Curried Pearls from California: No better way to start a Thursday

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2019 Summer AAD FRM F003: Pearls from Members
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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FRM F003: 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: bhatiaharbor@gmail.com
Pearl #1: How to get the most out of Crisaborole Ointment to maximize outcomes

- 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 #2: Get to know Tapinarof: therapeutic aryl hydrocarbon receptor modulator

Adults with stable plaque psoriasis for ≥6 months
- 18–65 years
- BSA ≥1%–≤15%
- PGA ≥2
(N=227)

Double-blind treatment (12 weeks)

Tapinarof 1% BID (n=38)
Tapinarof 1% QD (n=38)
Tapinarof 0.5% BID (n=38)
Tapinarof 0.5% QD (n=38)
Vehicle BID (n=38)
Vehicle QD (n=38)

Follow up (4 weeks)

Off-treatment

Bhatia, N, Rubenstein, D, Tallman, A, Lee, J, “Patient-reported outcomes in subjects with plaque psoriasis treated with tapinarof cream: Results from a phase 2b, randomized parallel-group study,” (Poster) Fall Clinical Dermatology Conference, Las Vegas, NV Oct 2018
Overall mean change in selected weekly average PSD scores at Week 12

Bhatia, N, Rubenstein, D, Tallman, A, Lee, J, “Patient-reported outcomes in subjects with plaque psoriasis treated with tapinarof cream: Results from a phase 2b, randomized parallel-group study,” (Poster) Fall Clinical Dermatology Conference, Las Vegas, NV Oct 2018
Pearl #3: Dermoscopy can help predict patient responses to Ingenol Mebutate gel

- Are there dermoscopic features of AK? N=55 pts, 245 AKs
  - 25 (45.4%) poor/partial and 30 (54.5%) complete responders
  - per-lesion approach to 66 (26.9%) and 179 (73.1%) AKs
  - Dermoscopy reclassified 14 patients in the per-patient and 48 AKs in the per-lesion analysis from complete to poor/partial responders.

- AKs on the face characterized by red pseudonetwork associated with a complete dermoscopic response to 0.015% IngMeb therapy, while microerosions were negative predictors.

Dermoscopy patterns in AK

- **Grade 1 AKs:**
  - pink to red pseudo-network surrounding hair follicles and discrete white scales;

- **Grade 2 AKs:**
  - erythematous background intermingled with white to yellow, keratotic, and enlarged follicular openings (strawberry pattern);

- **Grade 3 AKs:**
  - enlarged follicular openings filled with keratotic plugs in scaly and white/yellow-appearing background or marked hyperkeratosis
Pearl #4: Forgive Minnie

- Minocycline tablets with too many refills
- Minocycline Biphasic Gel 1% & 2%
- Minocycline 1% Foam
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

Transition from Oral to Topical Minocycline

- 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*

Jones, T, Ellman, H, deVries, T, “Pharmacokinetic Evaluation of Once-Daily Topical 4% Minocycline Foam in Adult and Pediatric Subjects with Moderate to Severe Acne in Two Phase 1 Studies,”
Improvement measured at 12 weeks

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

Study 04

- Reduction vs Baseline (%)
- Weeks
- FMX101 4% (n=307) blue line
- Vehicle (n=159) grey line
- LSM difference: 10.24 (95% CI: 3.41, 17.07) P=.0033
  - week 12:
    - 34%
    - 44%

Study 05

- Reduction vs Baseline (%)
- Weeks
- FMX101 4% (n=333) blue line
- Vehicle (n=162) grey line
- LSM difference: 9.16 (95% CI: 2.22, 16.11) P=.0097
  - week 12:
    - 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
- 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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<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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</tbody>
</table>
Biphasic Delivery of Minocycline: Reaches $T_{max}$ Faster: Fasting or Fed

- Can be taken any time of day with or without food, and in both cases maximum concentration is reached faster with MinoLira than Solodyn.
- Delivered maximum minocycline concentration twice as fast as Solodyn under fasting conditions (2 vs 4 hours)
- When taken with food, there is a delay in reaching maximum minocycline concentration with available forms, but new Biphasic Delivery tablets (105 mg, 135 mg) achieves $T_{max}$ 1.5 hours faster
Lesion Count and Percent Clear or Almost Clear

Mean Percentage Improvement in Inflammatory Lesions

- Tablets: 43.1%* (Trial 1), 45.8%* (Trial 2)
- Placebo: 31.7%, 30.8%

Percent Clear or Almost Clear

- Tablets: 17.3%**, 15.9%*
- Placebo: 7.9%, 9.5%

*P < .01
**P < .006
Antibiotics and Birth Control Pill Interactions: Fact or Fallacy?

Conclusion

There are no pharmacokinetic data at this time to support the contention that oral antibiotic use decreases the efficacy of OCs, except for antituberculosis drugs such as rifampin. There are also no prospective, randomized clinical trials of OC efficacy and antibiotic use. Lastly, case reports used to support an effect of antibiotics on OC efficacy are anecdotal and subject to recall bias and lack adequate controls and medication documentation. Thus, there


J Am Acad Dermatol 2002;46:917-23
PDT for Acne instead of Antibiotics

ALA-PDT vs. Doxycycline + Adapalene

- N= 46 moderate inflammatory acne patients (18-30 years old)
- ALA-PDT: 20% ALA solution (90 min w/ occlusion); red light illumination (37J/cm²) with 0.1% adapalene gel 1X daily for 6 wks
- Antibiotics: 100mg/day doxycycline with 0.1% adapalene gel 1X daily for 6 wks

Timecourse

ALA-PDT vs. Doxycycline + Adapalene

**Median Reduction in Number of Lesions**

- **Photodynamic Therapy Group**
- **Antibiotics Group**

<table>
<thead>
<tr>
<th>Time</th>
<th>Total lesions</th>
<th>Inflammatory lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 wk</td>
<td></td>
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</tbody>
</table>

**Adverse Events**

**With PDT/adapalene:**
- pain during treatment (3/10)
- erythema
- desquamation
- edema
- mild sterile pustular eruption
- transient acne flare

**With doxycycline/adapalene:**
- abdominal pain
- nausea/vomiting
- photosensitivity
- scaling
- erythema
- stinging/burning
Pearl #5: Current In-Office Use of PLA

- 100% of PLA+ results were clinically managed with surgical biopsies (n=51).
  - Number needed to biopsy 2.7
- 99% PLA - results were clinically managed with surveillance (n=330)
  - None of 3 follow-up biopsies performed after 3-6 months were diagnosed as melanomas histopathologically (follow-up 1 year for 187 PLA- cases, no melanomas)
  - Real-world performance 95% sensitivity and 91% specificity
  - Commercial performance ~20,000 cases, 88% negative

As of Sept. 2018 (n=522): 461 cases have been followed for 6 months
  - 272 cases have been followed for 1 year

Ferris et al, Melanoma Research, 2018
Collects ~1.5 mg of stratum corneum tissue capturing signatures from epidermal keratinocytes, T cells, dendritic cells, melanocytes...

23ng of human skin RNA
28ng of human skin DNA
600pg of microbiome DNA

Also harvests proteins & lipids
Lesion margins can be identified on patch if needed
Tissue embedded in adhesive and does not require fixation or special refrigerated shipping
**LINC00518**

Long Intergenic Non-Coding RNA 518

- Novel Marker-discovered by DermTech - Overexpressed in melanoma
- Member of a rapidly growing family of regulatory RNA molecules
- Important regulator of oncogenesis - melanoma proliferation and invasion

**PRAME**

Preferentially Expressed Antigen in Melanoma

- Promotes tumor progression by interfering with retinoic acid receptor signaling
- Overexpressed in melanoma
- Independently validated- Haqq, Myriad, Castle

Pearl #6: Take a breath before addressing Negative Reviews
Customers or Patients?

- Customers choose to do business with a certain establishment
  - As a result, the establishment’s revenue increases.
- Customer service is a business idea developed to attract and retain profits.
- Physician-Patient relationship is profit driven
- Patients needing health care may positively, neutrally or even negatively affect revenue.
  - Patients may carry good, poor or no insurance.
  - Institutions are legally obligated to care
- Physicians’ obligations for their patients does not translate to the language of customer service.
Where does patient care end and customer service begin?


- There is a fine line between customer service and people taking advantage of you.

- “Remember that you run your business, you make the rules, you follow your contract obligations, and you should never have to lose money on any claim because a patient tells you to…”
88% of consumers trust online reviews as much as a personal recommendation

- Countless other studies have proved the same thing over and over again – “consumers” trust online reviews and those reviews heavily influence their “purchasing” decisions.

- 72% of consumers, will make purchasing decisions ONLY after they’ve read a positive review. If you can have both a high volume and a good score, you become the defacto choice for many consumers
One Star Reviews: Weapon of retaliation?

- 91% of consumers read online reviews before a purchase
- According to a survey performed by Softwareadvice.com in 2013 and 2014, the percentage of patients using online reviews to find their physician increased from 25% to 42%

- 1 star review from misunderstanding of healthcare system?
- How Soon Is Now?
  - Prior Auths, processing referrals, additional path stains all take time, regardless of efforts to ensure good patient experience

Table 1. Characteristics of 152 Five-Star Reviews

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedside manner</td>
<td>40 (26.3)</td>
</tr>
<tr>
<td>Knowledge</td>
<td>33 (21.7)</td>
</tr>
<tr>
<td>Results</td>
<td>26 (17.1)</td>
</tr>
<tr>
<td>Honesty/pressure</td>
<td>17 (11.2)</td>
</tr>
<tr>
<td>Office staff</td>
<td>17 (11.2)</td>
</tr>
<tr>
<td>Wait time/scheduling</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>Cost</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Consultation fee</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Characteristics for 112 One-Star Reviews

<table>
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<th>Characteristic</th>
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<tr>
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<tr>
<td>Office staff</td>
<td>20 (17.9)</td>
</tr>
<tr>
<td>Results</td>
<td>15 (13.4)</td>
</tr>
<tr>
<td>Cost</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Wait time/scheduling</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Knowledge</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Consultation fee</td>
<td>3 (2.7)</td>
</tr>
</tbody>
</table>

842 reviews were examined—200 reviews were included for analysis some with more than 1 comment why a patient gave the rating they did—264 comments, comprised of 152 comments for 5-star reviews, and 112 comments for 1-star reviews.
Put out the fire…but does this solve burnout?

- Contact the reviewer directly
  - If you can get people on the phone, they’ll see you as a human and not a faceless business.

- Take the proper tone
  - The right tone can turn a complaint into a positive review.
  - Don’t make excuses. Don’t get defensive.

- Never threaten a lawsuit
  - Technically, you can sue someone for online defamation
  - Lawsuits draw negative attention, and the media backlash from suing a consumer will scare off other clientele.