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Disclosures

Aclaris**#
Allergan**#
Anacor**
Aqua/Almirall**
Bayer Dermatology***
BioPharmX**
Celgene**
Cutanea#
Dermira*
Ferndale**
Foamix#
Galderma***

Genentech+
LeoPharma**#
Novartis**
Novan#
Valeant***
Pharmaderm**
Promius**
Sebacia#
SunPharma**#
Unilever**

Consultant* / Speaker* / Researcher#
(Updated as of 6-10-16)
Recent References on Rosacea

**American Acne & Rosacea Society**

- Cutis March 2013 publication from AARS

- Cutis 5-Part Article Series from AARS
  - Nov 2013: General Measures/Skin Care
  - Dec 2013: Topical Therapies
  - Jan 2014: Systemic Therapies
  - Feb 2014: Physical Modalities
  - Mar 2014: Consensus Recommendations on Management

**Rosacea International Study Group**

- Publication from RSIG on rosacea
  - Studied information from multiple dermatologists with strong interest in rosacea from the United States, Canada, Sweden, Germany, Ireland, and other countries over the past 3 years
  - Included multidisciplinary information presented by ophthalmologist, gastroenterologist, and basic scientists
  - Supplement publication in J Am Acad Dermatol (December 2013)
The AARS Rosacea Initiative Publications
Multiple Levels of Review (AARS, Peer Review)

Cutis March 2013
AARS Supplement

Cutis 5-Part Article Series

Consensus Recommendations From the American Acne & Rosacea Society on the Management of Rosacea, Part 1: A Status Report on the Disease State, General Measures, and Adjunctive Skin Care

PARTS 1-5
Nov 2013: General Measures/Skin Care
Dec 2013: Topical Therapies
Jan 2014: Oral Therapies
Feb 2014: Physical Modalities
Mar 2014: Consensus Recommendations on Management
Clinical Manifestations of Cutaneous Rosacea

**INTERMITTENT**

*Present during flares*

*Absent between flares*

- Acute vasodilation (flushing)
- Inflammatory lesions
  - Papules
  - Pustules
- Perilesional erythema
- Diffuse central facial erythema that is related to acute inflammation of rosacea and *NOT* related to chronically enlarged superficial blood vessels

**PERSISTENT**

*Present during and between flares*

- Diffuse central facial erythema related to chronically enlarged superficial blood vessels*
- Telangiectasias
- Phymatous changes

*Increases in magnitude during a flare of rosacea*

Rosacea-Prone Skin: A Plethora of Dysregulations

Exogenous Triggers
Inflammatory Signals
Vascular Signals & Response
Sensory Response

Endogenous Predispositions

TLR2

TRPV

Heat, capsaicin, RTX
Na⁺, Ca²⁺

Closed

Open
PKC, Ca²⁺

Dilated

TLR2

Callicidin
(CAMP mRNA / nCAP18)

Altered peptides
(LL-37/FA-29, etc.)

Inflammation
Angiogenesis
Telangiectasia
Rosacea-Prone Skin: A Plethora of Dysregulations

Pathophysiological Pathways Correlate with Signs and Symptoms of Rosacea

Potential Triggers

- UV light, *Demodex*, Food, Genetic predisposition, Emotional factors, Beverages, Physical activity, Temp and weather, Skin-care products, etc

Cathelicidin Cascade
- LL-37
- MMPs

Leukocyte Recruitment

Potential Triggers

- *Neuroinflammation associated with Neurovascular Dysregulation*

Vascular Dilatation/Proliferation Angiogenesis

Inflammatory Cascades
- TNF + IL-1β
- PGE2
- ROS Vasorelaxation

- Inflammation
- Pain
- Erythema*

Inflammasome Pathways
- Nitric Oxide
- MMPs

- Vasodilation
- Tissue Remodeling

*Neuroinflammation associated with Neurovascular Dysregulation*
Pathophysiologic Pathways Correlate with Signs and Symptoms of Rosacea

**Rosacea-Prone Skin**

TLR2 → MMP → KLK5 → Cathelicidin LL37

- **Augmented Immune Detection & Response**
  - NALP3 → Inflamasome → IL-1β (Caspase-1 Activation)

- **Neurovascular Dysregulation**
  - TRPV Ion Channels → Neuropeptides → Sensory Symptoms

- **MMP, NO, ROS**
  - Vascular Effects / Vasodilatation
  - MMP, NO, ROS

- **Inflammation**
  - TNF → Inflammation

- **Macrophage/Leukocyte Chemotaxis**
  - IL-8 → Neutrophil Chemotaxis → Pustules Papules

- **Angiogenesis**
  - VEGF → Angiogenesis

- **Symptoms**
  - Sensory Symptoms

- **Fibrosis Activation**
  - Mast Cell → Fibroblast → Fibrosis Activation
ROSACEA FACIAL
ERYTHEMA
CENTRAL FACE
DIFFUSE
MACULAR
+/- EDEMA
AT ONSET
AND/OR PERSISTENT
AFTER THERAPY

ROSACEA DERMATITIS
SC dysfunction
Increase in “jump start” cytokines

AUGMENTED INNATE IMMUNE RESPONSE
- Increase in TLR2
- Increased Cathelicidin (LL-37)
- Increased KLK-5

ALTERED VASCULATURE
- LL-37 → VEGF
- Increased Nitric oxide → Dilation
Increased flow

ANGIOGENESIS
Increased VEGF
Increased mast cells
Downstream effects of LL-37

DERMAL MATRIX DEGRADATION
Increase in ROS → Decreased
Antioxidant reserve
Increased MMPs

NEUROVASCULAR DYSREGULATION
Vascular Response/Vasodilation
Changes in Superficial Facial Vasculature in Rosacea Progressively Develop Over Time

Facial Cheek Skin Evaluated by Videocapillaroscopy (n=30)

Over time with repeated flares, facial skin blood vessels increase in number & size. Diffuse background redness persists between flare ups especially of the central face.

Kallikrein 5-Mediated Inflammation in Rosacea
Clinically Relevant Correlations with Acute and Chronic Manifestations in Rosacea and How Individual Treatments May Provide Therapeutic Benefit

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*Division of Dermatology, Department of Medicine, University of California, San Diego, La Jolla, California; ‡Touro University College of Osteopathic Medicine, Henderson, Nevada; JDRx Dermatology LLC, Las Vegas Skin and Cancer Clinics/West Dermatology Group, Henderson, Nevada

ABSTRACT
Rosacea is a chronic inflammatory condition of facial skin estimated to affect more than 16 million Americans. Although the pathogenesis of rosacea is not fully understood, recent evidence in vitro as well as in vivo has supported the role of increased levels of the trypsin-like serine protease, kallikrein 5, in initiating an augmented inflammatory response in rosacea. The increase in the quantity and magnitude of biological activity of kallikrein 5 leads to production of greater quantities of cathelicidin (LL-37), an antimicrobial peptide associated with increases in innate cutaneous inflammation, vasodilation, and vascular proliferation, all of which are characteristic features of rosacea. In this article, the authors review the literature supporting the role of kallikrein 5 in the pathophysiology of rosacea, including how therapeutic interventions modulate the effects of kallikrein 5, thus providing further support for this pathophysiological model that at least partially explains many of the clinical features of cutaneous rosacea. (J Clin Aesthet Dermatol. 2014;7(1):20-25.)
Two Studies Completed in Humans with Papulopustular Rosacea Show Biomarker Correlation with Response

**AZELAIC ACID 15% GEL BID**

- High Baseline
- Low Baseline

\[ r^2 = 0.7935 \quad p = 0.0008 \]
\[ r^2 = 0.1421 \quad p = 0.5317 \]

**DOXYCYCLINE 40MG-MR ONCE DAILY**

- Treatment Successes (S)
- Treatment Failures (F)

\[ n = 20 (S) \quad n = 150 (F) \]
\[ n = 41 (S) \quad n = 127 (F) \]
\[ n = 45 (S) \quad n = 119 (F) \]
\[ n = 49 (S) \quad n = 111 (F) \]