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REVIEW

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Rosacea: Epidemiology, pathogenesis, and treatment

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ABSTRACT

Rosacea is a chronic relapsing inflammatory skin disease with a high prevalence among adults of Northern European heritage with fair skin. Symptoms present in various combinations and severity, often fluctuating between periods of exacerbation and remission. Based on morphological characteristics, rosacea is generally classified into four major subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. Diverse environmental and endogenous factors have been shown to stimulate an augmented innate immune response and neurovascular dysregulation; however, rosacea's exact pathogenesis is still unclear. An evidence-based approach is essential in delineating differences between the many available treatments. Because of the diverse presentations of rosacea, approaches to treatment must be individualized based on the disease severity, quality-of-life implications, comorbidities, trigger factors, and the patient's commitment to therapy.

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Introduction

Rosacea (L. *rosaceus*, rosy) is a common chronic inflammatory dermatosis affecting approximately 10% of the population.[1] Symptoms present in various combinations and severity, often fluctuating between periods of exacerbation and remission.

Based on morphological characteristics, rosacea is generally classified into four major subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.[2,3] Erythematotelangiectatic rosacea is characterized by a transient facial erythema (flushing), combined with a background of persistent centrofacial erythema, with telangiectasia also present in most patients. The clinical definition can be challenging due to an overlap with the cutaneous findings of chronic actinic damage in fair-skinned individuals (dermatoheliosis). Papulopustular rosacea presents with variable intensity of central facial erythema and a variable number of small erythematous papules and pustules. Phamatous (Gr. *phyma*, growth) rosacea most commonly affects the nose (rhinophyma), and presents with tissue hypertrophy manifesting as skin thickening and hyperplasia of sebaceous glands. Symptoms of ocular rosacea consist of nonspecific complaints of dryness, gritty sensations, tearing, itching, as well as frequent styes. More active ocular rosacea presents as blepharitis, often with conjunctival injection, lid margin telangiectasia, chalazion or hordeolum formation.[4]

In daily clinical practice, patients often have morphological characteristics of more than one rosacea subtype and may complain of increased sensitivity of the facial skin with symptoms of burning, stinging, and itch.[3] The diversity of clinical presentations has made rosacea's pathophysiology elusive. Various environmental stimuli and endogenous factors have been shown to stimulate an augmented innate immune response and aberrant neurovascular signaling.[5-11] Downstream of these events various mediators orchestrate vascular and inflammatory effects that characterize the disease. Here, we review the current knowledge of the epidemiology, pathophysiology, and treatment of rosacea with an emphasis on the most recent literature.

Epidemiology

Caucasians with fair sun-sensitive skin (skin phototypes I and II) appear to have the greatest risk for

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rosacea.[12-14] It is unknown whether factors such as masking of facial redness by abundant skin pigment, protective effects of melanin against ultraviolet radiation (an exacerbating factor for rosacea), or genetic differences in susceptibility to rosacea contribute to the lower rate of diagnosis in people with darker skin.[15-17] Estimates of the prevalence of rosacea in fair-skinned populations range from 2 to 22 percent.[18-21] A recent prospective study from Germany reported an overall rosacea prevalence of 12 percent, with erythematotelangiectatic and papulopustular subtypes making up 9 and 3 percent, respectively.[1] Prevalence rates for ocular involvement in rosacea patients range from less than 10 percent to more than 50 percent.[12,22,23] Cutaneous rosacea exhibits a strong female predominance, with the exception of phymatous rosacea, and is usually diagnosed after the age of 30 years.[12,18]

Associated diseases

Rosacea is considered a disease that is limited to the skin; however, there is accumulating evidence of significant associations between rosacea and systemic comorbidities.[24-30]

A recent case-control study (n = 130) showed that patients with rosacea had significantly

higher odds of having allergies (airborne and food), respiratory diseases, gastrointestinal (GI) diseases, hypertension, metabolic diseases, urogenital diseases, and female hormone imbalance compared with age-, sex-, and race-matched control subjects without rosacea.[12] Moderate to severe rosacea has been associated with hyperlipidemia, hypertension, metabolic, cardiovascular, and GI diseases.[12] Population-based cohort studies confirmed these findings[31-33] and reported further associations of rosacea and type 1 diabetes mellitus, celiac disease, multiple sclerosis, rheumatoid arthritis[34], Parkinson disease,[35] and migraine.[36,37] In addition to physical comorbidities, rosacea was associated with a disease severity-dependent, increased risk of depression and anxiety disorders.[30,38] Thus, assessing cardiovascular risk factors, GI and psychiatric morbidity in patients with rosacea seems prudent, especially in those presenting with more severe disease.

Psychosocial impact

Rosacea occurs predominantly in the face and therefore affects the patients' physical appearance. In a survey conducted by the National Rosacea Society with more than 400 participants, approximately 75 percent of rosacea patients feel low self-esteem, 70 percent feel embarrassed, and 69 percent feel frustrated. Among rosacea patients with severe symptoms, 88 percent cited the disorder as adversely affecting their professional interactions, and 51 percent had missed work because of their condition. In addition, 41 percent experienced anxiety over their condition and 25 percent suffered depression, stemming from cosmetic disfigurement, painful burning sensations, and decreases in quality of life.[39-42]

Genetics of rosacea

It has been observed that individuals with a family history of rosacea were more likely to develop rosacea.[13] A study in twins suggested a 46 percent genetic contribution,[43] which is in accordance with other cross-sectional studies reporting a family history of rosacea in up to 50 percent of patients.[12] Recently, genomic association studies identified three human leucocyte antigen (HLA) alleles and two single-nucleotide polymorphisms (SNPs) to be associated with rosacea.[44] Interestingly, these rosacea-associated HLA (human leukocyte antigen) genes have links to autoimmune diseases, including type I diabetes mellitus and celiac disease. Together, recent studies support the hypothesis of a genetic component in rosacea, but future studies are needed to further investigate specific genetic factors associated with rosacea risk, and to identify mechanistic links between the gene variants and the expressed rosacea phenotype.

Integrative concepts of rosacea pathophysiology

The exact molecular mechanisms involved in rosacea's pathophysiology are unknown, and a multifactorial etiology with a genetic preposition is likely. There is accumulating evidence that triggers such as microbes, ultraviolet (UV) radiation, nutrition, extremes of temperatures, (skin) barrier disruption, psychosocial stress, and hormones may stimulate an augmented innate immune response and/or neurovascular dysregulation.[6,45-47] Multiple cell types have been implicated in promoting rosacea, including keratinocytes, mast cells, neurons, endothelial cells, macrophages, fibroblasts, and Th1/Th17 cells.[11,46,48,49] Accumulating evidence points to activation of cellular pattern recognition receptors like the toll like receptor (TLR) 2 and

transient receptor potential (TRP) ion channels, and release of inflammatory mediators within the skin as key steps that lead to the clinical manifestation of rosacea. However, the precise interplay of the different dysregulated systems (immune, vascular, nervous) is still poorly understood.

Aberrant innate immune response and antimicrobial peptides

The innate (non-specific) immune system protects epithelial surfaces against infection, physical or chemical trauma. Among multiple detection systems, toll-like receptors (TLRs) respond to microbial components, chemical and physical trauma, including tissue damage, and ultraviolet-induced apoptotic cells. Activation of TLR leads to the induction of conserved anti-pathogen signaling cascades including the secretion of antimicrobial peptides (AMPs) such as cathelicidin, and the production of proinflammatory cytokines and chemokines.[50] One member of the TLR family, TLR2, is highly expressed in rosacea skin, which correlates with increased TLR2 activation to extrinsic stimuli.[10,51] Consistent with this finding, rosacea patients also have increased expression of the AMP cathelicidin, and kallikrein (KLK) 5, the predominant serine protease responsible for cleaving cathelicidin into LL-37, its active peptide form.[8,9] LL-37-induced effects, including leukocyte chemotaxis, promotion of angiogenesis, and activation of NF-kB[7,8] which collectively correlate with morphologic characteristics od rosacea, such as facial erythema, telangiectases, and papules and pustules.

In addition to these innate immune receptors and molecules, neuronal dysregulation, including vascular dysfunction, and release of proinflammatory neuropeptides have been shown to contribute to rosacea's pathophysiology.

Neurogenic inflammation and vascular hyperreactivity

The concept of cutaneous neurobiology includes a complex network of closely related mono- and/or bidirectional pathways that link the skin with the nervous, the immune, and the endocrine system.[52-55] This network regulates a variety of physiological and pathophysiological functions including cellular development, growth, differentiation, vasoregulation, pruritus, and immunological processes and leukocyte recruitment or neurogenic inflammation.[56] Mediators involved in these processes are defined as neuropeptides, neurotransmitters, neurotrophins, and neurohormones, which target various skin cells including keratinocytes, mast cells, Langerhans cells, vascular endothelial cells, fibroblasts, and infiltrating immune cells.[11,52,57-60] Stressors including UV radiation,[61] microbial antigens, trauma, emotional stress, endogenous hormones may stimulate the release of neurotransmitters and contribute to the vasodilatation, flushing, and increased skin sensitivity, stinging, itch, and lower pain thresholds in patients with rosacea.[6] Interestingly, sensory neuron density was increased in erythematotelangiectatic rosacea.[11,62] Transient receptor potential (TRP) vanilloid type (TRPV)1 and 4, and TRP ankyrin 1 (TRPA) ion channels expressed on nerves, keratinocytes, mast cells and/or immune cells are highly reactive to thermal, chemical and/or mechanical stimuli.[49,63,64] A recent study showed increaed density of TRP ion channels on sensory neurons, vascular cells and immune cells across all cutaneos rosacea subtypes (erythematotelangiectatic, papulopustular, and phymatous). TRPVs have an impact on local immune function, vascular regulation, nociception, and epidermal barrier integrity.[62]

Activation of TRP results in release of vasoactive neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP), which were elevated in rosacea.[11,65,66] Substance P is involved in local blood flow regulation and induces mast cell degranulation leading to increased levels of pro-inflammatory cytokines (e.g., IL1, IL3 and IL 8), chemokines, (e.g., CCL2, CXCL9, CXCL10, CCL5, and CXCL8), and tumor necrosis factor (TNF)-α, suggesting that neurogenic inflammatory processes are also likely active in rosacea.[56,60]

Update on the management of rosacea

Historically, rosacea was treated by bloodlettings and application of leeches on rosacea-affected skin.[67] Rosacea therapy has changed since then, but a curative treatment approach has not yet been developed. Thomas Bateman's quote holds true to date: *"The perfect cure of [acne] rosacea is, in fact, never accomplished"* (from *Delineations of cutaneous diseases, 1812*).

Current rosacea treatment is focused on symptom suppression to improve patients' quality of life, to prevent progression, and to sustain remission. Most

current guidelines are based on the identification of the rosacea subtype to select the appropriate therapy. However, in reality there is often an overlap of clinical features across rosacea subtypes in each patient, requiring several therapeutic strategies for optimal outcome. Thus, there is no single best way to treat all rosacea patients.[68-70] Usually a set of interventions is needed including avoidance of trigger factors, the use a daily skin care regimen, the use of topical or systemic therapies, and physical modalities. Key messages for the individualized management of rosacea are displayed in Table 1. In this article, we review the management of rosacea based on currently available evidence.

General measures

It is important to educate the patient at the initial consultation as to the chronic relapsing nature of the disorder and the likelihood of exacerbations, and to advise the patient to avoid recognized triggers. To our knowledge, no controlled studies have been conducted to recommend any specific skin care products for rosacea patients. General recommendations include a gentle skin care regimen to maintain skin hydration and barrier function, and photoprotection (sun exposure avoidance and sunscreen with a sun protection factor of 30 or greater). Additionally, cover-up or color-correcting powders can be helpful to mitigate the psychosocial impact of rosacea. Since the psychosocial impact of rosacea tends to be underestimated by physicians, this issue should be raised with every patient and considered in the therapeutic plan. Several topical drugs including topical metronidazole, azelaic acid, ivermectin, and brimonidine tartrate are approved for rosacea by the United States Food and Drug Administration (FDA). The only approved oral drug for rosacea is low-dose doxycycline. Most treatments are generally effective at inhibiting the inflammatory pathways involved in rosacea.

Table 1. Key messages for the individualized management of rosacea.

- Confirm diagnosis and severity of disease
- Evaluate treatment history and exacerbating factors
- Routinely screen for risk factors and comorbidities associated with rosacea
- Raise quality of life concerns: self-esteem, social impairment, work activities
- General recommendations: chronic disease needing life-long treatment intervention, avoidance of trigger factors, gentle skin care regimen, and photoprotection
- Range of treatment modalities

Topical therapies

In mild to moderate disease of rosacea, topical therapeutic approach is considered to be the first-line.[45,47,71,72] Metronidazole 0.75% (gel, cream, and lotion; twice-daily application), metronidazole 1% (gel and cream; once-daily application), azelaic acid 15% gel (twice-daily application),[73] and ivermectin1% cream (once-daily application)[74] are US FDA approved to treat inflammatory lesions of rosacea, and are generally well tolerated by most patients.[75] According to the current Cochrane review published in 2015, topical metronidazole, azelaic acid, and ivermectin compared with placebo were all associated with improvements primarily for papulopustular rosacea.[76,77] Topical ivermectin appeared to be slightly more effective than topical metronidazole for papulopustular rosacea (high quality evidence).[76,78]

Brimonidine tartrate 0.33% gel (once-daily application) was approved by the FDA as the first medication for the topical treatment of persistent facial erythema associated with rosacea. Brimonidine gel is a selective α2-adrenergic receptor agonist with vasoconstrictive activity, which leads to reduction of persistent facial erythema in the majority of patients.[79,80] Based on a systematic review, topical brimonidine tartrate gel was associated with two grades of improvement in facial erythema among 114 of 227 participants (50%) compared with 54 of 276 participants (20%) with vehicle alone (risk ratio [RR], 2.11 [95% CI, 1.60–2.78]; high-quality evidence].[76] Topical brimonidine tartrate gel is generally well tolerated; the most common side effects are skin related, including burning sensation, contact dermatitis, and rebound erythema.[81-84]

However, caution is recommended in patients with concomitant depression, cardiovascular disease, Raynaud's phenomenon, and orthostatic hypotension among others.[85]

Although sodium sulfacetamide 10%, with or without 5% sulfur, formulations (ie, cleanser, cream, gel, lotion) have long been used to control papulopustular rosacea,[86] they are not approved by the FDA due to limited efficacy data. Various other topical therapies are used as off-label treatments for rosacea, such as macrolids and macrolide analogues,[87,88] permethrin,[89] retinoids[90], topical calcineurin inhibitors[91] and others, often only based on anecdotal evidence.[75] These alternative non-FDA approved therapies may be helpful in specific patients based on the assessment of the physician.

Systemic therapies

Despite the widespread use of oral tetracycline and doxycycline in various dose regimens for treatment of rosacea, the only oral agent approved by the FDA to treat inflammatory rosacea lesions is a modified-release doxycycline (40 mg once-daily), which was approved in 2006.[75] This once-daily 40 mg doxycycline dosing (30 mg immediate-release and 10 mg delayed-release beads) provides anti-inflammatory, without antimicrobial effects; *in vivo* microbiological studies demonstrated no long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.[92-95] Based on most current evidence, oral tetracycline (moderate quality evidence) and doxycycline (high quality evidence) were both associated with improvements in papulopustular rosacea compared with placebo.[76] There was no difference in effectiveness between 100 mg and 40 mg doxycycline, but there was evidence of fewer adverse events with the lower dose (RR 0.25, 95% CI 0.11 to 0.54) (low quality evidence).[76,94] Of note, oral tetracycline was compared with topical metronidazole and showed no difference between the two treatments (low to moderate quality evidence).[96] In patients with inflammatory rosacea who cannot use tetracyclines, oral azithromycin appears to be an alternative, though efficacy and safety data are limited.[76,97]

In more severe or persistent cases of papulopustular and early phymatous rosacea, oral isotretinoin therapy may be required. Low dose isotretinoin (0.3 mg/kg daily) was shown to be associated with improvement in papulopustular rosacea compared with doxycycline 50–100 mg (high quality evidence).[98,99] However, relapse after discontinuation is common – unlike isotretinoin in acne vulgaris.

Ocular rosacea

Patients with mild ocular rosacea often present with a dry gritty feeling in the eyes; they can usually be treated by lid hygiene and lubricating eye drops. Patients with more severe ocular rosacea present with burning or stinging of the eyes, crusting of the lid margins, or formation of chalazia and hordeola. They frequently need topical or systemic antibiotics, or cyclosporine.

Topical cyclosporine 0.05% ophthalmic emulsion has been shown to be more beneficial than artificial tears in the treatment of ocular rosacea (low quality evidence).[76,100] For the more severe ocular rosacea, referral to an ophthalmologist is prudent.

Physical modalities

Telangiectasia

Reduction in telangiectasia is not to be expected with any of the currently available topical agents for rosacea. However, these features frequently become a psychological burden and can substantially impact rosacea patients' quality of life.

Destruction of dilated vessels by vascular lasers or intense pulse light is the primary therapy to reduce telangiectasia. Light energy is absorbed by hemoglobin in cutaneous vessels, leading to vessel heating and coagulation. Most commonly used for the treatment of erythema and telangiectasia in rosacea patients are the pulsed dye laser (PDL, pulsed dye laser, 585–595 nm) and intense pulse light (IPL) devices.[101,102] According to the latest Cochrane Systematic Review, pulsed dye laser and intense pulsed light therapy were each associated with erythema and telangiectasia improvement, but without difference between treatments (moderate-quality evidence).[76]

Phymatous rosacea

Mild rhinophyma may be responsive to systemic treatment with isotretinoin. Isotretinoin shrinks sebaceous glands, but long-term remission of phymatous changes does not occur when isotretinoin is discontinued.[103] More severe disease with deformity responds best to surgical excision, electrosurgery, and CO2 laser therapy.[102,104,105] However, randomized-controlled trials to address treatment of phymatous rosacea are lacking.[76]

Conclusion

Rosacea is an inflammatory skin disease characterized by immune dysfunction and neurovascular dysregulation. By rationally choosing among the many potential interventions, physicians can help most patients to alleviate the symptoms of rosacea, but none of these therapies is curative.

An increasing number of studies showed a relationship between rosacea and systemic comorbidities; however, the pathophysiologic connections remain to be defined. It is likely that these connections involve mechanisms that underlie chronic inflammatory conditions including inflammatory cytokines, and

metabolic, immune, and endocrine changes. The associations between rosacea and diseases involving barrier tissues such as the intestinal, respiratory, reproductive, and urinary tracts, and the skin, raise the suspicion that some form of dysbiosis may contribute to the development of rosacea. Future research needs to investigate how the tissue environment interface is altered in patients with rosacea.

Assessing and understanding the relationship between comorbid physical and mental disorders with rosacea is important and necessary to provide integrated care and enhance the quality of life for rosacea patients.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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