What’s New in Rosacea

JULIE C HARPER MD
Conflict of Interest

- Almirall
- BioPharmX
- Cutera
- Cassiopea
- EPI
- Galderma

- Journey
- LaRoche-Posay
- Ortho
- Sun
- Vyne
Rosacea Subtypes

1. Subtype **lesions/signs** of rosacea; don’t try to subtype patients
2. Treat everything that you see
3. Different lesions/signs of rosacea **will** require multiple modes of treatment
Rosacea Triggers:

- UV
- Spices
- Stress
- Exercise
- Heat

Neurogenic inflammation

Demodex / S. epidermidis

ROS
FGF2
VEGF2

TRPV/TRPA1 channels

Pro-KLK5
MMPs

Inflammation through innate immunity

Cathelicidin → LL-37

Rosacea Pathophysiology:
- Inflammation
- Angiogenesis

Rosacea Manifestations:
- Flushing
- Stinging
- Papules/Pustules
- Phymatous Changes
- Telangiectasias
- Erythema

**FIGURE 1.** Potential contributory inflammatory pathways in rosacea.\(^6\text{-}^{13}\)

<table>
<thead>
<tr>
<th>COMMON TRIGGERS</th>
<th>INFLAMMATION PATHWAY</th>
<th>PATHOLOGY</th>
<th>PHENOTYPE</th>
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<td>FLUSHING/ERYTHEMA</td>
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Erythema in Rosacea

- Flushing (transient erythema)
- Persistent facial erythema (non-transient erythema)
- Telangiectasia
- Perilesional erythema
Flushing
Beta-blockers

- Carvedilol, Nadolol, Propanolol (oral)
- Cause vasoconstriction in the skin by blocking $\beta_2$-receptors on smooth muscle of cutaneous arterial vessels
- All studied in rosacea but none are FDA-approved for rosacea
- Adverse events:
  - Decreased heart rate
  - Low blood pressure
  - Feeling weak
  - Dizziness, vertigo

Carvedilol

- 5 patients with either severe frequent flushing episodes or persistent erythema and burning sensations

- Prior treatments included cetirizine and doxycycline or isotretinoin combined with a topical application of metrogel or ivermectin without noticing sufficient improvement in erythema

- Carvedilol was added to the above treatments and titrated up to 12.5mg BID and continued for at least 6 months

Propanolol and/or doxycycline

- N=78
- ETR and PPR
- Propanolol
  - N=22
  - ETR:PPR =19:3
- Doxycycline
  - N=15
  - ETR:PPR=4:11
- Propanolol and doxycycline
  - N=26
  - ETR:PPR=9:17

72 yr old
ETR
propanolol

41 yr old
PPR
doxycycline

55 yr old
PPR
combination group

Propanolol and/or doxycycline

- PGA (patient global assessment) and IGA (investigator global assessment) decreased in all groups
  - Propanolol and combo group showed more rapid improvement (weeks 4 and 8) but there was no statistically significant difference by week 12

- Rosacea clinical scores also increased in all groups
  - Reduction of rosacea clinical scores (ARCS) was 51%, 52.2% and 57.3% in the propranolol, doxy, and combo groups respectively (NS)

2 cases of refractory flushing and erythema of rosacea

36 year old woman with persistent facial erythema for over 2 years

Prior treatments: minocycline, antihistamines, carvedilol, methylprednisilone, topical tacrolimus, topical metronidazole

Two treatments of intradermal botulinum toxin at 1-week interval

Fig. 1. a Pronounced erythema and flushing on the whole face. b Marked improvement of the lesions after two rounds of intradermal botulinum toxin injections.
Fig. 2. a Prominent erythema and flushing on both cheeks. b Marked improvement of the lesions after two rounds of intradermal botulinum toxin injections.
Botulinum toxin blocks mast cells and prevents rosacea like inflammation

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\textsuperscript{2}School of Medicine, University of California, San Diego, California, U.S.A.

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Persistent facial erythema (PFE)
Brimonidene 0.33% gel

- α-2 adrenergic receptor agonist (α2:α1 ≅ 1000:1)
- FDA-approved in 2014 for persistent facial erythema of rosacea
  - Does not treat telangiectasia
  - Not approved for flushing (transient erythema)
- Phase 3 pivotal trials excluded individuals with more than 2 papules
- A composite (investigator and subject reported) 2 grade improvement was seen as early as 30 minutes after application on Day 1
- Reduced erythema for 9-12 hours
- QAM

Brimonidine 0.33% gel

**Figure 3** Standardized photos of a representative subject before and at 30 minutes, 3 hours, 6 hours, 9 hours, and 12 hours after the application of brimonidine tartrate gel on day 1.


**Abbreviations:** CEA, clinician’s erythema assessment; PSA, patient’s self-assessment.

Oxymetazoline 1% cream

- α1a adrenergic receptor agonist
- FDA-approved in 2017 for persistent facial erythema of rosacea
- Phase 3 trials excluded individuals with more than 3 inflammatory papules or pustules
  - Does not treat telangiectasia
  - Not approved for flushing (transient erythema)
- A composite (investigator and subject reported) 2 grade improvement was seen as early as 1 hour after application on Day 1
- Reduced erythema for 9-12 hours
- QAM

Oxymetazoline 1% cream

**FIGURE 4.** Representative images of a female patient before and after treatment with oxymetazoline, days 1 and 29 (cross-polarized images).  
- 1 Hour Postdose
- 3 Hours Postdose
- 6 Hours Postdose
- 9 Hours Postdose
- 12 Hours Postdose

Day 1
Baseline Day 1
Predose

CEA: 3
SSA: 3

Day 29

Oxymetazoline 1% cream

- No head-to-head studies comparing oxymetazoline to brimonidine
- Different receptor selectivity may explain why there is more reported worsening of erythema with brimonidine than with oxymetazoline
- $\alpha_1$ receptors located ONLY post-synaptically in vascular smooth muscle
- $\alpha_2$ receptors located
  - Pre-synaptically (can inhibit norepinephrine and lead to vasodilation)
  - Post-synaptically in vascular smooth muscle
  - Endothelial wall (can mediate nitric oxide release and cause vasodilation)

Efficacy and safety of oxymetazoline cream 1.0% for treatment of persistent facial erythema associated with rosacea: Findings from the 52-week open label REVEAL trial

Zoe Diana Draelos 1, Michael H Gold 2, Robert A Weiss 3, Leslie Baumann 4, Steven K Grekin 5, Deanne Mraz Robinson 6, Steven E Kempers 7, Nancy Alvandi 8, Emily Weng 8, David R Berk 8, Gurpreet Ahluwalia 8
Draelos et al. JAAD 2018;78:1156-63.
Ocular rosacea
Fig. 1 Ocular rosacea. Bilateral blepharitis with chalazion and angiectasia.

Fig. 2 Ocular rosacea. Stye on lower lid.

Fig. 3 Ocular rosacea. Meibomian inspissation visible as pale streaks perpendicular to the lid margin, telangiectasia on bulbar conjunctiva and lid margin.
Ocular Rosacea

- International Workshop on Meibomian Gland Dysfunction (MGD):
  - Warm compresses
  - Lid massage
  - Artificial tears
  - Topical azithromycin
  - Topical emollient lubricant or liposomal spray
  - Oral doxycycline
  - Topical cyclosporine
  - Topical steroid (monitoring intraocular pressure)

Topical Ivermectin for ocular rosacea

- 50 year old male with papulopustular rosacea and blepharoconjunctivitis
- Ivermectin 1% cream applied every night (total of five pea-sized amounts spread over the entire face)
- Ivermectin 1% cream was also applied to the closed upper lid and lid edge (1/2 pea-sized amount on each lid)
- At week 35 both the skin and ocular IGA were completely clear
- No relapse 20 months after the end of treatment

Fig 1. Blepharoconjunctivitis in a 50-year-old patient: (a) before treatment, (b) clinical improvement after 14 weeks and (c) after 35 weeks' treatment with topical ivermectin 1% cream once daily.
Inflammatory lesions
Minocycline 1.5% foam

- The only minocycline FDA-approved (2020) to treat rosacea
  (no oral minocycline approved)
- Tetracyclines likely DO NOT work in rosacea by killing bacteria
- Tetracyclines likely work in rosacea by:
  - Inhibiting neutrophil chemotaxis
  - Inhibiting MMP and thus KLK5 and LL37
  - Inhibit pro-inflammatory cytokines
  - Down-regulate ROS
  - Inhibit angiogenesis

Sapadin et al. JAAD 2006;54:258-65.
Minocycline Foam 1.5%

- Two 12-week, phase 3, randomized, multicenter, double-blind, vehicle-controlled 2 arm study in patients with moderate to severe rosacea

- N=1522
- Baseline IGA 3 or 4 (moderate to severe)
- Baseline inflammatory lesion count≈30
- Co-primary endpoints:
  - Absolute inflammatory lesion reduction
  - IGA treatment success

Stein Gold et al. JAAD 2020;82:1166-73.
Minocycline Foam 1.5%

Stein Gold et al. JAAD 2020;82:1166-73.
Minocycline 1.5% Foam

Minocycline 1.5% foam

- Yellow; may stain fabric
- Contains coconut oil, soybean oil and light mineral oil
- Prefer QHS
Microbiology profile for topical foam minocycline 4% FMX101

- With MIC\textsubscript{90} values of 0.25 µg/mL, FMX101 4% was four-fold more potent than bacitracin and tetracycline, eight-fold more potent than clindamycin, and ≥32-fold more potent than neomycin, erythromycin, fucidic acid, and mupirocin.
- C. acnes lack many of the mechanisms to confer resistance to tetracyclines.
- The frequency of second-step mutation in C. acnes is less than 10\textsuperscript{-10}.
- Low plasma concentration makes systemic resistance unlikely.
- High concentrations on skin and in pilosebaceous apparatus mean that resistance evolution may be mitigated.

<table>
<thead>
<tr>
<th></th>
<th>Plasma $C_{\text{max}}$</th>
<th>Skin (epidermis) $C_{\text{max}}$</th>
<th>Skin/Plasma Ratio</th>
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<tbody>
<tr>
<td>FMX101 4%</td>
<td>1.3 ng/mL</td>
<td>560,000 ng/g</td>
<td>&gt;400,000</td>
</tr>
<tr>
<td>Oral Minocycline</td>
<td>1000 ng/mL</td>
<td>8000 ng/g</td>
<td>8</td>
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What’s New...
Benzoyl peroxide

- Mechanism of action in rosacea unknown??
- Is there a bacterial pathogen after all??
- Does benzoyl peroxide have an impact on Demodex???
5% microencapsulated benzoyl peroxide cream

- Phase 3 clinical trials complete
- N=733
- Baseline inflammatory lesion count ≈ 26
- Baseline IGA
  - IGA 3 (moderate) 86-92%
  - IGA 4 (severe) 9-13.6%
# 5% encapsulated benzoyl peroxide cream

## Proportion of Subjects Achieving “Clear” or “Almost Clear” at Week 12

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<th>SGT 54-02</th>
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<tr>
<td>BPO n=243</td>
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<td>BPO n=250</td>
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<td>Vehicle n=118</td>
<td>16.1%</td>
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<td>Vehicle n=122</td>
<td>25.9%</td>
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## Absolute mean change in ILC from baseline at week 12

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<td></td>
<td>-17.4</td>
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Press release, July 8, 2019; Sol-Gel Technologies Ltd.
Thank you!