Rosacea: Epidemiology, pathogenesis, and treatment

Barbara M. Rainer, Sewon Kang, and Anna L. Chien

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.

INTRODUCTION
Rosacea (L. rosacea, rosy) is a common chronic inflammatory dermatosis affecting approximately 10% of the population. 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. 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. Phymatous (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.

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. 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. 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...
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. Estimates of the prevalence of rosacea in fair-skinned populations range from 2 to 22 percent. 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. Prevalence rates for ocular involvement in rosacea patients range from less than 10 percent to more than 50 percent. Cutaneous rosacea exhibits a strong female predominance, with the exception of phymatous rosacea, and is usually diagnosed after the age of 30 years.

**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.

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. Moderate to severe rosacea has been associated with hyperlipidemia, hypertension, metabolic, cardiovascular, and GI diseases. Population-based cohort studies confirmed these findings and reported further associations of rosacea and type 1 diabetes mellitus, celiac disease, multiple sclerosis, rheumatoid arthritis, Parkinson disease, and migraine. In addition to physical comorbidities, rosacea was associated with a disease severity-dependent, increased risk of depression and anxiety disorders. 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.

**Genetics of rosacea**

It has been observed that individuals with a family history of rosacea were more likely to develop rosacea. A study in twins suggested a 46 percent genetic contribution, which is in accordance with other cross-sectional studies reporting a family history of rosacea in up to 50 percent of patients. Recently, genomic association studies identified three human leucocyte antigen (HLA) alleles and two single-nucleotide polymorphisms (SNPs) to be associated with rosacea. 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. Multiple cell types have been implicated in promoting rosacea, including keratinocytes, mast cells, neurons, endothelial cells, macrophages, fibroblasts, and Th1/Th17 cells. 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-kB7,8 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 increased density of TRP ion channels on sensory neurons, vascular cells and immune cells across all cutaneous 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 inhibitors91 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 inter-

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.

References

[1] Tan J, Schofer H, Araviiskaia E, Audibert F, Kerrouche N, Berg M. RISE study group. Prevalence of rosacea in the general population of Germany and Russia – The RISE study. J Eur Acad Dermatol Venereol. 2016;30:428-34. https://doi.org/10.1111/jdv.13556. PMID:26915718

[2] Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, Powell F. Standard classification of rosacea: Report of the national rosacea society expert committee on the classification and staging of rosacea. J Am Acad Dermatol. 2002;46:584-7. https://doi.org/10.1067/mjd.2002.120625. PMID:11907512

[3] Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, Odom R, Powell F. National Rosacea Society Expert Committee. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. J Am Acad Dermatol. 2004;50:907-12. https://doi.org/10.1016/j.jaad.2004.01.048. PMID:15153893

[4] Akpek EK, Merchant A, Pinar V, Foster CS. Ocular rosacea: patient characteristics and follow-up. Ophthalmology. 1997;104:1863-7. https://doi.org/10.1016/S0161-6420(97)30015-3. PMID:9373118

[5] Steinhoff M, Bergstresser PR. Pathophysiology of rosacea: introduction. J Investig Dermatol Symp Proc. 2011;15:1. https://doi.org/10.1038/jidsymp.2011.3. PMID:22076320

[6] Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. J Am Acad Dermatol. 2013;69:S15-26. https://doi.org/10.1016/j.jaad.2013.04.045. PMID:24229632

[7] Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol. 2015;72:749-58; quiz 59-60. https://doi.org/10.1016/j.jaad.2014.08.028. PMID:25890455

[8] Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, Dorschner RA, Bonnart C, Descargues P, Hovnanian A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med 2007;13:975-80. https://doi.org/10.1038/nm1616. PMID:17676051

[9] Yamasaki K, Gallo RL. The molecular pathology of rosacea. J Dermatol Sci. 2009;55:77-81. https://doi.org/10.1016/j.jdermsci.2009.04.007. PMID:19481425

[10] Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity. J Investig Dermatol Symp Proc. 2011;15:12-5. https://doi.org/10.1038/jidsymp.2011.4. PMID:22076322

[11] Schwab UD, Sulk M, Seelig S, Nowak P, Aubert J, Mess C, Rivier M, Carlavan I, Rossio P, Metze D, et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. J Investig Dermatol Symp Proc. 2011;15:53-62. https://doi.org/10.1038/jidsymp.2011.6. PMID:22076328

[12] Rainer BM, Fischer AH, Luz Felipe da Silva D, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. J Am Acad Dermatol, 2015;73:604-8. https://doi.org/10.1016/j.jaad.2015.07.009. PMID:26256428

[13] Abram K, Silm H, Maaros HI, Oona M. Risk factors associated with rosacea. J Eur Acad Dermatol Venereol. 2010;24:565-71. https://doi.org/10.1111/j.1468-3083.2009.03472.x. PMID:19874433

[14] Tan J, Berg M. Rosacea: current state of epidemiology. J Am Acad Dermatol. 2013;69:S27-35. https://doi.org/10.1016/j.jaad.2013.04.043. PMID:24229634

[15] Rosen T, Stone MS. Acne rosacea in blacks. J Am Acad Dermatol. 1987;17:70-3. https://doi.org/10.1016/S0190-9622(87)70173-X. PMID:2956299

[16] Alexis AF. Rosacea in patients with skin of color: uncommon but not rare. Cutis. 2010;86:60-2. PMID:20919596

[17] Melnik BC. Rosacea: The blessing of the celts – an approach to pathogenesis through translational research. Acta Derm Venereol. 2016;96:147-56. https://doi.org/10.1038/jidsymp.2011.4. PMID:22076328

[18] Rainer BM, Fischer AH, Luz Felipe da Silva D, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. J Am Acad Dermatol, 2015;73:604-8. https://doi.org/10.1016/j.jaad.2015.07.009. PMID:26256428

[19] Abram K, Silm H, Maaros HI, Oona M. Risk factors associated with rosacea. J Eur Acad Dermatol Venereol. 2010;24:565-71. https://doi.org/10.1111/j.1468-3083.2009.03472.x. PMID:19874433

[20] Tan J, Berg M. Rosacea: current state of epidemiology. J Am Acad Dermatol. 2013;69:S27-35. https://doi.org/10.1016/j.jaad.2013.04.043. PMID:24229634

[21] Schwab UD, Sulk M, Seelig S, Nowak P, Aubert J, Mess C, Rivier M, Carlavan I, Rossio P, Metze D, et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. J Investig Dermatol Symp Proc. 2011;15:53-62. https://doi.org/10.1038/jidsymp.2011.6. PMID:22076328

[22] Rainer BM, Fischer AH, Luz Felipe da Silva D, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. J Am Acad Dermatol, 2015;73:604-8. https://doi.org/10.1016/j.jaad.2015.07.009. PMID:26256428
[23] Ramelet AA. Rosacea: a reaction pattern associated with ocular lesions and migraine? Arch Dermatol. 1994;130:1448. https://doi.org/10.1001/archderm.1994.0169011018022. PMID:7979452

[24] Parodi A, Paolino S, Greco A, Dragó F, Mansi C, Rebora A, Parodi A, Savarino V. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. Clin gastroenterol hepatol. 2008;6:759-64. https://doi.org/10.1016/j.cgh.2008.02.054. PMID:18456568

[25] Gravina A, Federico A, Ruocco E, Lo Schiavo A, Masarone M, Tuccillo C, Peccerillo F, Miranda A, Romano L, de Sio C, et al. Helicobacter pylori infection but not small intestinal bacterial overgrowth may play a pathogenic role in rosacea. United European Gastroenterol J. 2015;3:17-24. https://doi.org/10.1177/2050640614559262. PMID:25653855

[26] Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. J Eur Acad Dermatol Venereol. 2014;28:1165-9. https://doi.org/10.1111/jdv.12234. PMID:23909954

[27] Spoendlin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of developing rosacea: a population-based study within the United Kingdom. J Am Acad Dermatol. 2013;69:399-406. https://doi.org/10.1016/j.jaad.2013.03.027. PMID:23643255

[28] Spoendlin J, Voegel JJ, Jick SS, Meier CR. Risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs. J Investig dermatol. 2013;133:2790-3. https://doi.org/10.1038/jid.2013.225. PMID:23657502

[29] Spoendlin J, Bichsel F, Voegel JJ, Jick SS, Meier CR. The association between psychiatric diseases, psychotropic drugs and the risk of incident rosacea. Br J Dermatol. 2014;170:878-83. https://doi.org/10.1111/bjd.12734. PMID:24236423

[30] Gupta MA, Gupta AK, Chen SJ, Johnson AM. Comorbidity of rosacea and depression: an analysis of the national ambulatory medical care survey and national hospital ambulatory care survey–outpatient department data collected by the U.S. National Center for Health Statistics from 1995 to 2002. Br J Dermatol. 2005;153:1176–81. https://doi.org/10.1111/j.1365-2133.2005.06895.x. PMID:16307654

[31] Hua TC, Chung PI, Chen YJ, Wu LC, Chen YD, Hwang CY, Chu SY, Chen CC, Lee DD, Chang YT, et al. Cardiovascular comorbidities in patients with rosacea: A nationwide case-control study from Taiwan. J Am Acad Dermatol. 2015;73:249-54. https://doi.org/10.1016/j.jaad.2015.04.028. PMID:26004520

[32] Egeberg A, Weinstock LB, Thyssen EP, Gislason GH, Thyssen JP. Rosacea and gastrointestinal disorders: a population-based cohort study. Br J Dermatol. 2017;176 (1):100-106. https://doi.org/10.1111/bjd.14930.

[33] Wu CY, Chang YT, Juan CK, Shieh JJ, Lin YP, Liu HN, Lin JT, Chen YJ. Risk of inflammatory bowel disease in patients with rosacea: Results from a nationwide cohort study in Taiwan. J Am Acad Dermatol. 2017;76:911-17. https://doi.org/10.1016/j.jaad.2016.11.065. PMID:28073582

[34] Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Clustering of autoimmune diseases in patients with rosacea. J Am Acad Dermatol. 2016;74:667-72 e1. https://doi.org/10.1016/j.jaad.2015.11.004. PMID:26830864

[35] Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Exploring the association between rosacea and Parkinson disease: A Danish nationwide cohort study. JAMA Neurol. 2016;73:529-34. https://doi.org/10.1001/jamaneurol.2016.0022. PMID:26999031

[36] Egeberg A, Ashina M, Gaist D, Gislason GH, Thyssen JP. Prevalence and risk of migraine in patients with rosacea: A population-based cohort study. J Am Acad Dermatol. 2017;76:454-8. https://doi.org/10.1016/j.jaad.2016.08.055. PMID:27817869

[37] Spoendlin J, Voegel JJ, Jick SS, Meier CR. Migraine, triptans, and the risk of developing rosacea: a population-based study within the United Kingdom. J Am Acad Dermatol. 2013;69:399-406. https://doi.org/10.1016/j.jaad.2013.03.027. PMID:23643255

[38] Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with rosacea have increased risk of depression and anxiety disorders: A danish nationwide cohort study. Dermatology. 2016;232:208-13. https://doi.org/10.1159/000444082. PMID:26954304

[39] Kini SP, Nicholson K, DeLong LK, Dannemann T, Estraris J, Foster J, Chen SC. A pilot study in discrepancies in quality of life among three cutaneous types of rosacea. J Am Acad Dermatol. 2010;62:1069-71. https://doi.org/10.1016/j.jaad.2009.08.020. PMID:20466185

[40] Su D, Drummond PD. Blushing propensity and psychological distress in people with rosacea. Clin Psychol Psychother. 2012;19:488-95. https://doi.org/10.1002/cpp.763. PMID:21698719

[41] Nicholson K, Abramova L, Chren MM, Yeung J, Chon J, Kini SP, Nicholson K, DeLong LK, Dannemann T, Estraris J, Foster J, Chen SC. A pilot study in discrepancies in quality of life among three cutaneous types of rosacea. J Am Acad Dermatol. 2010;62:1069-71. https://doi.org/10.1016/j.jaad.2009.08.020. PMID:20466185

[42] Veronese N, Piccardo M. Rosacea – global diversity and optimized outcome: proposed international consensus from the European Society of Dermatology. J Eur Acad Dermatol Venereol. 2014;28:1165-9. https://doi.org/10.1111/jdv.12234. PMID:23909954

[43] Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, Gotow E, Cooper KD, Mann M, Popkin DL. Genetic vs environmental factors that correlate with rosacea: A cohort-based survey of twins. JAMA Dermatol. 2015;151:1213-9. https://doi.org/10.1001/jamadermatol.2015.2230. PMID:26307938

[44] Chang AL, Raber I, Xu J, Li R, Spitalte R, Chen J, Kiefer AK, Tian C, Eriksson NK, Hinds DA, et al. Assessment of the genetic basis of rosacea by genome-wide association study. J Investig Dermatol. 2015;135:1548-55. https://doi.org/10.1038/jid.2015.53. PMID:25695682

[45] Elewski BE, Draelos Z, Dreno B, Jansen T, Layton A, Piccardo M. Rosacea – global diversity and optimized outcome: proposed international consensus from the...
Rosacea International Expert Group. J Eur Acad Dermatol Venereol. 2011;25:188-200. https://doi.org/10.1111/j.1468-3083.2010.03751.x. PMID:20586834

[46] Steinhoff M, Buddenkotje J, Aubert J, Sulk M, Novak P, Schwab VD, Mess C, Cevikbas F, Rivier M, Carlavan I, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. J Investig Dermatol Symp Proc. 2011;15:2-11. https://doi.org/10.1038/jidsymp.2011.7. PMID:22076231

[47] Del Rosso JQ, Gallo RL, Tanghetti E, Webster G, Thiboutot D. An evaluation of potential correlations between pathophysiological mechanisms, clinical manifestations, and management of rosacea. Cutis. 2013;91:1-8. PMID:23833998

[48] Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol. Exp Dermatol. 2017;26(8):659-667. https://doi.org/10.1111/exd.13143. PMID:27376863

[49] Chen Y, Moore CD, Zhang JY, Hall RP, 3rd, MacLeod MK, Ansel JC, Paus R, Scholzen TE. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. J Investig Dermatol. 2006;126:1957-47. https://doi.org/10.1038/sj.jid.5700429. PMID:16912691

[50] Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. Nature. 2006;442:39-44. https://doi.org/10.1038/nature04946. PMID:16823444

[51] Schaub J, Gallo RL. Antimicrobial peptides and the skin immune defense system. J Allergy Clin Immunol. 2008;122:261-6. https://doi.org/10.1016/j.jaci.2008.03.027. PMID:18439663

[52] Peters EM, Ericson ME, Hosoi J, Seiffert K, Hordinsky MK, Ansel JC, Paus R, Scholzen TE. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. J Investig Dermatol. 2006;126:1957-47. https://doi.org/10.1038/sj.jid.5700429. PMID:16912691

[53] Zouboulis CC. The skin as an endocrine organ. Dermatolendocrinol. 2009;1:250-2. https://doi.org/10.4161/derm.1.5.9499. PMID:20808511

[54] Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. J Investig Dermatol. 2006;126:1697-704. https://doi.org/10.1038/sj.jid.5700104. PMID:16845409

[55] Peters EM. Stressed skin? – a molecular psychosomatic update on stress-causes and effects in dermatologic diseases. J Dtsch Dermatol Ges. 2016;14:233-52. PMID:26972185

[56] Gerber PA, Buhren BA, Steinhoff M, Homey B. Rosacea: The cytokine and chemokine network. J Investig dermatol Symp Proc. 2011;15:40-7. https://doi.org/10.1038/jidsymp.2011.9. PMID:22076326

[57] Ansel JC, Armstrong CA, Song I, Quinlan KL, Olerud JE, Caughman SW, Bunnett NW. Interactions of the skin and nervous system. J Investig Dermatol Symp Proc. 1997;2:23-6. https://doi.org/10.1038/jidsymp.1997.6. PMID:9487011

[58] Legat FJ, Armstrong CA, Ansel JC. The cutaneous neurosensory system in skin disease. Adv Dermatol. 2002;18:91-109. PMID:12528403

[59] Muto Y, Wang Z, Vanderbergh M, Two A, Gallo RL, Di Nardo A. Mast cells are key mediators of cathelicidin-initiated skin inflammation in rosacea. J Invest Dermatol. 2014;134:2728-36. https://doi.org/10.1038/jid.2014.222. PMID:24844861

[60] Kulka M, Sheen CH, Tancowny BP, Grammer LC, Schleimer RP. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology. 2008;123:398-410. https://doi.org/10.1111/j.1365-2567.2007.02075.x. PMID:17922833

[61] Salzer S, Kresse S, Hirai Y, Koglin S, Reinholz M, Ruzicka T, Schaub J. Cathelicidin peptide LL-37 increases UVB-triggered inflammasome activation: possible implications for rosacea. J Dermatol Sci. 2014;76:173-9. https://doi.org/10.1016/j.jdermsci.2014.09.002. PMID:25306296

[62] Sulk M, Seeliger S, Aubert J, Schwab VD, Cevikbas F, Rivier M, Nowak P, Voegel JJ, Buddenkotje J, Steinhoff M. Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. J Investig Dermatol. 2012;132:1253-62. https://doi.org/10.1038/jid.2011.424. PMID:22189797

[63] Mascarenhas NL, Wang Z, Chang YL, Di Nardo A. TRPV4 Mediates mast cell activation in cathelicidin-induced rosacea inflammation. J Investig Dermatol. 2017;137:972-5. https://doi.org/10.1016/j.jid.2016.10.046. PMID:27908695

[64] Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci. 2001;24:487-517. https://doi.org/10.1146/annurev.neuro.24.1.487. PMID:11283319

[65] Helfrich YR, Maier LE, Cui Y, Fisher GJ, Chubb H, Fligel S, Sachs D, Varani J, Voorhees J. Clinical, histologic, and molecular analysis of differences between erythematotelangiectatic rosacea and telangiectatic photoaging. JAMA Dermatol. 2015;151:825-36. https://doi.org/10.1001/jamadermatol.2014.4728. PMID:25798811

[66] McAleer MA, Powell FC. Rosacea and neuropeptides. In: Zouboulis CC, editors. Pathogenesis and treatment of acne and rosacea. Berlin Heidelberg: Springer-Verlag; 2014. https://doi.org/10.1007/978-3-540-69375-8_82

[67] Debersaques J. Historical notes on (Acne) rosacea. Eur J Dermatol. 1995;5:16-22.

[68] Reinholz M, Ruzicka T, Steinhoff M, Schaller M, Gieler U, Schöfer H, Homey B, Lehmann P, Luger TA. Pathogenesis and clinical presentation of rosacea as a key for a symptom-oriented therapy. J Dtsch Dermatol Ges. 2016;14 Suppl 6:4-15.

[69] Gauwerkery K, Klövekorn W, Korting HC, Lehmann P, Meigal EM, Reinel D, Ruzicka T, Schaller M, Schöfer H, Tietze J. J Dtsch Dermatol Ges. 2009;7(11):996-1003. https://doi.org/10.1111/j.1610-0387.2009.07119.x

[70] Tan J, Almeida LM, Bewley A, Cribier B, Dlova NC, Gallo R, Kautz G, Mannis M, Oon HH, Rajagopalan...
M, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea Consensus (ROSCO) panel. Br J Dermatol. 2017;176:431-8. https://doi.org/10.1111/bjd.15122. PMID:27718519

[71] van Zuuren EJ, Fedorowicz Z. Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments. Br J Dermatol. 2015;173:651-62. https://doi.org/10.1111/bjd.13956. PMID:26999423

[72] Reinholz M, Tietze JK, Kilian K, Schaller M, Schörer H, Lehmann P, Zierhut M, Klövekorn W, Ruzicka T, Schauben J. Rosacea – S1 guideline. J Dtsch Dermatol Ges. 2013;11:768-80; -79. https://doi.org/10.1111/ddg.12101

[73] Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. J Am Acad Dermatol. 2003;48:836-45. https://doi.org/10.1067/mjd.2003.308. PMID:12789172

[74] Stein L, Kircik L, Fowler J, Tan J, Draelos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Liu H, et al. Efficacy and safety of ivmecin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. J Drugs Dermatol. 2014;13:316-23. PMID:24595578

[75] Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part II. Topical and systemic therapies in the treatment of rosacea. J Am Acad Dermatol. 2015;72:761-70; quiz 71-2. https://doi.org/10.1016/j.jaad.2014.08.027. PMID:25890456

[76] van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MM, Charland L. Interventions for rosacea. 2015; 28(4):CD003262. https://doi.org/10.1002/14651858. CD003262.pub5. PMID:25919144

[77] Taieb A, Passeron T, Ruzicka T, Berth-Jones J, Jacovella J, Huang MY, Wertheimer A. Ivermectin cream improves health-related quality of life in patients with rosacea: data from a randomized trial. Br J Dermatol. 2016;175:1366-8. https://doi.org/10.1111/bjd.14665. PMID:27061926

[78] Taieb A, Ortonne JP, Ruzicka T, Roszkiewicz J, Berth-Jones J, Peirone MH, Jacovella J. Ivermectin Phase III study group. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. Br J Dermatol. 2015;172:1103-10. https://doi.org/10.1111/bjd.13408. PMID:25228137

[79] Fowler J, Jarratt M, Moore A, Meadows K, Pollack A, Steinhoff M, Liu Y, Leoni M, Brimonidine Phase II Study Group. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. Br J Dermatol. 2012;166:633-41. https://doi.org/10.1111/j.1365-2133.2011.10716.x. PMID:22050040

[80] Layton AM, Schaller M, Homey B, Hofmann MA, Bewley AP, Lehmann P, Nohlgard C, Sarwer DB, Kerrouche N, Ma YM. Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study. J Eur Acad Dermatol Venereol. 2015;29:2405-10. https://doi.org/10.1111/jdv.13305. PMID:26416154

[81] Holmes AD, Waite KA, Chen MC, Palaniswamy K, Wiser TH, Draelos ZD, Rafal ES, Werschler WP, Harvey AE. Dermatological adverse events associated with topical brimonidine gel 0.33% in subjects with erythema of rosacea: A retrospective review of clinical studies. J Clin Aesthet Dermatol. 2015;8:29-35. PMID:26345379

[82] Cookson H, McFadden J, White J, White IR. Allergic contact dermatitis caused by Mirvaso(R), brimonidine tartrate gel 0.33%, a new topical treatment for rosacea erythema. Contact Dermatitis. 2015;73:366-7. https://doi.org/10.1111/cod.12476. PMID:26768997

[83] Lowe E, Lim S. Paradoxical erythema reaction of long-term topical brimonidine gel for the treatment of facial erythema of rosacea. J Drugs Dermatol. 2016;15:763-5. PMID:27272086

[84] Ilkovitch D, Pomerantz RG. Brimonidine effective but may lead to significant rebound erythema. J Am Acad Dermatol. 2014;70:e109-10. https://doi.org/10.1016/j.jaad.2014.01.853. PMID:24742853

[85] Johnson AW, Johnson SM. The role of topical brimonidine tartrate gel as a novel therapeutic option for persistent facial erythema associated with rosacea. Dermatol Ther (Heidelb). 2015;5:171-81. https://doi.org/10.1007/s13555-015-0078-1. PMID:26112098

[86] Del Rosso JQ, Evaluating the role of topical therapies in the management of rosacea: focus on combination sodium sulfacetamide and sulfer formulations. Cutis. 2004;73:29-33. PMID:14959943

[87] Mills OH, Jr., Kligman AM. Letter: Topically applied erythromycin in rosacea. Arch Dermatol. 1976;112:553-4. https://doi.org/10.1001/archderm.1976.01630280071021. PMID:131516

[88] Ozturkcan S, Ermentcan AT, Sahin MT, Afsar FS. Efficiency of benzoyl peroxide-erythromycin gel in comparison with metronidazole gel in the treatment of acne rosacea. J Dermatol. 2004;31:610-8. https://doi.org/10.1111/j.1346-8138.2004.tb00566.x. PMID:15492433

[89] Raoufnejad K, Mansouri P, Rajabi M, Naraghi Z, Jebraili R. Efficacy and safety of permethrin 5% topical gel vs. placebo for rosacea: a double-blind randomized controlled clinical trial. J Eur Acad Dermatol Venereol. 2016;30:2105-17. https://doi.org/10.1111/jdv.13801. PMID:27600257

[90] Chang AL, Alora-Palli M, Lima XT, Chang TC, Cheng C, Chung CM, Amir O, Kimball AB. A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks. J Drugs Dermatol. 2012;11:333-9. PMID:22395584

[91] Bamford JT, Elliott BA, Haller IV. Tacrolimus effect on inflammatory lesions of rosacea. J Am Acad Dermatol. 2015;72:761-70; -79. https://doi.org/10.1016/j.jaad.2014.08.027. –
[92] Rashid M-U, Panagiotidis G, Backstrom T, Weintraub A, Nord CE. Ecological impact of doxycycline at low dose on normal oropharyngeal and intestinal microflora. Int J Antimicrob Agents. 2013;41:352-7. https://doi.org/10.1016/j.ijantimicag.2012.11.014. PMID:23332619

[93] Thomas J, Walker C, Bradshaw M. Long-term use of sub-antimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. J Periodontol. 2000;71:1472-83. https://doi.org/10.1902/jop.2000.71.9.1472. PMID:11022778

[94] Del Rosso JQ, Webster GF, Jackson M, Rendon M, Rich P, Torok H, Bradshaw M. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. J Am Acad Dermatol. 2007;56:791-802. https://doi.org/10.1016/j.jaad.2006.11.021. PMID:17367893

[95] Walker C, Preshaw PM, Novak J, Hefti AF, Bradshaw M, Powala C. Long-term treatment with sub-antimicrobial dose doxycycline has no antibacterial effect on intestinal flora. J Clin Periodontol. 2005;52:1163-9. https://doi.org/10.1111/j.1600-051X.2005.08840.x. PMID:16212578

[96] Schachter D, Schachter RK, Long B, Shifman N, Lester R, Miller S, Bargman H, Haber R, Bourgouin J. Comparison of metronidazole 1-percent cream versus oral tetracycline in patients with rosacea. Drug Invest. 1991;3:220-4. https://doi.org/10.1007/BF03259568

[97] Modi S, Harting M, Rosen T. Azithromycin as an alternative rosacea therapy when tetracyclines prove problematic. J Drugs Dermatol. 2008;7:898-9. PMID:19112809

[98] Sbidian E, Vicaut E, Chidiack H, Anselin E, Cribier B, Dréno B, Chosidow O. A randomized-controlled trial of oral low-dose isotretinoin for difficult-to-treat papulopustular rosacea. J Invest Dermatol. 2016;136:1124-9. https://doi.org/10.1016/j.jid.2016.01.025. PMID:26854486

[99] van Zuuren EJ, Fedorowicz Z. Low-dose isotretinoin: An option for difficult-to-treat papulopustular rosacea. J Invest Dermatol. 2016;136:1081-3. https://doi.org/10.1016/j.jid.2016.03.003. PMID:27212646

[100] Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. Adv Ther. 2009;26:651-9. https://doi.org/10.1007/s12325-009-0037-2. PMID:19551353

[101] Hofmann MA, Lehmann P. Physical modalities for the treatment of rosacea. J Dtsch Dermatol Ges. 2016;14 Suppl 6:38-43.

[102] Tanghetti E, Del Rosso JQ, Thiboutot D, Gallo R, Webster G, Eichenfield LF, Stein-Gold L, Berson D, Zaenglein A, American Acne & Rosacea Society. Consensus recommendations from the American acne & rosacea society on the management of rosacea, part 4: a status report on physical modalities and devices. Cutis. 2014;93:71-6. PMID:24605343

[103] Jansen T, Plewig G. Clinical and histological variants of rhinophyma, including nonsurgical treatment modalities. Facial Plast Surg. 1998;14:241-53. https://doi.org/10.1055/s-2008-1064456. PMID:11816064

[104] Schweinzer K, Koffer L, Spott C, Krug M, Schulz C, Schnabl SM, Breuninger H, Hänner HM, Eberle FC. Surgical treatment of rhinophyma: experience from a German cohort of 70 patients. Eur J Dermatol. 2017;27:281-5. PMID:28524054

[105] Goktay F, Erfan G, Celik NS, Öztürk C, Doruk T, Albayrak H, Yanik ME, Albayrak S. Early cosmetic results and midterm follow-up findings of rhinophyma patients treated with high-frequency electrosurgery and a discussion on the severity assessment of the disease. J Cutan Med Surg. 2017;21(3):221-226. doi: 10.1177/1203475417694860. PMID:28300449