Treatment of Actinic Keratosis: Timed Sequential Therapy

Gary Goldenberg, MD
Assistant Clinical Professor of Dermatology
Mount Sinai School of Medicine
Medical Director of the Dermatology Faculty Practice
• DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY
  • Abbvie
  • Allergan
  • Amgen
  • Aqua/Almirall
  • Bayer
  • Castle
  • Celgene
  • Dermira
  • Galderma
  • Genentech
  • GSK/Stiefel
  • Janssen
  • LEO
  • Novartis
  • Pharmaderm
  • Pfizer/Anacor
  • Regeneron/Sanofi
  • SUN
  • TEVA
  • Valeant
  • Xoft

• Off-label medication use
Outline

• Why treat AK?
  – Progression to SCC
  – Field cancerization

• Timed Sequential Therapy (TST) with
  – Imiquimod 3.75%
  – Ingenol mebutate
  – 5-FU 0.5%
  – Photodynamic therapy
Gene Expression Patterns of Normal Human Skin, Actinic Keratosis, and Squamous Cell Carcinoma

A Spectrum of Disease Progression

R. Steven Padilla, MD, MBA; Sheldon Sebastian, MD; Zeyu Jiang, PhD; Ingo Nindl, PhD; Richard Larson, MD, PhD

Objectives: To identify and compare the gene expression profiles of actinic keratosis (AK) and squamous cell carcinoma (SCC) and to further clarify critical genetic alterations in the evolution of SCC from normal sun-damaged human skin.

Design: Observational study.

Setting: University practice.

Patients: Skin biopsy specimens were obtained from 16 patients. The specimens included 14 normal non-sun-exposed skin samples, 14 normal sun-exposed skin samples, 5 AKs, and 15 cutaneous SCCs.

Main Outcome Measures: Gene expression profiles from normal non-sun-exposed skin, normal sun-exposed skin, AKs, and SCCs.

Results: Using a highly stringent shrunken centroid threshold of 6.52 and the prediction analysis of micro-arrays, we identified 89 unique genes that most likely contribute to the molecular evolution of SCC. Our model was cross-validated using data from a separate study and clearly distinguishes between skin tumors (AK and SCC) and normal skin independent of sun exposure. Genes that were upregulated in AK and SCC were downregulated in normal skin, and genes that were downregulated in AK and SCC were upregulated in normal skin.

Conclusions: The finding of similar differentially expressed genes in AK and SCC confirms that AK is a precursor lesion of SCC and indicates that they are closely related genetically. Clear elucidation of these relationships will be critical to improving therapeutic approaches.

Arch Dermatol. 2010;146(3):288-293
Actinic Keratosis

• Larson and colleagues examined
  – 14 normal non–sun-exposed skin samples
  – 14 normal sun-exposed skin samples
  – 5 AKs
  – 15 cutaneous SCCs
  – High-density gene microarray studies were performed on isolated RNA samples

Actinic Keratosis

• Direct correlation of abnormal gene expression in the progression of normal skin to AK to SCC

Actinic Keratosis

• 186 genes statistically significant
  – 101 - expressed progressively higher along the spectrum
  – 85 - expressed progressively lower along this spectrum of disease
  – AK and SCC - most evident degree of gene expression
    • Normal skin - minimal alteration of gene expression

Evaluation of the Prognostic Significance of Follicular Extension in Actinic Keratoses

SHAILY PANDEY, BA; STEPHEN E. MERCER, MD, PhD; KAI DALLAS, BS;
PATRICK O. EMANUEL, MD; GARY GOLDENBERG, MD

Mount Sinai School of Medicine, New York, New York; Departments of Dermatology and Pathology, Mount Sinai School of Medicine, New York, New York; Consultant Dermatopathologist Diagnostic Medlab, Auckland, New Zealand
Actinic Keratosis - Follicular Extension

- Examined 1000 AKs
  - 104 with follicular extension
  - Determine the prognostic significance of follicular extension in AK

Actinic Keratosis - Follicular Extension
## Actinic Keratosis - Follicular Extension

<table>
<thead>
<tr>
<th></th>
<th>Squamous cell carcinoma</th>
<th>Basal cell carcinoma</th>
<th>Melanoma</th>
<th>No cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With follicular extension</strong></td>
<td>64 (52%)</td>
<td>40 (54%)</td>
<td>11 (61%)</td>
<td>30 (41%)</td>
</tr>
<tr>
<td><strong>Without follicular extension</strong></td>
<td>60 (48%)</td>
<td>34 (46%)</td>
<td>7 (39%)</td>
<td>44 (59%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>124</td>
<td>74</td>
<td>18</td>
<td>74</td>
</tr>
</tbody>
</table>
## Table 2: Univariate odds ratio comparing previous history of skin cancer in patients with AKs without follicular extension to patients with AKs with follicular extension.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>1.18</td>
<td>0.67-2.04</td>
<td>0.57</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1.30</td>
<td>0.72 - 2.27</td>
<td>0.38</td>
</tr>
<tr>
<td>Melanoma</td>
<td>11.1</td>
<td>1.56-111</td>
<td>0.04</td>
</tr>
<tr>
<td>Overall</td>
<td>1.81</td>
<td>1.01-3.22</td>
<td>0.043</td>
</tr>
</tbody>
</table>
Actinic Keratosis - Follicular Extension

Table 4: Significant variables in a multivariable logistical regression model for predicting the increase in probability of having AK with follicular extension versus AK without follicular extension.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.001</td>
<td>1.044</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>0.004</td>
<td>2.51</td>
</tr>
<tr>
<td>Leg</td>
<td>0.012</td>
<td>5.40</td>
</tr>
</tbody>
</table>
Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

- n=149 excision specimens BCC, SCC & MM

Table 1: Incidence rates of AK by cutaneous malignancy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th># of Cases Examined (% of Total Cases)</th>
<th># of Cases with AKs Observed (% by Cancer Type)</th>
<th># of Cases with Marginal AKs (% of Previous Column Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>64 (43%)</td>
<td>21 (33%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>SCC</td>
<td>61 (41%)</td>
<td>35 (57%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>MM</td>
<td>24 (16%)</td>
<td>6 (33%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>149 (100%)</td>
<td>62 (42%)</td>
<td>35 (56%)</td>
</tr>
</tbody>
</table>

Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

Table 2: Study population and specimen statistics

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Average Age (Standard Deviation)</th>
<th>% Male (% Female)</th>
<th>Average Specimen Size in cm² (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>72 (13)</td>
<td>53% (47%)</td>
<td>2.7 (2.2)</td>
</tr>
<tr>
<td>SCC</td>
<td>63 (13)</td>
<td>57% (43%)</td>
<td>2.1 (2.3)</td>
</tr>
<tr>
<td>MM</td>
<td>75 (13)</td>
<td>58% (42%)</td>
<td>6.2 (5.5)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (14)</td>
<td>56% (44%)</td>
<td>3.0 (3.3)</td>
</tr>
</tbody>
</table>

Table 3: Significant variables in predicting the presence of an AK in the near vicinity of a re-excised cutaneous malignancy as determined by multiple variable regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
<th>Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer type = SCC</td>
<td>P = .007</td>
<td>2.61</td>
</tr>
<tr>
<td>Cancer location = Head</td>
<td>P = .044</td>
<td>2.39</td>
</tr>
<tr>
<td>Cancer location = Arm</td>
<td>P = .042</td>
<td>2.55</td>
</tr>
</tbody>
</table>

Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

• Of 149 cases, chi-square analysis determined that AKs were observed significantly more often (p=.0125) in SCC re-excisions (57% of 61 SCCs) than BCC (33% of 64 BCCs) or MM (33% of 24 MMs) re-excisions

• Multivariate regression analysis determined the following variables to be significant in prediction of AKs near malignancies: cancer type of SCC (p=.007) and any type of cutaneous cancer located on the head (p=.044) or on the arms (p=.042)

Actinic keratosis as a marker of field cancerization in excision specimens of cutaneous malignancies

Figure 1: Actinic Keratosis and Adjacent Squamous Cell Carcinoma
On the left, an actinic keratosis demonstrates atypical keratinocytes along the basal layer with hyperchromatic nuclei and atypical maturation. On the right, a squamous cell carcinoma is seen which is separated from the AK by a section of histologically normal epithelium.

Figure 2: Actinic Keratosis and Basal Cell Carcinoma
A) Residual basal cell carcinoma B) Actinic keratosis from the same excision with notable parakeratosis and solar elastosis in the dermis.

Figure 3: AK and MM
A) Malignant melanoma B) Incidental actinic keratosis in the same excision specimen; both images exhibit a lymphocytic infiltrate.

Actinic Keratosis:
Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

Actinic Keratoses
Natural History and Risk of Malignant Transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial

Vincent D. Criscione, AB, MD, PhD, Martin A. Weinstock, MD, PhD, Mark F. Naylor, MD, Claudia Luque, MD, Melody J. Eide, MD, MPH, and Stephen F. Bingham, PhD, for the Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group
Actinic Keratosis:
Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

• Oklahoma City VA site
• 169 patients
• Mean follow up – 42 months, 7 visits
Actinic Keratosis: Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

- 7784 distinct AKs identified during the study
- 411 lesions biopsied
  - 122 (30%) – primary SCC (91 invasive and 31 in situ)
  - 76 (18%) – primary BCC
  - 159 (39%) – AK
  - 16 (4%) – recurrent carcinoma (SCC or BCC)
  - 16 (4%) – seborrheic keratoses
  - 22 – other, nonspecific, or no pathology

• Risk of progression of AK to primary SCC (invasive or in situ)
  – 1 year – 0.60%
  – 4 years – 2.57%

• Risk of progression of AK to primary invasive SCC
  – 1 year – 0.39% (95% CI, 0.26%-0.57%)
  – 4 years – 1.97%

Actinic Keratosis: Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

- The risk of progression of AK to primary BCC
  - 1 year – 0.48%
  - 4 years – 1.56%

- The risk of progression of AK to any KC (SCC or BCC)
  - 1 year – 1.08%
  - 4 years – 4.10%

Actinic Keratosis: Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

- Baseline AKs had a significantly greater risk of progression to primary SCC (invasive or in situ; P = .02)

- 88/169 patients applied topical tretinoin
  - Rate of malignant transformation did not differ from control group

Actinic Keratosis:
Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial

• 187 primary SCCs on the face or ears (139 invasive and 48 in situ)
  – 65% arose in previously documented AK
• 210 primary BCCs on the face and ears
  – 36% arose in previously documented AK

• CONCLUSIONS: In the current study, the authors quantified the malignant potential of clinically diagnosed AKs for both SCC and BCC, although many did not persist, and the results suggested that AKs may play a greater role in the overall burden of keratinocyte carcinomas than previously documented.
What does TST stand for?

Timed sequential therapy

allacronyms.com
Imiquimod and Cryotherapy

- Multi-center (US/Canada)
- N = 247 subjects
- 126 Cryo followed by Imiq 3.75%
- 121 Cryo followed by Placebo

- Baseline ≥ 10 AKs on the face
- Cryo some AKs (5-14)
- Leave ≥ 5 AKs for field treatment
- Wait until sufficiently healed (1-2 weeks)
- Average wait time: 12 days
AK Lesion Counts & Cryosurgery
Baseline Visit

Baseline = 16 AK lesions (protocol requires ≥ 10)

<table>
<thead>
<tr>
<th></th>
<th>Cryo/3.75%</th>
<th>Cryo/Placebo</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>16.1</td>
<td>15.8</td>
<td>16</td>
</tr>
<tr>
<td>Range</td>
<td>(10-39)</td>
<td>(10-50)</td>
<td>(10-50)</td>
</tr>
</tbody>
</table>

7 Lesions Cryo’ d (Mean) (protocol requires 5 -14)

9 lesions remain (Mean) (protocol requires ≥ 5)
Primary Endpoints
WK 26 (End of Study)

### AKs Treated w/ Cryosurgery

<table>
<thead>
<tr>
<th>Change from Baseline (%)</th>
<th>Cryo/Imiq 3.75%</th>
<th>Cryo/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-100%</td>
<td>-80.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>-83.9%</td>
<td>-73.1%</td>
</tr>
<tr>
<td>P value</td>
<td>.0008</td>
<td></td>
</tr>
</tbody>
</table>

### ALL AKs*

<table>
<thead>
<tr>
<th>Change from Baseline (%)</th>
<th>Cryo/Imiq 3.75%</th>
<th>Cryo/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-86.5%</td>
<td>-50.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>-77.4%</td>
<td>-43.3%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

*All AKs = AK lesions treated w/ cryosurgery at baseline and AK lesions not treated w/ cryosurgery (baseline, recurrent or new)
## Additional Endpoints
### WK 26 (End of Study)

<table>
<thead>
<tr>
<th>AKs Treated w/ Cryosurgery</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryo/Imiq 3.75%</td>
<td>Cryo/Placebo</td>
</tr>
<tr>
<td>% of Patients w/ Complete Clearance</td>
<td>59.5%</td>
<td>29.8%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

### All AKs*

<table>
<thead>
<tr>
<th>All AKs*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryo/Imiq 3.75%</td>
<td>Cryo/Placebo</td>
</tr>
<tr>
<td>% of Patients w/ Complete Clearance</td>
<td>30.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*All AKs= AK lesions treated w/ cryosurgery at baseline and AK lesions not treated w/ cryosurgery (baseline, recurrent or new)
Median AK Lesion Counts Over Time

- **Cryo**
- **Visit**
- **Start med**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Median AK Lesion Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

Cryo/Imiq 3.75%  Cryo/Placebo
An Investigator-initiated Study to Assess the Safety and Efficacy of Imiquimod 3.75% Cream When Used After Cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

GARY GOLDENBERG, MD; RITA V. LINKNER, MD; GISELLE SINGER, BS; AMYLYNNE FRANKEL, MD
Mount Sinai School of Medicine, Department of Dermatology, New York, New York
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• 20 subjects with at least 3 HAKs on each dorsal hand or forearm underwent cryotherapy treatment to HAKs
• Randomized to have either their right or left dorsal hand or forearm treated with imiquimod 3.75% cream
• Begin on the same day as cryotherapy
• 2 wks on, 2 wks off, 2 wks on
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

The number of HAKs in both treatment groups decreased over time with a more pronounced effect observed at weeks 10 and 14 in the cryotherapy/imiquimod group (P < 0.0094).
Imiquimod 3.75% and cryotherapy in the Treatment of Non-Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

The number of non-HAKs in the combination therapy group increased at week 6 and then decreased over time. Lesion rates decreased in the cryotherapy alone group.
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

Incidence of Hypertrophic AKs on the Dorsal Hands and Forearms

- Baseline:
  - Imiquimod + Cryotherapy: 6.3
  - Cryotherapy Only: 5.5

- Week 14:
  - Imiquimod + Cryotherapy: 3.235
  - Cryotherapy Only: 2.94

* P-value = 0.0094; P-values were for the comparison, by way of ANOVA with factors of patient and treatment, of mean change from baseline at each week post baseline for the cryotherapy + Imiquimod group compared to the corresponding week in the cryotherapy only group.
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• Baseline
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• Week 2
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

- Week 6
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

- Week 14/EOS
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• Baseline
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

- Week 2
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• Week 4
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

• Week 6
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms

- Week 14/EOS
Imiquimod 3.75% and cryotherapy in the Treatment of Hypertrophic Actinic Keratoses on Dorsal Hands and Forearms
Field treatment with ingenol mebutate gel, 0.015%, 3 weeks after cryosurgery of actinic keratosis is safe and effective

Berman B¹, Swanson N², Goldenberg G³, Hanke W⁴, Tyring S⁵, Werschler W⁶, Knudsen KM⁷, Larsson T⁷

¹University of Miami Miller School of Medicine, Miami, FL, and Center for Clinical and Cosmetic Research, Aventura, FL; ²Oregon Health and Science University, Portland, OR; ³Mount Sinai School of Medicine, New York, NY; ⁴Laser and Skin Surgery Center of Indiana, Carmel, IN; ⁵University of Texas Health Science Center, Houston, TX; ⁶University of Washington School of Medicine, Seattle, WA and Premier Clinical Research, Spokane, WA; ⁷LEO Pharma, Ballerup, Denmark
Study Design

Figure 1. Study Design Diagram

- **Arm A**: Cryotherapy and Ingenol mebutate, 0.015% gel
- **Arm B**: Cryotherapy and Vehicle gel

Visit No.: 1, 2, 3, 4, 5, 6, 7, 8, 9

Time From Initial Cryotherapy:
- 0, 3 wk, 3 wk + 3 days, 5 wk, 7 wk, 11 wk, 6 mo, 9 mo, 12 mo
Complete clearance rates were significantly higher with ingenol mebutate.
• Partial clearance (>75%) rates were higher with ingenol mebutate
• At week 5 mean composite LSR score in the ingenol mebutate group return to a score similar to that of earlier visits
What if you do another 3 day cycle?

First treatment cycle

<table>
<thead>
<tr>
<th>Total population</th>
<th>Complete clearance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks after initial treatment</td>
<td>61.6%</td>
</tr>
</tbody>
</table>

Second treatment cycle

<table>
<thead>
<tr>
<th>AKs present at 8 wks</th>
<th>Complete clearance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks after randomization</td>
<td>46.7%</td>
</tr>
<tr>
<td>12 mths</td>
<td>18.4% (IngMeb), 18.5% (Vehicle), 4.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emergent AKs</th>
<th>Complete clearance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks after randomization</td>
<td>59.5% (IngMeb), 25.0% (Vehicle), 31.0% (Vehicle)</td>
</tr>
<tr>
<td>12 mths</td>
<td>15.0% (Vehicle)</td>
</tr>
</tbody>
</table>
• An Investigator-Initiated Study to Assess the Safety and Efficacy of Ingenol Mebutate 0.05% Gel when used after Cryotherapy in the Treatment of Hypertrophic Actinic Keratoses (AK) on Dorsal Hands.
Design

• n=16
• Split hand
• All HT-AK treated with LN2: 2 sprays each 5 seconds with a 5 second interval between
• LN2 not used for any nonHT-AK
• IM 0.05% gel applied same day as LN2
## Results: HT-AK

<table>
<thead>
<tr>
<th>Type</th>
<th>Outcome</th>
<th>Picato</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT</td>
<td>Baseline # AK’s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.4 (3.14)</td>
<td>4.6 (2.13)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.5</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>2, 13</td>
<td>1, 10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from Baseline to Day 57 in #AK’s</th>
<th>Picato</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-4.6 (2.66)</td>
<td>-2.5 (1.37)</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td>-4.3 (0.22)</td>
<td>-2.8 (0.22)</td>
</tr>
<tr>
<td>Median</td>
<td>-4.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-10, -2</td>
<td>-5, 0</td>
</tr>
<tr>
<td>p-value vs. Control</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent Change from Baseline to Day 57</th>
<th>Picato</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-86.34 (16.642)</td>
<td>-51.89 (19.091)</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td>-86.1 (4.58)</td>
<td>-52.1 (4.58)</td>
</tr>
<tr>
<td>Median</td>
<td>-100.00</td>
<td>-58.57</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-100.0, -57.1</td>
<td>-75.0, 0.0</td>
</tr>
<tr>
<td>p-value vs. Control</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of subjects CLEAR on Day 57</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>9 (56.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of subjects with ≥75% reduction from Baseline to Day 57</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>11 (68.8%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0016</td>
</tr>
</tbody>
</table>
## Results: nHT-AK

<table>
<thead>
<tr>
<th>Type</th>
<th>Outcome</th>
<th>Picato</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON-HT</td>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>4.4 (3.24)</td>
<td>3.7 (2.27)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>1, 13</td>
<td>1, 9</td>
</tr>
<tr>
<td></td>
<td>Change from Baseline to Day 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-4.1 (3.38)</td>
<td>0.0 (0.00)</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>-3.8 (0.37)</td>
<td>-0.3 (0.37)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-3.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>-13, -1</td>
<td>0, 0</td>
</tr>
<tr>
<td></td>
<td>p-value vs. Control</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>
Efficacy of Cryosurgery and 5-Fluorouracil Cream 0.5% Combination Therapy for the Treatment of Actinic Keratosis

William D. Hoover III, MS; Joseph L. Jorizzo, MD; Adele R. Clark, PA-C; Steven R. Feldman, MD, PhD; Judy Holbrook, LPN, CCRC; Karen E. Huang, MS
Cryosurgery and 5-FU 0.5% Cream

- $n=60$
- Cryosurgery followed by 5FU 0.5% cream vs vehicle for 1 week
- 28 week follow up
Cryosurgery and 5-FU 0.5% Cream

• Week 8: cryosurgery and 5-FU cream 0.5% more likely to result in complete clearance versus cryosurgery alone

• Week 26: no statistical difference was found in the complete clearance of AK lesions in the treatment group compared to cryosurgery alone
0.5% 5-FU Following Cryotherapy

- Multicenter, randomized, double-blind, vehicle-controlled trial
- 144 patients with ≥5 visible or palpable AKs (face)
- 0.5% 5-FU or vehicle qd x 7 d, residual lesions cryosurgery
- Results at 4 wk
  - Mean AK lesion count reduced by 62.4% with 5-FU vs 28.8% with vehicle ($P<.001$)
  - Complete clearance: 16.7% with 5-FU vs 0% with vehicle ($P<.001$)
- Results at 6 mo
  - Mean lesion count reduced by 67% with 5-FU plus cryosurgery vs 45.6% with vehicle plus cryosurgery ($P=.01$)
  - Complete clearance: 30% with 5-FU plus cryosurgery vs 7.7% with vehicle plus cryosurgery ($P<.001$)

PDT with Ingenol mebutate vs Ingenol mebutate alone

Treatment of Facial Actinic Keratoses With Aminolevulinic Acid Photodynamic Therapy (ALA-PDT) or Ingenol Mebutate 0.015% Gel With and Without Prior Treatment With ALA-PDT

Brian Berman MD PhD, Mark S. Nestor MD PhD, Jessica Newburger DO, Huynhee Park DO, and Nicole Swenson DO
The Center for Clinical and Cosmetic Research, Skin and Cancer Associates, Aventura, FL
PDT with Ingenol mebutate vs Ingenol mebutate alone

- **N=24**, randomized, single center
- 4-8 AKs in a discrete facial area (25 cm²)
- **Treatment groups:** (N=8 per group)
  1. ALA-PDT x 2 (4 weeks apart)
  2. ALA-PDT → IM 0.015% for 3 days (2 weeks apart)
  3. IM x 1 (0.015% for 3 days)*
- **ALA-PDT protocol**
  - 20% ALA solution, 1-hour incubation, double-coat applied to 25 cm² area
  - Blue light: 16:40
- AKs counted at baseline and study end (day 57 or day 71)

*treatment applied in-office
• All treatment groups had statistically significant AK lesion reductions compared to baseline
  – The ALA-PDT x 2 group had the greatest numerical reduction, but this was not statistically significant vs. the sequential ALA-PDT group or the IM alone group (p=0.90, p=0.136 respectively)
• Composite LSR score was calculated from the sum of the individual LSR categories, with a maximum severity score of 24

Peak Composite LSR Score

<table>
<thead>
<tr>
<th></th>
<th>ALA-PDT x 2</th>
<th>ALA-PDT → IM</th>
<th>IM x 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSR score</td>
<td>4.625</td>
<td>10.375</td>
<td>12.625</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.0011</td>
<td>p=0.0001</td>
<td>p=0.0004</td>
</tr>
</tbody>
</table>

Day 0: **4 AKs present**, LSR= 2

Day 4, LSR=2

Day 14, LSR=1

Day 29: day of 2nd PDT, **2 AKs present**, LSR=2

Day 43: 14 days post 2nd PDT, **LSR=7**

Day 71: 42 days post 2nd PDT – **Zero AKs**, LSR=0
Day 0: **5 AKs present**, LSR= 2

Day 14: **2 AKs present**, LSR= 1

Day 16: Day 2 post IM, LSR= 8

Day 18: Day 4 post IM, LSR= 4

Day 22: Day 8 post IM, LSR= 4

Day 29: Day 15 post IM, LSR= 1, **Zero AKs**
Day 0: 6 AKs present, LSR= 2

Day 2: LSR= 7

Day 4: LSR= 9

Day 15: LSR= 3

Day 29: LSR= 2

Day 29: 1 AK present, LSR= 1
SEQUENTIAL TREATMENT: ALA-PDT → Imiquimod

Treatment of Actinic Keratoses With Sequential Use of Photodynamic Therapy and Imiquimod 5% Cream

Michael Shaffelburg MD FR.CPC
Valley Professional Center, Kentville, Nova Scotia, Canada
PDT followed by imiquimod 5%

- Randomized, vehicle-controlled, split-face study
- N=25
- Adults with ≥ 10 facial AKs
- ALA-PDT Protocol
  - Baseline & Month 1: ALA-PDT
    - Acetone scrub $\rightarrow$ microdermabrasion $\rightarrow$ 20% ALA solution broad area $\rightarrow$ 1-hour incubation $\rightarrow$ blue light x 8 minutes
  - Month 2: Imiquimod, split-face (vehicle on other side)
    - 2 times per week x 16 weeks

Results: 6 months

Reduction in AK Lesion Count (% median)

Results: 12 months

AK Lesion Reduction

<table>
<thead>
<tr>
<th>[split face]</th>
<th>ALA-PDT $\rightarrow$ IMQ</th>
<th>ALA-PDT $\rightarrow$ Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AK (median)</td>
<td>23.5</td>
<td>21.5</td>
</tr>
<tr>
<td>Month 12</td>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td>AK Lesion Reduction (mean)</td>
<td>89.9% (p=0.0023)</td>
<td>74.5%</td>
</tr>
<tr>
<td>Complete Clearance</td>
<td>N=2</td>
<td>N=2</td>
</tr>
</tbody>
</table>

- **Safety**
  - **Common:** erythema, flaking/scaling, scabbing/crusting
  - **Erythema:** 87.5% (N=21) during IMQ treatment
  - **Local skin reaction rest periods:** 1 week (N=1), 2 weeks (N=2)
  - **No discontinuations**
  - **No systemic AEs**, including flu-like AE’s

BF-200 10% ALA Gel
Photodynamic Therapy
**Nano-vesicle Technology**

**Electrostatic Interaction between ALA with Lecithin**

- **Lecithin (Phosphatidylcholine)**

- **5-aminolevulinic acid**

**Stabilization of ALA by binding to the outside of the nanovesicles**

- Penetration studies in a porcine ex-vivo skin model
- Nanoemulsion BF-200 optimizes transport of 5-ALA through the Stratum Corneum
- Significantly deeper PpIX induction with this formulation (down to basal membrane)
- No PpIX induction below the basal membrane layer

Maisch & Szeimies, Study report, 2008
Red Light Source (BF-RhodoLED)

Red Light Increases the Depth of Penetration

Kochevar et al., Fitzpatrick's Dermatology in General Medicine, 2012
Complete Patient Clearance – per US PI Data for PDT Drugs

Vegter & Tolley EU naive analysis

U.S. PI Data

Prospective, Case-Based Assessment of Sequential Therapy With Topical Fluorouracil Cream 0.5% and ALA-PDT for the Treatment of Actinic Keratosis

George Martin, MD
Dermatology and Laser Center of Maui, Kihei, HI
• Case Report
• N=3
• Aged 66-81, Fitzpatrick skin types I, II and III
• Numerous AK
  – 2 patients: >100 AKs, flat or minimally keratotic
  – 1 patient: >50 AKs on arms
• AK locations
  – 2 patients: Forehead and cheek
  – 1 patient: Forehead, scalp, hands and dorsal forearms

MARTIN – Results

- 7 days after 5-FU, no AK lesion reduction, moderate erythema and crusting
- 4 days after PDT, 5-FU pretreated side had more pronounced response, although erythema, edema, crusting were present at AK sites

- 3 months after PDT
  - 5-FU + ALA-PDT: 100% clearance
  - ALA-PDT alone: substantial AK reduction, with scattered, residual lesions present

- 6 months after 5-FU re-challenge
  - No visible AKs
  - Improved skin texture (decreased wrinkling, softer feel)

---

**INITIAL TREATMENT**

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 66, Fitzpatrick type I</td>
<td>Age 71, Fitzpatrick type II</td>
<td>Age 81, Fitzpatrick type II</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Face: Left Side</th>
<th>Forehead/Scalp: Left Side</th>
<th>Left Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU cream 0.5%</td>
<td>Untreated</td>
<td>5-FU cream 0.5%</td>
</tr>
<tr>
<td>once daily for 7 days</td>
<td></td>
<td>once daily for 7 days</td>
</tr>
</tbody>
</table>

**TREATMENT 2**

- Short-contact ALA-PDT (1-hour incubation) to entire treatment area: assess tolerability/response 3-4 days later
- Short-contact ALA-PDT (2-hour incubation) to both arms; assess tolerability/response 3-4 days later

- 7 days
- 10 days
- 7 days

- 3 months
- 7 months
- 3 months

**Follow-up:** 6 and 18 months after diagnostic rechallenge

---

ALTERNATIVE TREATMENTS

• Why do we need other options?

• PRICE:
  – 5FU 0.5% - over 2,500.00
  – 5FU 1% - over 1,000.00
  – Imiquimod 3.75% - over 1,000.00
  – Ingenol mebutate – Over 1,000.00
1927-nm Fractional resurfacing of facial actinic keratoses: A promising new therapeutic option

Elliot T. Weiss, MD, a,d Jeremy A. Brauer, MD, a Robert Anolik, MD, a Kavitha K. Reddy, MD, a Julie K. Karen, MD, a,b Elizabeth K. Hale, MD, a,b Lori A. Brightman, MD, a Leonard Bernstein, MD, a,d and Roy G. Geronemus, MD a,b,c

New York, New York

Background: Actinic keratoses (AK) are precancerous epidermal proliferations commonly present on chronically sun-damaged skin. These lesions are among the most often treated dermatologic conditions.

Objective: We sought to investigate the 6-month safety, tolerance, and efficacy of nonablative 1927-nm fractional resurfacing of facial AK.

Methods: This was a prospective clinical trial of 24 individuals with facial photodamage and AK receiving up to 4 treatments with the fractionated 1927-nm nonablative thulium laser.

Results: At 6 months, an 86.6% reduction in absolute number of lesions was noted by independent physician assessment. In addition, at this same time point, patients reported marked or noticeable improvement in overall photodamage.

Limitations: This prospective study does not provide safety, tolerance, and efficacy data beyond 6 months of follow-up, nor does it identify the precise mechanism of action involved in AK clearance after 1927-nm resurfacing.

Conclusion: The clinical and histologic findings, as well as the reported patient satisfaction and safety, suggest that the treatment of AK and photodamage with a fractionated 1927-nm nonablative thulium laser is a promising new therapeutic option. (J Am Acad Dermatol 2013;68:98-102.)

Key words: actinic keratosis; laser; nonablative resurfacing; photodamage; rejuvenation.
Dermatologic Surgery

Nonablative fractional photothermolysis for facial actinic keratoses: 6-month follow-up with histologic evaluation

Tracy M. Katz, MD, Leonard H. Goldberg, MD, Denise Marquez, PA-C, Arash Kimyai-Asadi, MD, Kristel D. Polder, MD, Jennifer M. Landau, BS, and Paul M. Friedman, MD

Houston, Texas

Background: A number of epidermal and papillary dermal skin conditions can be treated safely and effectively with fractional photothermolysis (FP).

Objective: We sought to evaluate the effectiveness of FP with a 1550-nm fractionated erbium-doped fiber laser for the treatment of facial actinic keratoses (AKs).

Methods: Fourteen men, ages 59 to 79 years, underwent 5 laser treatments (2- to 4-week intervals) at an energy fluence of 20 to 70 mJ and treatment level of 11 (8-10 passes), corresponding to 32% to 40% surface area coverage. AK counts and photographs were taken at baseline, before each treatment, and at 1-, 3-, and 6-month follow-ups after the last treatment. Biopsies were performed at baseline and at the 3-month follow-up. The clinical improvement of the actinic lesions was evaluated by a dermatologist using digital photography and lesion counts at all 3 follow-up visits.

Results: The AK count for each patient was reduced on average by 73.1% (67.5%-77.7%) at the 1-month, 66.2% (60.0%-71.5%) at the 3-month, and 55.6% (43.9%-64.8%) at the 6-month follow-up visit. Excluding two cases, all biopsy specimens (baseline and at the 3-month follow-up) were positive for histologic features of AK and/or squamous cell carcinoma.
Conclusions

• Importance of timed sequential therapy

• Need for field therapy
Thank you