NOVELTIES IN THE MANAGEMENT OF ROSACEA

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Summary

Rosacea is an inflammatory disease with centrofacial localization and a prevalence between 1 and 22%, and it predominantly affects women. Clinically, it is manifested by erythema, telangiectasia, papules and pustules, concomitantly or in independent stages. Rosacea features 4 stages of evolution: stage I erythematotelangiectatic, stage II papulopustular, stage III phymatous and stage IV with ocular damage. The following are among the factors involved in the aetiology of the disease: age, skin phototype, gender, alcohol consumption, exposure to UV radiation, vascular, digestive and psychoemotional factors.

Analysing the studies published in the specialty literature for a period of 6 years, I have synthesized the therapeutic realities and the main therapeutic lines recommended by the new international guidelines for rosacea acne.

Treatment of rosacea is complex and varies depending on the stage of the disease. The use of SPF50 photoprotective creams is recommended for all stages of the disease. In topical treatment, a beneficial effect can be obtained by applying azelaic acid gel 15%. The most commonly used systemic treatments are antibiotics, more frequently in the cycline class for a period of 3 months and retinoids. Modern methods such as Nd:YAG laser and IPL are also easy to access and beneficial for the treatment of erythematous lesions.

Treatment of rosacea needs to be individualized, with several local and systemic therapeutic lines available.

Key words: *rosacea, etiology, risk factors, management, treatment.*

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Introduction

Rosacea is an inflammatory condition of the face, commonly found in dermatological pathology, having a recurrent, sometimes transient, sometimes persistent character, in the absence of proper treatment. It is clinically characterized by polymorphic lesions, with erythema, telangiectasia, papules and pustules occurring simultaneously or in independent stages. Most commonly rosacea starts after the third decade of life in women (F:M ratio is 3: 1), with phenotype 1 and 2, with irritable and xerotic skin. (1) The term "rosacea" dates back to the Middle Ages, and the 19th century French writers, such as Balzac and later Proust, admirably described the red faces, which always announced a difficult, violent temper or were the sign of the working class. (2)

Epidemiological studies show that rosacea affects about 10% of the population, and in Romania up to 40% of women are diagnosed with this condition. The onset of rosacea takes place at about 30 years of age, with a peak incidence at 30-40 years and a 3-fold higher frequency in women. (3)

Rosacea is a condition with a significant impact on the patients' quality of life, as facial erythema is sometimes perceived as a disability in terms of social relationships. Treatment is complex and difficult, being adapted for each stage of the disease. In addition to local and systemic treatment, general skin care measures, which have special requirements, are also extremely important. If a-adrenergic receptor agonists, metronidazole, neuronal calcium inhibitors associated with laser therapy are

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recommended for the erythematotelangiectatic form, in the more advanced, papulopustular forms, antibiotic or retinoid treatment is recommended up to low-dose corticosteroids in rosacea fulminans. In the rosacea forms affecting the eyes, besides the dermatological therapy, the intervention of an ophthalmologist with specific therapy is also necessary. Low-dose retinoids and surgery are required in the phimatous form. (1, 10) In order to achieve therapeutic success, the combined use of local, systemic and modern treatment methods is recommended.

The aim of the paper is to synthesize the etiopathogenic and therapeutic novelties that allow a good management of rosacea.

Material and method

I have analysed 3 reviews, the updated treatment guidelines and other clinical trials published in the literature over the last 3 years (2016 Ţ 2018). I have used Pubmed and Medscape as search engines by introducing keywords such as "rosacea etiopathogenesis", "risk factors", "rosacea treatment guide", "modern rosacea therapies".

Results and discussions

Plewig and Kligman classify rosacea in 4 evolutionary stages: **Stage I** (erythematotelangiectatic) with persistent erythema and telangiectasia, **Stage II** (papulopustular) and **Stage III** (rhinophyma) with intense persistent erythema, dense telangiectasia, pustules and nodules (Figure 1). The lesions are associated with hyperplasia of the sebaceous glands at the level of the nose. Sebaceous gland pores are dilated and sebum plugs are removed by compression. **Stage IV**, with ocular damage, occurs in both sexes more frequently in the age group 60-70 years. Ocular rosacea may be asymptomatic in the beginning, then it progresses with pruritus and local burning sensation. The most common ocular manifestations are blepharitis, dysfunction of the meibomian glands (chalazion formation) and conjunctival erythema (4). Although rare, rosacea keratitis is a severe condition that can lead to corneal ulceration (5, 6). **Other particular forms** of rosacea are granulomatous rosacea, rosacea fulminans, steroidal rosacea, and drug-induced rosacea. The etiopathogenesis of this condition is still incompletely elucidated, but several factors involved in the onset and maintenance of the disease are known.

The **vascular factor** is of great importance because transient erythema (flush) is the initial symptom, triggered by heat, alcohol, spice, and exposure to emotional factors. Venous dilatations with increased parietal permeability occur as early as onset, and the topography of the lesions coincides with the facial vein drainage area (6).

The **inflammatory factor** occurs through the proliferation of the pro-inflammatory cathelicidin-related peptides (7), a family of proteins with a role in the antimicrobial defence that are normally present on the skin and overexpressed in rosacea patients. They promote and regulate leukocyte chemotaxis, angiogenesis and expression of extracellular matrix components. LL-37 is the only antimicrobial peptide derived from cathelicidin identified in humans that has been shown to exhibit a broad

Figure 1 Papules-pustular rosacea in a patient with chronic C virus hepatitis.

spectrum of antimicrobial activity. This cathelicidin is typically found in neutrophils, and in the case of rosacea patients LL-37 is generated in the epidermis by an abnormal serine protease action. (8)

Genetic research has led to the identification of a gene defect localized on an arm of chromosome 6 and three HLA alleles significantly associated with rosacea: HLA-DRB1 03: 01, HLADQB1 02: 01, HLA-DQA1 05: 01 (9).

Environmental factors include exposure to extreme hot/cold temperatures. The main mechanism by which ultraviolet rays interfere with the pathogenesis of rosacea is the induction of reactive oxygen species and thus the degradation of the extracellular matrix, favouring the development of the inflammatory process. UVB increases the synthesis of endothelial growth factor in keratinocytes, and UVA stimulates degradation of dermal collagen. It also increases the amount of skin pro-inflammatory mediators (IL1β, IL6, IL10, TNFα, CXCL8).

CXCL8 plays a role in maintaining recruitment of neutrophils at the site of inflammation (10).

Demodex folliculorum is an acarian that lives in the face areas rich in sebaceous glands (forehead, cheeks, nose, eyelid edge) and plays a sure role in the etiopathogenicity of the disease.

The involvement of this acarian is more important in the granulomatous rosacea (6). There are few dermatoscopic data on Demodex, the main dermatoscopic aspect are Demodex tails and oval or triangular follicular plugs. (11)

Bacillus oleronius is a commensal bacterium of the sebaceous glands that can trigger an exaggerated response in rosacea patients, being considered to play a role in triggering the disease. It is usually sensitive to the antibiotics used to treat rosacea. (12)

Helicobacter Pylori is a factor that stimulates the development or maintenance of rosacea. There are some fundamental arguments regarding this relationship, namely: the typical spring relapse of rosacea and peptic ulcer, the frequency of gastrointestinal problems in rosacea patients, and the efficacy of metronidazole and several antibiotics in both Helicobacter pylori infection and in rosacea. Rosacea may be considered the primary extragastric manifestation of H pylori infection. (13) **Other factors** recognized in rosacea are the psychological factor and the vitamin B2 deficiency.

Treatment is difficult, complex and varies depending on the stage of rosacea. For all clinical forms, photoprotection with SPF 50 creams is recommended, with both UVB and UVA blocking (14). As a general measure, it is advisable to identify and avoid risk factors by adopting a hygienic-dietary regimen without food and drink with vasodilatory effects, avoiding exposure to solar radiation and heat sources. Treatment of rosacea needs to be individualized and several local and systemic therapeutic lines are currently available.

Local treatment consists of applications of **azelaic acid gel 15%**. It is a saturated dicarboxylic acid with antimicrobial activity, which reduces the inflammatory response and inhibits the proliferation of keratinocytes. It is applied twice daily for 3-6 months. **Metronidazole gel** or **cream 0.75-1%,** 1 application/day, has antibacterial and antioxidant action, suppressing the production of reactive oxygen species by neutrophils, molecules that favour inflammation. **Brimonidine gel 0.33-1%** (an alpha adrenergic vasoconstrictor initially used in the treatment of glaucoma), 1 application/day, has vasoconstrictor action over a period of 6-8 hours. The most common side effects are burning sensation, severe reactive erythema and contact dermatitis. (15)

Calcineurin inhibitors cream 0.1%, 2 applications daily for 4 weeks, are effective for and well tolerated by patients with mild to moderate inflammatory lesions. (16) In ocular damage, topical treatment consists of artificial tears, warm compresses, eyelid hygiene, fusidic acid (ointment) applied to the palpebral edges 1x/evening for 4 weeks, steroids (fluorometholone 0.1%, prednisolone 0.5%) 4x1 drops/day. (17)

In January 2017, the FDA approved **oxymetazoline hydrochloride** cream 1%, 1 application/day for 1 month. This is an alpha-1 adrenoceptor agonist that reduces facial erythema by vasoconstriction (18). It should be used with caution in patients with severe or unstable cardiovascular and neurological disease

and those with glaucoma because alpha-adrenergic agonists may affect blood pressure. (19)

Ivermectin cream 1% is a new agent indicated for the local treatment of inflammatory lesions in rosacea. By its broad spectrum anti-inflammatory and anti-parasitic properties, Ivermectin reduces the manifestations of the disease. It is applied locally 1x/day in the evening for 12-16 weeks. It shows few side effects, including pruritus, burning sensation and dry skin. (20)

It is advisable to avoid irritating products such as astringent solutions, menthol, camphor, waterproof cosmetics requiring removal solvents or products containing sodium sulphate. (14)

In systemic treatment, **antibiotics** have proven to be very effective. In the treatment of rosacea, doxycycline administered at doses of 100 mg/day or 200 mg/day has similar results but with higher adverse effects than the 40 mg/day dose. (21)

In a randomized clinical trial that looked at the response of erythema and telangiectasia to the selected antibiotic therapy, there was no difference between 250 mg clarithromycin twice daily for 4 weeks, then 250 mg once daily for 4 weeks versus doxycycline 100 mg twice daily for 4 weeks, then 100 mg once daily for 4 weeks. (21) Also, the comparison between oral azithromycin (500 mg three times a week for 4 weeks, followed by 250 mg three times a week for 8 weeks) and doxycycline 100 mg daily, has demonstrated equal efficacy in both therapeutic regimens. (21)

Tetracycline at a dose of 1-1.5g/day divided into 3-4 intakes, leads to symptom relief, then the dose is progressively reduced to 250-500 mg/day (5). Because of the risk of photosensitization during tetracycline therapy, it is advisable to avoid direct exposure to sunlight and ultraviolet radiation. Oral **Ivermectin** is effective at the single dose of 12 mg po in case of massive infestation with Demodex. (5)

1064 nm Nd:YAG laser is a complementary method in the treatment of rosacea. The wavelength is adapted for the treatment of vascular lesions due to increased haemoglobin absorption of this wavelength. A study published in 2017 compared the efficacy of Nd:YAG and PDL (Pulse dye laser) lasers in the treatment of rosacea-related nasal telangiectasia. Patients with rosacea who had erythema and telangiectasia in the nose were included. Each patient was treated with PDL on the left side of the nose and Nd:YAG on the right, three sessions at 4 week intervals. At the end of the treatment there were no significant differences between the groups, the overall improvement was similar. However, Nd:Yag induced a greater response at the level of the thick, dilated vessels, while erythema with mild telangiectasia was more responsive to PDL. (22) The luminous energy emitted by PDL is primarily absorbed by the oxyhemoglobin contained in the blood vessels, thus reducing the thermal destruction of other structures. Intense pulsed light (IPL 540-950 nm) is a safe and effective treatment especially for perilesional erythema in rosacea. (23) In a randomized study involving 9 rosacea patients the efficacy of IPL compared to PDL was evaluated using the same duration and exposure time. The treatment consisted of four sessions three weeks apart. Efficacy was assessed by the level of erythema, the melanin index, the subjective assessment of the physician and the patient satisfaction. The results of the study showed that there are no significant differences between IPL and PDL treatments; also there were no adverse reactions. (24)

In a case study, a post-steroid rosacea patient treated for 8 weeks with **tacrolimus** ointment 0.03% associated with oral anti-histamine 2x day for 2 weeks combined with 3 PDL sessions, experienced a significant reduction of the inflammatory response and an almost total remission of the facial erythema. Tacrolimus inhibits the initiation of cytokine transcription and T cell activation by binding tacrolimus molecules to immunophilins as well as blocking neuronal calcium (25).

Recent studies have demonstrated the possible effect of attenuation of the facial erythema of the **botulinum toxin**. It functions as a neuromuscular modulator at the level of the neuromuscular junction.

The intradermal injection of botulinum toxin is indicated especially for patients with refractory erythema, in the absence of a therapeutic response to other therapies. (23)

Conclusions

Rosacea is a centrofacial skin inflammation with a great impact on the quality of life of patients. Rosacea patients can experience frustration, reduced self-esteem, sometimes with social and professional isolation. Treatment of rosacea needs to be individualized, with more than one therapeutic line being available, both local and systemic, which should be standardized and applied depending on the disease stage. The avoidance of risk factors, the use of local, systemic treatments, as well as modern methods of laser treatment, favour the therapeutic success in rosacea.

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Conflict of interest
NONE DECLARED

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