ROSACEA - IMMUNOMODULATION BY ANTIBIOTICS, LASER THERAPY AND NANOTECHNOLOGY
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HEALTH AND BEAUTY

BREAKING NEWS

First impressions

First impressions

LAST
SKIN = The first aspect evaluated when we meet someone...
1. History,
2. Epidemiology,
3. Quality of Life,
4. Associated diseases,
5. Pathogeny,
6. Holistic approach of rosacea,
7. Treatment - immunomodulatory aspects,
8. Conclusions.
HISTORY OF ROSACEA

• images in Louvre from 15th century.


• psychiatric illness and alcoholism = causes of rosacea,

• facial erythema = social stigma.


Definition / signs / symptoms

- chronic inflammatory skin disease,
- erythema, papules, telangiectasia, edema, pustules, or a combination (1)
- central face - cheeks, forehead, chin, and nose (2).
- facial flushing, stinging, pain, burning sensations.


Epidemiology - Rosacea

- Prevalence = **1.5% to 10%** - northern European countries (1,2,5)
- Prevalence = **5%** - USA (3,4,5)

5. BE Elewski et al 2011.
Classification

- erythematotelangiectatic (1), papulopustular (2), phymatous (3), and ocular (4),

- the severity = 1 (mild), 2 (moderate), or 3 (severe).


Quality of life can be defined either by the absence of disease or through productive and enjoyable life.

1984 Calman :,, Quality of life is present when hopes are appropriate with individual experience,,,
• skin disorders have a negative impact on the psychological and emotional health,
• depression,
• a decreased sense of body image and self-esteem,
• sexual and relationship difficulties,
• a general reduction in quality of life.


Experience of patients with rosacea (1-4)

- embarrassment (70%),
- low self-esteem (75%),
- frustration,
- impaired social functioning,
- social and professional isolation.


ROSACEA - CARDIOVASCULAR DISEASES

- High total cholesterol (>200 mg/dL), LDL (>130 mg/dL) and CRP (>0.8 mg/L) levels,
- A family history of premature CVD,
- A history of smoking and alcohol consumption,

**CVD - significantly more common in the rosacea patients compared to controls.**

• a higher risk of cardiovascular comorbidities - hypertension, dyslipidemia, coronary artery disease (1-3)

• rosacea severity related to cardiovascular comorbidities (3).


ROSACEA AND DIGESTIVE DISORDERS

- inflammatory bowel diseases,
- ulcerative colitis,
- Crohn’s disease,
- celiac disease,
- SIBO,


Comorbidities - autoimmune diseases

- Clustering of autoimmune diseases in patients with rosacea
- A Egeberg, PR Hansen, GH Gislason, JP Thyssen, J Am Acad Derm, DOI: [http://dx.doi.org/10.1016/j.jaad.2015.11.004](http://dx.doi.org/10.1016/j.jaad.2015.11.004)

- **women** = rosacea is associated with T1DM, celiac disease, multiple sclerosis, rheumatoid arthritis.
- **men** - rosacea is associated with rheumatoid arthritis.
PATHOGENESIS...UNCLEAR...

- **Neurovascular** changes, stimulation by various **microbes**, abnormal function of **innate immunity** in the skin,


- **Vascular** abnormalities, dermal matrix degeneration, **environmental** factors, **microorganisms**,

Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition
IMMUNE MODIFICATIONS - INNATE...

- disruption of epidermal barrier (direct effect of Demodex folliculorum),
- increased expression of TLR2 (consecutive production of IL-8, IL-1β, TNF-α),
- activation of KLK5 (Kallikrein-5) - lithic effects and production of cathelicidin LL-37 (with effects on immune modulation and inflammation),
- serum levels of vitamin D = higher.
TLR-2 and KLK-5

- the expression of TLR-2 is increased (acne, rosacea),


- TLR-2 (activated by external stimuli or triggering factors) - effects on keratinocytes (proinflammatory cytokines and chemokines).
• skin samples from patients with rosacea exhibit increased gene expression for proinflammatory cytokines (IL-8, IL-1β, and TNF-α).


• IL-8 = chemotaxis of neutrophils in the skin / the release of proteases including cathepsin G, elastase, and protease-3.


• IL-1β and TNF-α have an additional role as angiogenic factors VEGF.

• Demodex / Ultraviolet radiation = activated the expression of TLR-2.

• TLR-2 regulates the release of KLK-5 (disrupts the epidermal barrier/activates the cleavage of hCAP-18 into LL-37)


• the lesional skin of patients with rosacea express more KLK-5 than the skin of healthy controls.

LL-37/Cathelicidin

• increased expression of cathelicidin in the epidermis,


• only a single cathelicidin gene, cathelicidin AMP (CAMP),


• the propeptide of CAMP = LL-37,

LL-37 AND ROSACEA

• higher levels of LL-37 than controls,


• the higher molecular weight forms of LL-37,


LL-37 FUNCTIONS

- antimicrobial activity,
- immune modulation, neutrophil chemotaxis, induction of cytokine and chemokine release from mast cells.


- stimulates tissue inflammation, vasodilation, and angiogenesis in rosacea,
- facilitates the degranulation of mast cells (enhances the expression of MMP-1, MMP-9, and IL-6).
Vitamin D

• serum vitamin D levels were found to be higher than those of the control groups.

• the pathogenesis of rosacea appears to differ somewhat from that of other chronic cutaneous inflammatory diseases.

Dysregulation in Adaptive Immunity

• T Cell-Mediated Responses

1. increase of CD4+ over CD8+ T cells among the T cell population,
2. upregulation of Th1 and Th17.

Buhl, T.; Sulk, M.; Nowak, P.; Buddenkotte, J.; McDonald, I.; Aubert, J.; Carlavan, I.; Deret, S.; Reiniche, P.; Rivier, M.; et al. Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways. J. Investig. Dermatol. 2015, 135, 2198-2208.

• B Cell-Mediated Responses

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Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition
Changes
NEXT EXIT

CHANGE AHEAD

Presented in ICoMi 2017
The 3 steps in Rosacea - systematic approach

• ,, the team for rosacea ,, 
• Nobody is perfect, so we need a team!
• If YOU are NOT a dermatologist, please refer to a colleague in order to have an holistic approach!
YOU - Step 1

- Consultation (history / type and severity of rosacea / trigger / associated conditions / contraindication for laser),
- Assess patient concerns and expectations,
- Principles of skin care (gentle cleansing, moisturizing, photoprotection),
- Principles of diet,
- Plan of action,

TEAM - step 2

• Investigation for associated conditions / associated diseases.
ROSACEA AND IMAGISTIC

- bioengineering techniques (scanning laser doppler, video microscopy, skin surface temperature, pH, colorimetry, digital photography)
- noninvasive tool,
- first evaluation of the patient,
- monitoring the treatment.
YOU - step 3

• Diet = alimentary journal,
• Skin care = principles / photoprotection / make up,
• Local and general treatment,
• EBD treatments = IPL, NIR, vascular laser.
• educate and monitor for possible triggers,
• individual risk factor profile - "journal of patient", - 4 weeks.

The goals of treatment

• Healing and prevention of active lesions,
• Prevention of scar,
• Improving the quality of life of patients,
• Decreasing the negative psychological impact.
EVIDENCE...

• **High quality evidence** = topical azelaic acid, topical ivermectin, brimonidine, doxycycline and isotretinoin.

• **Moderate quality evidence** = metronidazole and oral tetracycline.

• **Low quality evidence** = low dose minocycline, laser and intense pulsed light therapy.

Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel


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Treatment goals in rosacea should be based on discussion of severity and the psychosocial burden.

The majority of panellists agreed that they would treat an individual feature when it bothered the patient, regardless of severity.
The triad of rosacea care

- Education,
- Skin care,
- Treatment.

BE Elewski et al 2011.
Principles of treatment - holistic approach

- Life style,
- Sun exposure,
- Diet,
- Skin care,
Principles of treatment-holistic approach

- Local treatment,
- General treatment,
• Some of the most efficient drugs used are characterized by immune modulation properties.
Topical Azelaic Acid

- inhibit the expression of KLK-5 in cultured keratinocytes
- treatment with azelaic acid induce the decrease of expression of KLK-5 and cathelicidin mRNA,


- anti-inflammatory properties,
- inhibiting the production of ROS and the UVB-induced upregulation of proinflammatory cytokines (IL-1, IL-6, and TNF-α).

**Doxycycline....**

- **inhibits MMP-9 (production, activity),**
  

- **inhibits other MMPs (conformational changes and functional abnormalities),**
  

- **indirectly inhibit the activation of KLK in vitro,**
  
Doxycycline....

- inhibit the NO synthase activity (inhibit vasodilatation),
- anti-inflammatory effects.


- sub-antimicrobial-dose decreased inflammatory lesion counts and erythema scores,


- a sub-antimicrobial-dose decrease the release of inflammatory cytokines and downregulate the production of ROS.

Macrolides...

- immunomodulatory activities,
- reducing chemotaxis and pro-inflammatory cytokine production,
- decreasing adhesion molecule expression,
- decreasing ROS production.
Immune modulation concept,

- It must be pointed out that immune modulation is the suppression of inflammation and immune hyperactivation without causing immune depression (immunosuppression).


- Interest in the immunomodulatory effects of macrolides began in the 1960s with the observation that the 14-member antibiotic, troleandomycin, was an effective “steroid-sparing” agent when used to treat patients with severe asthma.

Non antimicrobial effects,

- modify host functions apart from the antimicrobial potency.
- directly influence phagocyte and lymphocyte function, and chemotaxis.
- effects on the generation and release of various cytokines involved in the inflammatory process.

Rosacea = laser and light therapy


Laser treatment in rosacea

- the cause and pathogenesis of rosacea = unknown,
- FACT = strong vascular component.

Laser treatment...

• The best = **NO**!

• The best for moment / patient / health status / ,,problem,, = **YES**!
History....

- Vascular laser therapy for rosacea began in the early 1980s with the argon laser (488-514 nm).
Laser treatment - effects

- ablation of vascular anomalies (destroy small vessels and reducing the symptoms),
- decreasing erythema and telangiectasia, and the flushing symptoms,
- reorganization and remodeling of dystrophic dermal connective tissue,
- strengthening of the epidermal barrier.
- interruption of the release of inflammatory mediators.


Type-1 rosacea = erythematototelangiectatic type ETR

- Pulsed dye laser (PDL, 585-595 nm),
- Potassium titanyl phosphate (KTP, 532 nm),
- Intense pulsed light (IPL, 500-1200 nm),
- Dual-wavelength lasers,
- Long-pulsed neodymium:yttrium-aluminum-garnet laser (Nd:YAG, 1064 nm)
Papulo-pustular rosacea

- long-pulsed 1064-nm neodymium: yttrium-aluminum-garnet laser (LPND),


- review of laser and rosacea

Nd:YAG and Rosacea

- destruction of the follicular unit by Nd:YAG,


- Nd:YAG penetrate deeply / treatment of deeper vessels.

- more safely for darker skin,

- the risk for postinflammatory hyperpigmentation is very low.

reduction in inflammatory lesions.


a reduction in the dose of concurrent oral antibiotic therapy has been possible after PDL treatment.

• NOT cure / YES control!
• NOT favorable effects, overnight,
• NO best treatment!
My way...

- NOT laser treatment at the first visit,
- Complex and holistic evaluation,
- Change the life style of patient = diet, sun exposure, skin care,
- Local and general treatment,
- Indication and contraindication for laser,
- Follow up.
Practical approach....

• **NOT** laser treatment at the first visit,

• Complex and holistic evaluation,

• Change the life style of patient = diet, sun exposure, skin care,
• Local and general treatment,
• Indication and contraindication for laser,
• Follow up.
Immunity = important role in pathogeny,
Holistic approach (education, skin care, local and systemic treatment, vascular laser and nanotechnology),

Immunomodulation (local and general treatment, laser, nanotechnology) = FUTURE!!!