Curried Pearls from California: What could be better on a Saturday?

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2018 Summer AAD FRM F026: Pearls from Members
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Neal Bhatia, M.D.

FRM F026: Pearls from Members

DISCLOSURES

Affiliations with Abbvie, Aclaris, Almirall, Bayer, Biofrontera, BiopharmX, Dermira, Encore, EPI Health, Ferndale, Foamix, Galderma, Intraderm, ISDIN, LaRoche-Posay, Leo, Mayne, Menlo, Novartis, Ortho, Pfizer, Pierre-Fabre, Promius, Regeneron, Sanofi, SkinFix, Soligenix, SunPharma, and Vidac

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: bhatiaaharbor@gmail.com
PHOTOGRAPHY & VIDEOTAPING ARE STRICTLY PROHIBITED IN ALL EDUCATIONAL SESSIONS
CELL PHONES MUST BE PLACED ON VIBRATE OR TURNED OFF

Violations of this policy will result in removal from the session and possible revocation of meeting registration.
Session directors will be closely monitoring such occurrences.
Pearl #1: Stay Away Skin Cancer...

- Photolyases—sunscreen based
- Polypodium leucotomos extract
- Nicotinamide
- Photodynamic Therapy
- Retinoids
- NSAIDs
- Caffeine
Photolyases

- Naturally occurring enzymes
  - Repair UV-induced thymidine dimers
  - Absent in placental mammals
  - Active in organisms with high cumulative UV exposure.
  - Exogenous forms isolated from a cyanobacterium *Anacystis nidulans* in marine plants
- Long-term use improves:
  - Expression of MMP-1, Ki67, PCNA
  - Mutations of p53, p21

Preventative effects of photolyases compared to conventional sunscreens

- 9 month long study involving 30 patients after treatment with PDT on the face or scalp
- Sustained remission of previously treated AKs and in patients treated once with PDT
- All patients in the group treated with photolyases avoided a second PDT treatment vs. 10 of 15 subjects in the sunscreen only group needing a second treatment to stay clear

Polypodium leucotomos Extract: Yes it is natural but what is the dose?

- Marketed OTC as a food supplement: 240 mg capsule
  - Antioxidant effects through polyphenolic acids
- Use for daily photoprotection is different than incorporation into a treatment regimen
  - One capsule daily, add one before sun exposure
  - Higher doses~480-960 mg for treating vitiligo, melasma, and PMLE
- New data: patients with lighter skin types could benefit from more photoprotection from an extra dose than darker patients
  - “Measurable suppressive effects on UVB-induced erythema”

Good News and Bad News on using Retinoids for Chemoprevention

Good News:
- Retinoids stabilize differentiation and atypical keratinocyte replication
- Inhibit of ornithine decarboxylase
- Promote of dendritic cell activity and restoration of apoptosis

Bad News: Good luck finding a way to get them for your patients
- But if you can: Start slow 10 mg acitretin daily and increase as tolerated, 25 mg qod then qd
- Every systemic retinoid is considered off-label for chemoprevention
- 2018 Anthem and BC/B changes from Tier 2 to 3 → sub for methoxasalen

Pearl #2: Itchy and Scratchy

I'M GONNA NEED YOU TO STOP SAYING PSORIASIS IS "DRY SKIN"

MMMMKAY?
Itchy Rant about “Prants” and “Tants”

- **Setipiprant**
  - orally available antagonist of the prostaglandin D$_2$ receptor 2
  - Initially studied in asthmatics and for itch.
  - Also expressed at high levels in the scalp in males with androgenetic alopecia.
  - Phase 2A study studying oral setipiprant relative to a placebo and the active comparator, finasteride, in 18 to 41 years old males with androgenetic alopecia.

- **Tradipitant (VLY-686)**
  - neurokinin 1 receptor antagonist
  - Trials in motion: 100 mg of tradipitant (N=34) or placebo (N=35) once a day

- **Serlopitant (TCP-102) NK-1R**
  - 5 mg daily
  - Phase 2 trial prurigo nodularis n=127
  - 8 wks: 48% improved vs 26% placebo
  - New trials underway in US
Sebuderm Gel

- Hypochlorous Acid (HOCl)
  - Eradicates bacteria, viruses, fungus and spores
  - Reduce Inflammation via inhibition of mast cell degranulation
  - Increases Oxygenation and Breaks Down Biofilm

- Subject Efficacy Assessment
  - 25 patients with mild to moderate seborrheic dermatitis, apply bid
  - 19/24 improved at day 14. At day 28, 20/24 improved, none worsening.

- Overall disease activity decreased 33% at day 14 and 52% at day 28

Draelos, Z, poster submission 2017 Maui Derm
Other Biologics for atopic dermatitis

- **Lebrikizumab (Genentech): IL-13**
  - Studied extensively in asthma, no differences in changes in FEV$_1$
  - IL-13 blockade but does not improve lung function

- **Mepolizumab (GSK): IL-5**
  - Two single i.v. doses of 750 mg, one week apart, Significant decrease in peripheral blood eosinophils, Ineffective in reducing cutaneous eosinophils

- **Tralokinumab (Leo): IL-13**
  - Phase IIb trial week 12, significant improvement from baseline in EASI score and in DLQI

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**Therapeutics on the Horizon for AD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Target</th>
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<tbody>
<tr>
<td>AMG 157</td>
<td>TSLP</td>
</tr>
<tr>
<td>Apremilast</td>
<td>PDE4</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Jak1, Jak2</td>
</tr>
<tr>
<td>BMS 981164</td>
<td>IL-31</td>
</tr>
<tr>
<td>CIM-331</td>
<td>IL-31RA</td>
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<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
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<td>ILV 094</td>
<td>IL-22</td>
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<tr>
<td>MK 8226</td>
<td>TSLPR</td>
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<tr>
<td>OC 000459</td>
<td>CRTH2</td>
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<tr>
<td>OGE 031</td>
<td>IgE</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>IL-13RA</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12/IL-23p40</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; TSLP, thymic stromal lymphopoietin; PDE4, phosphodiesterase 4; Jak, Janus kinase; TSLPR, TSLP receptor; CRTH2, chemoattractant receptor-homologous molecule expressed on T helper cell 2 (T$_h$2).

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Czarnowicki, Tali, Guttman-Yassky, Emma “Revolution in Atopic Dermatitis, and How It Also Translates to Other Inflammatory Skin Diseases,” Cutis. 2016 September;98(3):145-146
JAK Inhibitors for Atopic Dermatitis

- **Baricitinib**: JAK 1-2 inhibitor
  - pro-inflammatory cytokine signaling
  - Ph 2, n=124, dose range 2-4 mg
  - 16 weeks, topical steroid rescue
  - 61% EASI 50 vs 37% placebo

- **ASN002**: JAK/SYK inhibitor
  - Reduce Th2/Th22 cytokine signaling
  - Ph 2 40mg and 80mg: all pts met EASI50: Ph 3 starting 2018

- **Upadacitinib**: JAK-1 inhibitor
  - Ph 2 completed, 7.5 mg-30 mg
  - EASI 90 by 50% of pts @ 30 mg; 26%@ 15 mg, 14%@ 7.5 mg vs 2% placebo

- **Sienna SNA-125**: JAK 3 inhibitor proof of concept 2018

- **PF-04965842 100mg-200mg**
  - JAK-1 starting phase 3


Fig 1

Emerging therapies for atopic dermatitis: JAK inhibitors

David G. Cotter, MD, PhD, David Schairer, MD, Lawrence Eichenfield, MD
Early Phase Studies for Atopic Dermatitis

- **Novan**: topical nitric oxide SB414 2%-6% cream bid x 2 wks
  - anti-staphylococcal activity and anti-inflammatory compared to betamethasone in mice models
  - Phase I: n=48, early PK study
- **Shaperon**: Taurodeoxycholic acid HY209 Gel 0.05%-0.5%; 28 days,
- **Takeda**: Roflumilast 0.5% cream
  - Applied bid x 2 wks
- **Dignity**: DS107 topical omega-6 fatty acid cream— further study
- **Incyte**: Ruxolitinib JAK 1-2, 1.5% cream BID for 8 weeks
  - Comparators against placebo and triamcinolone
- **Cutanea**: Omaganan peptide
  - N=80, 1%-2.5% gel
- **Dermavant**: RVT-501 0.5% Cerdulatinib oint BID x 28 days
- **Awaiting further study**: Anti-TSLP Ab (AMG157) Anti-OX 40 Ab (GBR 830)

Pearl #3: How to use Crisaborole Ointment

- What to remember about Crisaborole Ointment:
  - It is not a “steroid sparing” agent or cousin of calcineurin inhibitors
  - It does not work “upstream” but does shut off the cytokine faucet instead of mopping up the cytokine puddle
  - Use it anywhere on the body, ages 2 and up, for as long as needed

- Burning and Stinging? Are you serious?
  - Resolved in 78% study subjects by day #3
  - Inflamed skin is sensitive skin, and the same patient usually gives the same answer for burning/stinging/itching in a trial
  - If you are worried...have the patient try the sample, and on innocent skin, while they are in the exam room
Immunomodulatory effects of PDE inhibition

- cAMP-PDE activity in leukocytes is significantly elevated in patients with AD compared to healthy controls\(^1\)

- PDE4 increased cAMP conversion to AMP and increased cytokine production\(^2\)
  - Also expressed in keratinocytes and fibroblasts\(^4\)

- Increased PDE4 results in immune activation and overexpression:\(^3\)
  - Th2 cytokines (IL-4, IL-5, and IL-13)
  - Th1 cytokines; TNF-\(\alpha\), IL-12
  - Th22 cytokine IL-22; Th17 pathway

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What to remember about Boron

- Essential for inhibition of PDE4 activity
- “Presence of Boron and empty p-orbital allows formation of tetrahedral configuration within PDE4 active site”
  - Tetrahedral geometry allows close overlap to cAMP binding site in PDE4 active site
- Incorporation of boron contributes to low molecular weight → better penetration in lesional skin of AD

How to use Crisaborole Ointment

- Bathe daily for 5 minutes
  - Apply Hypochlorous acid gel to stubborn or high risk areas 5 minutes before shower
- Apply anti-itch lotions as needed throughout the day
- If the patient complains of stinging, have the patient try it on normal skin...if it still stings, then pull the plug, if not then set expectations for how it should feel when the flare subsides
- Apply Crisaborole Ointment at the first sign of new flare, just like the aura of a new acne papule or new flare of HSV labialis starts before lesions
- Treat through the disease like a golf swing
- Add steroids when it goes south, and the burning and stinging will go down
Pearl #4: Managing Reactions is Key for Compliance with the AK drugs

- Topical anesthetics as needed
- Sunscreens to reduce potential for dyschromia
- Moisturizers
- Topical antibiotics as needed to promote healing and resolution
- Weekly follow-up
What’s coming for AKs

- **KX2-391 Ointment**
  - inhibit T cell migration and endothelial tubule, lymphocyte infiltration, angiogenesis

- **VDA-1102 Ointment**
  - Placebo vs 5% vs 10% for 28 d
  - anti-neoplastic agent
  - selective modulation of VDAC/HK2, unique to glycolysis and mitochondrial
  - selectively triggers apoptosis in cancer cells

- **SR-T100 gel--antiproliferative**
  - Solanum lycocarpum alkaloidal extract and their constituents, solamargine and solasonine
  - 16 week treatment study, 8 wk F/U for recurrence evaluation

- **Actikerall (LAS41005)**
  - 0.5% 5-fluorouracil (5-FU) and 10% salicylic acid in film-forming base
  - Comparison trial against placebo and LAS106521 similar compound
Management Strategies

- Start slowly
- Wait at least a week after cryotherapy
- Consider regions instead of full face
  - Forehead MWF
  - Rest of face TuThSat
- Make sure there is no history of HSV labialis
- Bacteriostatic healing ointment
- Barrier restoration
- Pramoxine lotion
- Mix equal parts with moisturizer to maximize surface areas
- Spray sunscreens
- Turn the radio up or down but not off
Tips for Success

- Have patients fill prescriptions between Monday to Thursday—less likely to be switched than Fridays or weekends.
- Have patients start treatments on Sundays so that reactions occur mid week rather than on weekends.
- Take at least 4-7 days off before and after destructions or surgery.
- Use every adjunct possible except steroids.
Pearl #5: PDT Nuts and Bolts
What do we need to do before, during, and after?

- Pick the right patient
  - Knows the role of therapy, reads the pamphlet, and reviews potential outcomes.
  - Review any oral medications or using any topical prescription or non-prescription products on their face or scalp.
  - No upcoming social events, photo sessions, or vacations

- Prepare the staff
  - Adequate time for treatment allotted on everyone’s schedule to dedicate time
  - Discuss pre and post-treatment expectations
  - Provide patient education
  - Apply ALA and monitor light device for treatment
  - Reviews post-treatment plan

- Pain Control
  - 3 minute breaks
  - Fans and Cool mist sprays
  - Cool packs
  - Talkesthesia
Treatment Day

- There is no reason to stop meds that are sensitizing in the UV spectrum since PDT works in 410-417nm
  - Antibiotics, Diuretics, Anti-hypertensives
  - If you are worried, then have them hold the drugs on the day before and the day of treatment

**TABLE 2. Photodynamic Therapy General Treatment Protocol**

Patient washes the area to be treated with soap and water
Acetone- or alcohol-soaked 4 x 4 gauze is used to remove any remaining debris and oil
The photosensitizer is evenly applied to the entire area to be treated. A second coat of the photosensitizer can be applied, after the first coat has dried.
Allow the photosensitizer to incubate for 0.5–4 hours (see below for more comprehensive recommendations)
Activate the photosensitizer with the appropriate light source
Patient to wash the treated area with soap and water to remove any residual photosensitizer
The patient must stay out of the any direct sunlight for 48 h
Repeat as needed in 2–3 wk
Rationale for Antihistamines

- Anticipated ALA PDT Response: erythema and edema
  - Edema generated by mast cell degranulation
  - Erythema unaffected by H1 blockade
  - More mast cell related over 72 hours than lymphocytic, so steroids not as potentially helpful

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All PDT codes should be billed with the appropriate J code!
CPT Codes

96567

- Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (eg, lip) by activation of photosensitive drug(s), each phototherapy exposure session

- This code should now ONLY be used only when a physician does not directly participate in the PDT treatment delivery.

96573 and 96574

- The physician or other practicing clinician MUST apply the photosensitizer AND initiate the light illumination
## 2018 Fee Schedule Changes

<table>
<thead>
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<td>96573</td>
<td>Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s), per day</td>
<td>NEW</td>
<td>0.48</td>
<td>0.48</td>
<td>No</td>
</tr>
<tr>
<td>96574</td>
<td>Debridement of premalignant hyperkeratotic lesion(s) (i.e., targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s), per day</td>
<td>NEW</td>
<td>1.01</td>
<td>1.01</td>
<td>No</td>
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# 2018 Fee Schedule Changes

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<tr>
<th>CPT CODE</th>
<th>2017 Payment Amount</th>
<th>2018 Payment Amount</th>
<th>Percent Difference</th>
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<td>96567</td>
<td>$137.10</td>
<td>$116.61</td>
<td>-14.95%</td>
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<tr>
<td>96573</td>
<td>NA</td>
<td>$193.27</td>
<td>NA</td>
</tr>
<tr>
<td>96574</td>
<td>NA</td>
<td>$249.05</td>
<td>NA</td>
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</table>
Pearl #6: Give Minnie a new look

- Minocycline 1% Foam
- Minocycline Biphasic Gel 1% & 2%
What does Minocycline do that makes us worry?

- Vestibular side effects: less with longer-acting formulations
  - Minocycline Pigmentation
  - Minocycline-induced Lupus Erythematosus
    - 1990s first reports, 58 cases since 2000
  - Hypersensitivity/DRESS Syndrome
- Drug Reaction with Eosinophilia and Systemic Sx
- Immediate-release minocycline different concerns than extended-release or weight based dosing
- Resistance issues as with any antibiotic

Walsh, "Minocycline joins list of drugs causing lupus" Skin and Allergy News
Minocycline Hyperpigmentation

- Dermal and/or Epidermal pigment
  - Blue-black near scars
  - Blue-gray hyperpigmentation in normal skin of extremities
  - Diffuse brown pigment in photoexposed

- Pigmentation occurred in 4% of patients taking minocycline 200 mg/day
- All pigmentation cases occurred after a minimum treatment duration of 8 months and a minimum total cumulative dose of 70 g of minocycline

Minocycline 4% Foam safer than systemic

Pharmacokinetic Evaluation of Once-Daily Topical 4% Minocycline Foam in Adult and Pediatric Subjects With Moderate-to-Severe Acne in Two Phase 1 Studies

Terry M. Jones, MD¹; Herman Ellman, MD²; Tina de Vries, PhD²

¹J&S Studies, Inc., College Station, Texas, USA
²Foamix Pharmaceuticals, Inc., Bridgewater, New Jersey, USA
Study Design and Methods: Transition from Oral to Topical Minocycline Foam

- 2 Phase 1, single-center, nonrandomized, open-label studies (Figure 1)
- Adults (age 18 to 35 years) or pediatric subjects (age 9 years to 16 years, 11 months) with moderate-to-severe AV
  - **Adult Study** (FX2014-03) First received a single 1-mg/kg oral dose of oral extended-release minocycline HCl tablet (Solodyn®). Then, after 10 days, they received a once-daily topical application of 4 g FMX101 4% to the face, neck, upper chest, upper back, shoulders and upper arms for 21 days
  - **Pediatric Study** (FX2016-21) Received once-daily topical application of 4 g FMX101 4% to the face, neck, upper chest, upper back, shoulder and upper arms for 7 days

![Figure 1. Study Design](image-url)
Steady Concentration patterns with Foam

**Figure 2.** Mean Plasma Minocycline Concentration Over the First 24 Hours Following a Single Dose of Oral Minocycline and Topical Application of FMX101 4% (Semi-log Scale) in Adult Subjects (Study FX2014-03)

- **Oral**: FMX101 4%, days 1-2
- **Foam**: FMX101 4%, days 12-13, FMX101 4%, days 21-22

Concentration (ng/mL) vs. Time (hr)
The Efficacy and Safety of FMX101, Minocycline Foam 4%, for the Treatment of Acne Vulgaris: A Pooled Analysis of 2 Phase 3 Studies

Linda Stein Gold, MD\textsuperscript{1}; Sunil Dhawan, MD\textsuperscript{2}; Jonathan Weiss, MD\textsuperscript{3}; Zoe Diana Draelos, MD\textsuperscript{4}; Herman Ellman, MD\textsuperscript{5}

\textsuperscript{1}Henry Ford Health System; \textsuperscript{2}Center for Dermatology Clinical Research, Inc; \textsuperscript{3}Gwinnett Dermatology; \textsuperscript{4}Dermatology Consulting Services; \textsuperscript{5}Foamix Pharmaceuticals, Inc.
Improvement measured at 12 weeks

Figure 4. Percentage Change From Baseline to Week 12 in Inflammatory Lesions by Visit

Study 04

- LSM difference: 10.24 (95% CI: 3.41, 17.07) P=.0033*
- -34%
- -44%

Study 05

- LSM difference: 9.16 (95% CI: 2.22, 16.11) P=.0097*
- -34%
- -43%

*ANCOVA, ITT population, multiple imputation.
*P≤.0001; †P≤.001; *P<.01.
BPX-04 Minocycline Gel for Rosacea: Open Label Feasibility Study

- 12-week, open-label, single-site study
  - 20 pts with moderate-to-severe papulopustular rosacea
  - Once daily application to the face (10 at 1%; 10 at 2%)

- Efficacy Endpoints:
  - 2 grade reduction in IGA to clear or almost clear (0 or 1)
  - Change in lesion count from baseline to 12 weeks

- Safety & Tolerability Endpoints:
  - Investigator & patient assessed cutaneous tolerability
  - Hematology & chemistry lab tests
  - Treatment emergent AE’s
Minocycline 1% & 2% Biphasic gel for Rosacea

- **Primary Endpoints:**
  - To evaluate efficacy of BPX-01 1% and 2% topical gel in treatment of PPR (Improvement in IGA)
  - To evaluate safety of BPX-01 1% and 2% topical gel in terms of cutaneous tolerance and adverse events

- **Secondary Endpoint:**
  - To evaluate efficacy of BPX-01 1% and 2% topical gel in terms of lesion reduction
Early Onset of Lesion Reduction

PERCENTAGE REDUCTION VS BASELINE

<table>
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<tr>
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<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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<tr>
<td>1% BPX-04</td>
<td>0.00%</td>
<td>-79.79%</td>
<td>-84.72%</td>
<td>-93.40%</td>
</tr>
<tr>
<td>2% BPX-04</td>
<td>0.00%</td>
<td>-68.14%</td>
<td>-79.96%</td>
<td>-87.58%</td>
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Early Onset of Efficacy Using a 1% and 2% Topical Minocycline Gel for the Treatment of Rosacea: a Small Open Label Study

Bhatia N1, Ahmadyar M1, Hansra H2, Del Rosso JP, Baldwin H4, Daniels AM2

1Therapeutics Clinical Research, San Diego, CA; 2BioPharmX, Inc., Menlo Park, CA; 3JDR Dermatology Research, LLC, Las Vegas, NV; 4This Acne Treatment and Research Center, Morristown, NJ

Introduction
Rosacea is a chronic, benign, and recurring skin disorder that presents with a variety of clinical manifestations primarily on the central face. The pathophysiological subtype forms dome-like inflammatory papules, pustules, and papulopustules. Genital, immune, inflammatory, vascular, and environmental mechanisms may contribute to its development. Because no cure has been identified, current treatments are generally used chronically or intermittently and aim to suppress its symptoms.

Minocycline is effective as a first-line systemic therapy for rosacea. It has been shown to be effective in the treatment of rosacea but may induce significant side effects such as gastrointestinal distress and vertigo. Topical minocycline may offer a new therapeutic option with fewer systemic side effects and a more convenient delivery system. Topical minocycline has also been shown to have anti-inflammatory properties that may contribute to rosacea suppression.

The study medication: topical minocycline gel

The study medication is the first completely formulated minocycline gel for topical use. Its preliminary safety and efficacy profiles have been demonstrated in several clinical trials. Additionally, it has completed phase 2a and 2b testing for the treatment of rosacea.

Methods
This was a phase 2 open-label feasibility study of 1% and 2% formulations of a novel topical minocycline gel for the treatment of rosacea.

- Open-label, single-site study
- 25 patients with moderate-to-severe (Grade 3 or 4) papulopustular rosacea
- 12 weeks of treatment, including 2 arms: 1% (n=10) and 2% (n=15) with switching formulations of topical minocycline gel
- Treatment assignment was non-randomized
- Cessation of all acitvity and history of rosacea
- Concomitant use of oral antibiotics
- 2-grade reduction in IGA to clear or almost clear (0 or 1)
- Change in lesion count from baseline to 12 weeks
- Cutaneous tolerability (4-point severity scale: investigator and subject-reported)
- Adverse effects and adverse reactions

Results: Rapid and Effective

Reduction in Number of Lesions

Week 0 Week 12
0% 100% 100% 100% 100%
1% 90% 100% 100% 100%
2% 90% 100% 100% 100%

Percentage Change from Baseline

Week 0 Week 4 Week 8 Week 12
0% 40% 70% 90% 100% 100%
1% 50% 75% 90% 100% 100%
2% 60% 80% 90% 100% 100%

Satisfaction: Both 1% and 2% formulations show potential for high patient compliance

In conclusion,
The rapid rate of improvement has the potential to improve treatment compliance and improved patient satisfaction.

An important advantage of the topical minocycline formulation is its chronic use, which is feasible in this long-term drug use which long-term use is possible — may be in these factors associated with systemic exposure to this antibiotic.
Pearl #7: Onychomycosis and Treatment
Oral vs. Topical: How to Decide

- Lunula/matrix involvement
- Overall severity
- Patient risk factors: hepatic, cardiac, etc.
- Concomitant medications
  - Hepatotoxic, Cardiotoxic
  - Potential for CYP450 interactions
- Patient reliability for blood draws and F/U
- Patient preferences, concerns, fears
Systemic Therapy Considerations

- Discuss treatment risks to liver or heart
- Full medical history re: hepatic disease, heart failure symptoms, concomitant meds
- Importance of lab monitoring: screening and follow-up
- Lifestyle management: EtOH
- Risk of resistance to antifungal therapy
- Number of nails involved?
What are the numbers?

- 50% of all nail abnormalities are due to onychomycosis
- Average # of nails~5; Usually lasts 5 years, 15% progress to all
- Distal lateral subungual onychomycosis—most common
- Obvious risk factors (DM, PVD) need aggressive strategy
Treat first and ask questions later?

- Comparative analysis of costs and risks associated with 3 approaches to onychomycosis evaluation before treatment with oral terbinafine or efinaconazole, 10%
  - empirical therapy without confirmatory testing
  - pretreatment confirmatory testing with potassium hydroxide (KOH) stain followed by periodic acid–Schiff (PAS) evaluation if KOH testing is negative
  - pretreatment testing with PAS

- Cost savings of empirical terbinafine therapy without confirmatory testing
  - $47 compared with the KOH screening model
  - $135 compared with PAS testing
  - KOH screening and PAS testing before treatment with efinaconazole, 10%, saved $272 and $406 per patient per nail, respectively

Scrutinize the Efficacy Outcomes Review

- **Primary outcome: Complete Cure**
  - 100% totally clear target toenail and negative KOH/ fungal culture
  - Most conservative efficacy estimate→ trials are 1 yr long and nails take >1 yr to grow completely

- **Almost Complete Cure**
  - ≤5% clinical involvement and negative KOH/ fungal culture

- **Mycologic Cure: Negative KOH/negative fungal culture**

- **What do clinicians want: no more fungus**
- **What do patients want: normal looking nails**

Endpoint Failures in research trials are usually still success in the clinic.

Onychomycosis: Does Cure Equate to Treatment Success?

Boni E. Elawiski MD,⁎ Aditya K. Gupta MD PhD FRCPC,⁎ Ted Rosen MD,⁎ Bryan D. Caldwell DPM,† David M. Pariser MD,† Leon H. Kirch MD,‡ Neal Bhatia MD,§ and Antonella Tosti MD,†

TABLE 1.

Previous Definitions of Cure 1,2 When Assessing Patients With Onychomycosis

<table>
<thead>
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<th>Consensus Conference 2006¹</th>
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<tbody>
<tr>
<td>- 100% Absence of clinical signs of onychomycosis (mycology not required)</td>
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</table>

OR

- Negative mycological laboratory results with one or more of following clinical signs
  - Distal subungual hyperkeratosis or onycholysis leaving less than 10% of nail plate affected
  - Nail-plate thickening that does not improve with treatment because of comorbid condition

Proposed modifications 2013²

- The absence of clinical signs or presence of negative culture, with or without negative microscopy, assessed after an adequate washout period
  - Length of treatment 12 to 18
  - Longer washout period (3-6 months)

Do the eyes have it?

PCR:
Quick but expensive;
High false positive rate,
Not much better than Cx in one study (72% vs. 57%)

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Courtesy Ken Tomecki, MD
Thank You...and Cheers to Ken