Systemic Acne Treatment
Evidence Synthesis and Knowledge Translation for Clinical Dermatology: A Cochrane Skin Group Perspective (S017)

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Caroline Sousa Costa, MD, PhD, IFAAD
Member (review author) - Cochrane Skin Group
Dermatologist, International member – AAD and EADV
Member - Brazilian Society of Dermatology, Brazilian Society of Dermatologic Surgery
Professor of Dermatology – Federal University of Piauí, Brazil

DISCLOSURES:
I do not have any relevant relationships with industry.

Systemic Acne Treatment – Presentation Topics

1 – Background
2. Oral antibiotics
3. Hormonal agents
4. – Isotretinoin

Systemic Acne Treatment – Background - When is it used?

- Moderate to severe cases:
  - inflammatory lesions (papulopustular and nodulocystic acne);
  - higher risk of scarring;
  - less frequent and severe forms, acne conglobata and acne fulminans;
  - proneness to psychological sequelae and negative impact on QoL.

Systemic Acne Treatment – Oral antibiotics

- Most prescribed systemic acne treatment in daily clinical practice;”
- Mainstay: second-generation tetracyclines (minocycline, doxycycline, lymecycline) - single daily dosage, better adherence;”
- Limit duration of therapy to 3-4 months; concurrent use of other topical treatment - benzoyl peroxide (BP), fixed-formulation BP + retinoid, retinoid, azelaic acid;”
- Mechanism of action: - Cutibacterium acnes growth and proliferation;
  - anti-inflammatory (neutrophil chemotaxis, cytokines and matrix metalloproteinases release);”

Systemic Acne Treatment – Oral antibiotics

- Tetracyclines-class, adverse effects”:
  - gastrointestinal
  - photosensitivity
  - gram-negative folliculitis
  - pharyngitis
  - Candida vaginitis
  - cutaneous and intestinal dysbiosis
  - new-onset inflammatory bowel disease (IBD)
  - vertigo, headache and pseudo tumor cerebri syndrome
  - greyish blue tissues pigmentation (minocycline)
  - cutaneous rash

- Restrictions to use: pregnancy; breastfeeding; children < 8 yo (azithromycin and erythromycin - second-line therapy, off-label for acne).”

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY
Caroline Sousa Costa, MD, PhD, IFAAD
S017 Systemic Acne Treatment

Systemic Acne Treatment – Oral antibiotics

- Regarding evidence on oral antibiotics for acne, it is true that:
  1) There is a robust body of evidence to support the use of tetracycline and doxycycline instead of the other drugs from tetracyclines class;
  2) With basis on data from systematic reviews, extended-release tetracyclines formulas are safer and more efficacious than other tetracyclines preparations;
  3) According to RCTs (randomized clinical trials), sarecycline, a fourth-generation tetracycline, is more efficacious and safety than the second-generation ones;
  4) There is still a lack of high-certainty evidence to support optimal duration of therapy; most efficacious dosage regimens (i.e. q.d versus b.i.d; higher, full therapeutic dose, versus lower dose and tapering doses).*

Systemic Acne Treatment – Hormonal Treatment

- Combined oral contraceptives (COCs): used for teenager or adult women - early added to first-line acne treatment regimens (contraception or menorragia);*
  - Mechanism of effect: all COCs sebogenesis due to androgenic stimulus:
    - estrogen: ↑ free testosterone serum levels; ↑ LH secretion; ↑ androgen production, ↓ SHBG serum levels;
    - progestin: competitive blockage - androgen receptor sebaceous cells (only fourth-generation***);

- Spironolactone: originally to systemic arterial hypertension and heart failure management; since 1980’s – acne, alternative for teenager and adult women (off-label);*
  - Antiandrogen tailored approach - used alone or combined with COCs in the acne therapeutic regimen (concurrently with topical agents alone or plus systemic antibiotics).***

- Adverse effects - detailed medical history and blood pressure measurement:
  - risk of venous thromboembolic events
  - nausea, breast enlargement, headaches, and weight gain
  - risk of myocardial infarction and stroke (>45 yo, DM, hypertension or smoking)

**Adverse effects: abdominal pain, polyuria, fatigue and lethargy.

- Blood potassium measurements: unnecessary before and during therapy for young healthy acne patients;
  - Avoid pregnancy - risk of feminization of the male fetus (use of COCs helps).***

- Systemic Acne Treatment – Oral antibiotics

- Daily dosage: 100 to 200 mg/daily.*
  - Starting: 25 to 50 mg/day, escalating the dosage X 100 mg/day or greater, tapering when adverse effects present;***
  - Mechanism of action: antisebogenic activity (competitive blockage of the androgen receptors inside sebaceous cells of the skin, especially on the face).***
Systemic Acne Treatment – Hormonal Treatment

- Regarding evidence on hormonal treatment for acne, it is true that:
  1. There is a robust body of evidence to support the use of spironolactone, alone or combined with COCs, to treat teenage and adult women;
  2. There is not high-certainty evidence of the superiority of COCs containing progestins with antiandrogenic activity, such as cyproterone acetate, drosperine, or drospirenone, and danazol;
  3. According to RCTs (randomized clinical trials), COCs improve acne, but their efficacy and safety for acne in comparison to other systemic treatments is still a knowledge gap;
  4. There is a research gap of RCTs on effectiveness of spironolactone for acne, compared to oral antibiotics, COCs and isotretinoin.

Systemic Acne Treatment – Isotretinoin

- Isotretinoin (13-cis retinoic acid) – the single one systemic acne treatment used as monotherapy;
- FDA approved for severe recalcitrant acne since 1982;
- According to guidelines and consensus experts: also recommended for treatment-resistant moderate acne, and when there is physical scarring or significant psychosocial distress;
- Conventional daily dose – 0.5 mg/kg to 1 mg/kg, taken with meal.

Systemic Acne Treatment – Oral isotretinoin

- Regarding evidence on oral isotretinoin for acne, it is true that:
  1. There is a robust body of evidence to support the delay of superficial cosmetic procedures, biopsies, and dermatological surgeries without involvement of muscle planes until 6 months after the end of the therapy.
  2. With basis on data from systematic reviews, a causal link between isotretinoin use and serious psychiatric adverse events may exist.
  3. The best therapeutic regimen, cumulative dose and duration of therapy in order to achieve better efficacy outcomes and less adverse effects are still a gap in knowledge about isotretinoin.
  4. According to data from systematic reviews, laboratory monitoring (including cell blood counting, CPK, lipid and hepatic profile) should be performed monthly during treatment.

Systemic Acne Treatment – Evidence synthesis conclusion

- More RCTs on all systemic interventions for acne are still necessary:
  - well-designed, in accordance to CONSORT - on the top priorities on acne research!

MANY THANKS!

carolinencosta@terra.com.br
http://orcid.org/0000-0003-0281-6890

"Love Dermatology, make it one of the reasons of your life, and you will always have a reason to live." Prof. Sebastião de Almeida Prado Sampaio