Strategies in Topical Therapy of Eczema and Psoriasis

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Dr. Koo’s Conflict of Interest

- Abbott
- Amgen
- Astellas
- Celgene
- Janssen
- Galderma
- Eli Lilly
- Leo Pharma
- Novartis
- Pfizer/Anacor
- Strata Skin Science

Most Patients Have Localized Psoriasis.
They are still often dissatisfied with their treatment.


The Art of Optimizing Topical Therapy of Psoriasis
Why do we have to learn this art?
Reasons for Creative Use of Topical Agents

- **Increase Efficacy** - So that the efficacy of each agent is additive
- **Decrease Problems** - So that each agent can cover for other agents’ weaknesses
- **Or Both**

For successful therapy, both clearing and maintenance strategies are needed

### Beyond Monotherapy

**5 Topical Strategies**

1. Proactive flare prevention
2. Rotational therapy
3. Sequential therapy
4. Topical jump start using “rabbit”
5. Turtle stacking using “turtles”

### Topical Strategy #1

Proactive Flare Prevention
(Example: Eczema)
Proactive flare prevention study was conducted with pimecrolimus.
But Tacrolimus and Pimecrolimus have Black-Box Warnings about Cancer where proactive use is off-label.

However, we have a new non-steroidal topical agent that just got approved for eczema called crisaborole 2% ointment (EUCRISA®).

Crisaborole Topical Ointment: Boron-Based, Nonsteroidal, Anti-Inflammatory PDE4 Inhibitor

- Boron is essential for PDE4 inhibition and anti-inflammatory activity
- Boron is nontoxic and commonly found in fruits, vegetables and cosmetics

Crisaborole Topical Ointment, 2%, Decreases Atopic Dermatitis–Associated Inflammation by Inhibiting PDE4

Efficacy: % who are Clear or Almost Clear

- AD-301 AD-302
- P = 0.008
- P = 0.038

Crisaborole Vehicle

n = 503  n = 513  n = 250  n = 256
**Pruritus: Crisaborole vs. Placebo**

**Safety: Crisaborole Topical Ointment**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Crisaborole (n = 1012)</th>
<th>Vehicle (n = 499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>4.4%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

**Safety: Crisaborole Topical Ointment**

**Topical Strategy #1 Conclusion**

**Proactive Flare Prevention**

1. Tacrolimus
2. Pimocrolimus
3. Crisaborole

**Topical Strategy #2**

**Rotational Therapy**

(Example: Psoriasis)
Yin-Yang Strategy

Brodell RT et al. A multi-center, open-label study to evaluate the safety and efficacy of a sequential treatment regimen of clobetasol propionate 0.05% spray followed by calcitriol 3 mg/g ointment in the management of plaque psoriasis. JDD. 2011; 10: 158-164.

Clobetasol Spray to Calcitriol Ointment Rotational Therapy

With topical vitamin D, efficacy is maintained for 1 month after D/C clobetasol spray

Beyond 1 month, efficacy drops

Yin-Yang Strategy

Sequential Therapy

Rotational Strategy

Topical Strategy #3
Sequential Therapy
(Example: Psoriasis)

Sequential Therapy of Psoriasis: Introducing a New Therapeutic Paradigm for Better Clinical Results

Sequential therapy is a new therapeutic strategy involving the use of specific therapeutic agents in a deliberate sequence to optimize therapeutic outcome. It includes three steps: (1) the clearing or "quick fix" phase; (2) the transitional phase; and (3) the maintenance phase. The rationale for this strategy is that (1) psoriasis is a chronic disease that requires a long-term maintenance strategy as well as initial quick improvement; (2) various therapeutic options have different strengths and weaknesses; (3) some therapies are better suited for "quick fix" while others are better suited for long-term maintenance. The sequential therapeutic approach is designed to use a better or more tolerable agent during the clearing phase and a maintenance agent during the maintenance phase. It is expected that the strength of each agent will diminish over time.

Sequential Therapy of Psoriasis

- Step ①: Clearing Phase (*Quick Fix*)
  - Maximum Efficacy
- Step ②: Transitional Effect
  - Smooth Transition
- Step ③: Maintenance Phase
  - Maximum Safety
**Sequential Therapy Phase 1**

Why use both superpotent topical steroid and non-steroid together?

Because the combination is better than even superpotent topical steroid BID.

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**Sequential Therapy Phase 1**

Calcipotriol + Superpotent Topical Steroid > Either Agent Alone

<table>
<thead>
<tr>
<th>Combination</th>
<th>71%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superpotent topical steroid</td>
<td>57%</td>
</tr>
<tr>
<td>Calcipotriol</td>
<td>30%</td>
</tr>
</tbody>
</table>

Clear or Almost Clear (% patients)


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Topical Steroid and Calcipotriene should be Mixed Only Just Before Application
Sequential Therapy Phase 1

Combination Use of Superpotent Topical Steroid + Calcipotriene

V

Superpotent topical steroid BID

Sequential Therapy Phase 2

Why use non-steroid on weekdays and superpotent topical steroid on weekends?

Because weekday/weekend regimen has better maintenance than superpotent topical steroids on weekends only.

Sequential Therapy Phase 2

After 6 months, better maintenance with weekday/weekend than weekend only.


Phase 2: Transitional

After 6 months, better maintenance with weekday/weekend than weekend only

Topical Sequential Therapy with Other Agents

For example: Clobetasol foam (Olux®) + Calcipotriene (Dovonex®)

Sequential Therapy with Clobetasol Foam (Olux®)

A randomized, multicenter study of calcipotriene ointment and clobetasol propionate foam in the sequential treatment of localized plaque-type psoriasis: Short- and long-term outcomes

Sequential Therapy with Clobetasol Foam

Sequential Therapy of Psoriasis

Step ① Max Efficacy

Step ② Smooth Transition

Step ③ Max Safety

Topical Strategy #4
Topical Jump Start Using “Rabbit”
(Example: Psoriasis)

Jump Start with Clobetasol Spray
“Rabbit”

<table>
<thead>
<tr>
<th>Clobetasol Spray, the Fastest Rabbit?</th>
<th>% of Patients Clear or Almost Clear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td>Clobetasol Spray</td>
<td>51%</td>
</tr>
<tr>
<td>Clobetasol Cream</td>
<td>11%</td>
</tr>
<tr>
<td>Clobetasol Lotion</td>
<td>17%</td>
</tr>
<tr>
<td>Clobetasol Foam</td>
<td>28%</td>
</tr>
</tbody>
</table>

From US FDA Package Insert

The next graph shows data which was not collected in a “head to head” manner.

Disclaimer
Topical “Rabbits” can help jump start:

**Psoriasis**
- Apremilast
- Acitretin
- Etanercept
- UVB Phototherapy
- PUVA

**Eczema**
- Pimecrolimus
- Tacrolimus
- Crisaborole (just got approved)
- UVB Phototherapy
- PUVA

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**Topical Strategy #5**

*Turtle Stacking Using “Turtles” (Example: Psoriasis)*

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**Non-Steroids in Combination**
UVB + Calcipotriene

Calcipotriene makes 2x/week UVB as effective as 3x/week UVB

A multicenter, prospective, randomized, parallel-group, vehicle-controlled, single-blind study

Calcipotriene Cream BID with UVB 2x / week
N = 80

Vehicle Cream BID with UVB 3x / week
N = 79

Calcipotriene makes PUVA more effective

Calcipotriene + PUVA vs. vehicle + PUVA

- Fewer number of PUVA treatments: 10 vs. 15
- Lower cumulative UVA dose: 30 J/cm² vs. 57 J/cm²
- Shorter duration of treatment: 22 days vs. 34 days
- Greater average % decrease in PASI: 91.4% vs. 75.7%
- Greater % of patients achieving PASI 75: 87% vs. 64.4%

Side effects: No statistically significantly difference (P = 0.94)

### Calcipotriene + Oral Agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clear or almost clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriene + Acitretin</td>
<td>41.0%</td>
</tr>
<tr>
<td>Placebo + Acitretin</td>
<td>67.0%**</td>
</tr>
<tr>
<td>N = 69</td>
<td></td>
</tr>
<tr>
<td>Calcipotriene + CSA 2mg/kg</td>
<td>38.8%</td>
</tr>
<tr>
<td>Placebo + CSA 2mg/kg</td>
<td>13.8%</td>
</tr>
<tr>
<td>N = 135</td>
<td></td>
</tr>
<tr>
<td>Calcipotriene + MTX 6.5mg/ wk</td>
<td>11.8%†</td>
</tr>
<tr>
<td>Placebo + MTX 10.5mg/ wk</td>
<td>8.7%†</td>
</tr>
<tr>
<td>N = 98</td>
<td></td>
</tr>
</tbody>
</table>

*Calcipotriene + Acitretin vs. Placebo + Acitretin: p = 0.002*  
*Calcipotriene + CSA 2mg/kg vs. Placebo + CSA 2mg/kg: p < 0.001*  
*Calcipotriene + MTX 6.5mg/ wk vs. Placebo + MTX 10.5mg/ wk: p = 0.015*

**Calcipotriene + Acitretin vs. Placebo + Acitretin: p = 0.002**  
**Calcipotriene + CSA 2mg/kg vs. Placebo + CSA 2mg/kg: p = 0.002**  
**Calcipotriene + MTX 6.5mg/ wk vs. Placebo + MTX 10.5mg/ wk: p = 0.002**

### Tazarotene

**Topical Vitamin A for Psoriasis**

### Tazarotene and Topical Steroid (mometasone cream)

#### Tazarotene + Mometasone Cream vs. Mometasone Cream BID

- **Clinical Trial:** Investigator-masked comparison of tazarotene gel q.d. plus mometasone furoate cream q.d. vs. mometasone furoate cream b.i.d. in the treatment of plaque psoriasis
- **Authors:** John T. Y. Koo, MD, and Edelle Martin, MD

Tazarotene QD + Mometasone Cream QD > Mometasone Cream BID

Efficacy


Much Less Recurrence With Combination Tazarotene + Steroid


Tazarotene + Calcipotriene

Is calcipotriol and tazarotene
•Compatible?
•Synergistic?
When applied together
Tazorotene + Calcipotriene vs. Clobetasol BID

Study Protocol

- Right vs. Left comparison
- Tazorotene + calcipotriene vs. clobetasol
- 2 week study involving 28 target lesion pairs with 4 weeks post-treatment follow up

Tazarotene + UVB

Methods
2 week pre-UVB Phototherapy Period followed by 10 weeks of UVB phototherapy
- Both UVB and topical agent 3x/week
- Topical agent applied only after UVB
- Each patient’s lesions randomized to receive:
  - Tazarotene 0.1% gel
  - Vehicle
  - No treatment (control)
5 Strategies Beyond Monotherapy

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