Recognition and management of ocular rosacea

Chronic ocular discomfort and redness from ocular rosacea and facial erythema from cutaneous rosacea both respond to oral tetracyclines. Coexisting dry eye and blepharitis including meibomian gland dysfunction are common and must also be treated.

STEPHANIE L. WATSON
BSc(Med), MB BS(Hons), FRANZCO, PhD

MINAS T. CORONEO
BSc(Med), MB BS, MSc, MD, MS, FRACS, FRANZCO

Dr Watson is a Consultant Ophthalmologist at the Corneal Unit at Prince of Wales Hospital, Sydney Children's Hospital and Sydney Eye Hospital. She is also an Ophthalmologist in private practice in Bondi Junction, Sydney, NSW.
Professor Coroneo is Professor and Head of Department of Ophthalmology, Prince of Wales Hospital, Randwick, Sydney, NSW.

Rosacea is a chronic skin condition characterised by facial hyperaemia.[1] It is found in 10% of the population, most commonly affecting women aged in their thirties, forties and fifties who have Celtic and northern European ancestry.[2] Ocular rosacea occurs in about 50% of all patients with cutaneous rosacea and is an often undiagnosed cause of chronic ocular discomfort, redness and intermittent visual blurring.[3] Ocular rosacea may occur in children, but this is not common.[4,5]

A patient with ocular rosacea – including its presentation and management – is described in the box on page 26.

Diagnosis

There is no diagnostic test for rosacea. Diagnosis depends on identification of the typical symptoms and signs and may be overlooked because many patients only exhibit mild signs (such as telangiectasia) and/or have a history of easy facial flushing.[2] A family history of rosacea is reported by up to 30% of affected patients.[6]

Signs and symptoms

The main feature of rosacea is chronic facial hyperaemia that typically affects the nose, central forehead and upper cheeks (Figure 1). Drinking alcohol or eating spicy food usually causes flushing of these areas. Facial telangiectasia, papules and pustules and hypertrophic sebaceous glands leading to increased sebum production occur to varying degrees.[2] Patients may need to be examined when they are not wearing make up because this can hide the signs. Examination in dimly and artificially lit consulting rooms is suboptimal. Rosacea typically has a subtle onset and disease activity fluctuates over time, but it becomes more severe and rarely remits spontaneously. Hypertrophy and hyperaemia of the end of the nose (rhinophyma) is a late sign in men with rosacea.[3]

There is no association between the severity of cutaneous rosacea and the extent of ocular involvement. The skin signs typically precede the ocular signs, but patients sometimes present initially with ocular features. Therefore, the diagnosis should

IN SUMMARY

- **Rosacea, a chronic skin condition characterised by facial hyperaemia, is common and often undiagnosed. Ocular rosacea occurs in about 50% of all patients with cutaneous rosacea.**
- **There is no association between the severity of cutaneous rosacea and the extent of ocular involvement. Although skin signs typically precede ocular signs, a diagnosis of ocular rosacea should be considered in a patient who presents with ocular discomfort, redness and intermittent visual blurring.**
- **Coexisting dry eye and blepharitis including meibomian gland dysfunction are common with ocular rosacea. Educating patients on how to perform eyelid hygiene is an important part of the management of these associated conditions.**
- **Cutaneous and ocular rosacea respond to oral tetracyclines.**

Case presentation: a patient with red eyes and blurred vision

History and examination

A 40-year-old woman presented with a three-year history of red and uncomfortable eyes and intermittent blurring of her vision. She had been diagnosed as having dry eyes and was using preserved artificial tears. Recently she had had been troubled by recurrent eyelid chalazia and hordeolum. She was otherwise well, took no medication and had no significant ocular family history. Her visual acuity was 6/6 in each eye.

On examination, hyperaemia and telangiectasia of the nose, central forehead and upper cheeks were noted. Her skin was pale and she had blue eyes and fair hair. When questioned, she said that her face flushed when she drank alcohol and coffee and when she ate spicy food. Schirmer's test, performed without anaesthetic, showed that her aqueous tear production was within normal limits.

At the slit lamp, mild bulbar conjunctival injection was accompanied by eyelid margin telangiectasia and other signs of posterior blepharitis including blocked meibomian gland orifices, cheesy meibomian gland secretions – expressible by mild pressure on the eyelids – and posterior eyelid margin notching. The palpebral conjunctiva was injected and occasional follicles and calcific concretions were seen. Scarring of the tarsal plate was visible where incision and curettage of chalazia had been performed in the past. There was peripheral vascularisation of the inferotemporal and inferonasal quadrants of the right and left corneas; on the left cornea subepithelial infiltrates were present central to the vessels. Punctate epithelial erosions were seen, particularly in the inferior cornea, following instillation of topical fluorescein and viewing with the cobalt blue light on the slit lamp.

Diagnosis and management

A diagnosis of rosacea with ocular involvement and associated posterior blepharitis was made. The link between the patient's facial flushing and irritable eyes was discussed, and she was advised to avoid substances such as coffee that may trigger or exacerbate flushing. She was also advised of the chronic nature of rosacea and of the need for daily effort on her part (eyelid cleaning and efforts to identify and avoid rosacea triggers) to improve her condition.

Oral doxycycline, 100 mg daily for one month, was prescribed. Prior to commencing therapy, the patient was informed that doxycycline can cause gastrointestinal disturbances so she should take the tablet with food and eat yoghurt to prevent pseudomembranous colitis. She was also advised to wear sunglasses, sunscreen and a hat when outdoors because doxycycline can cause photosensitivity. Advice was also given that doxycycline can interfere with the oral contraceptive pill and that she should use alternate means of contraception. She was given instruction in eyelid hygiene, which she was encouraged to perform at least twice daily, and prescribed chloramphenicol ointment for the eyelids, to be administered twice daily for one month. Management of dry eye was not required because she had good aqueous tear secretion. Due to the presence of corneal vessels and infiltrates (signs of inflammation and hypersensitivity), she was referred to an ophthalmologist, who prescribed topical fluorometholone eyedrops and monitored her for potential side effects.

Follow up

At a review visit one month later, the patient reported a marked reduction in her ocular discomfort and redness and an improvement in her skin. Doxycycline was continued at 100 mg once day for another month and then reduced to 50 mg a day. Topical chloramphenicol and fluorometholone were ceased. Topical metronidazole, applied twice daily to the eyelids, was prescribed for three months to maintain remission. The chronic nature of her condition was reinforced and the need for daily eyelid hygiene, avoidance of triggers and for courses of doxycycline to control flare ups was discussed.

be considered in a patient presenting with ocular discomfort, redness and intermittent visual blurring. Patients may also complain of foreign body sensation or photophobia. Symptoms of ocular rosacea are typically worse on waking (unlike the symptoms of dry eye, which are worse at the end of the day) and may also occur when performing visual tasks that require focused attention, such as reading, driving or using a computer. The symptoms are mostly due to tear film dysfunction, as dry eye and blepharitis including meibomian gland dysfunction are commonly associated with rosacea.[7]

Ocular signs, which are variably present in patients with rosacea (see Figures 1 to 5),[1,2,8] are listed in Table 1.[9-12] The cornea may be involved in up to one-third of patients with cutaneous rosacea.[10] Coexistent acute staphylococcal blepharoconjunctivitis may be accompanied by mucopurulent discharge and inflammatory reactions of the sclera, limbus and cornea to staphylococcal endotoxins or cell-mediated hypersensitivity responses to staphylococcal antigens, such as marginal keratitis.

Aetiology

The aetiology of rosacea is not completely understood. Vasomotor lability is thought to underlie the condition and is aggravated by ingestion of coffee, tea and other hot beverages and foods, alcohol and spicy foods, as well as by endocrine abnormalities, menopause and anxiety. Gastric infection with *Helicobacter pylori* may stimulate flushing, possibly by raising gastrin levels, but there is no firm evidence for this.[13] Limited evidence from conjunctival specimens has suggested that a type IV hypersensitivity reaction may be involved.[14]

Recently it has been proposed that raised skin temperature in rosacea, due to vascular dilation, may alter protein production by resident bacteria (see the review by Stone and Chodosh).[8] The bacterial lipases produced may act on meibomian gland secretions to produce cleavage products that incite inflammation. The mite *Demodex folliculorum* has been found in facial lesions

of rosacea, but its role in the pathogenesis of rosacea has not been established.[15]

Differential diagnoses

Rosacea may be confused with a variety of conditions that produce ocular discomfort and redness; it may also occur in conjunction with these conditions. Toxic keratoconjunctivitis is caused by chemical trauma and by iatrogenic and, rarely, factitious disease (the result of mechanical trauma or abuse of toxic eyedrops). Management requires withdrawing the drug or replacing the current formulation with an alternative that is nonpreserved and less toxic.

Rarely, rosacea may be confused with meibomian gland carcinoma, which is typically unilateral and presents with localised eyelid thickening and madarosis (loss of eyelashes). Some patients have a history of recurrent chalazia at one site requiring multiple surgeries.

The differential diagnoses of ocular rosacea are listed in Table 2.[9]

Management

Management of ocular rosacea should be tailored to disease severity. Four steps may be involved concurrently:

- treatment of the underlying condition (rosacea)
- treatment of associated conditions, such as dry eye and blepharitis
- control of bacterial growth on the eyelids
- treatment of ocular inflammation and hypersensitivity reactions.

This approach to management, which is discussed below, is summarised in the box on page 28.

Treatment of rosacea

Cutaneous and ocular rosacea respond to oral tetracyclines.[16] These agents are thought to favourably alter sebum secretions or may have a positive effect on interactions between the secretions and bacteria. We use a regimen of doxycycline, 100 mg daily for two months then reduced to 50 mg a day. It is important to warn patients that tetracycline therapy is suppressive, not curative, that prolonged courses are often needed and that a therapeutic response may take several weeks. If long term therapy is needed, tetracycline 'vacations' can be taken for two to three months.

A patient's general health and concurrent medications must be considered because tetracyclines can interact with anticoagulants, penicillins, antacids and iron preparations. Tetracyclines are contraindicated in patients with severe renal insufficiency, pregnant women, nursing mothers and children under 8 years of age. There is also emerging evidence from a large case–control study that long term antibiotic therapy may be linked to an increased risk of breast cancer; however, a causal role has not been established.[17]

Side effects of tetracycline therapy include gastrointestinal upset and photosensitivity. It is important to advise patients to take the medication with food, to eat yoghurt to prevent pseudomembranous

Table 1. Signs of ocular rosacea

Conjunctiva and eyelids

Chronic conjunctival hyperaemia, typically in the interpalpebral area (Figure 1) with palpebral follicles

Small grey vascularised nodules on the interpalpebral conjunctiva

Thickened erythematous eyelid margins with telangiectatic vessels (Figure 2) and plugging of the meibomian gland orifices by thickened yellowish secretions

Calcific concretions (Figure 3) and the sequelae of chalazia – treated and untreated – on the palpebral conjunctiva

Trachoma-like cicatrising conjunctivitis (rare, Figure 4)[9]

Episclera and sclera

Recurrent episcleritis (common)

Scleritis (rare)

Cornea

Punctate epitheliopathy on the inferior two-thirds of cornea, particularly if accompanying blepharitis and meibomian gland dysfunction are present

Peripheral corneal vascularisation, especially in the inferotemporal and inferonasal cornea (Figure 5), which may be associated with subepithelial infiltrates central to vessels

In severe cases, pannus formation on the cornea which may obscure the visual axis and be accompanied by lipid deposits, scarring and opacification of the cornea

In chronic cases, broad areas of pannus with usually inferior 'spade-shaped' peripheral scars and stromal thinning

Circumferential inflammation of the limbal stroma with vascularisation (less common)

Corneal thinning and ulceration, which may occur with the potential for perforation and/or microbial superinfection

Pseudokeratoconus (uncommon)[10]

Recurrent corneal erosion[11]

Dendritic keratopathy[12]

Table 2. Ocular rosacea: differential diagnoses

Dry eye syndrome

Anterior and posterior blepharitis

Allergic conjunctivitis

Toxic keratoconjunctivitis

Microbial conjunctivitis

Atopic keratoconjunctivitis

Herpes simplex blepharoconjunctivitis

Superior limbic keratoconjunctivitis

Idiopathic blepharospasm

Cicatrising conjunctivitis[9]

Psoriasis

Meibomian carcinoma

continued

Managing ocular rosacea: a summary

Principles

Tailor therapy to disease severity

Review patient to reinforce the need for compliance and chronic nature of the condition

Warn patient to return for review immediately if eyes become red and uncomfortable and vision is reduced as there is a risk of corneal involvement

Treat the rosacea*

Treat with oral tetracyclines (or erythromycin if tetracyclines are not tolerated)

Consider use of topical skin preparations: metronidazole ointment or azelaic acid cream

Identify and modify lifestyle factors that trigger exacerbations

Suggest measures to improve cosmesis (green eyeliner, green-tinted foundation)

Treat dry eye and blepharitis

Educate patient about eyelid hygiene

Consider use of artificial tear substitutes and punctal occlusion

Provide advice about increasing intake of omega-3 fatty acids

Control bacterial growth on the eyelids

Educate the patient about eyelid hygiene

Consider topical antibiotics (chloramphenicol ointment), applied to the eyelids

Treat ocular inflammation and hypersensitivity reactions

Treat with topical corticosteroids or progestational steroids† (with monitoring by an ophthalmologist for side effects)

Consider topical cyclosporin

Refer promptly to an ophthalmologist if there is corneal involvement (topical corticosteroids and, less commonly, corneal scrape and culture, corneal gluing and/or grafting may be required)

* Additional therapies (e.g. isotretinoin, retinoids, laser therapy) may be considered if there is no response to treatments listed.

† Must be produced by a hospital pharmacy.

colitis, and to wear sunglasses, sunscreen and a hat when they are outdoors. Reducing the tetracycline dose may improve tolerability. Oral tetracyclines can interfere with absorption of the oral contraceptive pill, so women who are of childbearing age should be advised to use other means of contraception.

A trial of oral erythromycin (DBL Erythromycin, Eryc) can be undertaken for a patient who cannot tolerate tetracyclines. Patients resistant to tetracyclines may respond to low-dose oral isotretinoin and topical retinoids; however, these must be

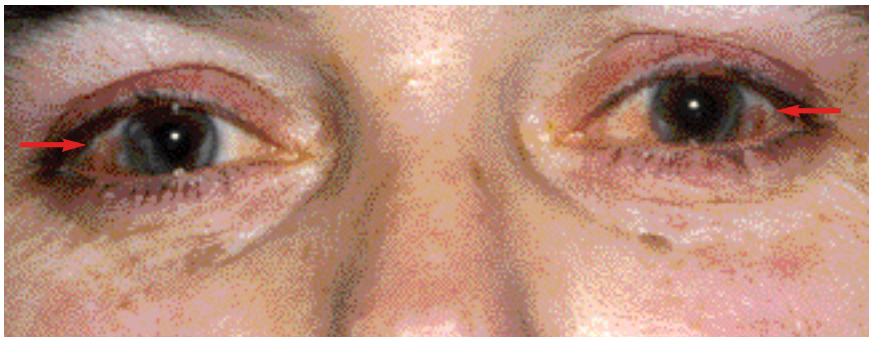

Figure 1. Mild facial hyperaemia and conjunctival hyperaemia (arrows).

Figure 2. Thickened eyelid margin with telangiectasis.

Figure 3. Calcific concretions in the palpebral conjunctiva.

FIGURES 1 AND 3 REPRODUCED FROM: LEONARD J, DART JKG. THE SKIN AND THE EYES [CHAPTER 64]. IN: BURNS DA, BREATHNACH S, COX N, GRIFFITHS C (EDS). ROOK'S TEXTBOOK OF DERMATOLOGY, 7TH ED, 2004. WITH PERMISSION FROM BLACKWELL PUBLISHING.

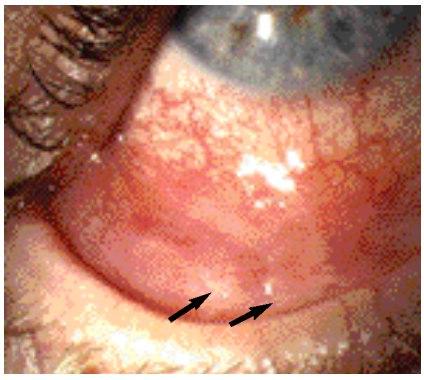

Figure 4. Cicatrisation (arrows) of the lower forniceal conjunctiva.

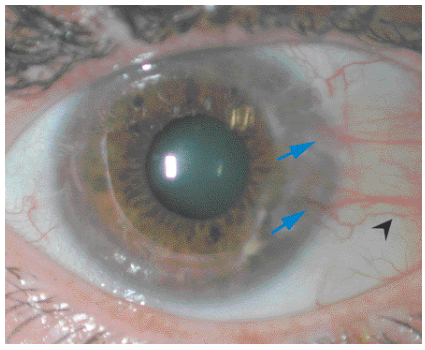

Figure 5. Conjunctival hyperaemia (arrowhead) and inferotemporal and nasal (arrows) peripheral corneal vascularisation.

used with caution because they have not been evaluated fully for rosacea,[8] and they may worsen the ocular disease by causing ocular surface drying and keratitis.

Topical metronidazole ointment (Metronidazole Gel, Rozex Gel) can be prescribed with oral therapy, typically twice a day for three months, for use on facial skin, including the eyelids and periorbital area; it can be continued in order to maintain remission when oral therapy is stopped.[2,18] Topical azelaic acid cream (Finacea)[19] and a sodium sulfacetamide–sulfur preparation (not available in Australia)[20] have also been shown to be effective for rosacea.

Lifestyle factors that may trigger exacerbations should be identified and avoided. Patients should keep a diary of daily activities, food and drink to link possible trigger factors to episodes of flushing. A list of common triggers can be found on the website for the US National Rosacea Society (www.rosacea.org/patients/materials/triggersgraph.php). Protection from climatic influences (hot and cold), such as with sunscreen, should be advised.[1]

To improve cosmesis, women may use a green eyeliner or green-tinted foundation to counteract the redness of the telangiectasis, along with a skin-tone foundation with natural yellow tones. Foundations with pink or orange hues should be avoided. Further information is available on the internet (www.rosacea.org/patients/materials/coping/tripwires.php#Skin). Laser therapy can be used to treat prominent telangiectatic vessels,[1] and it may reduce erythema.[21]

Treatment of dry eye and blepharitis including meibomian gland dysfunction

Eyelid hygiene is an important part of management for rosacea patients with coexisting dry eye and blepharitis including meibomian gland dysfunction. It involves a cleaning protocol which should be performed twice daily and should include the following steps:

- applying heat to the eyelids with a warm cloth to melt the meibomian gland secretions (2 minutes)
- massaging the upper and lower eyelids using a finger in a stroking motion directed towards the eyelid margin to encourage meibomian gland drainage (2 minutes)
- removing discharge from the meibomian gland openings using a cottonbud soaked in a solution of bicarbonate soda (one pinch of bicarbonate in a glass of warm water),[22] to minimise meibomian gland obstruction and improve lipid flow into the tear film (4 minutes).[23]

For an illustrated patient handout entitled

'Blepharitis: a guide to active management' refer to the January 2005 issue of *Medicine Today*.[23]

Artificial tear substitutes are useful for improving ocular surface wetting, punctate epitheliopathy and variable vision during prolonged visual tasks. Punctal occlusion (temporary or permanent) is useful if aqueous tear deficiency is associated with rosacea.[24]

Oral omega-3 fatty acids are helpful in managing dry eye and blepharitis. They are thought to reduce inflammation and therefore pro-inflammatory cytokines on the ocular surface.[25]

Topical and systemic androgens and/or oestrogens have been suggested as adjunctive therapy in dry eye because they may promote secretion by the lacrimal and meibomian glands and modulate ocular surface inflammation.[26] However, these agents are not in routine clinical use.[27]

Control of bacterial growth

The growth of ocular microflora may be inhibited by tetracycline therapy, which may ameliorate the inflammatory response to the cleavage products of bacterial lipases. Other measures that may reduce bacterial growth include eyelid hygiene (as discussed above) and topical antibiotics. In the first month of treatment for rosacea, topical antibiotics can be used to reduce bacterial flora – particularly if there is acute mucopurulent blepharoconjunctivitis, marginal corneal infiltrates or peripheral ulcerative keratitis. We use chloramphenicol ointment (Chloromycetin Eye Ointment, Chlorsig), applied twice daily to the eyelids.

Treatment of inflammation and hypersensitivity reactions

In the first month of treatment for rosacea, mild topical corticosteroids may be used to reduce ocular surface inflammation, particularly if there are marginal corneal infiltrates, peripheral ulcerative keratitis without progressive thinning and/or vascularisation. Patients with rosacea who are using corticosteroids should be followed closely by an ophthalmologist to monitor for side effects, including corneal melting.[28]

Topical medroxyprogesterone 1% may be used by the ophthalmologist if peripheral ulcerative keratitis with progressive thinning and progressive vascularisation are present. Progestational steroids are thought not to induce corneal melting (unlike corticosteroids) but are not widely available because they must be produced by a hospital pharmacy.

Topical cyclosporin, an inhibitor of T-cell function, may be used as an alternative to topical corticosteroids. However, although it has been shown to be of

benefit for dry eye[29] and meibomian gland disease,[30] a benefit in rosacea has not been established. Topical ophthalmic cyclosporin can be formulated by hospital pharmacies. Alternatively, an ophthalmic preparation of cyclosporin (Restasis) is available on the Special Access Scheme, but it is only approved for use in treating dry eye.

Topical tacrolimus, a potent inhibitor of T-cell activation and cytokine production that penetrates the skin more readily than cyclosporin, has recently been suggested for use in cutaneous rosacea.[31,32] It reduces facial erythema and minimises the need for topical glucocorticoids and their potential side effects, such as skin atrophy, but there is an increased risk of systemic absorption due to disruption of the skin barrier. However, it is not available as an ophthalmic preparation and larger studies are needed to establish its safety and efficacy in cutaneous rosacea.[33]

If corneal ulceration does develop, a scraping should be performed to rule out microbial infection. Small perforations can be managed with corneal glue and a bandage contact lens or amniotic membrane. Large perforations or excessive corneal scarring and vascularisation may require corneal grafting.

Follow up

Patients should be reviewed four weeks after commencing treatment so that compliance with therapy and daily eyelid hygiene can be ascertained. If an improvement is seen at this visit, we recommend that patients continue treatment with oral doxycycline 100 mg daily for another four weeks and then reduce the dosage to 50 mg daily; the patient is assessed again six weeks later to review the response and to determine whether doxycycline therapy should be continued. At each visit, the patient is reminded of the chronic nature of the condition and the need for increased therapy when a flare up occurs. MT

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STEPHANIE L. WATSON BSc(Med), MB BS(Hons), FRANZCO, PhD **MINAS T. CORONEO** BSc(Med), MB BS, MSc, MD, MS, FRACS, FRANZCO

References

1. Powell FC. Clinical practice. Rosacea. N Engl J Med 2005; 352: 793-803.
2. Wilkin JK. Rosacea. Pathophysiology and treatment. Arch Dermatol 1994; 130: 359-362.
3. Starr PA. Oculocutaneous aspects of rosacea. Proc R Soc Med 1969; 62: 9-11.
4. Lacz NL, Schwartz RA. Rosacea in the pediatric population. Cutis 2004; 74: 99-103.
5. Nazir SA, Murphy S, Siatkowski RM, Chodosh J, Siatkowski RL. Ocular rosacea in childhood. Am J Ophthalmol 2004; 137: 138-144.
6. Rebora A. The red face: rosacea. Clin Dermatol 1993; 11: 225-234.
7. Lemp MA, Mahmood MA, Weiler HH. Association of rosacea and keratoconjunctivitis sicca. Arch Ophthalmol 1984; 102: 556-557.
8. Stone DU, Chodosh J. Ocular rosacea: an update on pathogenesis and therapy. Curr Opin Ophthalmol 2004; 15: 499-502.
9. Ravage ZB, Beck AP, Macsai MS, Ching SS. Ocular rosacea can mimic trachoma: a case of cicatrizing conjunctivitis. Cornea 2004; 23: 630-631.
10. Dursun D, Piniella AM, Pflugfelder SC. Pseudokeratoconus caused by rosacea. Cornea 2001; 20: 668-669.
11. Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. Eye 2006; 20: 635-644.
12. Lee WB, Darlington JK, Mannis MJ, Schwab IR. Dendritic keratopathy in ocular rosacea. Cornea 2005; 24: 632-633.
13. Szlachcic A. The link between *Helicobacter pylori* infection and rosacea. J Eur Acad Dermatol Venereol 2002; 16: 328-333.
14. Hoang-Xuan T, Rodriguez A, Zaltas MM, et al. Ocular rosacea. A histologic and immunopathologic study. Ophthalmology 1990; 97: 1468-1475.
15. Erbagci Z, Ozgoztasi O. The significance of *Demodex folliculorum* density in rosacea. Int J Dermatol 1998; 37: 421-425.
16. Sneddon IB. A clinical trial of tetracycline in rosacea. Br J Dermatol 1966; 78: 649-652.
17. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Tapin SH. Antibiotic use in relation to the risk of breast cancer. JAMA 2004; 291: 827-835.
18. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remissions of rosacea. Arch Dermatol 1998; 134: 679-683.
19. Elewski BE, Fleischer AB, Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. Arch Dermatol 2003; 139: 1444-1450.
20. Torok HM, Webster G, Dunlap FE, Egan N, Jarratt M, Stewart D. Combination sodium sulfacetamide 10% and sulfur 5% cream with sunscreens versus metronidazole 0.75% cream for rosacea. Cutis 2005; 75: 357-363.
21. Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. J Am Acad Dermatol 2004; 51: 592-599.
22. Coroneo M. Management of chronic blepharitis. Arch Ophthalmol 1989; 107: 951-952.
23. Chan DG, Francis IC. Blepharitis: an approach to management. Med Today 2005; 6(1): 56-59.
24. Tai MC, Cosar CB, Cohen EJ, Rapuan CJ, Laibson PR. The clinical efficacy of silicone punctal plug therapy. Cornea 2002; 21: 135-139.
25. Trivedi KA, Dana MR, Gilbard JP, et al. Dietary omega-3 fatty acid intake and risk of clinically diagnosed dry eye syndrome in women [abstract 811]. Invest Ophthalmol Vis Sci 2003; 44.
26. Sullivan DA, Sullivan BD, Ullman MD, et al. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci 2000; 41: 3732-3742.
27. Scott G, Yiu SC, Wasilewski D, Song J, Smith RE. Combined esterified estrogen and methyltestosterone treatment for dry eye syndrome in postmenopausal women. Am J Ophthalmol 2005; 139: 1109-1110.
28. Watson SL, Coroneo M. Steroids and the eye. Med Today 2001; 2(3): 78-85.
29. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology 2000; 107: 967-974.
30. Perry HD, Doshi-Carnevale S, Donnenfeld E, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea 2006; 25: 171-175.
31. Ruzicka T, Assmann T, Lebwohl M. Potential future dermatological indications for tacrolimus ointment. Eur J Dermatol 2003; 13: 331-342.
32. Bamford JTM, Elliott BAP, Haller IVP. Tacrolimus effect on rosacea. J Am Acad Dermatol 2004; 50: 107-108.
33. Woo DK, James WD. Topical tacrolimus: a review of its uses in dermatology. Dermatitis 2005; 16: 6-21.