Chapter 13

Acne Rosacea

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Additional information is available at the end of the chapter

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Abstract

Rosacea is a common chronic inflammatory cutaneous disorder with variable presentation and severity. Disease usually occurs between the ages of 30 and 50 years. Women are more commonly affected than men. Rosacea is divided into four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular, and one variant: lupoid or granulomatous rosacea. Erythematotelangiectatic rosacea is manifested as flushing and persistent centrofacial erythema, and papulopustular rosacea as papules and pustules in a centrofacial distribution. With disease progression, phymas consisting of sebaceous gland hypertrophy can develop. Ocular rosacea can result in blepharitis and conjunctivitis. Diagnosis is made clinically. Management of rosacea consists of protective measures such as sun protection and gentle skin care and topical and systemic treatments to suppress inflammation and erythema.

Keywords: rosacea, acne, perioral dermatitis, rhinophyma, ocular rosacea

1. Introduction

Rosacea is a common chronic inflammatory cutaneous disorder with variable presentation and severity. Facial flushing, telangiectasia, papules, and pustules are the main features of cutaneous rosacea.

2. Epidemiology

Rosacea can be seen in any age, but the onset usually occurs between the ages of 30 and 50 years. Women are more commonly affected than men; however, the development of

phymatous skin changes is more commonly observed in men. Although the disease is more common in fair-skinned people of Celtic origin, patients of any ethnic group can be affected [1]. Up to 1/3 of the patients report a family history [2]. Rhinophyma, bulbous nose due to increased connective tissue and hyperplastic sebaceous glands, is almost exclusively seen in men over 40 years of age [3]. The prevalence is highly variable as the methods used and the populations studied vary greatly from one study to another [4]. A Swedish study reported a prevalence of 10% with a female-to-male ratio of 3:1 [5]. Eye involvement may be observed in more than 50% of patients [1].

3. Pathogenesis

Pathogenesis of rosacea is not well understood. Abnormalities in innate immunity, role of cutaneous microorganisms, and UV damage and vascular dysfunction may play a role in pathogenesis of rosacea.

Recent studies have shown the dysregulation of innate immune response in rosacea. Due to an exacerbated innate immune response, patients develop inflammatory reactions to stimuli that do not affect normal individuals. Patients with rosacea have high levels of cathelicidin, an antimicrobial peptide with vasoactive and proinflammatory properties and local protease kallikrein 5 (KLK5), which controls the production of cathelicidin peptides in epidermis. Injection of mouse skin with cathelicidin peptides from patients with rosacea led to skin changes similar to those observed in rosacea confirming the hypothesis [6]. Toll-like receptors (TLRs) work by triggering inflammation in response to recognized microbial patterns and elevated TLR2 activity, leading to an increase in KLK5 level which may also contribute to enhanced inflammatory responses responsible for rosacea signs [7].

Some microorganisms have been proposed to stimulate inflammatory reaction in cutaneous rosacea. *Demodex folliculorum* is an obligatory parasite found in pilosebaceous unit. Although almost all adults are infested with *Demodex*, patients with rosacea have increased density of *Demodex* mites supporting a significant association between *Demodex* infestation and the development of rosacea [8]. Correlation of gastrointestinal *Helicobacter pylori* infection and rosacea is controversial. The prevalence of *H. pylori* infection is shown to be increased or not different in patients with rosacea compared to control subjects. Treatment of *H. pylori* infection with antibiotics has been shown to improve rosacea, but this may be the benefit of anti-inflammatory effects of the antibiotics used for treatment [9].

UV and sun exposure are among the exacerbating factors for rosacea. UV-B has been shown to induce cutaneous angiogenesis in mice. In skin, UV-B increases vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) secretion from human keratinocytes promoting angiogenesis. UV irradiation also produces reactive oxygen species, causing a damage in dermal matrix and thus leading to inflammation [6].

Vascular hyperreactivity may also play a role in disease pathogenesis. Dermal expression of VEGF, CD31, and lymphatic endothelium marker D2-40 has been shown to be elevated in rosacea, leading to stimulation of vascular and lymphatic endothelial cells [10].

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4. Classification and clinical features

Rosacea is manifested as erythematous flushing, papules, and pustules in a centrofacial distribution. Intermittent or chronic facial edema may also occur. With disease progression, some patients may develop yellow-orange plaques called phymas consisting of sebaceous gland hypertrophy [11].

There are four stages: pre-rosacea and stages I through III. Patients with frequent flushing are considered in pre-rosacea group. In stage I, there is erythema that lasts from hours to days and telangiectasias. In stage II, persistent erythema is accompanied by multiple inflammatory papules and pustules. In stage III, large inflammatory nodules and connective tissue hyperplasia occur [4] (**Table 1**).

Pre-rosacea	**Frequent flushing**
Stage 1	Transient facial erythema that becomes more persistent telangiectasias
Stage 2	Persistent facial erythema
	Papules, pustules
	Ocular changes
Stage 3	Large inflammatory nodules
	Tissue hyperplasia, fibroplasias

Table 1. Stage symptoms and signs [11].

The National Rosacea Society (NRS) has classified rosacea into four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular, and one variant: lupoid or granulomatous rosacea.

4.1. Erythematotelangiectatic type

The erythematotelangiectatic type is the most common subtype of rosacea (**Figure 1**). It is characterized by flushing and persistent central facial erythema with sparing of periocular skin. The flushing of rosacea lasts longer than 10 min differentiating it from physiological flushing episodes. Telangiectasias are common but not essential for the diagnosis of this subtype. Stinging or burning sensations may be present [4].

4.2. Papulopustular type

Papulopustular rosacea is characterized by persistent central facial erythema: small, dome-shaped erythematous papules and surmounting pustules on the central face [4] (**Figure 2**). However, papules and pustules may also occur periorificially. The inflammation seen in papulopustular rosacea is similar to acne vulgaris, but comedones typical for acne vulgaris are absent in rosacea [12].

In a study, 15 patients with pustular rosacea and 15 age- and sex-matched control subjects were compared. A significantly increased growth of *S. epidermidis* was found in rosacea pustules and eyelid margins of rosacea patients suggesting a role of *S. epidermidis* in pathogenesis of pustular and ocular rosacea [13].

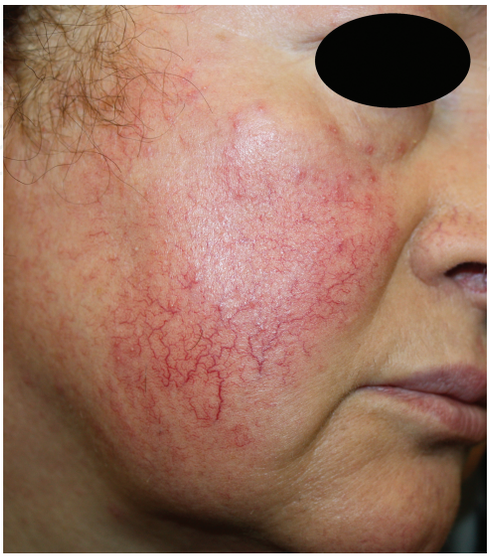

Figure 1. Erythematotelangiectatic type of rosacea. Prominent telangiectatic vessels and erythema on the cheek with characteristic sparing of periocular skin.

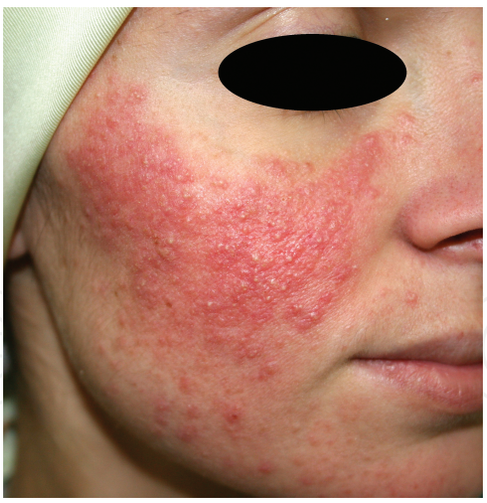

Figure 2. Papulopustular type of rosacea. Extensive papules and pustules on a background of persistent erythema.

4.3. Ocular rosacea

Ocular rosacea occurs in more than 50% of patients with rosacea. Eye involvement may follow, as seen in half of the patients, may precede as in 20%, or occur simultaneously with skin changes [12].

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Patients with ocular rosacea may complain of foreign body sensation, dryness, itching, photophobia, and tearing. If the cornea is involved by the disease, the visual acuity may be decreased [14]. Blepharitis and conjunctivitis are the most common findings. Blepharitis is characterized by the eyelid margin erythema, scale, and staphylococcal infections. Hypopyon, scleritis, keratitis, and iritis can also occur. Rosacea keratitis is a severe condition and has a poor prognosis. It can lead to corneal opacity, scarring, and loss of vision. The severity of ocular rosacea symptoms is often not related to the severity of cutaneous manifestations [4].

4.4. Phymatous rosacea

Phymatous rosacea shows tissue hypertrophy manifesting as thickened skin with irregular contours and prominent pores. Involvement most commonly occurs on the nose (rhinophyma), but the chin (gnathophyma), forehead (metophyma), and ears (otophyma) may also be affected [4]. Rhinophyma occurs mostly in men with a male/female ratio of 20:1. Although rhinophyma is often accepted as a presentation of last stage of rosacea, it may occur in patients with few or no other features of rosacea. One diagnosis is a clinical one, and biopsy is only indicated to rule out alternative diagnoses or in suspicion of a malignancy such as basal cell carcinoma or squamous cell carcinoma [15].

4.5. Granulomatous rosacea

Granulomatous rosacea was classified by the expert committee as a disease variant characterized by discrete yellow, brown, red papules, or nodules on periorificial facial skin [12] (**Figure 3**). Patients do not often have persistent erythema or flushing of the face and may not have their disease distributed to convexities of the face [16].

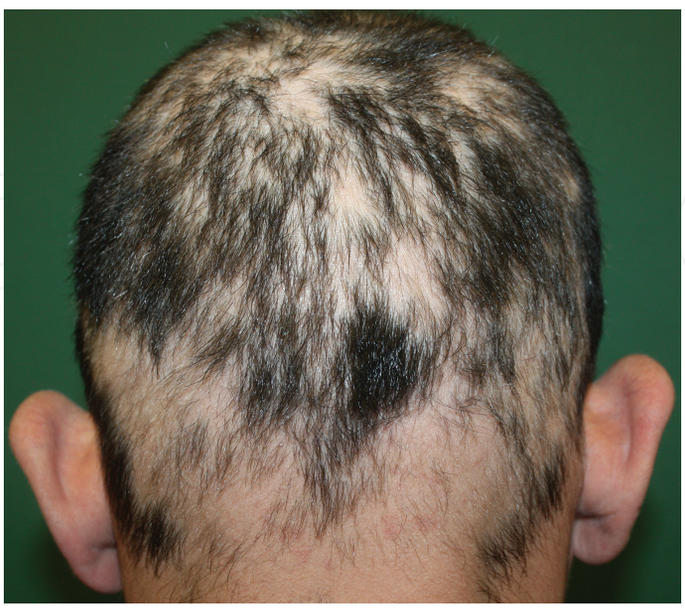

Figure 3. Granulomatous rosacea. Discrete yellow papules clustered periorficially.

5. Histopathology

In mild forms of rosacea, histologic findings are often limited to vascular ectasia and mild edema. A lymphohistiocytic infiltrate with perivascular and perifollicular distribution is observed in papulopustular form [17]. Solar elastosis is invariably found in histopathologic examination of biopsy specimens. In granulomatous variant, non-caseating epithelioid granulomas are seen within the dermis [18].

6. Diagnosis and differential diagnosis

Diagnosis of rosacea is made clinically; there is no laboratory test to confirm the diagnosis. A biopsy is only indicated to rule out alternative diagnoses [1] (**Table 2**).

Acne vulgaris
Seborrheic dermatitis
Keratosis pilaris
Dermatomyositis
Systemic lupus erythematosus
Photodermatitis
Sarcoidosis
Demodicosis
Haber syndrome
Basal cell carcinoma

Table 2. Differential diagnosis of facial rosacea [17, 19].

Acne vulgaris is the disease most commonly confused with rosacea, especially in middle-aged adults. Key distinguishing feature between acne vulgaris and rosacea is the absence of comedones in rosacea [4]. Patients with acne vulgaris are often younger patients, having oily skin with comedones, larger pustules, and less erythema with scarring [1].

Perioral dermatitis presents with micropustules and vesicles with scaling around the mouth. Seborrheic dermatitis often coexists with rosacea [17]. Scaling and erythema of the scalp, eyebrows, external auditory canals, and retroauricular folds serve as clues to the presence of seborrheic dermatitis [4].

The malar erythema of systemic lupus erythematosus can be difficult to distinguish from rosacea. Clinically, papules pustules and ocular symptoms are mostly absent in lupus [17]. Severe Demodex infection (demodicosis) may present with rosacea-like features, but flushing and telangiectasia are absent [4]. And also, photodermatitis is triggered by sun exposure and has similar skin manifestations to rosacea [4].

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7. Associated diseases

Rosacea patients may have increased risk of developing certain diseases as evidenced by case-controlled studies. Further studies are necessary to confirm these associations.

Patients with rosacea are more likely to have dyslipidemia and hypertension. They are also at increased risk of coronary artery disease after adjustment for cardiovascular disease risk factors [20]. There is a possible association between rosacea and an increased risk of thyroid cancer and basal cell carcinoma [21].

Rosacea was associated with a significantly increased risk of glioma in a Danish nationwide cohort [22]. In the same Danish cohort, patients with rosacea had an increased risk of autoimmune diseases, including type 1 diabetes mellitus, celiac disease, multiple sclerosis, and rheumatoid arthritis [23].

8. Treatment

8.1. Protective measures

Protective measures are of utmost importance in management of rosacea patients of all subtypes. These include avoidance of triggers of flushing, gentle skin care, and sun protection.

Most sufferers report worsening of the disease by factors such as hot or cold temperature, wind, hot drinks, exercise, spicy food, alcohol, emotions, and menopause [24]. A variety of medications may exacerbate flushing such as vasodilative drugs, nicotinic acid and amyl nitrite, calcium channel blockers, and opiates [1].

Cleansers containing acetone or alcohol should be avoided. Usage of abrasive or exfoliant preparations and vigorous rubbing of the skin should also be discontinued [1].

Daily application of combined ultraviolet-A and ultraviolet-B protective sunscreen with a sun protection factor of 15 or greater should be advised to every patient. Sun-blocking creams containing titanium dioxide and zinc oxide are usually well tolerated [1].

8.2. Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is the most treatment-resistant subtype of rosacea. Flushing and burning are the most difficult features to treat. Non-cardioselective β-blockers such as propranolol 40 mg twice daily or nadolol 40 mg daily can be tried, but provide rather limited benefit [25].

Topical or oral medications described below for papulopustular rosacea are often used, but evidence supporting their role in erythematotelangiectatic rosacea is lacking [1].

Treatment of erythema and telangiectasia with vascular lasers or intense pulse light can help in improving flushing and burning [4].

8.3. Papulopustular rosacea

Systemic and topical antibiotics are effective in treatment of papulopustular rosacea. Patients with moderate-to-severe papulopustular rosacea at initial presentation may require systemic therapy to achieve clearance of inflammatory skin lesions followed by topical treatment to avoid relapses. Topical medications alone can be used to control milder disease.

Main topical agents utilized for the treatment of rosacea include metronidazole, sulfacetamide-sulfur, azelaic acid, and topical antibiotics (clindamycin, erythromycin) [26]. Three varieties of 0.75% metronidazole and 1% metronidazole and several brands of 10% sodium sulfacetamide with 5% sulfur and 15% azelaic acid gel are medications that have been approved by the Food and Drug Administration (FDA) for rosacea. All are indicated for the papules, pustules, and erythema [4].

Topical metronidazole used once or twice daily is effective in treatment of inflammatory papules and pustules and improving erythema of papulopustular rosacea. Azelaic acid is a well-tolerated preparation that also reduces papules and pustules. It is available in 15% gel and 20% cream forms, applied twice a day; 10% sodium sulfacetamide with 5% sulfur is used to treat acne, rosacea, and seborrheic dermatitis. It has beneficial effects in reducing both inflammatory lesion counts and erythema scores in papulopustular rosacea [27]. Topical erythromycin used for acne vulgaris can help in reducing symptoms but may prove irritant on skin affected by rosacea [24]. Clindamycin gel, also developed for treatment of acne, may be better tolerated. A combined formulation containing 5% benzoyl peroxide and 1% clindamycin has proved effective and well tolerated in a placebo-controlled trial [4].

Topical retinoids have been used to treat rosacea, but the true efficacy has not been established. Adapalen, a relatively well-tolerated retinoid, has been shown to be an alternative treatment agent in management of papulopustular rosacea [28].

Effective systemic antibiotics include tetracyclines (e.g., tetracycline or oxytetracycline 250 mg twice daily) and erythromycin 250 mg twice daily. Second-generation tetracyclines, such as minocycline and doxycycline, are also effective and offer the advantages of once daily administration and less gastrointestinal side effects [24]. Doxycycline shows anti-inflammatory effects at doses as low as 40 mg daily [29]. Azithromycin was proven to be as effective as doxycycline in a number of studies [4]. In one series, azithromycin proved beneficial after 4 weeks at 250 mg/day, for 3 days each week (Monday, Wednesday, and Friday) [30].

Oral metronidazole is an effective alternative treatment for rosacea. Metronidazole (200 mg) taken twice daily for 12 weeks has been proved to be as effective in improving the inflammatory lesions of rosacea as 250 mg oxytetracycline taken twice daily [4]. Abstinence from alcohol during metronidazole therapy is necessary to avoid disulfiram-like reactions. Although relatively safe, metronidazole has been associated with potential side effects such as neuropathy and seizures [24].

Oral isotretinoin is a treatment option for severe rosacea. The onset of action of systemic retinoids is slow when compared with the oral antibiotics. It is effective both in erythematotelangiectatic and papulopustular rosacea. Oral istotretinoin can also be used for

granulomatous rosacea and rhinophyma. It has been shown that treatment-resistant patients taking isotretinoin experienced fewer papules and pustules, a reduction in erythema, and decreased nasal volume [31]. Daily doses of isotretinoin range from 0.2 to 1 mg/kg. It is usually given for 6 months. With low dose therapy, the common mucosal side effects of the drug are minimal and tolerable. However, due to its teratogenic effects, it is contraindicated in women of childbearing potential [4].

8.4. Ocular rosacea

Treatment of ocular rosacea depends on disease severity. Lid hygiene and warm compresses are the baseline treatment for all patients. For mild ocular rosacea, fucidic acid preparations and metronidazole gel are frequently used [4]. Systemic antibiotics such as oral tetracyclin or doxycyclin may be used in patients with a more severe involvement [32]. The keratitis associated with rosacea can be severe, and patients with potentially serious ocular symptoms should be referred to an ophthalmologist.

8.5. Rhinophyma

In patients with early rhinophyma, medical treatment with systemic isotretinoin may prove beneficial. In advanced cases, surgery is performed. Surgery can be done either as a complete excision or an incomplete excision made by cryosurgery, dermabrasion, electrosurgery, sharp blade excision, shaving with a razor, or laser surgery [32].

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References

[1] Powell FC: Clinical practice. Rosacea. N Engl J Med. 2005;352:793–803. doi:10.1056/NEJMcp042829

[2] Del Rosso JQ: Update on rosacea pathogenesis and correlation with medical therapeutic agents. Cutis. 2006;78:97–100

[3] Buechner SA: Rosacea: an update. Dermatology. 2005;210:100–108. doi:10.1159/000082564

[4] Tüzün Y, Wolf R, Kutlubay Z, Karakus O, Engin B: Rosacea and rhynophyma. Clin Dermatol. 2014;32:35–46 doi:10.1016/j.clindermatol.2013.05.024

[5] Berg M, Liden S: An epidemiological study of rosacea. Acta Derm Venereol. 1989;69:419–423.

[6] Yamasaki K, Gallo RL: The molecular pathology of rosacea: J Dermatol Sci. 2009;55:77–81. doi:10.1016/j.jdermsci.2009.04.007

[7] Yamasaki K, Kanada K, Macleod DT, et al: TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. J Invest Dermatol. 2011;131:688–697. doi:10.1038/jid.2010.351

[8] Zhao YE, Wu LP, Peng Y, Cheng H: Retrospective analysis of the association between demodex infestation and rosacea. Arch Dermatol. 2010;146:896–902. doi:10.1001/archdermatol.2010.196

[9] Tan J, Berg M: Rosacea: current state of epidemiology. J Am Acad Dermatol. 2013;69:27–35. doi:10.1016/j.jaad.2013.04.043

[10] Gomaa AH, Yaar M, Eyada MM, Bhawan J: Lymphangiogenesis and angiogenesis in non-phymatous rosacea. J Cutan Pathol. 2007;34:748–753. doi:10.1111/j.1600-0560.2006.00695.x

[11] Culp B, Scheinfeld N: Rosacea: a review. P T. 2009;34:38–45.

[12] Wilkin J, Dahl M, Detmar M, et al: Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2002;46:584–587.

[13] Whitfeld M, Gunasingam N, Leow LJ, Shirato K, Preda V: Staphylococcus epidermidis: a possible role in the pustules of rosacea. J Am Acad Dermatol. 2011;64:49–52. doi:10.1016/j.jaad.2009.12.036

[14] Vieira AC, Höfling-Lima AL, Mannis MJ: Ocular rosacea—a review. Arq Bras Oftalmol. 2012;75:363–369.

[15] Lazeri D, Colizzi L, Licata G, et al: Malignancies within rhinophyma: report of three new cases and review of the literature. Aesthetic Plast Surg. 2012;36:396–405. doi:10.1007/s00266-011-9802-0

[16] Crawford GH, Pelle MT, James WD: Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol. 2004;51:327–341. doi:10.1016/j.jaad.2004.03.030

[17] Webster GF: Rosacea. Med Clin North Am. 2009;93:1183–1194. doi:10.1016/j.mcna.2009.08.007

[18] Aroni K, Tsagroni E, Lazaris AC, Patsouris E, Agapitos E: Rosacea: a clinicopathological approach. Dermatology. 2004;209:177–182. doi:10.1159/000079886

[19] Fuller D, Martin S: Rosacea. J Midwifery Womens Health. 2012;57:403–409. doi:10.1111/j.1542-2011.2011.00156.x

[20] Hua TC, Chung PI, Chen YJ, et al: Cardiovascular comorbidities in patients with rosacea: a nationwide case-control study from Taiwan. J Am Acad Dermatol. 2015;73:249–254. doi:10.1016/j.jaad.2015.04.028

[21] Li WQ, Zhang M, Danby FW, Han J, Qureshi AA: Personal history of rosacea and risk of incident cancer among women in the US. Br J Cancer. 2015;113:520–523. doi:10.1038/bjc.2015.217

[22] Egeberg A, Hansen PR, Gislason GH, Thyssen JP: Association of Rosacea With Risk for Glioma in a Danish Nationwide Cohort Study. JAMA Dermatol. 2016;152:541–545. doi:10.1001/jamadermatol.2015.5549

[23] Egeberg A, Hansen PR, Gislason GH, Thyssen JP: Clustering of autoimmune diseases in patients with rosacea. J Am Acad Dermatol. 2016;74:667–672. doi:10.1016/j.jaad.2015.11.004

[24] Pelle MT, Crawford GH, James WD: Rosacea: II therapy. J Am Acad Dermatol. 2004;51:499–512. doi:10.1016/j.jaad.2004.03.033

[25] Wilkin JK: Effect of nadolol on flushing reactions in rosacea. J Am Acad Dermatol. 1989;20:202–205.

[26] Del Rosso JQ: Medical treatment of rosacea with emphasis on topical therapies. Expert Opin Pharmacother. 2004;5:5–13. doi:10.1517/14656566.5.1.5

[27] Gooderham M: Rosacea and its topical management. Skin Therapy Lett. 2009;14:1–3.

[28] Altinyazar HC, Koca R, Tekin NS, Eştürk E: Adapalene vs. metronidazole gel for the treatment of rosacea. Int J Dermatol. 2005;44:252–255. doi:10.1111/j.1365-4632.2004.02130.x

[29] Del Rosso JQ, Webster GF, Jackson M, et al: 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. doi:10.1016/j.jaad.2006.11.021

[30] Fernandez-Obregon A: Oral use of azithromycin for the treatment of acne rosacea. Arch Dermatol. 2004;140:489–490. doi:10.1001/archderm.140.4.489

[31] Baldwin HE: Systemic therapy for rosacea. Skin Therapy Lett. 2007;12:1–5.

[32] Gupta AK, Chaudhry MM: Rosacea and its management: an overview. J Eur Acad Dermatol Venereol. 2005;19:273–285. doi:10.1111/j.1468-3083.2005.01216.x

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