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REVIEW ARTICLE

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New Concepts in Rosacea Classification and Treatment

Ramadan S. Hussein[1,2*]; Walid Kamal Abdelbasset[3,4]

[1]*Department of Internal Medicine, College of Medicine Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia*
[2]*Department of Dermatology, Andrology and STDs, Assuit Plice Hospital, Assuit, Egypt*
[3]*Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia*
[4]*Department of Physical Therapy, Kasr Al-Aini Hospital Cairo University, Giza, Egypt*

Abstract

Rosacea is a chronic, persistent, inflammatory skin disease of the central face and eyes, caused by immune dysfunction and neurovascular dysregulation, that presents with recurrent flushing, erythema, telangiectasia, papules, or pustules. Rosacea affects quality of life and social and mental health. Recent research has linked rosacea to autoimmune, gastrointestinal, neurological, and psychiatric diseases and cancer risks. This review discusses the rosacea subtype-directed approach management, new topical and systemic formulations, and therapy combinations depending on new phenotype classification.(**International Journal of Biomedicine. 2022;12(4):515-520.**).

Keywords: rosacea • skin • classification • treatment

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Introduction

Rosacea is a chronic, persistent, inflammatory skin disease of the central face and eyes, caused by immune dysfunction and neurovascular dysregulation, that presents with recurrent flushing, erythema, telangiectasia, papules, or pustules. Rosacea affects between 0.09% and 22.41% of the general population and 5.46% of adults worldwide.[1] Phymatous alterations are uncommon, typically affecting the nasal area, and are more common in males. About 50% of rosacea individuals suffer eye dryness, conjunctivitis, blepharitis, and, rarely, keratitis.[2-4] Rosacea usually starts in adults but can occur at any age. Fair-skinned Celts are particularly susceptible. Because erythema and telangiectasia are more difficult to identify in deeper phototypes, rosacea is commonly misdiagnosed.[5,6] Rosacea affects quality of life and social and mental health.[7,8] Recent research has linked rosacea to autoimmune, gastrointestinal, neurological, and psychiatric diseases and cancer risks; whether these links are causative needs more study.[9] In addition to regular skin care and avoiding triggers, rosacea can be treated with active therapies. Topical brimonidine and oxymetazoline are approved for erythema, and ivermectin, azelaic acid, metronidazole, and doxycycline are for papules/pustules. Telangiectasia, erythema, and phyma can be treated with lasers and light. Phyma may need surgery.[3]

***Corresponding author:** Ramadan S. Hussein. Department of Internal Medicine, College of Medicine, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia. E-mail: ramadangazeera@yahoo.com*

Pathophysiology of rosacea

Dysregulation of immunological and neurocutaneous processes contributes to rosacea development.[10] The association of rosacea with SNPs in MHC genes suggests genetic vulnerability with changed immune reactivity.[11]

Microbes like *Demodex folliculorum* and *Bacillus oleronius* can elicit innate and adaptive immune activation.[12] Innate immunity activation upregulates keratinocyte-derived TLR2 and PAR2, which promote cathelicidin. KLK-5 protease converts cathelicidin to bioactive LL-37, producing erythema.[13] TLR2 activates the NLRP3 inflammasome, causing pustule development, discomfort, and vascular responsiveness via IL-1, PGE2, and TNF-α production. TLR2 also induces

inflammation, erythema, and telangiectasia through expression of chemokines, proteases, cytokines, and angiogenic factors. PAR2 activation causes itching, inflammation, and discomfort together with T-lymphocyte, neutrophil, mast cell degranulation, and release of chemokines, cytokines, and prostaglandins.[10] Activation of the acquired immune system, shown by TH1 and TH17 cells with immunological mediators, causes inflammation and subsequent immune activation.[14]

The ankyrin (TRPA) and vanilloid (TRPV) subfamilies of the transient receptor potential (TRP) channel superfamily may mediate neurocutaneous pathways in rosacea, which indicate responsiveness to ultraviolet light, temperature variations, spicy foods, and wine. Different environmental events may cause specific subfamily receptors to react, resulting in the production of vasoactive neuropeptides. TLR2 and PAR2 are also expressed in sensory neurons, and they can continue to activate inflammatory processes.[15]

Rosacea diagnosis and classification

One or more of the following major characteristics centered on the convex parts of the face are required for rosacea diagnosis: flushing, nontransient erythema, papules/pustules, and telangiectasia. The most crucial observation is persistent facial erythema lasting at least 3 months, sparing the periocular skin. This form of erythema is the only necessary diagnostic criterion for rosacea. Flushing, papules, pustules, and telangiectasia on the convex faces are supporting, but not required, diagnostic features. Burning or stinging sensations, edema, plaques, a dry look, ocular signs, and phymatous alterations are secondary symptoms. Polycythemia vera, connective tissue disorders, carcinoid, and mastocytosis must not be present. Long-term facial steroid users are also excluded. Extrafacial erythema is usually an excluding feature, photosensitivity and allergic contact dermatitis may be considered. There are four subtypes of rosacea: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PhR), and ocular rosacea (OR).[2,16]

ETR is characterized by prolonged flushing (lasting longer than 10 minutes). The center of the face is usually the reddest, although the periphery, ears, neck, and upper chest may also be affected. Periocular skin is sparied. Stress, hot beverages, alcohol, spicy meals, exercise, cold or hot temperatures, and hot baths can cause flushing. Episodes are sometimes unprovoked.

PPR patients have a red center face but continuous or episodic inflammation with little papules and pinpoint pustules. Symptoms may include edema. Periocular skin is seldom affected, usually in midlife women. Inflammation can cause persistent edema and phymatous changes.

PhR is characterized by pronounced skin thickening and uneven surface nodules; they can appear on the nose (rhinophyma), chin (gnathophyma), forehead (metophyma), one or both ears (otophyma), as well as the eyelids (blepharophyma). Four forms of rhinophyma (glandular, fibrous, fibroangiomatous, and actinic) are clinically distinguishable and have unique histopathologic characteristics.[16]

In OR patients with ocular symptoms, blepharitis and conjunctivitis are the most prevalent findings. Recurrent chalazion and meibomian gland irritation may occur. Hyperemia, telangiectasia, and watery or dry, itchy eyes might develop. OR frequently causes burning, stinging, itching, light sensitivity, and a feeling there is a foreign body in the eye. Keratitis, scleritis, iritis, and consequences are rare.[16]

In 2017, the worldwide ROSacea COnsensus (ROSCO) group developed a revised schema on patient attributes that incorporated clinical manifestations. This phenotypic method focused on observable traits, which can be altered by environmental or genetic causes.[17] The ROSCO panel included ophthalmologists and dermatologists from different countries all over the world to make sure that the whole world was represented. In this model, accepted by the National Rosacea Society, either one of two separate signs is diagnostic of rosacea: persistent redness in the center of the face that gets worse from time to time due to possible triggers, phymatous changes. In the absence of these signs, if two or more major signs are present (transient erythema, inflamed papules/pustules, telangiectasia, conjunctivitis/blepharitis/telangiectasia of the lids) we can make a diagnosis. Minor characteristics (edema, burning, and dry sensation of the skin) could also potentially be diagnostic or important.[5,17]

Next step, management options were aligned with the phenotypic approach to enhance patient outcomes and well-being by addressing the most problematic features.[2,18]

Therapy

General advice for patients with rosacea

The disease picture varies over time, and the aggravating factors differ from person to person. Good patient information and knowledge of the condition are prerequisites for good treatment results. Worsening of the condition can be reduced by avoiding known triggers. The literature states that sun exposure worsens the condition by up to 80%, and the use of a high sun-protection factor is generally recommended; however, because patients with rosacea have sensitive skin, a variety of skincare products, including sunscreens, moisturizers, and cosmetics, can worsen the condition. There will often be individual variations, so patients are welcome to try their hand at finding effective skin care. Creams with a green cream base will be able to camouflage redness, and mineral oils and silicone-containing preparations are generally tolerated. As a rule, people with rosacea should avoid topical steroids on the face, as these can worsen the condition. Some foods, coffee, tea, citrus fruits, red wine, blue cheese, and spices can cause rosacea to flare up because they contain vasodilators. Flare-ups are also seen with significant temperature variations and intense physical activity. There are significant differences in how patients respond to various triggers.[8]

Sunscreen and cosmetics

Choosing UVA and UVB sunscreens is very important. Titanium dioxide and zinc oxide are physical blockers best tolerated. Protective silicones should be in cosmetics and sunscreens. A light, easy-to-apply foundation can be set with powder. Foundations that have sunscreen with UVA and UVB

protection are encouraged. Green cosmetics or sunscreen can mask redness. Products should be avoided that have sodium lauryl sulfate, astringents, toners, menthol, camphor, and toners. Waterproof makeup and thick foundations that are difficult to apply and remove should also be avoided. Cleansers should be soap-free.[8]

Medical treatment

The medical treatment is primarily aimed at reducing inflammation and the symptoms it causes. Erythema persisting after anti-inflammatory treatment can be treated with lasers, intense pulsed light, or medication. Mild and moderate forms of rosacea can often be treated topically. Widespread inflammatory and PhR require oral treatment, possibly surgical treatment, and laser treatment.[2]

Topical medications

Metronidazole: A 0.75% metronidazole topical cream is recommended twice daily. Metronidazole is equally effective as low-dose tetracycline, but it works faster.[2]

Ivermectin: It is not sufficiently well documented that one type of topical treatment is significantly better than another, although a comparative study with topical ivermectin and metronidazole showed that the effect of ivermectin was somewhat better.[19]

Sodium sulfacetamide and sulfur: 10% sodium sulfacetamide and 5% sulfur have resurged in acne and rosacea therapy: cleansing twice a day with a 10% sodium sulfacetamide and a 5% sulfur solution.[3]

Azelaic acid: FDA-approved for mild-to-moderate rosacea. Azelaic acid is a saturated dicarboxylic acid. Like metronidazole, azelaic acid may suppress neutrophils' ROS generation. Pregnancy category B.[10]

Benzoyl peroxide: Some rosacea patients with barrier failure and sensitive skin can be stung by benzoyl peroxide. Non-sensitive people can quickly resolve erythematous papules and pustules. Phymatous and glandular rosacea patients take benzoyl peroxide or benzoyl peroxide–clindamycin combination treatment effectively. Pregnancy category C.[14]

Topical antibiotics: Cleaning with topical clindamycin or erythromycin twice daily for four weeks is comparable to oral tetracycline. Stinging and dryness are side effects. Clindamycin and erythromycin both are in pregnancy category B.[2]

Topical tacrolimus treats steroid-induced rosacea-like lesions. Tacrolimus is a macrolide immunosuppressant produced by the fungus *Streptomyces tsukubaensis*. Most patients clear within 1 to 2 months of using tacrolimus 0.1% and minocycline 100 mg twice daily.[14]

Brimonidine tartrate: Symptomatic improvement of erythema can be achieved by topical application of the alpha-2 agonist brimonidine tartrate. The drug can be used in parallel with anti-inflammatory rosacea treatment and has a rapid onset of action.[10] The incidence of relapse is highest in the first two weeks after starting brimonidine treatment, and the patient must be given good information about the use of the drug. Daily application over time can have a better effect than occasional use, in terms of tackling side effects.[20]

Topical tretinoin: Chronic topical tretinoin treatment enhances dermal connective tissue remodeling and reduces skin inflammation. Clinical response is delayed, typically not apparent for two or more months. The use of tretinoin in rosacea may cause telangiectasia by increasing cutaneous neovascularization; if so, avoid it. Pregnancy category C.[20]

Oral therapy

Tetracyclines: Tetracycline has long been used to treat rosacea. Symptoms normally improve after 3 to 4 weeks of oral tetracycline. Subantimicrobial-dose tetracycline has been demonstrated to be an effective treatment for rosacea, due to its inherent anti-inflammatory properties (250 mg daily or every other day for maintenance). Minocycline, doxycycline hydrate, and doxycycline monohydrate are also beneficial for rosacea, they have a longer half-life, increased bioavailability, and may be taken with meals, decreasing gastrointestinal adverse effects. Slow-release doxycycline 40mg daily has documented the same effect as doxycycline 100 mg daily, but with a lower incidence of side effects. All long-term antibiotic usage can cause resistance, even if this has not been documented for low-dose doxycycline. The treatment time for rosacea with oral tetracyclines is usually 4-12 weeks, but there are large individual variations in response.[19]

Macrolides: Oral erythromycin treatment is used for rosacea when there is tetracycline intolerance, allergy, resistance, pregnancy, breastfeeding, or age younger than 12 years. Clarithromycin and azithromycin are beneficial for rosacea. Clarithromycin: 250mg twice daily for 4 weeks, followed by 250 mg once daily for 4 weeks.[14]

Metronidazole: Metronidazole 200mg twice a day with alcohol abstinence during treatment prevents disulfiram-induced headaches. The drug is safe to use during pregnancy (category B) and is an alternative to tetracyclines.[19]

Isotretinoin: Daily low-dose isotretinoin (0.3 mg/kg) as long-term therapy should be considered where the patient needs continued oral treatment beyond three months of continuous tetracycline use. In comparison to usual treatments, isotretinoin's effect on resistant rosacea can be delayed. Isotretinoin also reduces rhinophyma nasal volume.[21]

Miscellaneous oral therapies: Oral contraceptive monotherapy for women with "historical and clinical hormonal imbalances" requires 4 months of treatment. Effects of low-dose spironolactone antiandrogenic have been studied for rosacea (50 mg daily). In refractory rosacea, flushing-blocking drugs can help. Anecdotally, beta-blockers, clonidine, and naloxone have helped reduce flushing and erythema in rosacea sufferers.[19]

Vascular laser/Intense pulsed-light (IPL) treatment

Currently, vascular lasers with short wavelengths are used to treat telangiectasia and erythema. Standard pulsed dye lasers, long-pulsed dye lasers (595 nm, 0.5 to 40 milliseconds), potassium-titanyl-phosphate lasers (532 nm, 1 to 50 milliseconds), and the diode-pumped, frequency-doubled laser (532 nm) destroy vessels without collateral tissue injury. IPL is also effective in ETR.[21] In PhR, there are good results with treatment with CO_2 laser and surgery.[13]

Combination therapy

Dermatologists frequently recommend a combination therapy, although relatively minimal data support its usefulness.[21] Topical metronidazole 1% gel in combination with doxycycline 40-mg modified-release capsules (DMR) can

help with a variety of symptoms. Over 16 weeks, doxycycline 20 mg twice daily with metronidazole 0.75% gel resulted in more improvement than did a placebo.[22] The effect of adding 0.33% brimonidine gel to 1% ivermectin cream was supported by a decrease in redness and inflammation. Topical ivermectin and DMR alleviate rosacea inflammation. The combination therapy showed a more rapid beginning of action and improved erythema, stinging, burning, flushing, and ocular symptoms. Both groups reported few adverse effects.[23]

Rosacea management: A subtype-directed approach

The fundamentals of sun avoidance and sunscreen selection have been explored in rosacea. Avoiding triggers is an essential preventative measure. Patients should be taught about recognized triggers, and if possible, should identify and avoid their own triggers. Finally, patients may be advised to use nonirritating cosmetics to mask the signs and symptoms of rosacea.[2]

Standard medical treatments for rosacea have mostly centered on reducing inflammation. Repair of vascular and connective tissue dysfunction has only lately been a treatment goal for rosacea. Topical retinoids reorganize skin collagen and blood vessels and reduce inflammation.[10]

In ETR, first-line treatment may include IPL or lasers. Symptomatic improvement of erythema can be achieved by topical application of the alpha-2 agonist brimonidine tartrate. Most ETR individuals show barrier disruption and sensitivity to topical treatments. Education on cosmetic and sunscreen options is crucial. In the morning, one or a combination of topical anti-inflammatory agents, such as metronidazole or sodium sulfacetamide–sulfur, followed by sunscreen may be administered. If irritating responses are predominant in the history of an ETR patient, or if scaling and intense erythema are present, a barrier emollient may be used in the evening. While starting oral antibiotics, using a physical sunscreen and a barrier-protective emollient twice day may be helpful.[21]

In PPR, initial therapy (generally lasting 2-3 months) frequently needs a combination of oral and topical antimicrobials. Rapid control can be obtained in 1 to 3 months using oral and topical antimicrobials. In PPR, skin sensitivity is less common; therefore, all topical therapy alternatives are well tolerated in at least half of the patients. PPR seldom requires isotretinoin. Oral tetracyclines and topical antimicrobials manage disease in these people. Long-term PPR therapy frequently involves topical medications only. Metronidazole, sodium sulfacetamide–sulfur, azelaic acid, or benzoyl peroxide, followed by sunscreen every morning, could be part of a good combination topical regimen. A protective emollient, followed by tretinoin cream, might be used in the evening. Vascular lasers and IPL are supplementary therapeutic options for erythema and telangiectasia. IPL may also reduce bouts of flushing, but more research is needed in this area.[2]

Individuals with PhR may have overlapping acne and rosacea. Topical antimicrobials have a positive effect on them. These individuals respond effectively to benzoyl peroxide and benzoyl peroxide–antibiotic combinations. In addition to the topical regimen, oral tetracyclines are necessary for the early treatment of papules and pustules. Oral medication is typically continued for one to three months. The majority of PhR patients do not develop telangiectasia; however, they may have flushing. In the initial care of mild-to-moderate PhR, topical retinoids can be used in conjunction with topical or oral antibacterial therapy. Isotretinoin can be used to treat severe inflammatory or nodulocystic illness, which should be followed by long-term treatment with topical tretinoin. Increased sebum production, big pores, and thicker skin are common complaints among females with glandular rosacea. They may have mostly perioral papules and pustules. In such instances, low-dose spironolactone (25 to 50 mg daily) or oral contraceptives, or both, may assist. Isotretinoin is also beneficial in the short-term reduction of sebum production.[2]

In mild-to-moderate PhR, there are benefits from isotretinoin monotherapy. Surgery or a combination of surgery and isotretinoin treatment should be used to treat advanced phyma. Surgical techniques that have been used to reshape rhinophyma include a heated scalpel, laser ablation, tangential excision mixed with scissor sculpturing, and radiofrequency electrosurgery. Typically, these methods are combined to provide the greatest cosmetic effect.[14]

New treatments

Minocycline Foam: FDA authorized minocycline foam 1.5% in May 2020. The US began selling the foam in October 2020. A dose-ranging, randomized, double-blind experiment investigated the safety and efficacy of minocycline foam for PPR. No treatment-related adverse events occurred. Itching was the most common skin side effect, while respiratory infection was the most common overall adverse event. More trials are needed to compare topical minocycline to other available topical therapy.[24]

Encapsulated Benzoyl Peroxide Cream: The FDA accepted for review benzoyl peroxide 5% in September 2020.[25] Concerns about skin irritation prevented research on rosacea. Encapsulating it in silica may reduce discomfort.[26]

Erenumab: Erenumab is a monoclonal antibody against the receptor of the neuropeptide CGRP, which has been implicated in migraine pathophysiology. CGRP affects nociceptive and vasodilatory signals. In June 2020, there began an open-label phase II study of erenumab 140 mg administered subcutaneously every 4 weeks for rosacea redness and flushing.[27]

Rifaximin: Rifaximin is a gut-active antibiotic for traveler's diarrhea, IBS, and hepatic encephalopathy. Rosacea and gastrointestinal illness are linked. Research on small intestine bacterial overgrowth (SIBO) in rosacea patients found that eradicating SIBO with rifaximin 400mg three times daily for 10 days resolved rosacea in 78% of patients. In a study by Weinstock & Steinhoff, 51% of 63 patients with rosacea had SIBO. Rosacea and SIBO patients took 400mg rifaximin three times daily for 10 days; 46% of patients indicated clear or notable improvement, 25% - moderate, and 11% - mild.[28]

Hydroxychloroquine: Hydroxychloroquine is used to treat systemic autoimmune disorders. It modulates costimulatory molecules and reduces pro-inflammatory cytokine. In a rosacea mouse model, hydroxychloroquine reduced pro-inflammatory factors and proteases of the mast

cells.[29] In a study of six adults with moderate to severe rosacea, hydroxychloroquine 200 mg twice a day reduced inflammatory lesions by 67% and erythema by 83%. Long-term hydroxychloroquine usage can induce permanent retinopathy.[30]

Conclusion

Individualization of the diagnostic approach to rosacea has resulted in advancements in our knowledge of the pathogenesis, therapeutic methods, and how to care for patients. Greater knowledge of the pathogenesis, innovative topical methods for active treatments, and repurposing of established dermatologic medications have led to new rosacea treatments. These innovations might enhance rosacea sufferers' results. Despite treatment adherence, not all patients obtain complete or near-complete rosacea clearance. Thus, more effective treatments, particularly combination therapies, are needed. To thoroughly meet the requirements of all rosacea patients, more pathophysiology and therapy advancements are required.

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Competing Interests

The authors declare that they have no competing interests.

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