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Rosacea pathogenesis and topical treatment options – a review

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Abstract

Introduction: Rosacea is a chronic inflammatory condition primarily affecting the central facial areas and eyes, with subtypes including erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. While not life-threatening, rosacea significantly impacts quality of life, contributing to psychological distress.

Materials and methods: This article reviews the pathogenesis and treatment of rosacea, incorporating data from PubMed, Google Scholar, and Web of Science using keywords such as “rosacea,” “Demodex,” “topical treatment,” and “pathogenesis.”

Summary: Rosacea is driven by multifactorial mechanisms, including neurovascular hyperreactivity, immune system dysregulation, sebaceous gland dysfunction, microbial imbalances, and genetic predisposition. Triggers like UV radiation, stress, and certain foods exacerbate symptoms by activating pathways such as transient receptor potential (TRP) channels and inflammatory mediators like IL-6 and TNF-α. Effective treatments focus on symptom management and include topical agents like ivermectin, metronidazole, azelaic acid, calcineurin inhibitors, retinoids, alpha-adrenergic receptor agonists and sodium sulfacetamide. These therapies target inflammation, erythema, and microbial factors, with clinical trials demonstrating improvements in erythema, papules, and pustules.

Conclusions: While current treatments offer significant relief, the article emphasizes the importance of further research into the underlying mechanisms to develop more advanced therapeutic options.

Key words: rosacea, pathogenesis, demodex, topical treatment

Introduction

Rosacea is a chronic inflammatory condition that primarily impacts the central facial areas, including the cheeks, chin, nose, forehead, and eyes, with specific variations in lesion characteristics based on age and gender. [1] Rosacea was originally classified by the National Rosacea Society Expert Committee according to a subtypes approach, with 4 predominant subtypes: erythrotelangiectatic, papulopustular, phymatous, and ocular. Erythrotelangiectatic rosacea is marked by facial redness, frequently accompanied by telangiectasias. Papulopustular rosacea is characterized by facial redness along with varying numbers of red papules and pustules. Phymatous rosacea involves skin thickening and sebaceous gland hyperplasia. Ocular rosacea typically manifests as blepharitis, conjunctivitis, and chalazion.[2]

Phymatous changes are rare and predominantly affect the nose (rhinophyma), occurring more often in men. [3,4] Over half of rosacea patients exhibit ocular symptoms such as dryness, a foreign-body sensation, photophobia, conjunctivitis, blepharitis, and, in rare cases, keratitis, which can impair vision. [3] Severe ocular rosacea may result in corneal inflammation, scarring, and potentially corneal perforation, leading to a loss of visual acuity. [5] Rosacea is linked to a compromised skin barrier, leading to increased transepidermal water loss. This results in dry skin that is prone to scaling, peeling, and heightened sensitivity, often accompanied by sensations of burning and stinging. [6] While rosacea is not life-threatening, it significantly impacts patients' quality of life, often contributing to depression, social phobia, and anxiety. [7] In the United States alone, over 16 million people are affected by rosacea, with global incidence rates reaching up to 18%, particularly among populations with predominantly Celtic heritage, such as those in Ireland. [8] However, in individuals with darker skin tones, rosacea is often underdiagnosed and overlooked due to the difficulty in detecting erythema and telangiectasia. [9] An analysis of the US National Ambulatory Medical Care Survey from 1993 to 2010 revealed that among patients diagnosed with rosacea, 3.9% were Hispanic, 2.3% were Asian or Pacific Islander, and 2.0% were Black. [10] Worldwide, rosacea prevalence is estimated to exceed 5%, with males and females affected equally. [11] While rosacea typically begins between the ages of 30 and 50, it can occur at any age. [12] Although no direct causal relationships have been established, recent studies suggest potential links between rosacea and an increased risk of cardiovascular, gastrointestinal, neurological, autoimmune, psychiatric disorders, and certain cancers. [13] Research indicates that the pathogenesis of rosacea is driven by a combination of genetic and environmental factors, including immune dysfunction, chronic inflammation, microbial imbalances, and vascular neurological dysregulation. [14,15] Additionally, triggers such as ultraviolet radiation, heat, intense emotions, spicy foods, and alcohol consumption can exacerbate the condition. [16] Understanding and addressing the underlying mechanisms of rosacea are essential for improving management outcomes. [17]

The aim of this article is to systematically summarize, analyze, and synthesize existing research and knowledge in order to explore and elucidate the underlying mechanisms and factors contributing to rosacea, and assess the efficacy, safety, and limitations of current treatment modalities, such as topical therapies, providing a comprehensive overview for clinical practice. To find relevant articles, we conducted a literature review of the latest works available in bibliographic databases such as PubMed, Google Scholar, and Web of Science. We used the following keywords and their combinations: "rosacea", "demodex", "topical treatment","pathogenesis", "microbiome", "ivermectin". Based on the collected data and relevant literature, this work will serve as a foundation for advancing understanding and improving the management of rosacea.

Hyperreactive neurovasculature

Studies have linked vasodilation and lymphatic dilation to the "flushing" (acute neurogenic inflammation) and "blushing" (sympathetic-driven transient facial redness in the central face and cheeks due to emotion or stress) reported by patients, as well as the observed erythema and telangiectasias. [18,19] Current research suggests that individuals with rosacea exhibit increased expression and density of nonspecific cation channels on sensory neurons and keratinocytes. These channels, known as transient receptor potential channels (vanilloid 1 [TRPV-1] and ankyrin 1 [TRPA-1]), mediate various rosacea triggers and are activated by stimuli such as spices, temperature extremes, exercise, and possibly alcohol. [19] Activation of TRPV1 specifically leads to painful burning sensations. [20] Furthermore, TRP activation

initiates vasodilatory pathways, contributing to the flushing and erythema characteristic of rosacea. Once triggered, cells release vasoactive peptides, including substance P, pituitary adenylate cyclase-activating polypeptide (PACAP), vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP). [19]

Deregulation of the immune system

The activation of immune-mediated inflammatory pathways plays a central role in the pathogenesis of rosacea, involving the coordinated activity of various cell types such as mast cells and macrophages, and the release of proinflammatory mediators, including IL-6, IL-1β, IL-18, and TNF-α. [13, 21] Recently, a novel molecule, koebnerisin (S100A15), has been identified in the pathology of rosacea. Koebnerisin is an antimicrobial peptide implicated in immune-mediated inflammatory responses in multiple dermatological conditions, including rosacea. Regulated by TH1 and TH17 cells, koebnerisin functions as a chemoattractant for leukocytes, and skin biopsies from rosacea patients have shown elevated levels of this molecule. In vitro studies reveal that human keratinocytes exposed to koebnerisin secrete MMP-9 and VEGF, suggesting a potential role in promoting angiogenesis. [22] Additionally, skin biopsies from rosacea patients demonstrated increased CD4+ T-cells, particularly Th1 and Th17 subtypes, with the papulopustular subtype showing the highest elevation. [23] Ultraviolet (UV) light has also been implicated in rosacea pathogenesis by stimulating matrix metalloproteases (MMPs), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and generating free radicals, all of which exacerbate the innate immune response. [24,25]

Sebaceous glands

Sebaceous glands are intradermal structures found throughout the body that produce sebum—a mixture of lipids and cellular debris essential for preventing skin dryness and contributing to the hydrolipidic film on the skin's surface. [26] The connection between sebaceous glands and rosacea became evident when oral isotretinoin, a retinoid originally prescribed for acne that inhibits sebum secretion, was found to unexpectedly reduce erythema and papulopustules in patients with rosacea. [27] Rosacea-affected skin has been shown to exhibit an altered composition of fatty acids. [28] Sebocytes, the cells of sebaceous glands, play a role in the inflammatory response in rosacea by releasing proinflammatory factors and adipokines, such as IL-6. [29] Dysbiosis within the sebaceous environment may trigger sebocyte-driven inflammation and alter the local microenvironment, including changes in sebum composition. Additionally, these alterations in the sebaceous environment may influence the composition of resident microorganisms. [30]

Role of the microbiome

Several cutaneous microbes, particularly Demodex folliculorum and its associated bacterium Bacillus oleronius, have been implicated in the inflammatory response of rosacea. Demodex folliculorum, measuring approximately 0.3–0.4 mm in length, has an elongated shape and resides within hair follicles, often clustering in groups. Since its primary food sources are epidermal cells and sebum, these mites are predominantly found in sebaceous gland-rich areas such as the face—specifically the nose, cheeks, forehead, and chin. [31] While it is unclear whether Demodex contributes to the cause or is a result of rosacea, studies have shown higher mite densities in affected areas compared to healthy skin in the same individual and 5.7 times

higher in individuals with rosacea compared to healthy volunteers. [32,33] This increased density has been observed not only in patients with papulopustular rosacea but also in those with erythematotelangiectatic rosacea. [34] Additionally, Demodex has been linked to a high incidence of blepharitis in papulopustular rosacea. [35,36] Proteins associated with Demodex bacteria have been implicated in corneal inflammation in ocular rosacea. [37] Microbial products can be detected by innate immune system cells, activating receptors such as Toll-like receptors (TLRs) and proteinase-activated receptor 2 (PAR-2) expressed by keratinocytes, which further fuel inflammatory processes. [38] TLR-2 signaling, for example, can activate the NLRP3 inflammasome, amplifying inflammation through IL-1β and TNF-mediated pathways and promoting prostaglandin E2 synthesis, which contributes to pustule formation, pain, and vascular changes. [39]

Genetics of rosacea

The role of genetics in rosacea has long been suspected but remains unproven. Patients with rosacea are four times more likely to have a family member who also has the condition. [16] Twin studies suggest that genetics contribute to approximately half of the risk for developing rosacea. [40] A genome-wide association study involving 2,618 rosacea patients identified two single-nucleotide polymorphisms associated with the disease. The study revealed that rosacea was linked to three alleles of human leukocyte antigen (HLA) class II, molecules involved in presenting antigens to immune cells. [41] These findings support the hypothesis that genetic predisposition plays a role in rosacea development. Interestingly, a population-based case-control study revealed shared genetic risk loci between rosacea and autoimmune diseases, including multiple sclerosis, type 1 diabetes, celiac disease, and rheumatoid arthritis. [42]

Treatment

Rosacea is a chronic inflammatory condition for which there is currently no cure. However, several treatment options are available to help reduce symptoms. Since rosacea can be triggered by various factors, avoiding known triggers is an essential part of management. Patients are encouraged to keep a journal to track potential triggers, including environmental exposures, diet, and activities that lead to flare-ups. [43] For mild to moderate rosacea, topical agents are considered the first-line treatment. [44]

Ivermectin

Ivermectin 1% cream is an acaricidal agent that specifically targets Demodex folliculorum. Unlike many traditional topical treatments, ivermectin 10 mg/g cream has the convenience of once-daily application. [45] Inflammatory mechanisms are believed to play a key role in the formation of rosacea-related papules and pustules. [46] Ivermectin works by reducing both innate and adaptive immune responses, as well as inhibiting neutrophil chemotaxis and phagocytosis. Clinical trials have demonstrated its effectiveness in improving rosacea lesions after 16 weeks of use. [47] Additionally, ivermectin has been shown to be slightly more effective than topical metronidazole in both patient- and physician-assessed outcomes and in improving quality of life. [48]

Metronidazole

Metronidazole (MTZ) is believed to reduce oxidative stress and has been shown to effectively reduce erythema and inflammation in rosacea. [49] Topical MTZ is available as a 1% cream

applied once daily or a 0.75% cream applied twice daily. [50] By reducing papules, pustules, and erythema, MTZ is an effective treatment option for papulopustular rosacea. [51] Studies have found no significant differences in clinical efficacy between various formulations (gel, cream, or lotion) or concentrations (0.75% or 1%). Adverse effects are typically mild and include pruritus, irritation, and dryness. [43]

Azelaic Acid

Azelaic acid (AZA) is a dicarboxylic acid with anti-inflammatory, antioxidant, and antimicrobial properties, as well as mild antikeratinizing effects. [52] In topical formulations, AZA is present as a gel or cream where it is suspended solid, which limits its penetration into the skin. [53] Two topical formulations are currently available for rosacea treatment: a 15% gel and a 20% cream. Daily application of these formulations reduces erythema and decreases the number of inflammatory lesions, effectively improving rosacea symptoms. [54] Common side effects include irritation, dryness (xerosis), and a burning sensation; however, these effects are generally mild to moderate and transient, making the treatment well-tolerated by most patients. [55]

Calcineurin inhibitors

Cyclosporine, pimecrolimus, and tacrolimus are calcineurin inhibitors that are effective in treating rosacea due to their immunosuppressive properties. Cyclosporine is commonly used as an ophthalmic emulsion to manage ocular manifestations of rosacea, while pimecrolimus and tacrolimus are available as a cream and ointment, respectively, for treating cutaneous lesions. For instance, the effectiveness of cyclosporine is attributed to its ability to reduce the production of pro-inflammatory cytokines by T-lymphocytes in the conjunctiva. [56]

Retinoids

Retinoids, a class of vitamin A derivatives, are widely used to regulate skin cell turnover. Topical retinoids, such as the third-generation adapalene, have shown effectiveness in treating papules and pustules. [57] Multiple studies have reported that topical tretinoin, either as a monotherapy or in combination with other topical treatments, significantly reduces erythema, papules, pustules, and telangiectasias. [58, 59] Retinoids also support connective tissue remodeling, helping to repair damage caused by UV radiation that contributes to the pathogenesis of rosacea. [60]

Alpha-adrenergic receptor agonists

These agents specifically target the smooth muscles surrounding the vessels of the superficial and deep dermal plexuses. By binding to receptors on these muscles, they induce vasoconstriction [61] , redirecting blood flow away from the central face and thereby reducing the persistent centrofacial erythema characteristic of rosacea. The alpha-2 agonist brimonidine tartrate gel 0.5% (brimonidine gel 0.33%) has been approved by the FDA for once-daily use in treating rosacea-associated erythema. Clinical trials have demonstrated a reduction in baseline facial erythema as early as 30 minutes after application, with maximal erythema reduction lasting 6 to 7 hours following a single dose. [62, 63] Additionally, brimonidine 0.33% gel, typically recommended for daytime use, can also be safely combined with other topical rosacea treatments, such as ivermectin 1% cream. [64] Side effects, including flushing, paradoxical erythema, burning, skin irritation, allergic contact dermatitis, pruritus, skin

warming, and rebound erythema, may occur in up to 42% of patients. However, these reactions are generally mild, temporary, and confined to the application site. [65-68]

Sodium Sulfacetamide

A 10% lotion, either alone or combined with sulfur (5%), is available in various forms, including lotion, emollient foam, cream with sun protection, cleansers, and cleansing pads. Its efficacy stems from the antibacterial properties of sulfacetamide and the keratolytic and anti-inflammatory effects of sulfur. [69] This treatment is particularly beneficial for patients with inflammatory rosacea who also have seborrheic dermatitis. [70] It helps reduce inflammatory lesions and facial erythema. Common side effects include dryness, erythema, and irritation at the application site, which typically decrease in frequency over time. [60]

Summary and conclusions

This comprehensive review highlights the multifactorial pathogenesis of rosacea. Triggers such as UV radiation, emotional stress, spicy foods, and alcohol play a major role in exacerbating symptoms. Vasodilation and increased sensory neuron activity are central to rosacea. Transient receptor potential channels (e.g., TRPV-1) mediate responses to triggers. Immune-mediated inflammation involving mast cells, macrophages, and proinflammatory cytokines (e.g., IL-6, IL-1β) is pivotal. Molecules like koebnerisin and UV-induced factors such as VEGF and MMPs exacerbate inflammation. Sebocytes release inflammatory mediators and alter sebum composition, potentially influencing the microbiome and promoting dysbiosis. Demodex folliculorum mites, more abundant in rosacea-affected areas, and their associated bacterium Bacillus oleronius stimulate immune responses, further fueling inflammation. Family history and genome-wide association studies suggest a genetic predisposition to rosacea. While there is no cure for rosacea, symptom management focuses on using topical treatment such as ivermectin, metronidazole, azelaic acid, calcineurin inhibitors, retinoids, alpha-adrenergic receptor agonists and sodium sulfacetamide. Current treatments provide symptom relief and improve quality of life, but understanding underlying mechanisms remains crucial for advancing therapeutic options.

Disclosure

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