Photodynamic Therapy and Radiofrequency Energy. *Arch Facial Plast Surg*. 2004;6:374-378

Ingenol Mebutate 0.05% gel for two days for common warts

- Off-label independent study, n=16
- 2-5 common warts on palms or palmar surface of digits
  - Warts pared down on day 1, treated for two days
  - Largest wart occluded with adherent dressing for 24 hours, removed then replaced after second dose applied
- LSRs and tolerability assessments at Days 8, 29, and 57

Bhatia, N, “An open-label exploratory study evaluating the efficacy and safety of ingenol mebutate gel 0.05% for the treatment of verruca vulgaris,” J Amer Acad Dermatol, Vol 78, Issue 3, 595 – 596
Early Pearls from the Study

- Occlusion of warts on the digits gave the best results
- Paring of the warts is essential along with allowing the treatment to dry
- Would monthly cryo be of added benefit to prevent recurrence or persistence?
- Would extra treatment applications be useful?

Other Medical Treatments for Warts

- Aclaris Therapeutics’ A-101 45% Topical Solution Ph 2
  - N=159, 1-6 warts, 56 days of twice weekly application in office
  - PWA score measured diameter but not thickness or intact callus
  - Mean reduction in PWA score at Day 56 on the target warts was 0.87 points in A-101 45% treated group vs reduction of 0.17 points for placebo group (p<0.001)
  - Excluded plantar and periungual, ages 8 and up

- Cutanea CLS006 Furosemide Topical Gel, 0.125%
  - N=480, 1-6 warts, 3-10 mm
  - Daily application of gel at home
  - Ages 2 and up
  - Includes Periungual but not Plantar

  **Rationale:** Furosemide and Digoxin impair viral DNA synthesis by inhibition of cell membrane transport of Na⁺ and K⁺
  - Creates intracellular K⁺ depletion and slows HPV proliferation
Let’s Talk Cantharidin

- Cantharidin 0.7% preparation applied topically in office.
- MOA: Activates neutral serine proteases that cause degeneration of the desmosomoma plaque, leading to detachment of tonofilaments from desmosomes
  - ? Induces anti-viral immune response
- Repeat in-office applications within 14 -21 days may be necessary.
- Painless during (good for kids)
  - Risk of significant pain associated with swelling
- Not FDA approved (for now)

COVE-1: A Phase 2, Open-Label Study To Evaluate Efficacy, Safety, and Tolerability of a Proprietary Drug-Device Combination Product Containing 0.7% w/v Cantharidin (VP-102) for Topical Treatment of Common Warts

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aThe Indiana Clinical Trials Center, Plainfield, IN. bClarkston Skin Research, Clarkson, MI. cSolutions Through Advanced Research, Jacksonville, FL. dInstat Consulting, Chatham, NJ. eVerrica Pharmaceuticals Inc., West Chester, PA.

INTRODUCTION

- Verrucae vulgaris or warts are epidermal growths caused by the human papillomavirus (HPV). Approximately 50% of children and young adults have warts.1
- There are numerous treatments, but most are of limited efficacy.
- Compound cantharidin has been used for the treatment of warts since the 1950s but lacks large scale trials and a standardized formulation.2
- This Phase II study evaluated the safety and efficacy of VP-102, a drug-device combination with cantharidin (0.7% w/v) for the treatment of common warts.

METHODS

- Eligible subjects were 2 years or older and had 1-8 warts measuring ≤10 mm in diameter and ≤3 mm in height.

EFFICACY

- Percentage of VP-102-Treated Subjects With Complete Clearance of Common Warts
- Percentage Change in Number of Common Warts from Baseline in VP-102-Treated Subjects

SAFETY & TOLERABILITY

- Incidence of TEAEs ≥5%

CONCLUSIONS

- VP-102 demonstrated efficacy in the reduction of the percentage of common warts from baseline to Day 6 and as the rates of complete clearance of warts.
- VP-102 showed a favorable tolerability and safety profile. The most common treatment-emergent AEs were mild to moderate and included application site blistering, pain, pruritus, erythema, and scabbing. These were considered related to the pharmacodynamic action of cantharidin.
- Due to the higher complete clearance rate observed in Cohort 2 (51% complete clearance at Day 6), the treatment regimen of Cohort 2 will be utilized in future Phase 3 studies.

Disclosures

This study was sponsored by Verrica Pharmaceuticals Inc. Editorial support was provided by Versant Learning Solutions, and funded by Verrica Pharmaceuticals Inc.

References
CONCLUSIONS

• VP-102 demonstrated efficacy in the reduction of the percentage of common warts from baseline to D84 as well as the rates of complete clearance of warts.

• VP-102 showed a favorable tolerability and safety profile. The most common treatment-emergent AEs were mild to moderate and included application site blistering, pain, pruritus, erythema, and scabbing. These were considered related to the pharmacodynamic action of cantharidin.

• Due to the higher complete clearance rate observed in Cohort 2 (51% complete clearance at D84), the treatment regimen of Cohort 2 will be utilized in future Phase 3 studies.
Battle Molluscum

- CAMP-1: 46% of patients had achieved completion lesion clearance at day 84 vs. 18% of placebo
- CAMP-2: Pts on VP-102 54% clearance vs. 13% placebo
  - no issues in terms of safety, no serious adverse events (SAE)
Safety and Efficacy of VP-102 (0.7% w/v Cantharidin) in Molluscum Contagiosum by Lesion Location: Pooled Results of Two Multicenter, Randomized, Vehicle-Controlled Trials

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INTRODUCTION

- VP-102 is a proprietary drug-delivery device combination containing a controlled formulation of cantharidin (0.7% w/v) that has been investigated in two Phase 3 trials for the treatment of molluscum contagiosum (MC).
- Anatomical and epidermal differences across distinct areas of the body could lead to variations in efficacy and safety by body region.
- The objective of this exploratory analysis was to determine the safety and efficacy of VP-102 by analyzing pooled data segmented by the location of the lesions on the body.

METHODS

Body Regions With Lesions at Baseline (ITT Population)

<table>
<thead>
<tr>
<th>Body Region</th>
<th>No. of Patients</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>729</td>
<td>557</td>
</tr>
<tr>
<td>Chest/Abdomen</td>
<td>360</td>
<td>217</td>
</tr>
<tr>
<td>Back/Buttocks</td>
<td>92</td>
<td>57</td>
</tr>
<tr>
<td>Arms</td>
<td>120</td>
<td>92</td>
</tr>
<tr>
<td>Lower Extremities</td>
<td>159</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>1,300</td>
<td>994</td>
</tr>
</tbody>
</table>

- Segmentation of lesions by body region at baseline included the following areas:
  - Head/Neck
  - Chest/Abdomen
  - Back/Buttocks
  - Arms
  - Lower Extremities

- Lesion counts by body region were obtained at each visit (Days 1, 21, 42, 93, and 64). Efficacy was measured by complete clearance of baseline and new lesions in the identified region.
- Subjects could present with multiple body regions. Lesion locations occurring at baseline were tracked throughout the study. Lesions occurring in new regions after baseline were not tracked in this analysis.

A safety analysis was conducted for patients who had lesions treated in the identified region at a particular visit.
- This analysis included pre-specified application site TEAEs reported during or after Visit 1 and before Visit 2 (see figure in Safety section), in which all subjects had MC lesions treated in the coordinated areas.

CONCLUSIONS

- VP-102 treatment resulted in a statistically significantly greater percentage of subjects with clearance of all baseline and new MC lesions in all body regions compared to vehicle treatment.
- Rates and types of adverse events were similar in the six body regions. The most common TEAEs included application site vesicles, pruritus, scab, erythema, dryness, discoloration, pain, and edema.
VP-102

Percent of subjects with complete clearance of all treatable warts (baseline and new) at Day 84
Study drug (VP-102) is administered topically to each treatable wart to a maximum of 4 applications
Cohort 1 is treated until clear, Cohort 2 receives one additional treatment at the first visit clearance was observed up

to a maximum of 4 total applications
Hyperthermic effects on HPV

- Higher body temperatures can lead to high clearance rates of the HPV lesions (53% vs 11%)
- The PI3K Pathway (responsible for suppressing Langerhans activity) is downregulated during Hyperthermia: Allows Langerhans cells to detect the HPV infected cells
Microwave therapy for cutaneous human papilloma virus infection

**Background:** Human papilloma virus (HPV) infects keratinocytes of the skin and mucous membranes, and is associated with the induction of cutaneous warts and malignancy. Warts can induce significant morbidity and disability but most therapies, including cryotherapy, laser, and

- Non-ablative Immune Modulation IM (43-46°C)
- HSP70 release
- Inflammatory modulation
- Immunotherapy adjuvant

- ABLATION
- Tissue destruction

Less than 50°C

More than 50°C
Non-ablative Immune Modulation
FDA approval 2018

- MOA: rapidly elevating tissue temperature into the Hyperthermic Range: 43-46°C
- Microwaves produce dielectric heating and cause rapid temperature elevation in tissue
  - 50 J over a 7-mm diameter application area (130 J/cm²) over 5 seconds

this process. Conclusion: Keratinocyte-skin dendritic cell cross-talk is integral to host defence against HPV infections, and this pilot study supports the concept of microwave induction of anti-HPV immunity which offers a promising approach for treatment of HPV-induced viral warts and potentially HPV-related cancers.
Microwave energy rapidly elevates tissue temperature and creates precise, localized cell destruction.

Figure 1.
Infected tissue can exist several millimetres below the surface and can often be difficult to treat using traditional methods, resulting in either untreated tissue or significant damage.
Microwave energy rapidly elevates tissue temperature and creates precise, localized cell destruction.

Figure 1. Infected tissue can exist several millimetres below the surface and can often be difficult to treat using traditional methods, resulting in either untreated tissue or significant damage.

Figure 2. Swift delivers a precise, highly controlled energy dose. As microwaves travel into the tissue, water molecules begin colliding and creating localised heat energy - quickly destroying all infected tissue within a predetermined depth.
Microwave energy rapidly elevates tissue temperature and creates precise, localized cell destruction.

**Figure 1.** Infected tissue can exist several millimetres below the surface and can often be difficult to treat using traditional methods, resulting in either untreated tissue or significant damage.

**Figure 2.** Swift delivers a precise, highly controlled energy dose. As microwaves travel into the tissue, water molecules begin colliding and creating localised heat energy – quickly destroying all infected tissue within a predetermined depth.

**Figure 3.** In just seconds the treatment is complete and the healing cascade begins immediately. Treated tissue is quickly replaced, repaired and regenerated.
Intralesional Versus Intramuscular Bivalent Human Papillomavirus Vaccine in the Treatment of Recalcitrant Common Warts

- N= 44 adults with recalcitrant warts
- Intralesional bivalent human papillomavirus (HPV) 16, 18 vaccine
  - 2-week intervals up to 6 vs intramuscular bivalent HPV vaccine at 0, 1, and 6 months.
- Intralesional group (n=22), 81.8% complete clearance of warts compared vs 63.3% of those IM group (P=.287).
- Clearance rate of warts was significantly faster in the intralesional group (3.22 months vs 4.75 months; P=.005).
- AE: pain at the injection site and localized itching
HPV vaccines for Warts

- Indicated for prevention of HPV-related cervical, vulvar, vaginal and anal cancer: 16, 18, 31, 33, 45, 52, and 58
  - Cervical intraepithelial neoplasia (CIN) grade 2/3 & cervical adenocarcinoma in situ
  - Cervical intraepithelial neoplasia (CIN) grade 1
  - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
  - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3
  - Genital warts (condyloma acuminata) caused by HPV types 6 and 11

- Gardasil quadrivalent vaccine now approved for ages 9-45 but no evidence for treatment

Courtesy Adam Friedman, MD
So what are the pearls?

- Wait at least a week after cryotherapy to start any topicals
- Topical anesthetics as needed
- Encourage callus reduction between destroyions

But what about Freeze and go? Costs costs costs...