Update on Rosacea Pathogenesis and Correlation With Medical Therapeutic Agents

James Q. Del Rosso, DO

The pathogenesis of rosacea is poorly understood, though clinical features of the disease are well-recognized. This article updates current views on mechanisms potentially associated with rosacea. Although data is limited, correlation with therapies is reviewed.

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Rosacea is a chronic facial disorder estimated to affect at least 14 million people in the United States and 1.5% to 10% of people in Europe based on population studies.[1,2] The disorder is characterized by intermittent episodes of exacerbation and variable periods of remission.[1-4] Multiple trigger factors have been identified and may be operative in individual patients.[3-6] Epidemiologic data suggest a genetic predisposition for the development of rosacea, with several intrinsic and extrinsic factors potentially correlating with the phenotypic expression of the disorder; approximately one third of patients with rosacea report a family history of the disease.[4-7] Most individuals affected by rosacea are white adults, usually of northern European origin, with Fitzpatrick skin types I and II on the face.[3,6] Approximately 60% of cases of rosacea are diagnosed before the age of 50 years, with most cases presenting between the ages of 30 to 50 years.[1,3,5,6]

The major subtypes of rosacea include erythematotelangiectatic, ocular, papulopustular, and phymatous rosacea, with glandular and granulomatous presentations described as variant subtypes.[8] The clinical features of rosacea primarily affect sites of facial convexity and include transient erythema (flushing), nontransient erythema, papules, pustules, and telangiectases. Clinical signs and symptoms of rosacea include stinging, burning, pruritus, edema, and dry skin.[8] The varied clinical presentations of rosacea appear to reflect a spectrum of heterogeneous responses to multiple pathogenic factors.[7] It is important to recognize that subtypes of rosacea are not stages; there is no evidence of disease progression from one subtype to another.[8] However, a patient may express clinical features of more than one subtype of rosacea.

What are the medical therapies most predominantly used for the treatment of rosacea?

Comprehensive treatment for rosacea incorporates appropriate skin care, photoprotection, medical therapies, and physical modalities.[1,3,9-11] The major topical therapies for rosacea include azelaic acid, metronidazole, and sulfacetamide-sulfur. The predominant oral therapies used for rosacea are tetracycline antibiotics (ie, doxycycline hyclate or monohydrate, minocycline hydrochloride, tetracycline hydrochloride).[1,9-11] Selection of therapeutic agents and use of combination approaches primarily are dependent on severity of disease and factors related to individual history, such as previous therapies used, history of drug allergies, and medication history.[10] Although medical therapies, both topical and oral, are effective in reducing inflammatory lesions and perilesional erythema associated with rosacea, the mechanisms of action of these agents are poorly understood.[10,11]

Conventional use of tetracycline agents for rosacea, including doxycycline hyclate or monohydrate (100–200 mg daily), minocycline

From the Department of Dermatology, University of Nevada School of Medicine, Las Vegas.

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hydrochloride (100–200 mg daily), or tetracycline hydrochloride (500–1000 mg daily), produces both anti-inflammatory and antibiotic activity.[10,11] Recently, the use of anti-inflammatory–dose doxycycline (40-mg controlled-release tablet once daily) has been shown to be effective and safe for the treatment of rosacea in 2 double-blinded, randomized, placebo-controlled 16-week trials inclusive of 269 actively treated patients.[12] The mean total inflammatory lesion count declined by 61% and 46% in patients receiving active treatment, and 29% and 20% in patients receiving placebo; reduction in erythema also was observed. Anti-inflammatory–dose doxycycline produces multiple intracellular and extracellular biologic activities, including anti-inflammatory and anticollagenolytic effects, without antibiotic activity.[12] Consequently, antibiotic selection pressure and potential for emergence of resistant bacterial strains are avoided, especially with chronic administration that is commonly used for the treatment of rosacea.

The following reviews current perspectives on the pathogenesis of rosacea and attempts to provide a rational correlation with potential mechanisms of action of available medical therapies, including anti-inflammatory–dose doxycycline.

What is currently known about mechanisms involved with the pathogenesis of rosacea?

The pathophysiology of rosacea has not been well-defined, including mechanistic explanations that explain the clinical presentations of defined clinical subtypes.[3-7] Multiple intrinsic and extrinsic factors have been associated with the development of rosacea, suggesting a multifactorial pathogenesis. These potential etiologic mechanisms are summarized in the Table.[2,4,6,7,13-30]

Mechanisms Associated With the Pathogenesis of Rosacea

- Abnormalities of the pilosebaceous unit[7]
- Altered cutaneous oxidation/antioxidant balance[13]
- Altered vascular response to ambient and oral heat exposure[4,6,7,14,15]
- Changes in cutaneous blood flow[4,7,14-17]
- Degeneration of dermal matrix[7,18,19]
- Features also associated with photoaging[2,4,6,7,13,14,16-22]
- Immune response to microbial organisms, such as follicular *Demodex* mites[23-25]
- Impairment of epidermal barrier function involving predominantly centrofacial skin[26]
- Increased angiogenesis[7]
- Increased generation of reactive oxygen species[13,20]
- Increased production of reactive nitrogen species[21,27]
- Loss of vascular integrity[7]
- Oral-thermal flushing[4,6]
- Structural alterations of cutaneous vasculature[4,7,14-16,18]
- Telangiectasia formation[7]
- Temperature-dependent bacterial protein production[28]
- Up-regulation of several matrix metalloproteinase enzymes[27,29,30]

How might chronic photodamage contribute to the pathophysiology of rosacea?

Although rosacea is not associated with definitively diagnostic histologic features, actinic elastosis with dermal matrix degradation and vasodilation are the most prominent and commonly identified histologic findings identified from biopsy specimens of patients with rosacea.[7,8,31] Based on common clinical characteristics and dermatopathologic findings, it has been suggested that chronic photodamage significantly contributes to the pathogenesis of rosacea.[3,4,6,7,31,32] Persistent facial erythema and fine linear telangiectases are common features predominantly affecting facial convexities of fair-skinned whites.[2-7] It has been suggested that chronic dermal matrix degradation and degenerative changes to superficial cutaneous vasculature lead to leakage into perivascular tissue with accumulation of serum and proinflammatory mediators, fluid outflow in excess of dermal lymphatic capacity, and loss of perivascular structural support, all producing greater persistence of erythema, edema, and telangiectases over time.[4,6,7]

What role may up-regulation of matrix metalloproteinases (MMPs) play in the pathogenesis of cutaneous and ocular rosacea?

The degradation of extracellular dermal matrix with degeneration of collagen and perivascular support

associated with rosacea are believed to result from increased expression of specific MMPs, a group of enzymes involved in inflammation, collagenolysis, and angiogenesis. Up-regulation of certain MMPs has been correlated with UV light exposure and presence of *Demodex folliculorum*.[20,27,29,32,33] One specific enzyme, MMP-9, also referred to as *gelatinase B*, demonstrates up-regulation in inflammatory rosacea in the presence of *D folliculorum* identified histologically.[29] MMP-9 appears to be an important etiologic factor in ocular rosacea.[30]

How does nitric oxide synthetase activity correlate with mechanisms involved in the pathophysiology of rosacea?

Exposure to UVB has been shown to increase activity of both inducible and endothelial (eNOS) nitric oxide synthetase in human keratinocytes, leading to increased nitric oxide production.[12,21] Nitric oxide is a modulator of inflammation and vascular response, has been shown to up-regulate MMP expression, and inhibits synthesis of dermal matrix components such as collagen.[21,27] In addition, increased production of eNOS induces vasodilation. The multitude of described effects related to increased nitric oxide activity suggests a role in the pathogenesis of rosacea.[12,21]

How has cutaneous antioxidant activity been associated with the pathogenesis and clinical severity of rosacea?

UV light exposure also induces production of reactive oxygen species (ROS).[20] Increased ROS may degrade collagen by activating pro-MMPs and inactivating intrinsic tissue inhibitors of MMPs, and may directly damage facial follicles in rosacea.[2] Inadequate cutaneous antioxidant reserve in patients with greater clinical severity of rosacea has been suggested based on evaluation of the activity of superoxide dismutase, an intracellular enzyme that behaves biologically as an innate antioxidant.[13] Cutaneous superoxide dismutase activity increased in patients with mild rosacea, reflecting increased protection against ROS-induced oxidative tissue damage. This response was coupled with lower levels of malondialdehyde, the predominant lipid peroxidation product of cutaneous fatty acids. In patients with more severe rosacea, superoxide dismutase activity was reduced and malondialdehyde levels elevated. This indicated that as rosacea severity increased, the capacity of intrinsic antioxidant defense may have been exceeded.[13]

How do available medical therapies that are often used to treat rosacea influence mechanisms associated with the pathogenesis of this disorder?

Overall, the mechanisms of action of medical therapeutic agents used to treat rosacea are poorly understood. Metronidazole appears to mitigate signs and symptoms of rosacea because of antioxidant and anti-inflammatory properties, related at least partially to reduction in the generation of neutrophil-generated ROS.[34,35] Similar to topical metronidazole, the anti-inflammatory mechanism of azelaic acid for rosacea also appears to be at least partially related to the inhibition of neutrophil-mediated ROS.[36] Although the mechanism of action of sulfacetamide-sulfur in rosacea is not known, anti-inflammatory benefit has been implicated based on clinical studies and long-term experience, and reduction of *Demodex* mites has been suggested.[37]

The therapeutic agents most extensively studied with regard to anti-inflammatory and anticollagenolytic properties, which appear to correlate with clinical activity in rosacea, are tetracyclines (J.Q.D. et al, unpublished data, 2006).[12,27,38,39] Multiple biologic effects of tetracyclines (ie, doxycycline hyclate or monohydrate, minocycline hydrochloride, tetracycline hydrochloride) have been identified that are unrelated to dose-dependent antibiotic activity (J.Q.D. et al, unpublished data, 2006).[12,27,39] These effects include inhibition of activity of several MMPs (MMP-2, MMP-8, MMP-9, MMP-12, MMP-13), reduced activity of constitutive eNOS via inhibition of the Ca++/calmodulin pathway, down-regulation of the production of several pro-inflammatory cytokines (eg, tumor necrosis factor α, interleukin 1β) and reduced activity of ROS (J.Q.D. et al, unpublished data, 2006).[12,27,38,39] In the case of doxycycline, separation of antibiotic and anti-inflammatory activity based on pharmacokinetic and microbiologic parameters has been identified (J.Q.D. et al, unpublished data, 2006).[12,27,39] Anti-inflammatory–dose doxycycline produces anti-inflammatory and anticollagenolytic activities without exhibiting antibiotic effects, thereby avoiding antibiotic selection pressure, which may impact upon emergence of resistant bacterial strains and potential adverse reactions associated with alteration of commensal flora (eg, vaginal candidiasis)(J.Q.D. et al, unpublished data, 2006).[12,39]

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