Current Drug Therapies for Rosacea: A Chronic Vascular and Inflammatory Skin Disease

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ABSTRACT

BACKGROUND: Rosacea is a chronic skin disorder that presents with abnormal vascular and inflammatory conditions. Clinical manifestations include flushing, facial erythema, inflammatory papules and pustules, telangiectasias, edema, and watery or irritated eyes.

OBJECTIVE: To discuss the evolving pathophysiology of rosacea, factors involved in promoting the chronic vascular and inflammatory abnormalities seen in rosacea, and the available drug therapies for the condition.

DISCUSSION: Chronic inflammation and vascular changes are believed to be underlying factors in the pathophysiology of rosacea. Aberrant cathelicidin expression, elevated kallikrein 5 (KLK5) proteolytic activity, and altered toll-like receptor 2 (TLR2) expression have been reported in rosacea skin leading to the production of proinflammatory cytokines. Until recently, drug therapies only targeted the inflammatory lesions (papules and pustules) and transient erythema associated with these inflammatory lesions of rosacea. Brimonidine tartrate gel 0.5% was recently approved for the treatment of persistent (nontransient) facial erythema of rosacea, acting primarily on the cutaneous vascular component of the disease.

CONCLUSION: Rosacea is a chronic vascular and inflammatory skin disease. Understanding the role of factors that trigger the onset of rosacea symptoms and exacerbate the condition is crucial in treating this skin disease.

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Rosacea is a chronic skin disorder that affects approximately 16 million people in the United States.[1] Patients with rosacea present with clinical manifestations that include flushing, persistent facial erythema, dryness, burning and stinging of the skin, inflammatory papules and pustules, telangiectasia or dilation of blood vessels, edema, and watery or irritated eyes.[2] Four clinical subtypes of rosacea have been characterized: erythematotelangiectatic, papulopustular, phymatous, and ocular (Figure 1; Table 1).[3,4] It is common for patients with rosacea to present with clinical manifestations of more than 1 subtype.

Patients with the *erythematotelangiectatic* subtype of rosacea present with flushing and persistent facial erythema. Telangiectasias may also be visible in these patients. Patients with the *papulopustular* subtype present with papules and pustules. These patients may be misdiagnosed with acne vulgaris because of the similarity in appearance between the 2 skin disorders. Patients with the *phymatous* subtype present with thickening of the skin and irregular surface nodules. Because the skin thickening typically occurs in the nose, rhinophyma is a common condition of this subtype. It is estimated that the *ocular* subtype of rosacea affects up to 60% of patients with rosacea.[5] Patients with the ocular subtype present with eye irritation, which may appear as watery, swollen, and/or bloodshot.

Women are frequently more affected by rosacea than men.[6,7] The onset of this skin disorder generally occurs between age 30-50 years, although rosacea has been less frequently reported in the teenage years.[8,9] Heredity has also been implicated in the epidemiology of rosacea.[10] Rosacea is more prevalent in fair-skinned people of Northern and Eastern European descent but has also been reported in people of other ethnicities.[5,11,12] Some of the factors believed to trigger the onset of symptoms or exacerbate the condition include sun exposure, stress, hot and cold weather, and consumption of hot beverages or alcohol and spicy foods.[5,13,14]

The National Rosacea Society (NRS) conducted a survey with more than 400 patients with rosacea to evaluate the impact of rosacea on their daily lives.[15] The results of the survey revealed that most respondents felt rosacea had lowered their self-esteem (75%), made them feel embarrassed (70%) and frustrated (69%), and that they felt robbed of pleasure or happiness because of their rosacea (56%).[15] Patients with rosacea have also reported having depression and anxiety because of their disease.[16] Improvement of self-image is typically seen after successful therapy. Most of the patients (70%) who responded to the NRS survey reported that their emotional health improved with effective treatment.[15]

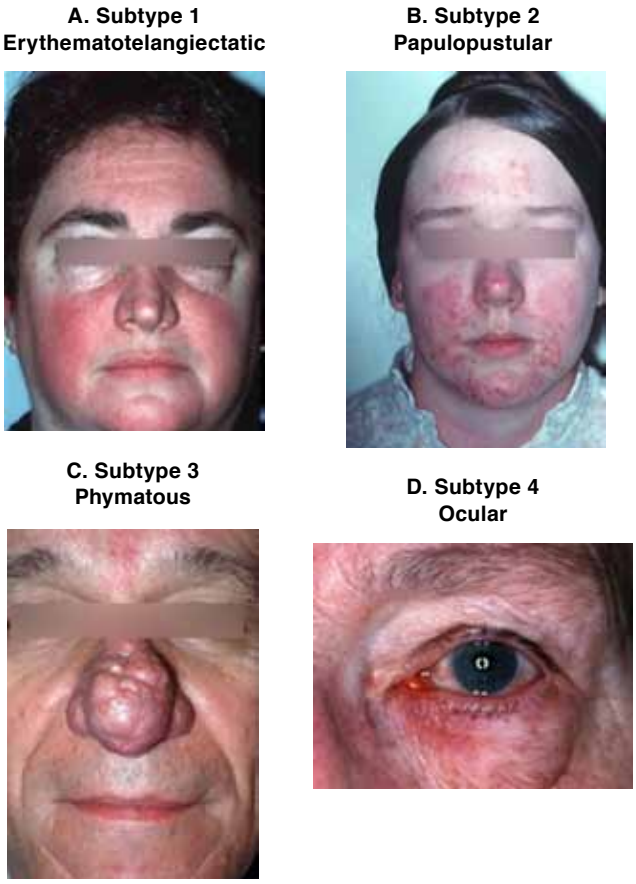
The pathophysiology of rosacea is poorly understood. While many mechanisms have been proposed, chronic inflammation and vascular changes are believed to be underlying factors (Figure 2).[17,18] An altered innate immune response may also play a role in the pathogenesis of rosacea.[19] Understanding the role of these factors and how they trigger the onset of rosacea symptoms and exacerbate the condition will be crucial in treating this chronic skin disease. Here, we discuss the evolving pathophysiology of rosacea, review factors involved in promoting the chronic vascular and inflammatory abnormalities seen in rosacea, and review the available drug therapies for the condition.

Pathophysiology of Rosacea

Chronic Inflammation

Antimicrobial peptides, processing enzymes, and toll-like receptors (TLR) may be involved in promoting inflammation in rosacea skin.[20] Cathelicidins were the first antimicrobial

FIGURE 1 Subtypes of Rosacea



peptides identified in the human skin and function in the innate defense against infectious pathogens.[21,22] Elevated levels of cathelicidins and abnormal forms of cathelicidins have been reported in patients with rosacea, as well as in those with other inflammatory skin conditions.[23-25] Some forms of these cathelicidin peptides have vasoactive and proinflammatory activities leading to modification of dermal structures through vascular changes and collagen degeneration.[26,27]

Cathelicidins are processed by an epidermal serine protease called kallikrein 5 (KLK5).[28] Patients with rosacea have elevated expression and elevated protease activity of KLK5.[28] Overexpression of serine proteases has resulted in increased skin inflammation in mouse models.[29] Elevated epidermal serine protease activity along with the deposition of cathelicidin-derived peptides in the skin have been identified in inflammatory lesions of patients with rosacea.[28]

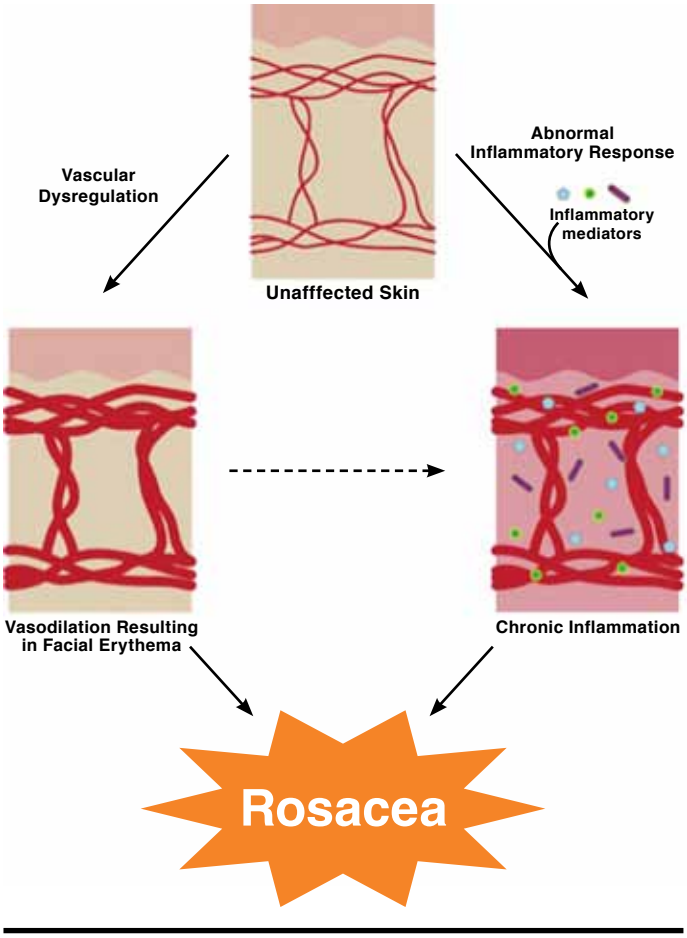
Elevated expression of TLRs has also been observed in skin biopsies from patients with rosacea.[30] TLRs are innate immune pattern recognition receptors that play a role in promoting inflammation when specific microbial products or products from a host injury are recognized.[31,32] Specifically, increased expression of TLR2 has been observed in the epidermis of patients with rosacea when compared with normal skin.[30] TLR2 expression is localized in the superficial layers of the epidermis and hair sheath in normal skin. TLR2 expression is localized throughout the epidermis and infiltrating cells of the dermis in rosacea skin. The localization of TLR2 expression coincides with KLK5 expression in skin biopsies from patients with rosacea.[28,30] Stimulating TLR2 results in elevated KLK5 activity, while TLR2-knockout models have reduced KLK5 activity.[30] Thus, recent studies support the current understanding that antimicrobial peptides, processing enzymes, and TLRs play a role in maintaining chronic inflammation in rosacea.

TABLE 1 Subtypes of Rosacea

Subtypes[a]	Clinical Features	Approved Drug Therapies
Subtype 1: Erythematotelangiectatic	• Persistent erythema • Prolonged flushing • Telangiectasias may be present	• Brimonidine tartrate 0.5%[48]
Subtype 2: Papulopustular	• Papules and pustules present • Persistent erythema • May resemble acne vulgaris (without comedones) • Facial edema may be present	• Metronidazole 0.75% and 1%[43,44] • Azelaic acid 15%[45] • Sodium sulfacetamide 10%-sulfur 5%[46,47] • Sub-antimicrobial dose doxycycline 40 mg MR[49]
Subtype 3: Phymatous	• Skin thickening • Irregular nodularities • Rhinophyma is common	No FDA-approved products
Subtype 4: Ocular	• Watery, bloodshot eyes • Dry eyes • Foreign body sensation • Irritation and inflammation may be present • Blepharitis, conjunctivitis, eyelid irregularities	No FDA-approved products

[a]*It is common for rosacea patients to present with clinical features of more than 1 subtype.*
FDA = U.S. Food and Drug Administration; mg = milligram; MR = modified release.

FIGURE 2 Chronic Vascular and Inflammatory Skin of Rosacea



Chronic Vasodilation

Rosacea has also been referred to as a vascular skin disorder because of its association with flushing, redness, and visible blood vessels. Mast cells may participate in a complex multifactorial process to promote localized vasodilation, angiogenesis, and tissue fibrosis.[33] Flushing may involve the nervous system, since symptoms of rosacea are triggered when patients are under emotional stress.[34-36]

One active form of cathelicidin found in rosacea is LL-37.[28] LL-37 is processed by the proteolytic activities of KLK5 and induces endothelial cell changes that may play a role in promoting the vascular effects of rosacea.[37] Neovascularization occurs when LL-37 is applied in a rabbit model, suggesting that LL-37 may play a role in creating a chronic vascular environment in rosacea skin.[26] Adrenergic receptors have also been implicated to play a role in neurovascular regulation.[38] Adrenergic receptor agonists have vasoconstrictive activity and have been shown to be effective at reducing erythema associated with rosacea.[38-40]

Treatment Options

Currently. there is no cure for rosacea.[41] Treatments are aimed at controlling the signs and symptoms that can worsen without treatment. The 4 topical agents approved by the U.S. Food and Drug Administration (FDA) for the topical treatment of rosacea are as follows:

- metronidazole gel 0.75% and 1%
- azelaic acid gel 15%
- sodium sulfacetamide 10%-sulfur 5% lotion and cream
- brimonidine tartrate gel 0.5%[38,41-48]

Metronidazole, azelaic acid, and sodium sulfacetamide-sulfur treat the papules and pustules associated with rosacea, while brimonidine tartrate treats persistent (nontransient) facial erythema of rosacea (Table 1). Currently, doxycycline 40 milligrams (mg) modified release (MR) is the only FDA-approved oral drug indicated for the treatment of inflammatory lesions (papules and pustules) of rosacea.[42,49]

Topical Therapies

Topical metronidazole is a synthetic agent with antimicrobial, antioxidant, and anti-inflammatory effects.[42,50] Topical metronidazole gel 0.75% and 1.0% is a nitroimidazole recommended by the American Acne and Rosacea Society (AARS) for the topical treatment of inflammatory lesions and transient erythema.[44,51,52] While the mechanism of action in rosacea is unclear, metronidazole may act through reducing neutrophil production in reactive oxygen species.[53] Significant decreases in inflammatory lesions have been reported in multiple clinical studies.[54-57] The most common adverse reactions (incidence >2%) of topical metronidazole are nasopharyngitis, upper respiratory tract infection, and headache.[58]

Azelaic acid is a naturally occurring saturated dicarboxylic acid with anti-inflammatory, antioxidant, and antimicrobial effects.[59,60] Azelaic acid gel 15% is recommended by the AARS for topical treatment of inflammatory papules and pustules of mild to moderate rosacea.[51] The exact mechanism of action is also unknown, but it may act through antikeratinizing and anti-inflammatory effects in rosacea.[53,61-66] Azelaic acid down-regulates cathelicidins by inhibiting serine protease KLK5 activity.[67,68] The most common treatment-related adverse events reported in 12-week and 15-week clinical trials were burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%), and erythema/irritation (4%).[69]

Another topical medication approved by the FDA and recommended by the AARS for the treatment of rosacea is sodium sulfacetamide 10%-sulfur 5%.[51] Sulfur has keratolytic, antifungal, and antibacterial activities.[70] Sulfacetamide-sulfur preparations reduce inflammatory lesions of rosacea when used as monotherapy or in combination with other agents.[71] While the mechanism of action of sulfur remains unclear, sulfonamides are believed to act as competitive antagonists to para-aminobenzoic acid, a component required for

bacterial growth.[46,47] The most common treatment-related adverse events reported with sodium sulfacetamide 10%-sulfur 5% were application site reactions (38%), which include dryness, erythema, and pruritus.[72]

Brimonidine tartrate is a highly selective α2-adrenergic receptor agonist with potent vasoconstrictive activity.[38] In 2 randomized, vehicle-controlled trials, topical brimonidine tartrate gel 0.5% was more efficacious at reducing moderate to severe persistent (nontransient) facial erythema than vehicle gel ($P < 0.001$) in patients with rosacea.[38,39] Slightly higher incidence of adverse events was observed for topical brimonidine tartrate than for the vehicle gel; however, most of the adverse events were dermatological, mild, and transient in nature. The most common adverse reactions reported in vehicle-controlled trials were erythema (4%), flushing (3%), skin burning sensation (2%), and contact dermatitis (1%).[48]

Oral Therapy

Tetracycline class antibiotics, the mainstay of oral antibiotic therapy for rosacea, has been used as an off-label treatment for rosacea since the 1950s.[73-75] Tetracyclines are believed to have effects on inflammation, immunomodulation, cell proliferation, and angiogenesis.[76] Tetracyclines may reduce the inflammation associated with rosacea by downregulating proinflammatory cytokines and directly inhibiting matrix metalloproteinases (MMPs).[77] One concern with the long-term use of tetracyclines has been antibacterial resistance.[78]

Doxycycline 40 mg MR is indicated for the treatment of inflammatory lesions of rosacea in patients aged at least 18 years.[49] Doxycycline 40 mg MR provides anti-inflammatory activity at a sub-antimicrobial dose with a reduced risk of bacterial resistance compared with higher doses of doxycycline.[75,76,79-81] Administration of this sub-antimicrobial dose doxycycline (40 mg) once daily for 9 months did not lead to the development of antibiotic resistance in subjects with periodontal disease.[82] The efficacy and safety of doxycycline 40 mg MR has been evaluated in multiple studies.[80,81,83,84] In 2 randomized, placebo-controlled, multicentered, double-blind, 16-week trials, rosacea patients on doxycycline 40 mg MR had a significantly greater reduction in total inflammatory lesion counts than the placebo control group at week 16 when compared with baseline ($P < 0.001$).[49] The most common adverse reactions reported in clinical trials (incidence >2% and more common than with placebo) are nasopharyngitis, sinusitis, diarrhea, hypertension, and aspartate aminotransferase increase.[49]

The mechanism of action by doxycycline is unclear, but doxycycline directly binds to MMPs and inhibits their activities.[85] MMPs are responsible for the degradation of extracellular matrix components when they are released after stimulation from proinflammatory cytokines. One potential mechanism of action for doxycycline in the treatment of rosacea is indirect inhibition of KLK proteolytic activities and cathelicidin peptide LL-37 production by inhibiting MMPs in keratinocytes.[37] Decreased KLK activity is reported when doxycycline or other MMP inhibitors are added to live keratinocytes during KLK production.[37]

Discussion

The clinical signs and symptoms of rosacea present predominantly in the facial region. Patients can suffer from emotional stress if the areas that are affected are visible.[86] Patients with rosacea perceive their physical appearance to negatively influence their emotional health, which can result in psychological comorbidities such as anxiety disorders and social phobias.[16] Previously, drugs approved by the FDA only treated the inflammatory lesions (papules and pustules) and the transient erythema associated with these inflammatory lesions of rosacea. Recently, brimonidine tartrate gel 0.5% was approved for the treatment of persistent (nontransient) facial erythema of rosacea, acting primarily on the cutaneous vascular component of the disease.

Examination of factors that trigger the onset of rosacea symptoms and exacerbate the condition is crucial in treating this skin disease. While external stimuli such as sun exposure, stress, hot and cold weather, and the consumption of hot beverages, alcohol, and spicy foods may trigger the onset of symptoms in some patients with rosacea, there are internal stimuli that may also play a role. Components of the immune system and changes in the innate immune response may trigger abnormal inflammatory responses. TLRs are innate immune pattern recognition receptors that play a role in promoting inflammation. Cathelicidins also play a crucial role in promoting abnormal inflammation and vascular responses.

Conclusion

While the pathophysiology of rosacea is still poorly understood, underlying factors that play a role in the pathogenesis of rosacea have been identified. Factors that promote chronic vascular and inflammatory abnormalities impact the evolving pathophysiology of rosacea. Understanding the mechanism of action in which these factors trigger the onset of symptoms and exacerbate the condition will be crucial in treating this chronic skin disease. Current drug therapies are effective in treating the inflammatory lesions (papules/pustules) and facial erythema associated with rosacea. Topical drugs such as metronidazole, azelaic acid, and sodium sulfacetamide-sulfur treat the papules and pustules associated with rosacea, while brimonidine tartrate treats persistent (nontransient) facial erythema of rosacea. Oral doxycycline 40 mg MR also treats inflammatory lesions of rosacea. Further examination of the factors that promote the abnormal vascular and inflammatory environment of rosacea may provide additional therapeutic benefits in the treatment of this chronic skin disease.

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