Rosacea Update 2018

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Relevant Disclosures

- Investigator/Consultant-Allergan
- Investigator-Galderma
Rosacea Is a Chronic Inflammatory Skin Disease

- Understanding of this disease is evolving\(^1\)

- Complex pathophysiology\(^1\)

- Usual age of onset is 30 to 50 years\(^2\)

- Affects approximately 16 million Americans\(^3,4\)

- 2x to 3x higher in women than men\(^2\)

- Can occur in any race or ethnic background\(^2\)
  - Typical patient is fair-skinned and of northern European descent\(^2\)
  - May be challenging to detect in dark-skinned patients\(^2\)

- High emotional impact\(^5\)

Subtype Classification System May Not Address Overlapping Symptoms

- Subtype classification system allows clinicians to focus on similar patients and evaluate treatment approaches\(^1,2\)
- However, manifestations of rosacea often overlap the defined subtypes\(^2\)
- Further, recent advances in understanding rosacea pathophysiology show inflammation is a key pathophysiologic feature across subtypes\(^3,4\)

**Inflammation**

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<tbody>
<tr>
<td>64%</td>
<td>36%</td>
<td>24%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Facial redness is the most common sign in rosacea patients, it is important to differentiate underlying erythema as management will differ\(^5\)

Rosacea Pathophysiology

Inflammation
Neurological dysfunction
Vascular dysfunction

Innate, adaptive, and neurogenic immune responses

Activated cells

Inflammatory mediators and processes
Cathelicidin-Mediated Inflammation Pathway in Rosacea

KLK-5 = Kallikrein 5.
Dual Anti-inflammatory and Antiparasitic Action of Topical Ivermectin 1% in Papulopustular Rosacea

Schaller M, Gonser L, Belge K, Braunschdorf C, Nordin R, Scheu A, Borelli C
Dual Anti-inflammatory and Antiparasitic Action of Topical Ivermectin 1% in Papulopustular Rosacea

- This study investigated the proposed dual mode of action of ivermectin *in vivo*.
- Twenty Caucasian subjects
  - Moderate to severe rosacea, IGA ≥ 3
  - Demodex density ≥ 15/cm²
- Treated with topical ivermectin 1% cream once daily for ≥12 weeks
- Demodex density was assessed via skin surface biopsies
- Inflammatory and immune markers were evaluated via:
  - RT-PCR
  - Immunofluorescence
- No subject reported adverse events

Schaller, J Eur Acad Dermatol Venereol. doi:10.1111/jdv.14437
Mean Demodex mite count at baseline was 99.9/cm² (SD 16.75)

Treatment resulted in a significant reduction in mite count

Schaller, J Eur Acad Dermatol Venereol. doi:10.1111/jdv.14437
Clinical Improvement

- Mean inflammatory lesion count at baseline was 57 (SD 36)
- Mean inflammatory lesion count at week 12 was 10 (SD 22, -81%)
- Subjects with high baseline demodex density showed a greater reduction
IVM Inhibits Inflammation and Demodex Density Associated with Rosacea

- This study reports the dual anti-inflammatory and antiparasitic efficacy of IVM.

- It is unclear from this study whether the anti-inflammatory effect is a consequence of demodex density reduction, or an independent effect.

- These results are consistent with the hypothesis linking the inflammatory process in some individuals with rosacea to the proliferation of demodex mites:
  - A baseline mean demodex density of 105.9/cm² was observed in moderate rosacea as compared to 81.6/cm² in severe rosacea.
  - This supports the idea of the inflammatory immune response in rosacea as a reaction intended to limit mite proliferation.
  - Subjects in this study showed a higher treatment success rate if they had a higher demodex density measured at baseline.
Efficacy and Safety of Ivermectin 1% Topical Cream Associated with Brimonidine 0.33% Topical Gel in the Treatment of Moderate to Severe Rosacea:

The MOSAIC Study
MirvasO Soolantra Association In the Treatment of Moderate to Severe Rosacea
Study Design

- Multi-center, randomized, double-blind, vehicle-controlled, and parallel-group comparison study, involving subjects with moderate to severe rosacea in terms of both persistent diffuse erythema and inflammatory lesions (papules and pustules).
- N = 190 subjects enrolled at 26 sites in the U.S. and Canada
  - n = 95 in the active groups
    - n = 49 on ivermectin (IVM) + brimonidine (Br), 12 wk
    - n = 46 on IVM + Br, 8 wk
  - n = 95 in the vehicle group

Data on file. Fort Worth, TX; Galderma Laboratories, L.P. RD 03 SPR 105069
Median Percent Change from Baseline in Inflammatory Lesion Counts

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>IVM + Br 8 wk</td>
<td>0.0</td>
<td>-34.8</td>
<td>-50.0</td>
<td>-65.5</td>
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<tr>
<td>IVM + Br 12 wk</td>
<td></td>
<td>-45.0</td>
<td>-56.4</td>
<td>-75.8**</td>
</tr>
<tr>
<td>Vehicle</td>
<td></td>
<td></td>
<td></td>
<td>-78.3**</td>
</tr>
</tbody>
</table>

*P < 0.01
**P < 0.001

Data on file. Fort Worth, TX; Galderma Laboratories, L.P. RD 03 SPR 105069
IGA Success at Week 12, Hour 3: Individual Arms (ITT population)

- **Vehicles H3**: 36.8% (34.7 almost clear, 2.1 clear)
- **IVM + Br 8w H3**: 50% (39.1 almost clear, 10.9 clear)
- **IVM + Br 12w H3**: 61.2% (44.9 almost clear, 16.3 clear)

\( P = 0.003^* \)

Data on file. Fort Worth, TX; Galderma Laboratories, L.P. RD 03 SPR 105069
IGA Success at Each Time Point, Hour 3: Individual Arms

IVM + Br 12 Weeks Was Significantly Superior to Both Vehicles as Early as Week 4

*P value vs vehicles

Data on file. Fort Worth, TX; Galderma Laboratories, L.P. RD 03 SPR 105069
Oxymetazoline

- A redness reducer
- Alpha 1 agonist
**Characterization of the In Vivo Pharmacology of Oxytetracycline and Brimonidine Using a Mouse Model of UV-Induced Erythema**

## Differential Features of $\alpha_1$- and $\alpha_2$-Adrenergic Receptors Modulating Cutaneous Vasculature

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$-Adrenergic Receptors</th>
<th>$\alpha_2$-Adrenergic Receptors</th>
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<tbody>
<tr>
<td>Location</td>
<td>Blood vessel</td>
<td>Nerves</td>
</tr>
<tr>
<td></td>
<td>• Smooth muscle</td>
<td>• Presynaptic terminal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood vessel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Smooth muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Endothelium</td>
</tr>
<tr>
<td>Effects</td>
<td>Vasoconstriction</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>• Smooth muscle</td>
<td>• Smooth muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Endothelium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Presynaptic terminal</td>
</tr>
</tbody>
</table>

Characterization of the In Vivo Pharmacology of Oxymetazoline and Brimonidine Using a Mouse Model of UV-Induced Erythema

Differential Expression of α-Adrenergic Receptor Subtypes

- α-Adrenergic receptor distribution
  - α\textsubscript{1} receptors are expressed postsynaptically on vascular smooth muscle cells (VSMC)
  - α\textsubscript{2} receptors can be expressed on presynaptic nerve terminals and/or postsynaptically on VSMC and vascular endothelium
- Vasoconstriction is induced upon activation of postsynaptic receptors located on VSMC by norepinephrine (NEP)
  - Mimicked by α-adrenergic agonists – basis of therapeutic effect.
Characterization of the in Vivo Pharmacology of Oxymetazoline and Brimonidine Using a Mouse Model of UV-Induced Erythema

$\alpha_2$-Adrenergic Agonists Can Act on Presynaptic Receptors to Promote Vasodilation

- In cutaneous vessels that lack postsynaptic $\alpha_2$-adrenergic receptors, an $\alpha_2$-adrenergic agonist acting on presynaptic receptors to reduce NEPI release will result in unopposed vasodilation.
- In contrast, an $\alpha_1$-adrenergic agonist will result in vasoconstriction in such vessels.

NEPI, norepinephrine.
Efficacy and Safety of Topical Oxymetazoline Cream 1.0% for Treatment of Facial Erythema Associated With Rosacea: Findings From Two Pivotal Phase 3 REVEAL Studies

Identical Study Design for Each of 2 REVEAL Studies

**Endpoints and Assessments**

Methods, cont’d

Randomize 1:1

Double-blind Treatment Period

Oxymetazoline (n=446)

A pea-sized amount of study medication was to be applied in a thin layer to the entire face, including the forehead, nose, cheeks, and chin, once daily in the morning.

Vehicle (n=439)

Post-treatment Follow-up Period

Incidence of rebound effect following treatment cessation assessed

Visit 1 Screening Day -45 to -1

Visit 2 Day 1 Randomize

Visit 3 Day 15

Visit 4 Day 29

Visit 5 Days 33-36

Visit 6 Day 57 Exit

- Adults age ≥18 years
- Moderate to severe persistent facial erythema associated with rosacea (CEA and SSA grade ≥3)

Reveal 1: Conducted at 20 centers in USA and enrolled 440 patients

Reveal 2: Conducted at 24 centers in USA and enrolled 445 patients

Primary efficacy: ≥2-grade improvement on both CEA and SSA (composite)∗

All efficacy analyses performed on the intent-to-treat population (all randomized patients). Safety analyses performed on the safety population (all randomized patients who received at least 1 application of study drug).

∗ Primary efficacy evaluations at day 29. Safety assessed throughout the study.
On day 29, improvements in the individual CEA and SSA components were each significantly greater with oxymetazoline vs vehicle at 3, 6, 9 and 12 hours post-dose ($P \leq 0.01$) and throughout the post-dose period ($P \leq 0.001$).
Patients using oxymetazoline experienced significantly decreased facial erythema for up to 12 hours post-dose compared with those who used vehicle, as assessed by digital image analysis at day 29 (throughout the post-dose period, $P<0.001$)
Rebound Assessment

- Following cessation of treatment, a low proportion of patients experienced worsening of erythema compared with baseline based on the CEA and SSA composite score.
  - For the entire post-treatment period from day 30 through day 57 (study exit), 6/355 patients (1.7%) in the oxymetazoline group and 2/349 patients (0.6%) in the vehicle group experienced worsening of erythema based on the CEA and SSA composite score.

- No patient had an unscheduled visit (for rebound assessment) during the 14-day post-treatment period.

- Based on these clinical data, there was no evidence of clinically relevant rebound effect following cessation of oxymetazoline treatment.
Doxycycline 40 mg Modified Release Capsules
Reduced Inflammatory Biomarker Expression
and Improved Clinical Outcomes in
Papulopustular Rosacea

Anna Di Nardo, MD, PhD¹, Anna D. Holmes, PhD², Yumiko Muto, BS ¹,
Eugene Y. Huang, MD, PhD³,⁴, Warren J. Winkelman, MD, PhD⁵,
Richard L. Gallo, MD, PhD¹

¹University of California San Diego, School of Medicine, Department of Dermatology, La Jolla, CA; ²Galdema Laboratories, L.P.,
Fort Worth, TX; ³Therapeutics Clinical Research, San Diego, CA; ⁴Veterans Affairs San Diego Health Care System, San Diego, CA.
⁵Nestlé Skin Health-SHIELD Center, New York, NY, Nestle Skin Health is an affiliate of Galderma Laboratories, L.P. which
markets Doxycycline 40mg Modified Release Capsules in the United States.
Doxycycline MR Treatment Results in Decreased Biomarker Gene Expression

Percent of baseline for CAMP, KLK5, and MMP9 mRNA measured in skin biopsies at week 12 for doxycycline MR and placebo groups (mean ± StDev; **P < 0.01; 2-way ANOVA)
Summary

- Protease activity and cathelicidin levels corresponded with rosacea severity
- Protease and cathelicidin levels were reduced following doxycycline MR treatment
  - This supports the hypothesis that the mechanism of doxycycline in the treatment of rosacea involves reduction of these biomarkers
Reported Comorbidities of Rosacea
Background

- Rosacea is associated with a range of reported comorbidities
  - Neurologic
  - Gastrointestinal
  - Cardiovascular
  - Autoimmune
  - Some forms of cancer

- Rosacea may be linked to these comorbidities through a number of factors
  - Genetic factors
  - Environmental factors
  - Common pathophysiology

- Characterizing common pathologic mediators may help identify new therapeutic targets
## Comorbidities with Reported Rosacea Associations

### Positive associations*

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Level of evidence†</th>
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<tbody>
<tr>
<td>Crohn’s disease</td>
<td>2A</td>
</tr>
<tr>
<td>Depression</td>
<td>2B</td>
</tr>
<tr>
<td>Migraine</td>
<td>2B</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2B</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>2B</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>2B</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>2B</td>
</tr>
<tr>
<td>Glioma</td>
<td>2B</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>2B</td>
</tr>
<tr>
<td>Dementia</td>
<td>2B</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>3B</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>3B</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>3B</td>
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<tr>
<td>Multiple sclerosis</td>
<td>3B</td>
</tr>
<tr>
<td>Allergy (food)</td>
<td>4</td>
</tr>
<tr>
<td>Allergy (airborne)</td>
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<tr>
<td>Urogenital diseases</td>
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<tr>
<td>GERD</td>
<td>4</td>
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<tr>
<td>Respiratory diseases</td>
<td>4</td>
</tr>
<tr>
<td>Female hormone imbalance</td>
<td>4</td>
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<tr>
<td>Metabolic diseases</td>
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### Possible associations

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Level of evidence†</th>
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<tbody>
<tr>
<td>CVD</td>
<td>+/-</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>+/-</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>+/-</td>
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</table>

*Associations based on limited studies and does not account for variations in study design and possible confounding

†Levels of evidence

- 2A: Systematic review of cohort studies
- 2B: Cohort study
- 3A: Systematic review of case-controlled studies
- 3B: Case-controlled study
- 4: Small or underpowered cohort/case-controlled study
- +/-: Conflicting evidence
Common Genetics and Comorbidities Associated with Rosacea

<table>
<thead>
<tr>
<th>Rosacea allele/SNP</th>
<th>PD</th>
<th>AD</th>
<th>MS</th>
<th>T1DM</th>
<th>CD</th>
<th>RA</th>
<th>IBD</th>
<th>CVD</th>
<th>Cancer</th>
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<td>HLA-DQB1*02:01</td>
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<td>GSTM1/GSTT1*0/0</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

- **PD** = Parkinson's disease
- **AD** = Alzheimer's disease
- **MS** = Multiple sclerosis
- **T1DM** = Type 1 diabetes mellitus
- **CD** = Celiac disease
- **RA** = Rheumatoid arthritis
- **IBD** = Inflammatory bowel disease
- **CVD** = Cardiovascular disease
Environmental Risk Factors and Triggers Associated with Rosacea

- **Risk factors**
  - Age
  - Lifetime UV exposure
  - Photosensitive skin type
  - Positive family history
  - Skin cancer history
  - High vitamin D levels
  - Not smoking
  - Body mass index

- **Triggers**
  - Sun exposure
  - Psychological stress
  - Heat
  - Wind
  - Heavy exercise
  - Alcohol consumption
  - Cold
  - Spicy foods
  - Humidity/osmotic changes
  - Skin care products/cosmetics
  - Hot beverages
  - Medications
  - Microorganisms (eg, Demodex, H. pylori)
Rosacea Shares a Common General Pathophysiology with Reported Comorbidities

**Inflammation**
- IBD
- Alzheimer’s
- Parkinson’s
- Anxiety/depression
- Migraine
- CVD
- RA
- Celiac
- T1DM
- MS
- Cancer

**Neurological**
- Alzheimer’s
- Parkinson’s
- Anxiety/depression
- Migraine
- MS

**Vascular**
- Alzheimer’s
- Cancer
- CVD
- IBD
- Migraine
- MS
- Parkinson’s
- RA
- T1DM
THANK YOU

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