

Rosacea: Pathophysiology, Differential Diagnosis and Treatment Modalities

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Abstract

Rosacea is a chronic cutaneous inflammatory disease that affects the facial skin. Clinically, rosacea can be categorized into papulopustular, erythematotelangiectatic, ocular, and phymatous rosacea. However, the phenotypic presentations of rosacea are more heterogeneous. Although the pathophysiology of rosacea remains to be elucidated, immunologic alterations and neurovascular dysregulation are thought to have important roles in initiating and strengthening the clinical manifestations of rosacea. In this article, we presented the possible molecular mechanisms of rosacea based on recent laboratory and clinical studies. We have also described the genetic predisposition for rosacea along with its associated diseases, triggering factors, and suggested management options in detail based on the underlying molecular biology. Understanding the molecular pathomechanisms of rosacea will likely aid in better comprehending its complex pathogenesis.

Keywords: - Rosacea; Inflammation; cutaneous disorder; Facial erythema; papules

INTRODUCTION

Rosacea is a common chronic facial dermatosis in the adult population. Rosacea is divided into four different subtypes. Transitory erythematous

episodes (flushing) are thought to be the early stage or pre-rosacea. Although, rosacea is a common disease, the cause of it is still a mystery. Endocrinological, pharmacological, immunological,

infectious, climatic, thermal, and alimentary factors are implicated as triggers of rosacea [1]. For the prevention of rosacea and for applying better causal treatment, it is important to know the aetiopathogenesis [2]. A common opinion is that rosacea mostly affects fair-skinned people of Celtic and northern European heritage, and sun exposure is an aggravating factor for rosacea, however, there is little evidence that proves this opinion. The relationship between rosacea and *Helicobacter pylori* infection has previously been investigated by several researchers. Nevertheless, these attempts to establish a link between *H. pylori* infection and rosacea are at present controversial, mainly based on case reports or small-scale studies. Some authors reckon that *H. pylori* probably constitutes a risk factor, at least in certain groups of individuals. Some beneficial effect of *H. pylori* eradication in rosacea has also been

found. Some other investigators contradict any associations between rosacea and *H. pylori* infection [3]. Although alcohol is recognized as a trigger of flushing episodes and rhinophyma is known as 'drinker's nose. No relation between alcohol consumption and rosacea was proved. The association between rosacea and caffeine intake was also not proved, although most doctors recommend avoiding hot beverages [4]. In addition, rosacea is predominantly known as a disease of non-smokers rather than active smokers.

TRIGGERS OF ROSACEA

Patients usually present with complaints of flushing, blushing, and sensitive skin. They may be unaware of these symptoms before diagnosis, but a variety of triggers or factors that induce or exacerbate rosacea are shown in **table 1** [5].

Table1: Triggering factors of Rosacea

Ingested/Iatrogenic	Environmental
Food and drinks: Cheese, spicy food, chocolate, soya sauce, vanilla, dairy products,	Temperature: Overheating, sun lamp, humidity, hot bath
Drugs: Niacin, nitroglycerine, tobacco	Emotion: Anger, stress, rage, embarrassment
Beverages: Red wine, hot drinks, alcohol	Weather: Sun, heat, cold, strong wind
Topical agents: Topical corticosteroids, retinoids, cosmetics, acetone, alcohol	Activity: Exercise, menopause, caffeine withdrawal

STAGES OF ROSACEA

There are different stages of rosacea that are reported according to several signs and symptoms in different stages as described in table 2 [6].

Table 2: Stages, sign, and symptoms of rosacea

Pre-rosacea	Stage 1	Stage 2	Stage 3
Frequent flushing; Irritation caused by topical preparations	Transient facial erythema that becomes more persistent; Slight telangiectasias; Increased skin sensitivity	Persistent, spreading erythema; Edema, papules, pustules; Enlarged pores; Ocular changes	Large inflammatory nodules and furuncles Tissue hyperplasia, fibroplasias Rhinophyma

DIFFERENTIAL DIAGNOSIS OF ROSACEA

Rosacea is somewhat similar to acne vulgaris as they have some common features such as the appearance of Papules, pustules, and erythema. However, features like comedones are predominant in acne vulgaris only. No telangiectasias or flushing is seen in acne vulgaris. Acne is reported to have an earlier onset and is not limited to the central third of the face [7].

Steroid rosacea is mostly found to result from topical application of corticosteroids, tacrolimus (Protopic, Astellas/Fujisawa), and pimecrolimus (Elidel, Novartis). The onset of erythema, papules, pustules, telangiectasias is found to be common in both steroid rosacea and rosacea. Both types

of rosacea are observed to affect most commonly the central third of the face [8].

Seborrheic dermatitis is another skin condition, if correlated with rosacea has some common manifestations such as blepharitis and erythema. However, scaling and eczematous changes prevail only in the case of seborrheic dermatitis. The distribution of seborrheic dermatitis is observed to be in paranasal, nasolabial, and extra facial parts of the skin. Rosacea has similar characteristics with perioral dermatitis such as the appearance of erythema and papules. However, smaller lesions are observed in perioral dermatitis. It has perioral distribution and telangiectasia; flushing or blushing is not observed, unlike rosacea.

Contact dermatitis has similar inflammatory indications like rosacea viz. erythema, papules, pustules, burning, and stinging. Contact dermatitis is observed to follow the size and shape of the causal agent along with the occurrence of scaling.

Photodermatitis is a seasonally occurring skin disease that has similar features to rosacea such as the development of erythema, papules, and plaques. It has the usual distribution in the extra facial area. Lupus has similar indications with rosacea viz. erythema. It usually has malar distribution and is photosensitive as well.

TREATMENT OF ROSACEA

Topical Therapy

FDA-Approved Topical Agents

The efficacy of topical therapy for rosacea relates primarily to the reduction in inflammatory lesions (papules, pustules), a decreased intensity of erythema, a decrease in the number and intensity of flares, and amelioration of symptoms, which may include stinging, pruritus, and burning. The list of standard topical agents used to treat rosacea includes topical antibiotics, such as clindamycin (Cleocin, Pfizer), erythromycin (Akne-Mycin, DTP Laboratories/Healthpoint Ltd.) and metronidazole, sulfacetamide-sulfur

(Sulfacet, Sanofi-Aventis), and azelaic acid (Azelex) [9].

Some studies have indicated efficacy for several treatments [10–12]. Topical metronidazole is more effective than a placebo in clinical studies. Between-patient and within-patient trials showed clear improvement in those using azelaic acid when compared with placebo. In a randomized trial comparing 15% azelaic acid and 0.75% metronidazole gel (MetroGel), azelaic acid was clinically superior in improving the inflammatory lesions and erythema associated with rosacea. However, studies show a greater potential for irritation from azelaic acid 15% than from metronidazole gel 0.75%, which had a significantly greater potential risk of irritation when compared with metronidazole 1% gel. However, three cases of allergic contact dermatitis resulting from topical metronidazole have been reported [13].

Other topical treatments include sulfur products, such as sodium sulfacetamide 10%/sulfur 5% combinations with or without a sun-blocking agent. These are available in lotions, creams, pledgets, short-contact preparations, and cleansers. Sodium sulfacetamide 10% alone may also be used [14].

Non-FDA-Approved Topical Agents

When used for four to eight weeks, pimecrolimus 1% cream (Elidel, Novartis), a topical calcineurin inhibitor, was no more efficacious than the vehicle creams. However, in an open-label, six-week pilot study in which patients used pimecrolimus 1% cream twice daily, nearly 50% of patients had clear skin and most showed at least modest improvement. Cutaneous adverse events, consisting of local burning, stinging, and itching occurred in fewer than 20% of patients. Symptomatic treatment with alpha-blockers has also been noteworthy. Patient using a topically administered selective α_1 -agonist showed a positive clinical response in treatment-resistant ETR rosacea.

ORAL THERAPY

FDA-Approved Oral Agents

The cornerstone of the oral treatment of rosacea involves the use of tetracyclines. Tetracycline (Sumycin) 500 mg twice a day is an effective treatment, but when it is taken with food, its absorption may be decreased. Doxycycline (Vibramycin, Pfizer) and minocycline (Minocin, Triax/Wyeth) 50–100 mg once daily to twice daily are the most currently used oral antibiotics by dermatologists for the treatment of rosacea. A new time-released form of minocycline (Solodyn, Medicis) at

doses of 45, 90, and 135 mg is indicated to treat only inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris in patients 12 years of age and older, but it can be used if another treatment has failed. It is the first weight-based antibiotic oral therapy for rosacea [15].

Non-FDA-Approved Oral Agents

Azithromycin (Zithromax, Pfizer), perhaps acting as an antioxidant, appears to be useful for treating rosacea in doses of 250 mg three times per week. If azithromycin, which is now available as a generic brand, is competitively priced with minocycline and doxycycline, its minimal side effects, lack of drug interactions, and three-times-weekly dosing could make it a good alternative for rosacea patients [16].

The systemic treatment of *Helicobacter pylori* infection has been advocated as a possible therapy for rosacea. In some studies, the two conditions are associated. Eradication of *H. pylori* can be achieved using a triple-therapy regimen lasting one to two weeks consisting of omeprazole (Prilosec, AstraZeneca) and a combination of two of the following: clarithromycin (Biaxin, Abbott), metronidazole, or amoxicillin (Amoxil, GlaxoSmithKline).

Although not commonly used clinically, other oral antibiotics with reported efficacy include penicillin 2.4 million units daily, erythromycin 250–500 mg two to four times daily, amoxicillin or ampicillin (Principen, Apothecon) 100–500 mg daily or twice daily, metronidazole at doses of 250 mg two to three times daily, and dapsone 50 to 200 mg once daily.

Combination Therapies

Effective treatments, including topical metronidazole and systemic antibiotics, have anti-inflammatory activity, which may be more important than their antimicrobial activity. For mild-to-moderate rosacea, an anti-inflammatory dose of doxycycline in combination with topical metronidazole gel 1% appears to be effective in reducing inflammatory lesion counts, and it is well tolerated [17].

Phototherapy

Several reports have found light-based treatments to be effective for the erythema of rosacea. Multiplexed laser appears to help in reducing erythema and telangiectasia. Intense pulsed light (IPL) at a wavelength of 550 to 670 nm may be effective for rosacea and solar lentigines, and it is particularly useful for ETR. Both the flashlamp-pumped, long-pulse dye laser and the potassium titanyl-phosphate

laser may be used to treat facial telangiectasias [18].

Nonmedical Therapies

Patients should be instructed about the regular use of sunscreens, the appropriate use of concealing makeup, and the need for careful follow-up of any ocular symptoms. Basic skin-care regimens, including the daily use of sunscreen, offer significant benefits. Clinical assessments, confirmed by biophysical measurements (electrical capacitance, transepidermal water loss, and lactic acid stinging test), indicated that moisturizers contributed to the restoration of the skin barrier. Skin dryness, roughness, and desquamation were much improved, and skin sensitivity was significantly reduced. Skin properties were enhanced, and skin discomfort was relieved.

CONCLUSION

This updated classification of rosacea is intended to provide accuracy and flexibility appropriate for the study, diagnosis, evaluation, and treatment of rosacea within the context of current scientific understanding and clinical experience. Growing knowledge of rosacea's pathophysiology has increasingly found that a consistent multivariate disease process appears to

underlie the various potential manifestations of the disorder, and its clinical significance may increase substantially as more is understood about the many comorbidities reported in recent studies. As with the original classification of rosacea, this updated standard system is considered provisional and may require modification as the etiology and pathogenesis of rosacea become clearer and its relevance and applicability are tested by investigators and clinicians.

REFERENCES

- I. Steinhoff M, Schmelz M, Schaubert J. Facial erythema of rosacea – Aetiology, different pathophysiologies and treatment options 2016; 96: 579–89.
- II. Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, et al. Standard classification of rosacea: Report of the National Rosacea Society expert committee on the classification and staging of rosacea 2002; 46: 584–87.
- III. Moustafa FA, Sandoval LF, Feldman SR. Rosacea: New and emerging treatments 2014; 74: 1457–65.
- IV. Guzman-Sanchez DA, Ishiuiji Y, Patel T, Fountain J, Chan YH, Yosipovitch G. Enhanced skin blood flow and sensitivity to noxious heat stimuli in papulopustular rosacea 2007; 57: 800–805.
- V. Sansare VA, Kanavaje AM. the Potential Advantages of Lipid Nanoparticles in Treatment of Acne 2019; 2: 6–13.
- VI. Maheshwari RGS, Tekade RK, Sharma PA, Darwhekar G, Tyagi A, Patel RP, et al. Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: A comparative assessment 2012; 20: 161–70.
- VII. Reinholz M, Ruzicka T, Steinhoff M, Schaller M, Gieler U, Schöfer H, et al. Pathogenesis and clinical presentation of rosacea as a key for a symptom-oriented therapy 2016; 14: 4–15.
- VIII. Sahni DR, Feldman SR, Taylor SL. Ivermectin 1% (CD5024) for the treatment of rosacea 2018; 19: 511–16.
- IX. Tirnaksiz F, Kayış A, Çelebi N, Adışen E, Erel A. Preparation and evaluation of topical microemulsion system containing metronidazole for remission in rosacea 2012; 60: 583–92.
- X. Arora D, Nanda S. Quality by design driven development of

- resveratrol loaded ethosomal hydrogel for improved dermatological benefits via enhanced skin permeation and retention 2019; 567.
- XI. Arora D, Khurana B, Nanda S. DoE directed optimization, development and evaluation of resveratrol loaded ultradeformable vesicular cream for topical antioxidant benefits 2020.
- XII. Khurana B, Arora D, Narang RK. QbD based exploration of resveratrol loaded polymeric micelles based carbomer gel for topical treatment of plaque psoriasis: In vitro, ex vivo and in vivo studies 2020; 59.
- XIII. Yu M, Ma H, Lei M, Li N, Tan F. In vitro/in vivo characterization of nanoemulsion formulation of metronidazole with improved skin targeting and anti-rosacea properties 2014; 88: 92–103.
- XIV. Patel NU, Shukla S, Zaki J, Feldman SR. Oxymetazoline hydrochloride cream for facial erythema associated with rosacea 2017; 10: 1049–54.
- XV. Jabbehdari S, Memar OM, Caughlin B, Djalilian AR. Update on the pathogenesis and management of ocular rosacea: an interdisciplinary review 2020.
- XVI. Kim JH, Oh YS, Choi EH. Oral azithromycin for treatment of intractable rosacea 2011; 26: 694–96.
- XVII. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: Part II. Topical and systemic therapies in the treatment of rosacea 2015; 72: 761–70.
- XVIII. Khurana S, Jain NK, Bedi PMS. Nanoemulsion based gel for transdermal delivery of meloxicam: Physico-chemical, mechanistic investigation 2013; 92: 383–92.