Acne Peer-to-Peer Educational Toolkit

A compilation of key content from select presentations at the 2020 South Beach Symposium and the Masters of Pediatric Dermatology

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Neonatal Acne

- **0-6 weeks of life**
- Small erythematous papules
- ? Acne --- maybe neonatal cephalic pustulosis
- Neonatal acne represents a heterogeneous set of conditions
- Controversy Pityrosporum (Malassezzia) – sometimes present and sometimes not
- Usually resolves over a few months
- Distribution: Forehead, Cheeks, Nose
  Less commonly: neck, chest, back

Neonatal Acne - Consensus

- Neonates may have true acne
- Many self-limiting papulopustular eruptions that occur on neonate faces
- Systemic abnormalities noted **(growth, precocity, virilization**), then referral to pediatric endocrinology
- *Eichenfield, LF, et al. Pediatrics 2013;131;S163*

Neonatal Acne - Treatment

- **Ketoconazole cream 2%**
- **Gentle cleanser**
- **If there are true comedones consider acne medications that you would use in infantile acne**
- **Usually not scarring, so can also not treat**

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Infantile Acne

- 0-1 year; usually see around 3-6 months
- Boys>girls
- May predispose to worse acne in teenage years*
- Increased sebum production
- Look more like classic acne – will see comedones
- Face where cheeks are mainly affected, also chin
- Less on the chest and back
- Should treat – can cause scarring
- Look for signs of hormonal abnormalities

- *Herane, MI. Acne in infancy and acne genetics. Dermatology 2003;206:24-28.

Infantile Acne - Consensus

- Most infantile acne is self-limited
- If there are signs of hormonal abnormalities, refer to pediatric endocrinologist

- Eichenfield, LF, et al. Pediatrics 2013;131;S163

- Combine treatments
- Watch for products that are appropriate for a baby
  - Topical antibiotics/benzoyl peroxide
  - Adapalene cream/low strength tretinoin
  - Avoid washes so that wash doesn't get into the eye
  - Oral erythromycin
  - Isotretinoin if severe, scarring
    - HOW YOUNG? I have seen case reports in the first months of life
    - DOSE ? 0.5mg/kg to 1mg/kg; cumulative dose 60-180mg/kg

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Mid-childhood Acne

- **Most likely time to have underlying hormonal abnormality**

- Newer concept
- **From 1-7(8) years of age**
- Androgens should be low and stable
- Evaluate for **Hyperandrogenism**
- Distribution – face, chest, back

Mid-childhood acne - consensus

- Acne in this age group is very **uncommon**

- Should warrant workup for cause of hyperandrogenism

Eichenfield, LF, et al. Pediatrics 2013;131;S163

Guide for Evaluation of Mid-Childhood Acne

- Bone age
- **Growth Chart**
  - **Height** crossing percentiles **upward in androgen excess**
  - **Weight** crossing percentiles **upward** and height downward in **Cushing's syndrome**
- Hormone Levels

Acne Vulgaris Editors, Shalita, AR., Del Rosso, JQ, Webster, GF, 2011 Informa Healthcare. Pp188-190

Which Hormones to check (Mild childhood acne)

- DHEA(s)
- Testosterone
- Cortisol
- 17 hydroxyprogesterone
- Androstenedione
- LH/FSH
- Prolactin
- **Pediatric Endocrinologist Referral – to ensure completeness**

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Pre-adolescent Acne

- **8-12 years of age**
- Treatments same as infantile/mid-childhood
- Adherence
- Once a day regimen
- Swallowing pills – use liquid forms
- Isotretinoin – uncommon but may need to repeat (early teen acne – young age they may need again)

Sometimes called Preteen acne

- Comedones
- Seborrhea
- Polycystic Ovarian Syndrome (PCOS) – can see at this age (8-12 years) in girls
- Distribution of acne:
  - Face (especially forehead)
    Conchae of ears may be involved
    Chest
    Back

- Pelvic Ultrasound is **not considered useful** for diagnosis of PCOS because it is considered non-specific

Rosenfield RL. Clinical review: Identifying children at risk for polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2007 Mar;92(3):787-96.

Acne Treatment Tips

Mild Acne

- Mild acne – topicals may suffice
- Benzoyl Peroxide or Retinoid
- Combination Products possibly including topical antibiotic

Moderate Acne

- Start with a combination therapy
- Use oral antibiotics
- Consider oral isotretinoin
- Hormonal therapy rarely

Severe Acne

- Use combination therapy AND systemic medications (oral antibiotics and/or hormonal therapy, rarely)
- Consider Isotretinoin

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TOPICAL RETINOIDS

Tretinoin 0.05% Lotion in Acne Vulgaris
Once Daily – 12-Week Phase III Monotherapy Studies

≥9 Years of Age
with Facial Acne
(N=1640)

Moderate to Severe
Acne at Baseline

Two Randomized (1:1) Controlled
Studies

Greater Improvements in Skin
Oiliness, Patient Satisfaction and QoL
with active vs vehicle
(Week 12 vs Baseline)

Figure 1: Percent Change in Mean Inflammatory Lesions from Baseline to Week 12 (ITT Population, LS Mean data). Study 301 in blue and 302 in red; vehicle data shown in corresponding dotted lines)

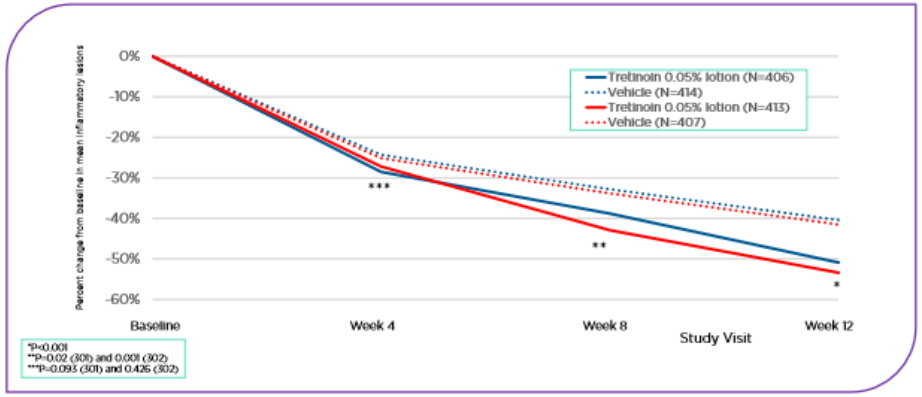
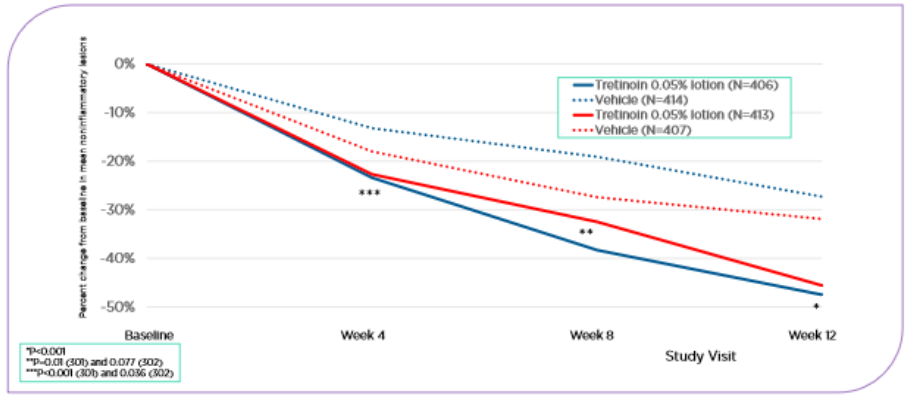


Figure 2: Percent Change in Mean Noninflammatory Lesions from Baseline to Week 12 (ITT Population, LS Mean data). Study 301 in blue and 302 in red; vehicle data shown in corresponding dotted lines)



WEEK 12

Mean % Reduction
Inflammatory Lesions
50.9% - 53.4%
(Tretinoin) vs
40.4% - 41.5%
(Vehicle)

Mean % Reduction
Comedonal Lesions
47.5% - 45.6%
(Tretinoin) vs
27.3% - 31.9%
(Vehicle)

All Comparisons
P<0.001

Del Rosso JQ, Pariser D, et al. Poster presentation, SCALE Meeting, Nashville, TN, May 2018

Harper JC, et al. J Dermatolog Treat. 2019 Apr 2:1-8.

TOPICAL RETINOIDS

POST HOC ANALYSES FROM PIVOTAL TRIALS

ASIAN POPULATION (N=69)
AGE 12-48 YRS
EFFICACY AND TOLERABILITY CONFIRMED
Han G, et al. J Drugs Dermatol. 2019;18(9):910-916

PREADOLESCENT POPULATION (N=154)
AGE ≤13 YRS
EFFICACY AND TOLERABILITY CONFIRMED
Eichenfield L et al. Ped Dermatol. 2019;36(2): 193-199

TRETINOIN 0.05% LOTION
ONCE DAILY
MODERATE-SEVERE ACNE

ADULT AND ADOLESCENT FEMALE POPULATION (N=909)
AGE 9-58 YRS
EFFICACY AND TOLERABILITY CONFIRMED
Kircik L, et al. J Drugs Dermatol. 2019;18(2): 178-188

HISPANIC POPULATION (N=766)
AGE 11-50 YRS
EFFICACY AND TOLERABILITY CONFIRMED
Cook-Bolden F, et al. J Drugs Dermatol. 2019;18(1):32-38

JAMES Q. DEL ROSSO, DO

TOPICAL RETINOIDS

Trifarotene Cream
Phase 3 Studies in Moderate Facial AND Truncal Acne

- Trifarotene is a RARγ-selective topical retinoid in a cream (50 µg/g)
- Development program evaluated efficacy and safety in both FACIAL and TRUNCAL ACNE
- Two 12-week, double-blinded, multicenter, vehicle-controlled studies
  - Once daily trifarotene cream (n=1209) or vehicle cream (n=1183)
  - Randomization pattern 1:1

TRUNCAL ACNE (Data at 12 Weeks)	Study 1	Study 2
Mean % Change Inflammatory Lesions	57.4% vs 50.0%	65.4% vs 51.1%
Mean % Change Non-Inflammatory Lesions	49.1% vs 40.3%	55.2% vs 45.1%

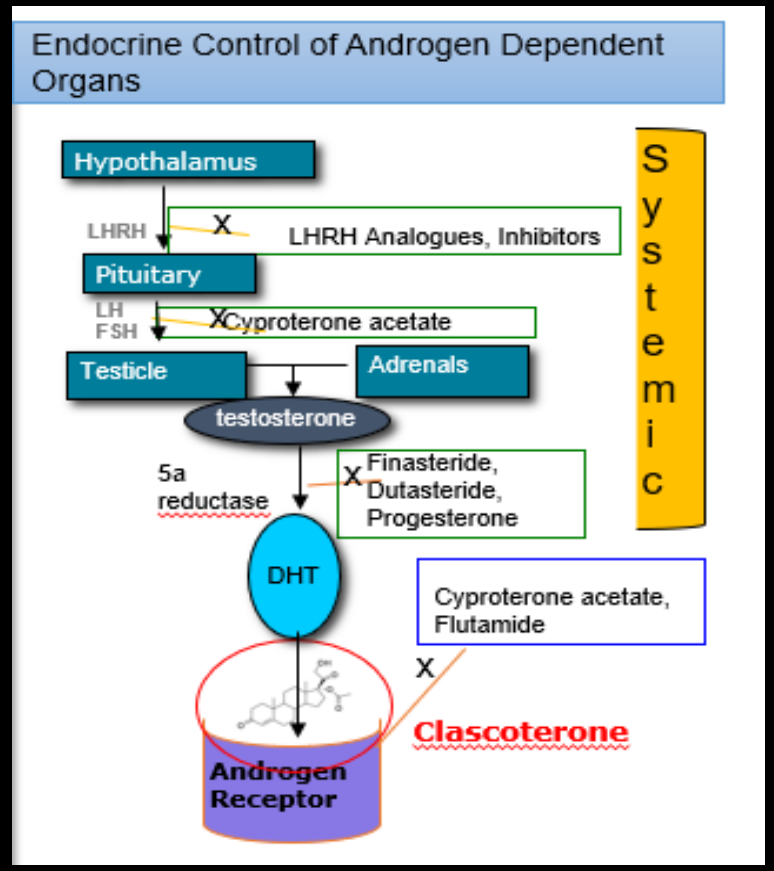
Majority of adverse events local tolerability reactions early in therapy

- Consistent with topical retinoid therapy – managed with proper skin care
- Fewer reactions on trunk

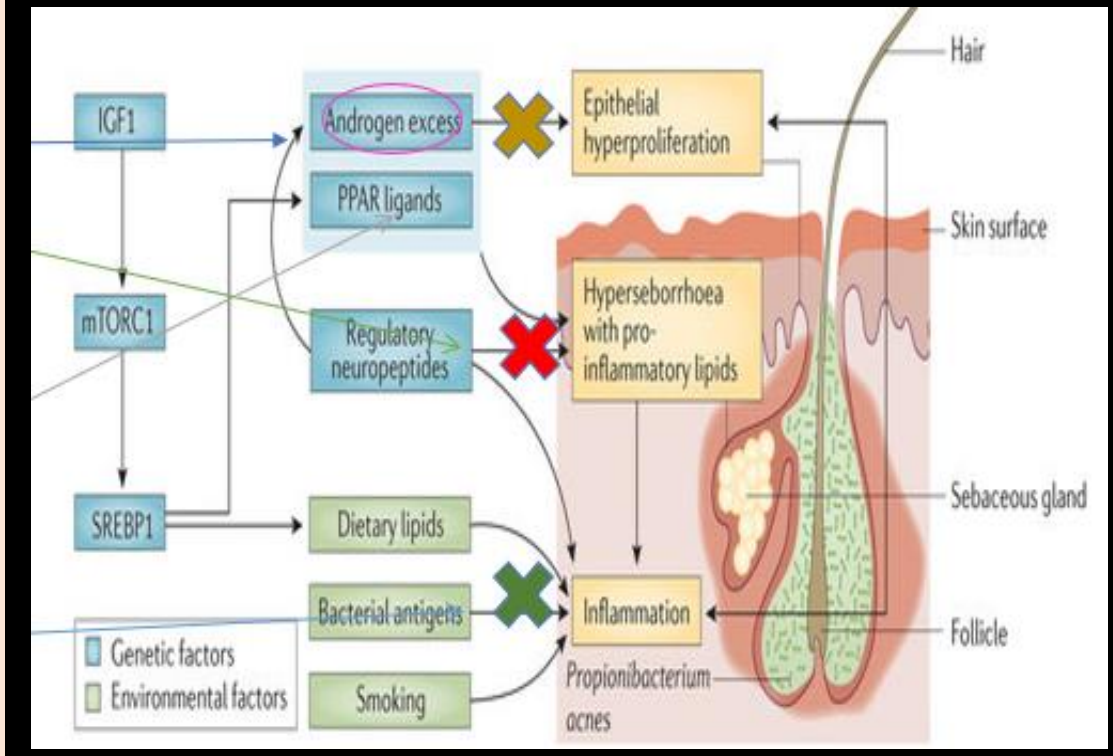
Tan J, Thiboutot D, Popp G, et al. J Am Acad Dermatol. 2019;80(6):1691-1699.

TOPICAL CLASCOTERONE

Clascoterone Targets Multiple Pathways Operative in Acne Pathophysiology



- **CLASCOTERONE Reduces**
  - **Sebum secretion[1]**
  - **Follicle cell keratinization[2]**
  - **Inflammation[1]**



1. Data on File. Clinical Study Report. Cassiopea SpA & Submitted manuscript to Investigative Derm.
2. Lai JJ et al. Arch Dermatol Res. 2012;304(7):499-510

Image from : Tuchayi SM et al. Acne Vulgaris. Nature Reviews: Disease Primers.2015; Sept. https://www.nature.com/articles/nrdp201529?WT.mc_id=TWT_NRDP

TOPICAL CLASCOTERONE

Topical Clascoterone Phase I/II Studies
Top Line Outcomes

First topical anti-androgen + anti-inflammatory properties

New Chemical Entity ~ New Mode of Action

Previously referred to as CB-03-01 and/or cortexolone 17-α propionate

Safety profile similar to vehicle (>1300 exposed in Phase I/II studies)

Statistical significance in Phase II primary end-points

35.7% Total Lesion Count reduction vs 13% with vehicle

Clinically superior / better tolerated than topical tretinoin (Phase IIa trial) 22% IGA improvement vs 11.5%, 66% Total Lesion Count reduction vs 52%

Anticipate use in combination with other acne therapies

Cannabidiol (CBD) [BTX 1503]

Mechanism of Action in Acne
BTX 1503 (Cannabidiol) Effects on Acne Pathophysiologic Factors

PRIMARY FACTORS IN ACNE PATHOPHYSIOLOGY:

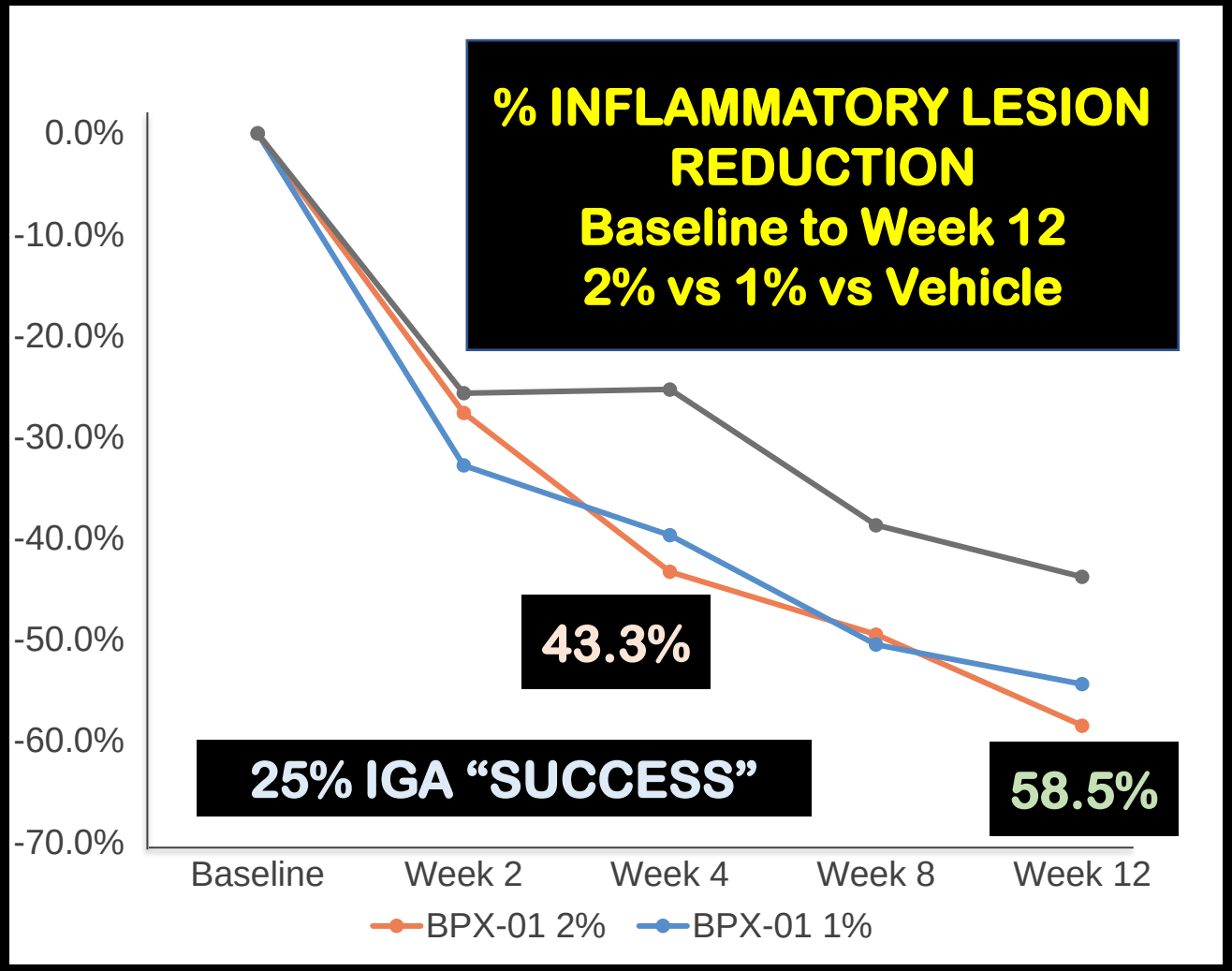
- Excess sebum production
- Follicular hyperkeratinization (microcomedo)
- *C. acnes* (formerly *P. acnes*) colonization
- Perifollicular inflammation

CBD SHOWN TO:

- Suppress sebocyte proliferation1
- Inhibit human keratinocyte proliferation, through a of the follicle non-CB1/CBs mechanism 2
- Have potent anti-microbial activity against gram-positive bacteria3
- Have anti-inflammatory effects on human sebocytes 1

1. Olah et al. *J Clin Invest*. 2014:124(9):3713-372;
2. Wilkinson & Williamson. *J Derm Sci*. 2007;45:87-92
3. Appendino et al. *J Natl Prod*. 2008;71:1427-1430;.

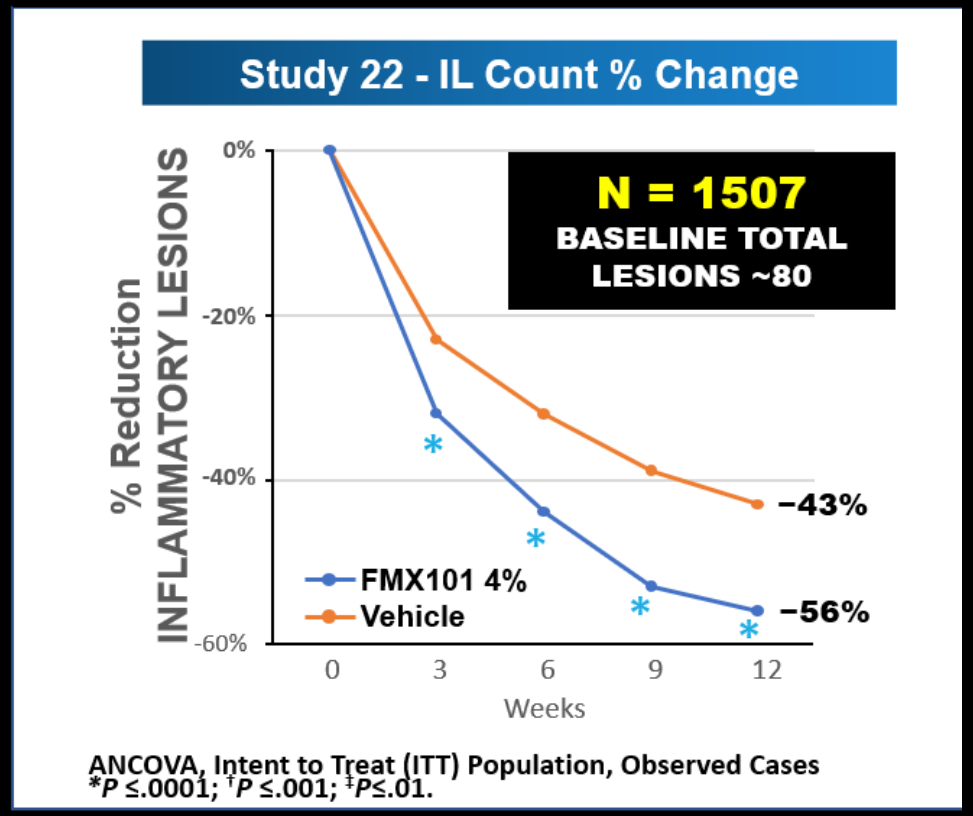
TOPICAL MINOCYCLINE FORMULATIONS



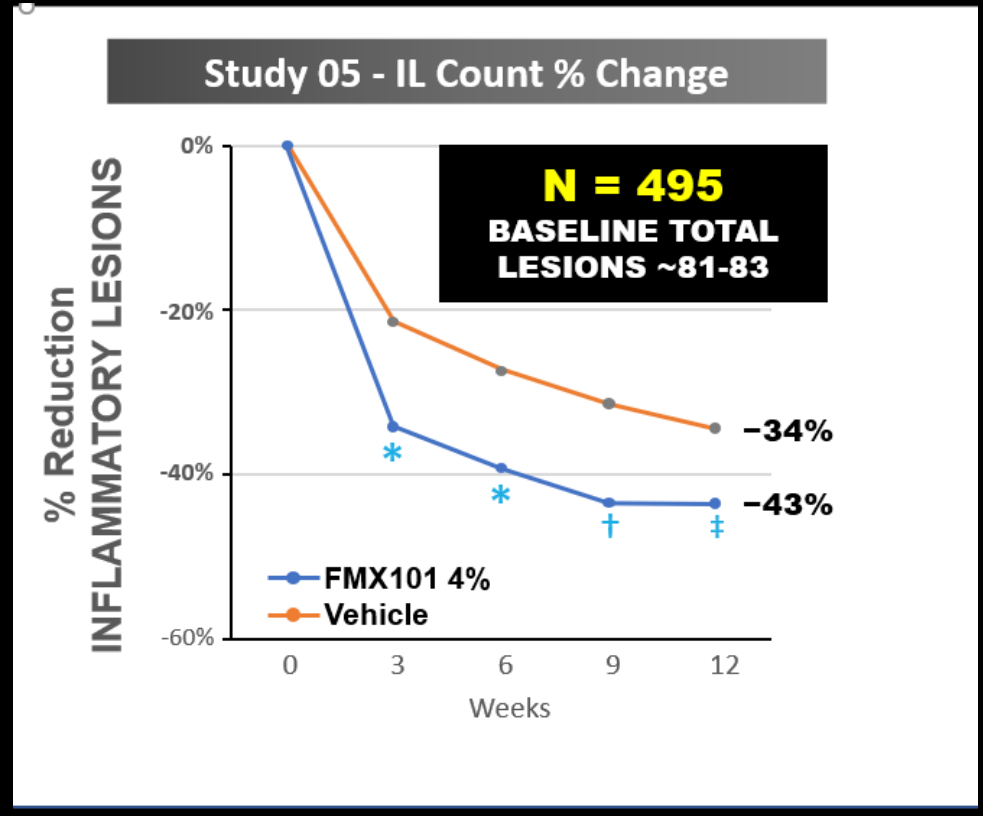
- 58.5% lesion reduction at Week 12 (2% dose)
- 43.3% lesion reduction at Week 4 (2% dose)
- 25% with ≥2-grade reduction in IGA + Clear or Almost Clear (2% dose)
- 25% lesion reduction at Week 4 *(Time to Onset)*
- Statistically significant lesion reduction *(P=0.0256)*

MINOCYCLINE 4% FOAM ONCE DAILY

PHASE 3 12-WEEK STUDIES – MODERATE/SEVERE ACNE
>9 YEARS OF AGE – CHANGE IN INFLAMMATORY LESIONS (ILs)



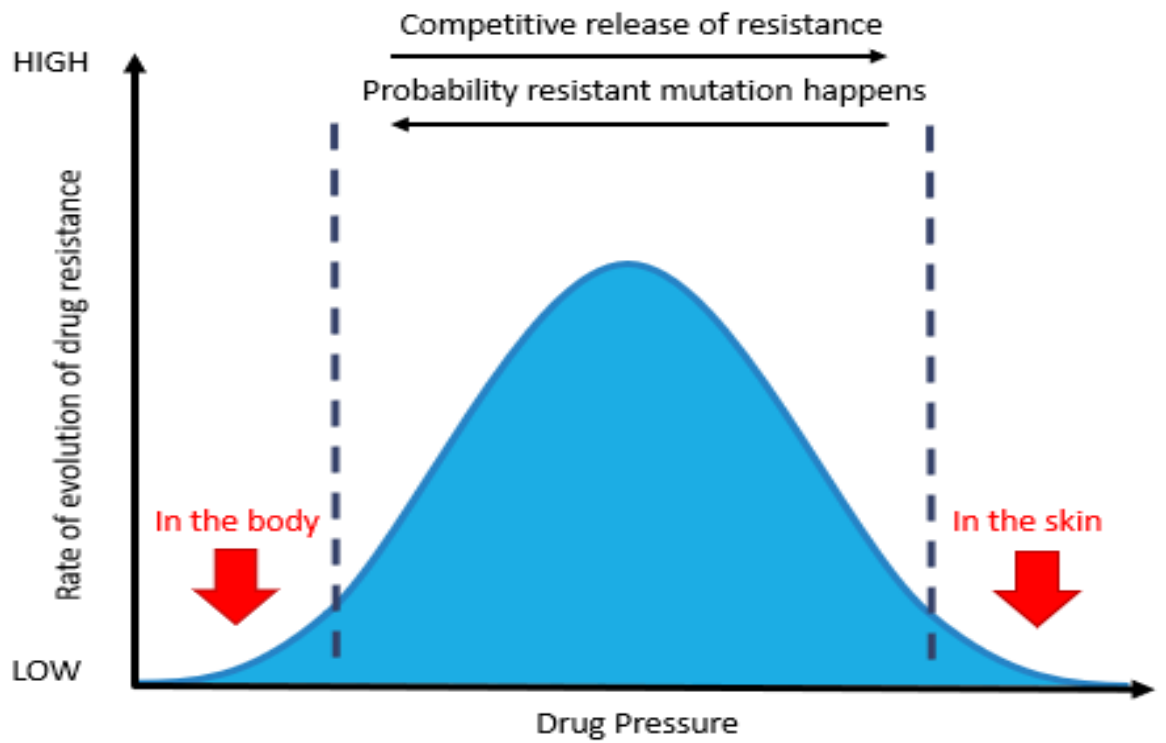
ANCOVA, Intent to Treat (ITT) Population, Observed Cases
*$P \leq .0001$; †$P \leq .001$; ‡$P \leq .01$.



1. Raoof TJ et al. *J Am Acad Dermatol.* 2019; doi: 10.1016/j.jaad.2019.05.078. [Epub ahead of print]
2. Gold LS et al. *J Am Acad Dermatol*. 2019;80(1):168-177.

TOPICAL VS ORAL ANTIBIOTIC USE

IMPLICATIONS FOR MINOCYCLINE 4% FOAM



	Plasma C_{max}	Skin (epidermis) C_{max}	Skin/Plasma Ratio
FMX101 4%	1.3 ng/mL	560,000 ng/g	>400,000
Oral Minocycline	1000 ng/mL	8000 ng/g	8

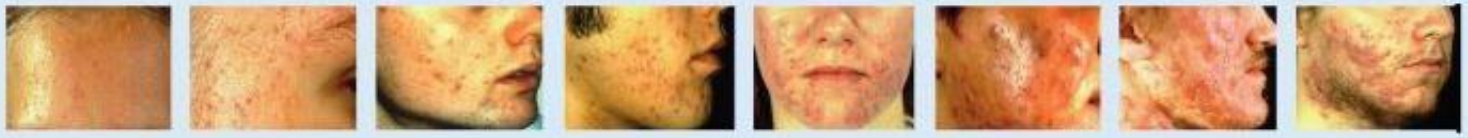
Therapeutic options for Moderate to Severe Acne

Therapy	Notes
Combination therapy	Oral antibiotics + topical retinoids ± BPO First line
Hormonal therapy	Women with moderate to severe acne, especially if contraception is desirable Used in combination with other modalities
Isotretinoin	Severe and/or recalcitrant acne Teratogenic; stringently regulated for women with childbearing potential

Gollnick H et al. *J Am Acad Dermatol*. 2003;49(1 suppl):S1-S37.

Acne Treatment Algorithm

Acne treatment algorithm

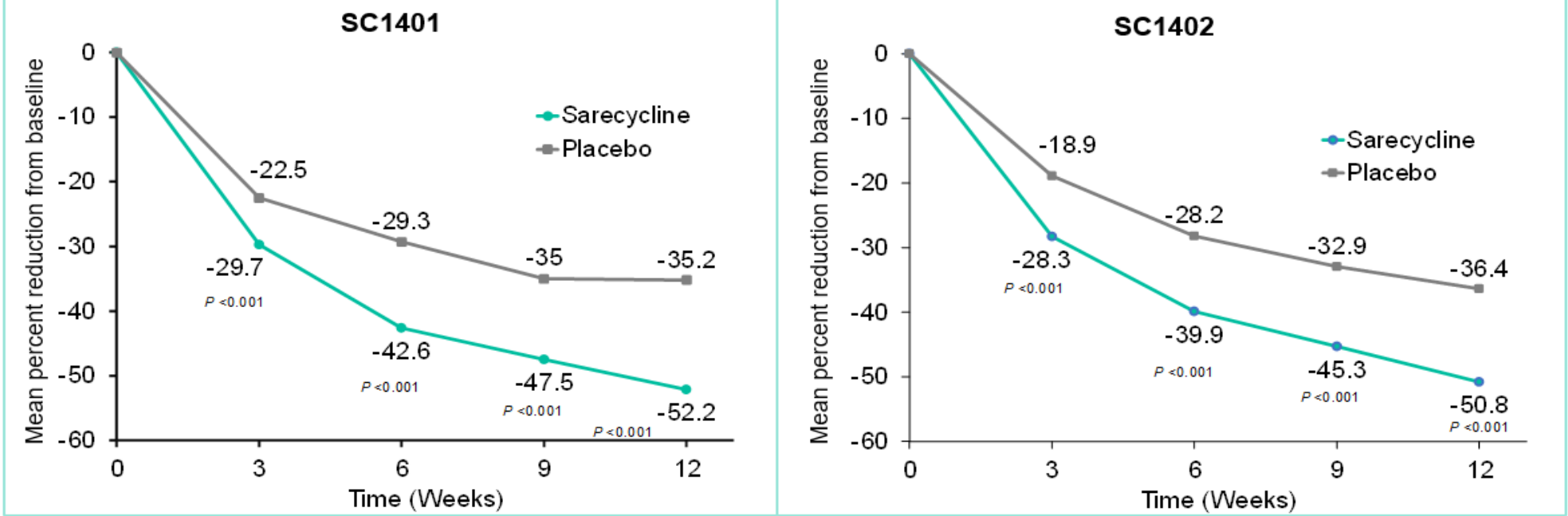


	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular†	Nodular/conglobate
First choice‡	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid +/- BPO	Oral antibiotic + topical retinoid +/- BPO	Oral isotretinoin§
Alternatives‡	Azelaic acid or salicylic acid	Alt. topical antimicrobial agent + alt. topical retinoid or azelaic acid¶	Alt. oral antibiotic + alt. topical retinoid +/- BPO	Oral isotretinoin or alt. oral antibiotic + alt. topical retinoid +/- BPA/azelaic acid¶	High-dose oral antibiotic + topical retinoid + BPO
Alternatives for females‡,#	See first choice	See first choice	Oral anti-androgen†† + topical retinoid/ azelaic acid¶ +/- BPO	Oral antiandrogen†† + topical retinoid +/- oral antibiotic +/- alt. antimicrobial	High-dose oral anti-androgen†† + topical retinoid +/- alt. topical antimicrobial
Maintenance therapy	Topical retinoid		Topical retinoid +/- BPO		

Sarecycline vs Placebo in Acne Vulgaris Inflammatory Lesion Count Reduction (%)

Sarecycline 1.5 mg/kg/day QD (n=1002) vs Placebo – 12-Weeks
Age Range 9-45 Years / ~25% Non-White Skin / 85% Moderate Severity

Mean Percent Change in Inflammatory Lesion Count from Baseline to Week 12



- Mean absolute reduction in lesion count was statistically significant at Week 12 and as early as Week 3

Moore A et al. *J Drugs Dermatol.* 2018;17(9):987-996.

MAY BE TAKEN WITH OR WITHOUT FOOD

Practical Considerations with Sarecycline

Concept of Narrow Spectrum Tetracycline

POTENTIAL CONSIDERATIONS RELEVANT TO CLINICAL PRACTICE

EFFICACY FOR ACNE VULGARIS
Inflammatory AND Comedonal Lesions
Face & Trunk

ADVERSE REACTION PROFILE
GI Side Effects / Photosensitivity /
Vaginal Candidiasis

ANTIMICROBIAL SPECTRUM
Reduced Risk of Antibiotic Resistance vs Some Organisms (especially Gram -)

REDUCE SELECTION OF GRAM (-) BACTERIA AND MULTI-DRUG RESISTANCE

Zhanel, George, et al. "Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris." *Antimicrobial agents and chemotherapy* 63.1 (2019).

Optimizing Use of Oral Antibiotic Therapy in Acne

A continued work in progress

Most data available with tetracyclines – "dual mechanisms"

Use in combination with *maximized topical regimen*

Incorporate benzoyl peroxide AND topical retinoid in regimen

AVOID antibiotic monotherapy or "unopposed" antibiotic use

Limit duration of oral antibiotic therapy *as best as possible*

Assess every 3 months

"Maximum" suggested ("hoped for") duration: 3 - 6 months

Consensus agreement: "…a subset of patients for whom alternative therapies are inappropriate and who may require a longer course of antibiotics even while taking topical medications."

1 Del Rosso JQ, Kim G. Derm Clinics. 2 Zanglein A, et al. J Am Acad Dermatol. 2016;74:945-973. Del Rosso JQ. Sem Cut Med Surg.

Adult Female Acne

Trigger Factors

Internal factors

Hormones

Genetic background

Endocrinopathies: POC

External factors

Cosmetics, Stress

Smoking

Sun

Medications (eg, benzodiazepin)

Williams C, et al. *Am J Clin Dermatol*. 2006;7:281-290..

Patient Factors to Consider when Treating Adult Female Acne

Clinical aspects: lesions type

Potential slow response to treatment

Maintenance therapy

Likelihood of high adherence

Emotional/psychological impact

Child- bearing potential

Potential of older skin to irritation

Cosmetic use

Photoaging/damage

Skin type

Ethnicity

Smoking

Dreno B, et al. *JEADV.* 2013;27:1063-1070.
Williams C, et al. *Am J Clin Dermatol.* 2006;7:281-290..

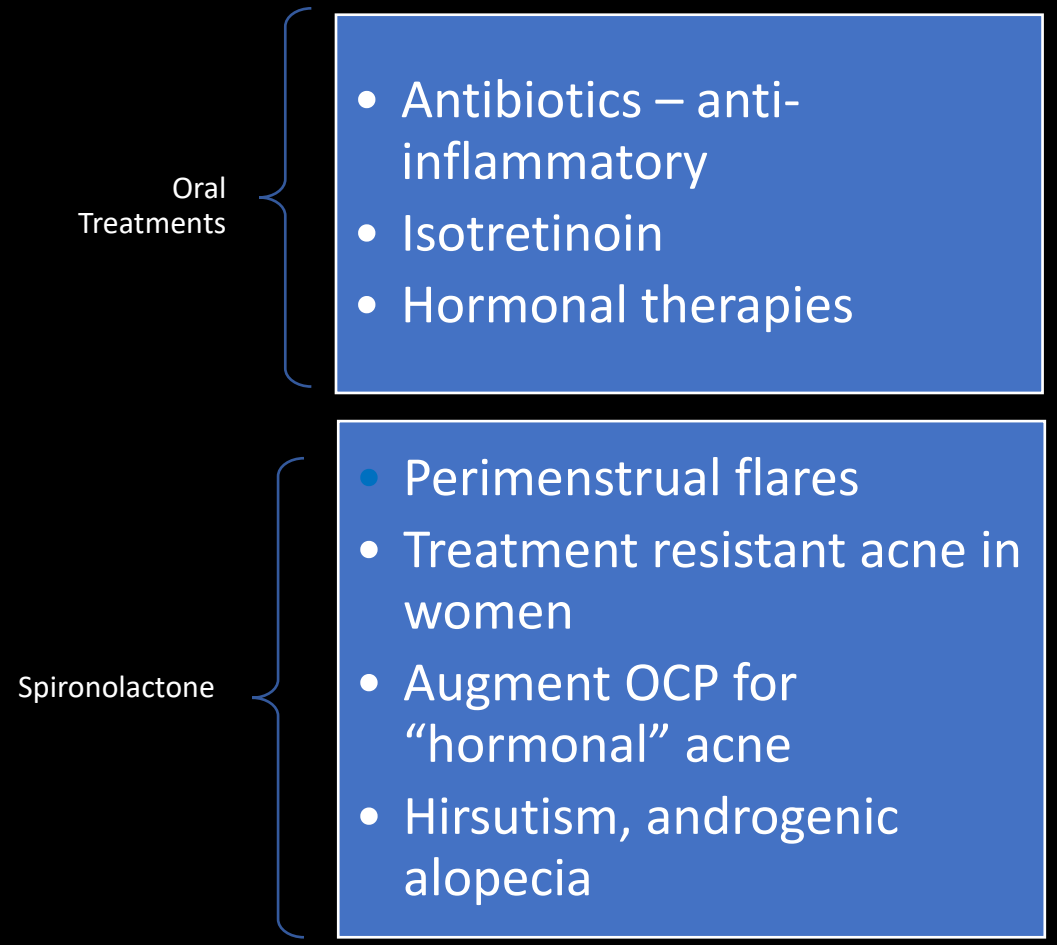
Adult Female Acne

Topical Treatments

Retinoids – first line, many formulations – photodamage,PIH	Benzoyl peroxide – no resistance – inflammatory lesions	Sulfone (Dapsone) – anti-inflammatory – vehicle
Azelaic acid – antimicrobial – anti – tyrosinase (PIH)	Antibiotics – fixed combinations – synergistic effects	Sodim sulfacetamide, sulfur

Diane S. Berson, M.D.

Adult Female Acne



Diane S. Berson, M.D.

Acne Laser & Light Therapy

Use of combination therapy is pathogenetically warranted, especially for patients who are genetically prone to the formation of post-acne scarring

A 650 microsecond 1064nm laser is effective at stimulating neocollagenesis without the risk of excessive heating of the skin or pain

Pathological scarring in acne was not observed. Improvement of preexisting acne scars was noticeable.

Combination therapy of a 650 microsecond 1064nm laser and isotretinoin at a low dosage (0.2-0.3 mg/kg/day) is safe, effective, and tolerable.