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Review

Ocular manifestations of rosacea: A clinical review

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ABSTRACT

Ocular rosacea is a chronic inflammatory condition that can occur in the absence of cutaneous features. The most common ocular features are chronic blepharoconjunctivitis with eyelid margin inflammation, and meibomian gland dysfunction. Corneal complications include corneal vascularisation, ulceration, scarring and, rarely, perforation. Diagnosis is largely based on clinical signs, although it is often delayed in the absence of cutaneous changes, particularly in children. It can also be associated with systemic disorders such as cardiovascular disease. Management ranges from local therapy to systemic treatment, depending on the severity of the disease. In this review, we describe the epidemiology, pathophysiology, clinical features and treatment of rosacea and ocular rosacea.

Keywords: Cornea, Staphylococcal blepharitis, Meibomian gland dysfunction, Keratitis, Dry eye

1. INTRODUCTION

Rosacea is a chronic, inflammatory dermatological condition that is associated with ocular disease in up to 58% of cases.[1] It is frequently under-recognised by ophthalmologists, as ocular signs precede cutaneous disease in 15% of cases.[1,2] While the ocular manifestations are usually mild, 41% of cases are associated with corneal involvement.[2] Ocular rosacea has a significant impact on ocular morbidity and on patients' quality of life, and therefore recognition of the condition is a key part to management. This is particularly the case in cases of paediatric ocular rosacea, where a delayed diagnosis is common.[3]

In this review, we explore the epidemiology, pathophysiology, clinical features of rosacea and ocular rosacea, and current treatment approaches.

2. EPIDEMIOLOGY

The global prevalence of rosacea has been estimated to be 5.46% of the adult population (range 0.09-24.1%) based on a meta-analysis of 32 studies.[4] The prevalence of ocular rosacea is reported to be much lower, ranging from 0.4-1.0%.[5,6] While rosacea is considered to be more prevalent amongst Caucasians with photosensitive skin types (Fitzpatrick skin phototypes I and II), it also affects other racial groups and those with Fitzpatrick skin phototypes III-VI.[7,8] In a United States national survey of known rosacea cases, 2% of cases were in African-Americans, 2% were in individuals of Asian background and 3.9% were in individuals of Hispanic backgrounds.[9] Epidemiological differences based on skin types may be due to the relative masking of facial flushing and erythema by the presence of skin pigmentation, the protective effects of melanin against ultraviolet (UV) radiation (as UV radiation can exacerbate rosacea) or genetic factors.[7] It is therefore important to consider the diagnosis of rosacea and ocular rosacea in patients of all races.

Rosacea is observed in all age groups, although it is most commonly diagnosed after the age of 30 years, with a peak between 40 and 59 years.[10] Females are commonly diagnosed earlier and more frequently than men, although this may represent

differences in the pattern of health seeking behaviours.[11] Phymatous skin changes occur more commonly in men,[10] with the more advanced change of rhinophyma usually occurring after the age of 40 years.[12] In contrast to rosacea, ocular disease occurs equally in both genders.[11]

Rosacea and ocular rosacea also occur in children. The reported incidence of rosacea in individuals aged less than 20 years in the United Kingdom was 0.89 per 1000 person years.[10] In a Chinese study of 13,215 adolescents aged between 12 and 20 years old, the prevalence of rosacea was 0.97%.[13] In a paediatric clinic in New Delhi, India, blepharoconjunctivitis was the most common diagnosis, accounting for 12% of 5,012 referrals, with a mean age of 6.7 years amongst affected children.[14]

3. PATHOPHYSIOLOGY

The pathophysiology of rosacea is likely multifactorial, involving a combination of immune-mediated and neovascular-mediated responses, environmental triggers and genetic factors.

3.1 Immune mediated

Dysregulation of the innate immune system has a role in the pathogenesis of rosacea. Levels of cathelicidin (an antimicrobial peptide) and kallikrein 5 (a serine protease) are increased in rosacea. Kallikrein 5 cleaves cathelicidin into LL-37, its active peptide form. LL-37, in turn, has a role in upregulating the immune-mediated response to promote inflammation and angiogenesis.[15-17] In patients with rosacea, LL-37 and kallikrein 5 are abundantly identified in the skin.[17,18] Gene array studies have also identified significant elevation of cathelicidin mRNA expression in all subtypes of rosacea.[19]

Elevated levels of pro-inflammatory markers in ocular rosacea patients have also been observed. Interleukin-1□and -□gelatinase B (matrix metalloproteinase, MMP-9), and collagenase-2 (MMP-8) have been identified in the tears of ocular rosacea patients.[20-23] Significant overexpression of intercellular adhesion molecule-1 (ICAM-1) and human

leukocyte antigen-DR (HLA-DR) isotype were also observed in conjunctival epithelial cells of rosacea patients,[24] while interleukin-1□, interleukin-16, stem cell factor, monocyte chemotactic protein-1 (MCP) and monokine induced by □-interferon, have all been found in skin biopsy specimens.[25]

3.2 Neurovascular dysregulation

The facial flushing, erythema and telangiectasia seen in rosacea may be due to an altered neurovascular response. Triggers, such as spicy foods, UV radiation and heat may promote release of inflammatory mediators which lead to vasodilatation, erythema and flushing, via a mechanism involving the transient receptor potential vallinoid (TRPV) family of cation channels.[26] Increased expression of TRPV has been identified on neuronal cells (TRPV1), smooth muscles of blood vessels, macrophages, mast cells (TRPV2), keratinocytes (TRPV2-4) and immune cells (TRPV2-4) in skin biopsy specimens from patients with different subtypes of rosacea compared with healthy skin.[26]

An increased expression of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGF-R1, VEGF-R2) has also been demonstrated in the skin of rosacea patients.[27] Interestingly, cathelicidin also modulates levels of VEGF within epidermal keratinocytes.[28] It is therefore likely that both vascular and immune-mediated processes contribute to the pathophysiology of rosacea.

3.3 Environmental risk factors

External triggers are believed to have a role in the activation of the vascular and immune-mediated responses in rosacea. These triggers include UV exposure, certain foods and drinks (including spicy foods, dairy products, alcohol and hot beverages), emotional stress, strenuous exercise, medications (including amiodarone, topical steroids and nasal steroids) and high doses of vitamins B6 and B12.[29,30] UV radiation may ~~have~~ trigger rosacea via several mechanisms: by activating vitamin D in keratinocytes, which in turn, induces cathelicidin expression in keratinocytes; by causing overexpression of MMP-1 in the skin,[31] which increases levels of kallikrein 5; and by inducing VEGF production from keratinocytes, leading to the increased

vascularity seen in rosacea.[32] UV radiation and other triggers may also lead to an increase in the levels of Toll-like receptor 2 (TLR2) in epidermal keratinocytes, as part of the innate immune response.[33] In turn, TLR2 leads to an increase in the production and activity of kallikrein 5, leading to increased expression of LL-37.[15]

3.4 Microorganisms

Microorganisms are postulated to play a role in rosacea. In particular, Demodex (Demodex folliculorum and Demodex brevis), a microscopic mite found on hair follicles and sebaceous glands, is found in higher density in rosacea compared to unaffected skin. In a meta-analysis of 1513 patients, Demodex mites were more commonly observed in rosacea patients compared to controls (OR 9.039; 95% confidence interval (CI), 4.827-16.925).[34] The Demodex count from eyelash samples is also significantly higher in patients with facial rosacea,[35] and was seen more commonly in paediatric and adult patients with chalazia compared to controls (69.2% vs 20.3%).[36] The presence of Demodex mites may lead to pro-inflammatory changes, or may act as a vector for other microorganisms, which activate TLR2 and the ensuing pro-inflammatory changes.[15,35,37] Additional microbes that may be implicated include Helicobacter pylori and *Staphylococcus epidermidis*, which is a normal skin commensal, however the effects of these additional microorganisms in the pathogenesis of rosacea remains controversial.[38] Interestingly, a reduced concentration of group IIA phospholipase A2, an antimicrobial protein which is secreted into tears by the lacrimal glands, has been observed in the tears of patients with ocular rosacea.[39]

3.5 Genetics

As the incidence of rosacea is more common in Caucasian populations, a genetic component is presumed to contribute to the pathogenesis of rosacea in up to 50% affected individuals.[40] However, the causative gene or genes have yet to be identified. In a genome-wide associations study in a mostly Caucasian population, a single-nucleotide polymorphism (SNP) rs763035 was identified, which is located between the ~~human leukocyte antigen-DRA (~~HLA-DRA~~)~~ and butyrophilin-like 2 (BTNL2) genes.[41]

4. CLINICAL FEATURES

The association between rosacea and ocular rosacea can vary between individuals. Facial changes may appear as the primary feature in 53% of cases; concurrent skin and ocular changes may occur in 27% of cases; and ocular changes may occur as the primary feature in up to 20% of cases.[42] There is also mounting evidence of systemic associations with rosacea.

4.1 Skin disease

Rosacea is characterised by vasomotor changes within blood vessels, primarily in the facial and periocular areas. It results in transient or persistent erythema, telangiectasia, papules, pustules and phymatous changes.[43] Symptoms of flushing, burning and stinging are characterised by periods of exacerbation and remission. It can also affect extra-facial locations, such as the neck, chest, scalp, ears and back.[44]

Rosacea is classified into four subtypes: subtype I - erythematotelangiectatic; subtype II - papulopustular; subtype III - phymatous; and subtype IV represents the presence of ocular features.[45] To diagnose rosacea, the global ROSacea COnsensus (ROSCO) panel defined criteria which are summarised in table 1. A minimum of one of the diagnostic ~~criteria~~ features, or two or more major ~~criteria~~ features are required for a diagnosis. Disease severity is independent of the extent of ocular disease.[46]

Table 1: Diagnostic, major and minor features of rosacea. From the recommendations of the global ROSacea Consensus (ROSCO) panel.[46]

Diagnostic Features	Major Features	Minor Features
Persistent centrofacial erythema associated with periodic intensification by potential trigger factors	Flushing/ transient centrofacial erythema	Burning sensation of the skin
Phymatous changes	Inflammatory papules and pustules	Stinging sensation of the skin

	Telangiectasia Ocular Lid margin telangiectasia Blepharitis Keratitis/ conjunctivitis/ sclerokeratitis	Oedema Dry sensation of the skin

~~While rosacea is typically considered a dermatological disorder, there is increasing evidence that it is associated with other systemic conditions, including gastrointestinal (coeliac disease, ulcerative colitis, Crohn's disease, *Helicobacter pylori* infection), neurological (depression, migraine, dementia, Parkinson's disease,) coronary artery disease, Type 1 diabetes mellitis and rheumatoid arthritis.[47] The association with other autoimmune disorders supports the possible shared genetic risk loci of rosacea with autoimmune disorders.[48]~~

4.2 Ocular rosacea

Ocular rosacea may occur in up to 58% of patients with rosacea.[1] However, the severity of ocular involvement may not directly correlate with the extent of cutaneous changes.[49] A diagnosis of ocular rosacea should therefore be considered in patients with diagnostic features, regardless of the presence of skin disease. The grading of ocular rosacea by the ROSCO panel is shown in Table 2:

Table 2: Grading of ocular rosacea. From the recommendations of the global ROSacea Consensus (ROSCO) panel.[46]

Severity	Features
Mild	Mild blepharitis with lid margin telangiectasia
Mild-to-moderate	Blepharoconjunctivitis
Moderate-to-severe	Blepharokeratoconjunctivitis
Severe	Sclerokeratitis, anterior uveitis

Ocular manifestations are typically seen bilaterally, however unilateral or sequential

changes can occur.[2] Symptoms are typically ocular irritation, itch, redness, photophobia and/or epiphora, and reduced vision in the presence of corneal involvement.[50] The signs are described in more detail in this section. It should be noted that neither symptoms nor signs are specific for the disease.[2]

4.3 Eyelid

The eyelid changes seen in ocular rosacea are well recognised and cause the symptoms of irritation and itch. The lid margin is typically erythematous with telangiectasia, Meibomian gland dysfunction (MGD) and posterior blepharitis are the most common findings.[11] (Figure 1) Meibomian gland secretions are produced in an excessive quantity and can be of turbid consistency, leading to the plugging of the meibomian gland and chalazion formation. It also results in an abnormal tear film, with a soapy, inferior tear meniscus, leading to evaporative dry eyes.[2] Anterior blepharitis with collarette formation around the eyelashes is also common, and Demodex mites may be seen on eyelashes.[11] An important differential diagnosis to consider in cases of eyelid involvement includes sebaceous gland carcinoma, which is typically unilateral and progressive.[51]

Figure 1: This 69 year-old male with rhinophymatous rosacea, presented with a 6 month history of decreased vision and epiphora. This photo shows eyelid margin telangiectasia, Meibomian gland dysfunction, and nasal and temporal areas of corneal neovascularisation associated with lipid keratopathy

4.4 Conjunctiva

The chronic inflammation associated with ocular rosacea can result in a non-specific, chronic conjunctivitis predominantly affecting the interpalpebral region.[52] An arcade of dilated vessels in the superficial limbal plexus, typically in the inferior quadrant may be observed.[1] Inferior conjunctival scarring and cicatrising changes, conjunctival granulomas and phlyctenulosis may occur.[2]

4.5 Cornea

Corneal involvement occurs in around one third of cases with ocular rosacea. It

typically involves the inferior cornea but can progress circumferentially and can involve the central cornea. Corneal pathology can range in severity from mild, inferior punctate epithelial erosions, to marginal keratitis, corneal vascularisation, scarring, peripheral thinning, ulceration and corneal perforation in the most severe cases. (Figure 1) Additional corneal changes include recurrent corneal epithelial erosions, Salzmann nodules and phlyctenules.[2] Episcleritis, scleritis and anterior uveitis have also been reported.[11]

4.6 Paediatric ocular rosacea

In contrast to adult cases where ocular manifestations may precede cutaneous disease in 15% of cases, ocular disease may precede skin disease in as many as 55% in affected children.[53] Dermatological features, where present, may also be more subtle compared to adults.[54] Thus, ophthalmologists may be the first to diagnose the condition in young patients. However, the absence of skin changes frequently results in a delayed diagnosis. In a case series of 27 children from London, United Kingdom, the mean time from onset of symptoms to presentation at a specialty anterior segment clinic was 1.9 years.[55] Ocular rosacea in the paediatric population also remains poorly recognised, in part, due to ambiguous diagnostic criteria and variable terms (including childhood blepharokeratoconjunctivitis, phlyctenular keratitis and staphylococcal blepharokeratitis) which are all used to describe a wide spectrum of manifestations of the same disease.[56]

On first presentation, most paediatric patients have bilateral disease, although it may be asymmetric. Signs include recurrent chalazia, lid margin telangiectasia, MGD, anterior and posterior blepharitis, conjunctival hyperaemia, inferior punctate epithelial erosions, corneal infiltrates and phylectnulosis.[3,57,58] (Figure 2) The presence of these signs and a positive family history of rosacea can provide clues to the diagnosis of ocular rosacea in this age group.[56] However, due to delays in the diagnosis, corneal complications such as ulceration, pannus formation, vascularisation and scarring are more common on first presentation in paediatric patients compared to adults.[57] Our own experience is that corneal vascularisation and scarring can be quite marked before the diagnosis is made, as associated lid disease is often subtle. In a case series

of 51 paediatric patients in Singapore, one third of eyes had poor vision (less than 0.3logMAR) at the time of presentation, and over 90% presented with corneal scarring or superficial vascularisation.[58] Therefore, timely diagnosis and treatment is crucial to reduce morbidity. It is frequently confused with Herpetic eye disease or allergic eye disease.

Figure 2: This 15 year-old male presented one year ago with 6-month history of conjunctival injection on a background of recurrent chalazia since the age of 18 months and a diagnosis of a papulopustular rosacea 2 years prior. At the time of presentation his visual acuity was 6/18 and he had posterior blepharitis, corneal vascularisation and lipid keratopathy. He was treated with oral doxycycline, topical corticosteroids and artificial tear supplements. He subsequently commenced a course of minocycline. At the time of this photograph, 8 months later, his visual acuity was 6/30.

4.7 Systemic associations

While rosacea is typically considered a dermatological disorder, there is increasing evidence that it is associated with other systemic conditions.[59] A meta-analysis found a higher prevalence of dyslipidaemia, hypertension, hypercholesterolaemia, raised low-density lipoprotein, triglycerides and fasting blood glucose, and systolic hypertension amongst patients with rosacea. However, no statistically significant association was found with ischaemic heart disease, stroke, diabetes and high-density lipoprotein.[60] It has also been associated with gastrointestinal disorders (coeliac disease, ulcerative colitis, Crohn's disease, *Helicobacter pylori* infection) neurological disorders (depression, migraine, dementia, Parkinson's disease,) and rheumatoid arthritis.[47] The association with other autoimmune disorders supports the possible shared genetic risk loci of rosacea with autoimmune disorders.[48]

5. INVESTIGATIONS

Rosacea and ocular rosacea currently remain a clinical diagnosis. The diagnosis of demodicosis is also based on clinical evaluation and can be confirmed by microscopic

detection of Demodex mites in epilated eyelashes or in skin scrapings, which can be sent on a glass slide for examination by a pathologist. Dermoscopy can also be performed by dermatologists where filaments surrounded by erythema or scales may be observed.[61] In vivo imaging of meibomian glands using meibography assists with morphology of the meibomian glands in MGD. While meibography can be performed using various techniques including confocal microscopy and direct transillumination, it is most commonly performed by capturing infrared images of meibomian glands, with commercial devices now available for this purpose. Using meibography, MGD can be graded as grade 0: no loss of meibomian glands; grade 2: gland dropout area less than one-third of the total meibomian glands; grade 2; gland drop out area one-third to two-thirds of the total meibomian glands; grade 3: gland drop out more than two-thirds of the total meibomian glands).[62] Impression cytology and confocal microscopy have been used for research purposes, with the latter finding an association between eyelid and skin changes, but not between eyelid and corneal changes.[63] In the future, tests may be available to assess the presence of bio-markers such as IL-1α and MMP-9 in tears of patients to aid with the diagnosis and assessment of treatment efficacy of rosacea[64,65] As rosacea is associated with systemic disorders including dyslipidaemia, hypertension and *H. pylori* infection, systemic investigations should be considered in conjunction with a general practitioner or physician, particularly if other risk factors for these diseases is present.

6. TREATMENT OF OCULAR ROSACEA

Depending on the severity of disease, treatment usually involves one or a combination of, conservative measures, topical agents, systemic agents and interventions. However, there is a lack of randomised, controlled trials assessing these treatments. Studies report small sample sizes, and many are not specific to ocular rosacea. A summary of the results of select studies specific to rosacea (where available) is listed in Table 3. Furthermore, there are few studies which specifically study treatment in the paediatric population.[66,67]

Table 3: Summary of select studies on topical, systemic and interventional treatment of ocular rosacea cited in this review.

Treatment	Study	Design	Condition	Dose	Follow-up	Outcome
Topical						
Ciclosporin 0.05%	Schechter et al[68]	Randomised (vs AT, n=37)	Rosacea	bd	3 months	↓ corneal staining ↑ Schirmer, OSDI
Lifitegrast 5% drops	Tauber[69]	Randomised (vs TP, n=50)	MGD	bd for 42 days	5 weeks	↓ symptoms, corneal staining, eyelid redness
Tacrolimus 0.03%	Sakassegawa-Naves[70] et al	Randomised (treatment n=18, placebo n=20)	Posterior blepharitis	bd for 28 days	28 days	↓ MG secretion, conjunctival hyperaemia, lid telangiectasia, corneal staining: ↓ symptoms of itch and dry eyes
Azithromycin 1.5% drops	Luchs[71]	RCT (vs compresses, n=21)	Posterior blepharitis	bd for 2 days then daily for 12 days	14 days	↓ in MG plugging, secretions, eyelid redness; symptoms
	Doan et al[72]	Retrospective case series, n=16	Ocular rosacea in children	bd for 3 days every 10 days then reduced; mean 6 months	Mean 11 months	15/16 ↓ redness, conjunctival hyperaemia. Resolution of phylectenules, corneal inflammation
Systemic						
Doxycycline	Sobolewska et al[73]	Retrospective case series (n=15)	Ocular rosacea	Slow release 40mg daily, for mean 8 months	Mean 9 months after ceasing treatment	↓ symptoms, blepharitis, conjunctival hyperaemia
Azithromycin (oral)	Greene et al[74]	Prospective case series (n=32)	meibomitis	1g per week for 3 weeks	Mean 5.6 months	75% symptomatic improvement
Erythromycin	Gonser et al[75]	Retrospective case series (n=9)	Ocular rosacea in children			7/9 remission 2/9 partial remission
Omega-3 fatty acids	Bhargava et al[76]	RCT (vs placebo, n=130)	Ocular rosacea in adults	Omega-3 FA* bd for 6 months	6 months	↓ symptoms, MG score, Schirmer score, TBUT
Interventional						
Thermal pulsation	Finis et al[77]	Randomised (vs warm compresses, n=31	MGD	Single treatment	3 months	↓ OSDI, no difference in expressible MG glands
IPL	Seo et al[78]	Prospective case series (n=17)	Ocular rosacea MGD	4 treatments at 3 weekly intervals	12 months	↓ lid vascularity, MG secretions, OSDI

* 180mg eicosapentaenoic acid (EPA) and 120mg docosahexaenoic acid (DHA)
AT artificial tears; bd twice daily; FA fatty acids; IPL intense pulsed light; MG meibomian gland; MGD meibomian gland dysfunction; OSDI ocular surface disease index; RCT randomised, controlled trial; TBUT tear break up time; TP thermal pulsation; ↓ reduction, ↑ improvement

6.1 Conservative measures

Patient education is essential, as affected individuals need to understand the chronicity of the condition, with periods of exacerbations and remissions. Patients should also be aware of the systemic associations with rosacea so that monitoring can be undertaken where appropriate. Exposure to potential triggers should be minimised, such as recommending the use of sun protection to minimise UV exposure, and minimising hot showers, spicy foods, alcohol and caffeine.[79] Conservative measures to treat MGD are encouraged, including digital massage or the use of warm compresses and lid hygiene, twice daily, to treat posterior and anterior blepharitis.[2] Any Demodex infection should be treated, for example, with tea tree oil therapy (weekly lid scrubs with 50% tea tree oil and daily lid scrubs with tea tree shampoo for a minimum of six weeks)[80,81], 4% pilocarpine gel (applied to the base of the eyelashes a night and removed in the morning, for two weeks[82] (not available in Australia), warm compresses, intense pulsed light, topical ivermectin (1% once daily for 12 weeks)[83] or systemic ivermectin (200µg/mL as a single dose, which can be repeated after 7 days).[80,84] If conservative measures are insufficient in treating eyelid disease, concurrent topical and systemic agents may be required.

6.2 Topical agents

The aim of topical treatments for ocular rosacea are to treat dry eyes, MGD and ocular surface inflammation. Preservative-free artificial tear supplements are recommended as it treats not only dry eyes but helps to reduce ocular surface inflammation.[79] In addition, topical steroids are frequently required during episodes of acute inflammation, however long-term use is generally not recommended due to the increased risk of microbial keratitis and other steroid-associated complications.[2,55]

Ciclosporin is a potent inhibitor of T-cell function by selectively inhibiting calcineurin, impairing the transcription of IL-2 and related cytokines in T-cells. It can be considered as an adjunct treatment for ocular surface inflammation in rosacea. In a randomised, controlled trial, twice daily instillation of topical ciclosporin 0.05% was more efficacious than artificial tear supplements after 3 months of treatment in improving Schirmer score, mean tear break-up score, corneal staining and Ocular Surface Disease Index (OSDI) score.[68] Use of higher concentrations of ciclosporin 2% have also been reported to be effective.[85] Topical ciclosporin has also been reported to improve ocular symptoms and tear production to a greater extent than oral doxycycline,[86] in part by increasing mucin production from goblet cells.[87] Stinging and irritation are common side effects, however it is generally well tolerated, with minimal long-term side effects reported.[88]

There is less information on the use of other anti-inflammatory agents for ocular rosacea. Lifitegrast 5% ophthalmic solution (Xiidra, Shire, Lexington, MA) is a first in class, selective antagonist to lymphocyte function-associated antigen-1 (LFA-1) and reduces T cell-medicated inflammation. Lifitegrast inhibits the interactions between LFA-1 and its ligand ICAM-1, which is expressed in vascular endothelial cells in the presence of infection or inflammation, and is overexpressed in corneal and conjunctival tissues in dry eyes.[89] While the original phase 3 studies were performed for dry eye disease, a recent prospective, randomised, single-masked study enrolled patients with inflammatory MGD. In this study, lifitegrast twice daily for 42 days was compared to a single treatment with thermal pulsation. At the end of the 6-week period, there was a greater improvement in symptoms, corneal staining and eyelid redness in the lifitegrast group compared to the thermal pulsation group.[69] However it should be noted that the study was funded by the manufacturers. There is also one prospective, randomised, double-masked interventional case series on the use of topical tacrolimus ointment 0.03% twice daily for refractory posterior blepharitis. After 28 days, there was an improvement in symptoms, meibomian gland secretion, conjunctival hyperaemia, lower lid telangiectasia and corneal staining.[70]

Topical azithromycin (for example, Azasite®, azithromycin 1% ointment, Inspire Pharmaceuticals and Azyter®, azithromycin 1.5% eye drops, Thea Pharmaceuticals) is approved to treat bacterial conjunctivitis. However, it may also be useful in treating MGD, although this indication is 'off-label'.[90] In a randomised trial comparing azithromycin 1% with warm compresses, azithromycin was been shown to improve eyelid signs, meibomian gland plugging and symptoms.[71] It can be used twice daily for two days then once daily for a total of 30 days, although dosing regimens vary. It has also been used in paediatric cases.[72]

6.3 Systemic agents

Oral antibiotics are commonly used in the treatment of ocular surface disease although evidence for their use is limited. Oral tetracyclines, such as doxycycline (a synthetic derivative of tetracycline), are beneficial in the treatment of rosacea through several potential mechanisms.[91] Tetracyclines inhibit the expression of MMPs and the activation of cathelicidin, which have as a role in the pathophysiology of rosacea as described previously. Furthermore, tetracyclines reduce bacterial flora on the eyelids and reduce the production of lipase enzymes by staphylococci, which can improve the quality of meibomian gland secretions.[92] Tetracyclines also inhibit collagenase enzymes and may protect the cornea from thinning and perforation in more advanced cases.[93]

Oral tetracycline and oral doxycycline have a similar mechanism and efficacy however, tetracycline has a shorter half-life and is taken at a four times daily dose.[93] Doxycycline is, therefore, generally more commonly used and better tolerated. There are various dosing regimens that can be used. It is typically prescribed as a dose of 100mg once daily, or 50mg twice daily for 6-12 weeks, or tapered to a lower dose after 2-4 weeks. It can also be prescribed at 100mg twice daily or 50mg daily.[94,95] It should be noted that the optimal dose and duration of treatment has not been established and little evidence exists for the 50mg daily dosing regimen to treat ocular rosacea.[96] Patients who have recurrent symptoms on discontinuation of the treatment may require longer term use. However, long term use of doxycycline may be associated with a higher side effect profile, including gastrointestinal symptoms, photosensitivity and lower

tolerance of the medication.[52] In 2006, a lower dose doxycycline capsule (Oracea, Galderma Laboratories L.P, TX, USA), was approved by the United States Food and Drug Administration (FDA) specifically for rosacea in adults. It consists of 30 mg immediate-release and 10 mg delayed-release doxycycline and is taken once daily. Treatment with doxycycline 40mg for a mean of 8 months resulted in an improvement in ocular rosacea symptoms and conjunctiva injection after a mean follow-up of 9 months. ~~Only one out of 15 patients ceased doxycycline due to gastrointestinal side effects.~~[73] Lower dose 40mg doxycycline is associated with fewer gastrointestinal side effects than conventional 100mg or 50mg doxycycline.[97] It also has the advantage that 40mg is a sub-microbial dose, whereas 50mg doxycycline once daily has a plasma concentration that exceeds the minimum inhibitory concentration for two to three hours.[98] Therefore, where available, the lower dose 40mg (30 mg immediate-release and 10 mg delayed-release) doxycycline should be used rather than 50mg immediate-release doxycycline.

~~Oral doxycycline is frequently used in ocular rosacea as an adjunct to topical and conservative management.~~ A combination of doxycycline and ciclosporin 0.05% have been shown to be more efficacious than doxycycline alone.[86] Another tetracycline, minocycline 100mg taken once daily is commonly prescribed by dermatologists for rosacea, due to the lower incidence of gastrointestinal side effects and photosensitivity than doxycycline. It has been found to be non-inferior to doxycycline 40mg once daily.[99] However, the evidence for minocycline in the treatment for ocular rosacea is lacking, and risks include drug-induced lupus and other hypersensitivity syndromes.[94] Minocycline is not currently FDA approved for rosacea, and rosacea is not an indication for doxycycline or minocycline in Australia under the Pharmaceutical Benefits Scheme.

The use of oral tetracyclines is not recommended in children under the age of 7 years, or in pregnancy and lactation. This is due to the potential complication of impaired bone growth and permanent discoloration of teeth, and its teratogenic potential.[53] In such cases, oral erythromycin may be used as an alternative,[100] at 500mg daily (as erythromycin base) for adults and 30-50mg/kg (ethyl succinate formulation) in divided doses for children. Alternatively, azithromycin can be prescribed 500mg orally, 3 days

a week for 3 or 4 weeks for adults and 5mg/kg/day for children.[101,102] Erythromycin and azithromycin are macrolide antibiotics, considered to have polymodal immunomodulatory effects which can be used for the management of posterior blepharitis. They are generally well tolerated, although gastrointestinal side effects may be reported.[103] In a randomised clinical trial, doxycycline (100mg twice daily for one month) and azithromycin (500mg for one day then 250mg for a further four days) have both been shown to improve symptoms and signs of MGD, with a relatively better effect observed following azithromycin. Together with the shorter duration of a course of treatment, azithromycin be a more preferable treatment than doxycycline.[104] However, it should be noted that azithromycin may be associated with an increased risk of cardiovascular death, although causality has not been established.[105] The relapse rate upon completion of a course of oral antibiotic treatment in children may be lower compared to adults.[75]

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which is involved in lipid secretion from skin sebaceous glands and hair follicles, has been found to be expressed in meibomian gland epithelial cells.[106] This has led to the postulation that the use of topical statins may be beneficial in meibomian gland disease. In a pilot study, treatment with topical atorvastatin (50μM, 8 times a day for 4 weeks) has been shown to improve symptoms of dry eyes and blepharitis.[107] Conversely, oral statins have not been shown to modify meibomian gland atrophy and meibum quality.[108]

6.4 Nutritional supplementation

A systematic review of randomised, controlled trials suggested supplementation with omega-3 and omega-6 fatty acids may reduce OSDI more so in patients with MGD and posterior blepharitis than dry eyes from other causes.[109] Omega-3 and -6 fatty acids may affect the quality and quantity of intracellular lipids.[110] In a randomised, controlled trial of omega-3 fatty acids taken for 6 months for ocular rosacea, meibomian gland function, Schirmer score, tear break up time and symptoms all improved at the end of the treatment.[76] It can also be used in paediatric ocular rosacea.[55] Conversely, the DREAM Study, a multi-centre, randomised, double-masked clinical trial did not find any benefit from omega-3 fatty acid supplementation

compared with an olive oil control for the management of dry eyes, although this larger study was not specific for MGD and posterior blepharitis.[111]

6.5 Interventions

In addition to the topical and oral medical treatment, interventional approaches, such as thermal pulsation (Lipiflow® Thermal Pulsation System, Johnson & Johnson), intense pulsed light (IPL) and intraductal Meibomian gland probing have gained popularity over recent years for the management of MGD.[77,112,113] Although the use of thermal pulsation has not been directly studied in ocular rosacea, the MGD associated with rosacea may be responsive to this treatment.[79] Thermal pulsation treatment consists of localised application of heat (42.5^0C) and mechanical stimulation of the eyelid to allow extrusion of blocked Meibomian glands. In a prospective, randomised, cross-over, observer-masked trial, a single treatment with thermal pulsation was at least as effective as a 3-month, twice daily, eyelid hygiene regimen in improving OSDI, but not in tear break-up time, tear osmolarity, corneal and conjunctival staining, Schirmer test values and tear meniscus height.[77] In other prospective studies, a single treatment of thermal pulsation led to a sustained improvement in OSDI and meibomian gland secretion scores after one year.[114,115]

IPL treatment consists of the use of a polychromatic light with a wavelength spectrum of 500–1200 nm. It leads to selective photothermolysis, whereby skin chromophores absorb light energy, leading to selective thermal damage of the target cell. In rosacea and MGD, IPL pulses are used in the peri-ocular area (while eye protection is worn), from the inner canthus to the temporal region below the lower and upper eyelids. Its potential mechanisms of action may be in coagulation of telangiectatic vessels, reducing inflammation, causing liquefaction of meibum and reopening of meibomian gland ducts and stabilising the tear film.[113] An American Academy of Ophthalmology Ophthalmic Technology Assessment concluded that IPL improves symptoms and signs of MGD despite methodological flaws in the studies examined. However, repeated treatments may be required.[116] For optimal results, IPL treatment should be combined with eyelid hygiene and warm compresses. While IPL may be an alternate option for ocular rosacea patients with MGD, its use is limited by its availability and cost. Further

studies are required to directly compare its use to the more standard topical and oral treatments in ocular rosacea.

Intraductal Meibomian gland probing is a simple, office-based procedure that can be performed at the slit lamp. Probes ranging from 1 to 4mm in length can be used to relieve obstructed Meibomian gland orifices. In one case series, all 25 patients whom were treated experienced symptomatic relief after 4 weeks, and 80% had continued improvement at 11.5 months after a single treatment.[112]

Further interventional procedures include the use of punctal plugs for dry eyes, although it is typically more useful for aqueous-deficiency dry eyes. Contrary to popular belief, the presence of ocular surface inflammation is generally not a contraindication to the use of punctal plugs.[117,118] Corneal involvement such as persistent epithelial defects may benefit from additional treatments including amniotic membrane grafts and corneal perforations may necessitate corneal transplantation.

6.6 Rosacea treatment

The management of skin disease is summarised in a recent Cochrane review.[94] The main treatments involve topical and systemic measures. As there is an overlap in the management between ocular rosacea, skin disease, and other systemic disorders, it should be co-managed with a dermatologist and a general practitioner or physician. Like the management of ocular rosacea, patients with skin disease should be encouraged to avoid any environmental triggers in addition to skin care. Topical treatments, including topical sulfacetamide, metronidazole (0.75% and 1% formulations) and azelaic acid (15% gel or 20% cream) are used in the treatment of mild to moderate papulopustular rosacea,[94] topical alpha-adrenergic receptor agonist, brimonidine (3.3mg/g), can be used to treat facial erythema and topical ivermectin can be used to treat both papulopustular rosacea and demodicosis. However, topical steroid treatment should be avoided as it can trigger steroid-induced rosacea.[119] If topical treatments are not sufficient in controlling the disease, systemic treatment with oral tetracyclines should be initiated.[94] Tetracyclines minocycline and doxycycline are commonly used; oral isotretinoin (0.3 to 1.0 mg/kg/day) can be used in recalcitrant

papulo-pustular rosacea, working via downgrading Toll-like receptor 2 (TLR2) expression, although the treatment is also associated with ocular side effects, most notably conjunctivitis.[120] The use of laser (eg. pulsed dye laser and 532nm potassium titanyl phosphate) and IPL treatments are reported in cases of persistent erythema or cutaneous telangiectasias.[121]

Given its chronic inflammatory nature, novel, future approaches targeting the causative inflammatory mediators involved in the pathophysiology of rosacea may become available in the future to help prevent the progression of the condition. Such approaches may include, targeting the pro-inflammatory interleukins, IL-17[122] and toll-like receptors.[79]

7. CONCLUSIONS

Ocular rosacea should be considered as a diagnosis in all age groups with chronic eyelid inflammation associated with conjunctival and corneal changes. It can be a diagnostic challenge, particularly in paediatric cases where there may be minimal, or no, associated skin changes. Early treatment will provide symptomatic relief and reduce the risk of corneal complications. Treatment should involve minimising environmental triggers, as well as a combination of conservative, topical, systemic and potentially, interventional therapies. The association of rosacea with systemic disorders such as dyslipidaemia and hypertension should be recognised.

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Figure 1:

This 69 year-old male with rhinophymatous rosacea, presented with a 6 month history of decreased vision and epiphora. This photo shows eyelid margin telangiectasia, Meibomian gland dysfunction, and nasal and temporal areas of corneal neovascularisation associated with lipid keratopathy

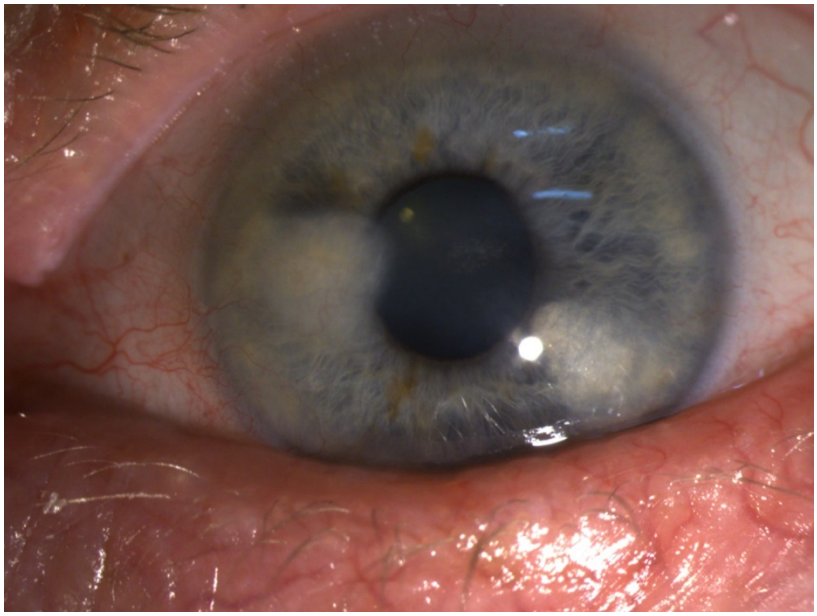

Figure 2

This 15 year-old male presented one year ago with 6-month history of conjunctival injection on a background of recurrent chalazia since the age of 18 months and a diagnosis of a papulopustular rosacea 2 years prior. At the time of presentation his visual acuity was 6/18 and he had posterior blepharitis, corneal vascularisation and lipid keratopathy. He was treated with oral doxycycline, topical corticosteroids and artificial tear supplements. He subsequently commenced a course of minocycline. At the time of this photograph, 8 months later, his visual acuity was 6/30.