Topical Therapy Pearls

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Outline

- Psoriasis
  - Historic perspective on combination therapy
  - New psoriasis combination therapy
- Actinic keratosis - Timed Sequential Therapy

Combination therapy for Psoriasis

Combined tar-anthralin versus anthralin treatment lowers irritancy with unchanged antipsoriatic efficacy. Modifications of short-contact therapy and Ingram therapy.

Schulze HJ, Schauder S, Mahrle G, Steigleder GK.

Degradation of anthralin by coal tar.

Whitefield M.

Salicylic acid increases steroid penetration as well as therapeutic effects and side effects

Salicylic acid ≠ Acetyl salicylic acid

Tell the pharmacist

Calcipotriene Stability: Effects of pH and Temperature

Calcipotriene Ointment

- 25°C, adjusted pH
- 5°C

Calcipotriene Ointment/Interceptone/Valeran Ointment

- 25°C
- 5°C

Concentration (μg/g) vs Hours

Concentration (μg/g) vs Hours


Concentration Varies When Products Are Compounded

effect of different topical medications on the concentration of calcipotriene immediately after mixing 2 commercially available preparations gram for gram


Combination Therapy: Increases Efficacy Over Calcipotriene Alone and Reduces Steroid Exposure

Calcipotriene BID (0.5%) 25%* 3% Halobetasol 3% 20% 10% 0 1 2 3 4 5 6 7 8 Clear or Almost Clear (% Patients)† at Day 14 of Treatment

Combination: Calcipotriene/Halobetasol

Calcipotriene/Halobetasol Combination Treatment

Baseline Day 14


Sequential Therapy

- After week 2 of calcipotriene in the morning and halobetasol in the evening, 40 patients who were at least moderately (≥50%) improved were randomized to 2 treatment arms:
  - Group A: n=20 halobetasol ointment BID weekends, and calcipotriene ointment BID weekdays
  - Group B: n=20 halobetasol ointment BID weekends, and placebo ointment BID on weekdays
- Patients were assessed at week 2 and at six monthly intervals
Mild-moderate Psoriasis: Plaque Elevation

Based on Wilcoxon rank sum test, scaling, thickness, overall severity and global assessment were significantly different between calcipotriene/halobetasol and placebo/halobetasol. The mean plaque elevation before and after treatment is shown in the figure.


P = .02

Sequential Therapy: Calcipotriol/Halobetasol


n = 20 n = 20

Baseline

Month 6

30%

40%

Baseline

Week 2

Month 6

Stability of Corticosteroids and Calcipotriene in Relation to pH

- Calcipotriene and betamethasone dipropionate are incompatible at similar pH
  - Betamethasone dipropionate is inactivated with high pH
  - Calcipotriene is inactivated with low pH

Solution to Stability: Mixing Unmixables

- Calcipotriene dissolved in an anhydrous vehicle
- Anhydrous environment eliminates pH concerns
- Secures equal distribution of the active component
- Betamethasone micronized suspended in the vehicle
- Results in a product with stable active constituents

A 2-Compound Product: Not 2 Compounds in a Product

Calcipotriene 0.005%
Betamethasone Dipropionate 0.064%

Calcipotriene & Betamethasone in separate solutions

Calcipotriene Dissolved
Betamethasone Micronized

Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% aerosol foam

LEO90100 provides greater skin penetration than Calcipot/Btmsn-dipr ointment

Calcipotriene from LEO90100
Calcipotriene from Calcipot/Btmsn-dipr ointment
Total content levels of betamethasone were significantly higher following LEO90100 application compared with Calcipot/Btmsn-dipr ointment (P=0.002)

Note: Study assessed the penetration of calcipotriene and betamethasone into the skin (ie applied skin) and through the skin (captured in a receptor fluid)


• Does increased penetration equal increased efficacy?

Evaluation of the vasoconstrictor potential of combination calcipotriene plus betamethasone dipropionate aerosol foam (Leo90100) versus other corticosteroid psoriasis treatments
A novel aerosol foam formulation of calcipotriene 0.005% (Cal) plus betamethasone dipropionate 0.064% (BD) is more efficacious than Cal and BD foam alone in treating psoriasis vulgaris: a randomized, double-blind, multicenter, three-arm, Phase II study

A greater skin blanching effect has been observed with Cal/BD aerosol foam than with Cal/BD ointment but less than with the very potent steroid, CP cream.

Efficacy: treatment success on PGA

Cal/BD aerosol foam was significantly more effective than its individual active components at week 4 on the body.

Cal/BD aerosol foam was significantly more effective than Cal aerosol foam at week 4 on the scalp.
Efficacy: mPASI score

Mean mPASI score (95% CI)

- Treatment success (% patients)
  - 20
  - 40
  - 50
  - 60
  - 70

At week 4, improvement in psoriasis of the body was significantly greater with Cal/BD treatment success versus those using aerosol foam vehicle at week 4.

PaGA – Patient’s global assessment

Mean mPASI scores improved in all groups for psoriasis of the body and scalp combined, with Cal/BD aerosol foam than with Cal aerosol foam (n=101) vs BD aerosol foam (n=101) at week 4.

Significantly more patients using Cal/BD aerosol foam achieved PaGA – Patient’s global assessment of disease severity (body and scalp combined) with Cal/BD aerosol foam (n=100) versus Cal aerosol foam (n=101).

Efficacy:

- Treatment comparison at end of treatment
  - Cal/BD foam vs foam vehicle
  - Cal/BD aerosol foam vs Cal aerosol foam (week 4)
  - Cal/BD aerosol foam vs BD aerosol foam (week 1)

- Odds ratio (95% CI)
  - Cal/BD aerosol foam vs Cal aerosol foam (week 4)
    - 0.11
  - Cal/BD aerosol foam vs BD aerosol foam (week 1)
    - 14.9 (6.5 to 34.0)

Multiple imputation applied for missing data. Odds ratio calculated using the Cochran–Mantel–Haenszel method adjusted for pooled centers. BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%.

Safety:

- ANCOVA, analysis of covariance; BD, betamethasone dipropionate 0.064%; Cal, calcipotriene 0.005%
- Odds ratio (95% CI)
  - Cal/BD foam vs foam vehicle (week 4)
    - 3.7 (2.0 to 6.9)
  - Cal/BD aerosol foam vs Cal aerosol foam (week 1)
    - 2.2 (1.3 to 4.0)

- Odds ratio (95% CI)
  - Cal/BD aerosol foam vs foam vehicle (week 4)
    - 30.3 (9.7 to 94.3)

PaGA – Patient’s global assessment

**Primary endpoint: treatment success (by PGA)**

Significantly more patients using Cal/BD aerosol foam achieved treatment success versus those using aerosol foam vehicle at week 4.

The mean mPASI score was significantly lower for Cal/BD aerosol foam versus aerosol foam vehicle, both at weeks 1 and 4.

- The mean percentage change in mPASI from baseline was ~38% at week 1 and ~72% at week 4 for Cal/BD aerosol foam.
### Patient-reported itch score

**Mean itch VAS score (95% CI)**

- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70

### Application-site ADRs

- Folliculitis: 1 (0.3%)
- Skin irritation: 1 (0.3%)
- Psoriasis: 1 (0.3%)
- Blood calcium increased: 1 (0.3%)

### ADRs, n (%) Cal/BD

- Erythema: 0 (0.0%)
- Dryness: 0 (0.0%)
- Irritation: 1 (0.3%)
- Pruritus: 1 (0.3%)
- Discoloration: 1 (0.3%)

### Safety

- 78.6% were reported in the trial
- Incidence was comparable between treatments (Cal/BD aerosol foam = 13.6% vs Aerosol foam vehicle = 13.9%)
- More than twice the proportion of patients using Cal/BD aerosol foam had no impairment in DLQI

### DLQI by visit and proportion of patients with no impairment (score ≤1; observed cases)

- Patients: n=322
- Patients: n=323
- Patients: n=103
- Patients: n=101

### Conclusion

- Reduction in itch-related sleep loss was observed as early as day 3 and was significantly greater with Cal/BD aerosol foam versus aerosol foam vehicle at all time points.

### Additional Information

- Definition of ADR: AEs for which the investigator had not described the causal relationship to trial medication as ‘not related’.
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
Leave ≥ 5 AKs for field treatment
Wait until sufficiently healed (1-2 weeks)
Average wait time: 12 days

AK Lesion Counts & Cryosurgery

Baseline = 16 AK lesions
(Protocol requires 5 -14)
7 lesions Cryo’d (Mean)
(Protocol requires ≥ 5)
9 lesions remain (Mean)
(Protocol requires ≥ 5)

Primary Endpoints

WK 26 (End of Study)

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<th>Cryo/Imiq 3.75%</th>
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<td>Median</td>
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% of Patients w/ Complete Clearance

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*All lesions treated with cryosurgery at baseline and all lesions treated with cryosurgery (baseline, recurrent or new)

Median AK Lesion Counts Over Time

Additional Endpoints

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*All lesions treated with cryosurgery at baseline and all lesions treated with cryosurgery (baseline, recurrent or new)
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

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.

Baseline

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

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, Worschler 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

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.

**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**

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<tbody>
<tr>
<td>Baseline</td>
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<tr>
<td>Change from Baseline to Day 37</td>
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<tr>
<td>N</td>
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<tr>
<td>Mean (SD)</td>
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<td>Min, Max</td>
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- Change from Baseline to Day 37: NHT-AK
- Place Value: 0.0001
- Control Value: 0.0001

**Results: nHT-AK**

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</table>

- Change from Baseline to Day 37: nHT-AK
- Place Value: 0.0001
- Control Value: 0.0001
The absolute reduction in LSR score is proportional to the composite LSR score on the day after the last application.

**Regression Analysis: Face**

Expected composite LSR score at week 1 through week 8 grouped by composite score at day 4 ($N=218$)

**Regression Analysis: Scalp**

Expected composite LSR score at week 1 through week 8 grouped by composite score at day 4 ($N=56$)

**Regression Analysis: Trunk & Extremities**

Expected composite LSR score at week 1 through week 8 grouped by composite score at day 3 ($N=209$)

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**Regression Analysis of Local Skin Responses to Predict Clearance of Actinic Keratoses on the Face in Patients Treated With Ingenol Mebutate Gel**

S Jim On1, KM Knudsen2, T Skov2, M Lebwohl1

1Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 2LEO Pharma A/S, Ballerup, Denmark

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**Results**

- The peak composite score was observed at day 4, one day after the third and last application of ingenol mebutate gel, 0.015%.

**Summary of AK Clearance and LSR ($N=12$)**

<table>
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<tr>
<td>All count reduction from baseline (%)</td>
<td>Mean (95% CI)</td>
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<tr>
<td>Median (range)</td>
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<tr>
<td>LSR composite score at day 4</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Median (range)</td>
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Regression Analysis of AK Counts vs Day 4 Composite LSR Scores

Composite LSR Scores Assessed on Day 4 Were Predictive of Efficacy

Expected percent reduction from baseline in AK count based on day 4 composite LSR scores: 3 examples

- Higher LSRs predicted greater rates of response
- At low scores, the LSR had no predictive value
  - It predicted neither treatment success nor treatment failure

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 84.4% with 5-FU vs 28.8% with vehicle (P<0.001)
  - Complete clearance: 16.7% with 5-FU vs 0% with vehicle (P<0.001)
- Results at 6 mo
  - Mean lesion count reduced by 87% with 5-FU plus cryosurgery vs 43.5% with vehicle plus cryosurgery (P<0.01)
  - Complete clearance: 30% with 5-FU plus cryosurgery vs 7.7% with vehicle plus cryosurgery (P<0.001)

THANK YOU!
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