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Clinical manifestations and treatment of ocular rosacea

Introduction

Rosacea is a common chronic inflammatory skin condition primarily affecting the central face, including the cheeks, nose, chin, forehead, and eyes.¹ The prevalence of rosacea is higher in middle-aged individuals and those with light skin phototypes (Fitzpatrick skin types I-II).² Ocular symptoms occur in up to 58% to 72% of those with rosacea.^{1,3} Clinical manifestations of ocular rosacea include chronic blepharitis; conjunctivitis; meibomian gland dysfunction (MGD); corneal vascularization; infiltration; and scarring.⁴ Patients may report symptoms of ocular dryness, burning and stinging, sensitivity to light, blurred vision, and foreign body sensation.¹ Clinical signs include telangiectasias of the lid margin, conjunctival telangiectasias, MGD, and chalazia.¹

Delay to diagnosis

Unfortunately, the diagnosis of ocular rosacea is often delayed leading to a delay in treatment.⁵ Diagnosis is challenging as the symptoms of ocular rosacea are not specific to the disorder alone, and other ophthalmic disorders may present with similar findings.⁶ The Global Rosacea Consensus Panel highlights that even with minimal skin involvement, ocular rosacea can be identified by specific features like lid margin abnormalities, corneal issues, or scleral inflammation (**Table 1**).⁴

For effective diagnosis of ocular rosacea in patients presenting with ocular symptoms with or without cutaneous features, a systematic approach is recommended. The assessment includes history taking, physical examination, and asking about the patient's subjective experience through questionnaires like Ocular Surface Disease Index (OSDI). Assessment tools such as the OSDI help in establishing a diagnosis,

Ocular rosacea features	Description
Lid margin telangiectasias	Visible blood vessels on the eyelid margin.
Blepharitis	Erythema and inflammation of the eyelid margin, most commonly arising from meibomian gland dysfunction.
Keratitis	Inflammation of the cornea that can lead to defects and in severe cases loss of visual acuity.
Conjunctivitis	Inflammation of the mucosa lining the inner surface of the eyelids and bulbar conjunctiva. Typically associated with conjunctival injection or vascular congestion.
Anterior uveitis	Inflammation of the iris and/or ciliary body.

Table 1. Features of ocular rosacea.⁴

grading of symptoms and evaluating the subjective effectiveness of treatments.^{1,4,7}

Notably, the severity of ocular symptoms is often not related to the severity of the cutaneous findings in patients with rosacea.^{6,8} In 20% of patients with rosacea, ocular findings may precede cutaneous involvement, and in up to 90% of cases of ocular rosacea, skin findings may be subtle, posing a further challenge to accurate diagnosis.⁹

A recent systematic review of ocular rosacea in children showed that over half (55%) of patients presented with ocular signs and symptoms prior to cutaneous manifestations.⁵ Unfortunately, ocular rosacea in children is often misdiagnosed as a viral or bacterial infection and patients may go undiagnosed for years until cutaneous features of rosacea arise. Consequently, the majority of children with ocular rosacea (83%) experienced a delay in diagnosis,

with a mean of approximately two years, with some experiencing a delay of up to 10 years.⁵

Ocular rosacea also presents a diagnostic challenge given its non-specific manifestations. Longstanding ocular rosacea left untreated may lead to corneal inflammation, scarring and possibly even corneal perforation with loss of visual acuity.¹ Therefore, diagnosis in the early stages of the disease is crucial to prevent complications.

Treatments

Given the multifactorial nature of ocular rosacea, a variety of treatment modalities have been utilized to target the etiologic factors associated with this condition. Contributing factors to ocular rosacea include staphylococcal infection; innate immune response; meibomian gland inflammation; *Demodex folliculorum*; vascular dysfunction; and environmental triggers such as sunlight. Commonly employed treatment options for ocular symptoms in rosacea include lid hygiene; topical and oral antibiotics; cyclosporine ophthalmic emulsion; ivermectin; isotretinoin; and intense pulsed light (IPL).

Lid hygiene

Lid hygiene is safe and often recommended as a first-line therapy for ocular rosacea and dry eye disease. Lid hygiene involves the use of warm compresses and artificial tears as a treatment for ocular rosacea. A recent systematic review concluded that 64% of patients treated with lid hygiene routines alone showed a positive treatment response, with 34% of patients showing a complete response (Figure 1). It is likely that for patients with mild symptoms, lid hygiene is sufficient to provide relief – however, for those with moderate or severe symptoms, lid hygiene alone may not be adequate and should be used in combination with other treatments.¹⁰

Compliance with lid hygiene can also pose a challenge. A survey study of lid hygiene and subjective patient response of dry eye symptoms showed that of 188 patients surveyed, only 55% reported compliance.¹¹ However, of those who adhered to treatment, 92% (n=96/104) described an improvement in dry eye symptoms. Furthermore, a Cochrane systematic review of treatments for chronic blepharitis concluded that lid hygiene routines may provide symptomatic relief.¹²

Various approaches to lid hygiene have been described, and generally involve the use of warm compresses alone or in combination with gentle shampoo lid scrubs using a cotton pad, cotton tip applicator or washcloth. Convenient over-the-counter lid scrubs, including OcuSoft (Rosenberg, Texas),

Eye Scrub® (Novartis, Switzerland) and LidHygenix (Advanced Eye Care Products, Inc. Atlanta, GA), among others, may be used in place of gentle shampoos for eyelid cleansing.¹¹ Lid hygiene may improve dry eye symptoms via removal of inflammatory debris from the eyelid margin and through an improvement of tear film stability.¹³

Topical antimicrobials

The use of topical antimicrobials on the eyelids and/or ocular surface has been reported for metronidazole, azithromycin and povidone iodine. A recent systematic review showed that overall, topical antimicrobials achieved a partial response in 39% of treated patients and a complete response in a further 52% (**Figure 1**).¹⁰ Topical antimicrobials may provide benefits via a decrease of eyelid flora, anti-inflammatory properties, or by helping to soften collarettes on the eyelid margin.⁶

Cyclosporine ophthalmic emulsion

The use of cyclosporine ophthalmic emulsion is commonplace in optometry and ophthalmology, and has been reported previously for patients with ocular rosacea.¹⁴ A recent systematic review with a pooled analysis of 46 patients showed that overall, cyclosporine ophthalmic emulsion achieved a complete response in 30% of treated patients, and a partial response in a further 57% (**Figure 1**).¹⁰

There are likely two mechanisms by which cyclosporine exerts a beneficial effect in ocular rosacea and MGD in general. First, cyclosporine inhibits trafficking of T-lymphocytes and thereby decreases inflammation of the meibomian glands.¹⁵ Second, cyclosporine modulates immune cell populations in the conjunctiva and lacrimal gland, thereby ameliorating dry eye symptoms.¹⁶ Importantly, in contrast to corticosteroids, cyclosporine ophthalmic emulsion is safe with no significant adverse effects, no risk of microbial overgrowth, and no increased risk of ocular infection reported.¹⁶

Oral antimicrobials

The use of a variety of oral antimicrobial agents has been reported for the treatment of ocular rosacea, including tetracyclines, nitroimidazoles, macrolides, and lincosamides. A recent systematic review found that oral antimicrobials as a class lead to a complete response in 20% of treated individuals and partial response in 70% (**Figure 1**).¹⁰

Overall, doxycycline was the most commonly reported oral antimicrobial agent used in ocular

rosacea dosed at 50 mg daily to 100 mg twice daily for treatment courses ranging from 1 to 3 months.^{14,17-19} A commonly used treatment regimen involves doxycycline 100 mg twice daily for the first month and once daily for the following two months.^{14,18} A recent pooled analysis of 206 patients showed that doxycycline led to a complete response in 23% of treated patients with a partial response in 64% (**Figure 1**).¹⁰ Doxycycline may be effective in treating ocular rosacea by decreasing the growth of ocular microflora and inhibiting enzymes such as metalloproteinases, collagenases and bacterial lipases.⁶ The most common adverse event reported with doxycycline is gastrointestinal upset, occurring in up to 52% of treated individuals.²⁰ Successful use of a 3-month course of oral metronidazole at a dose between 20 and 30 mg/kg per day has been reported as an alternative to oral doxycycline in children with ocular rosacea.²¹

Although the effectiveness and safety of doxycycline 40 mg (30 mg immediate release and 10 mg delayed release) once daily for the treatment of papulopustular rosacea has been demonstrated, its efficacy in ocular rosacea has not yet been established.²² A randomized, single-blind, noninferiority trial demonstrated that minocycline 100 mg is noninferior to doxycycline 40 mg in efficacy over a 16-week treatment period in rosacea patients.²³ However, the effects on ocular rosacea specifically have not been investigated.

Ivermectin

Ivermectin is an anti-parasitic drug that is proposed to manage ocular rosacea by targeting *Demodex folliculorum* mites and through its anti-inflammatory properties. The use of oral ivermectin in the treatment of ocular *Demodex folliculorum* has been demonstrated.²⁴ In addition, a single dose of oral ivermectin led to complete resolution in a 12-year-old girl with severe ocular and cutaneous rosacea unresponsive to oral doxycycline.²⁵

Topical ivermectin 1% cream once weekly in combination with eyelid hygiene significantly improved ocular symptoms, redness, swelling, and telangiectasia compared to eyelid hygiene alone.²⁶ A recent randomized trial compared ivermectin 1% cream and doxycycline 40 mg modified release capsules vs ivermectin 1% cream and placebo in patients with severe rosacea and with >40% having ocular symptoms. Both treatments reduced the proportion of participants with ocular signs and symptoms from baseline to week 12: -60.0% with combination therapy and 60.7% with monotherapy.²⁷ Thus, topical ivermectin 1% cream is safe, well tolerated, and may be effective

in patients with ocular rosacea by decreasing *Demodex folliculorum* mites at the eyelid margin.²⁸

Isotretinoin

The use of isotretinoin for ocular rosacea is reported in several clinical studies in the literature. Despite the beneficial role of low-dose isotretinoin in select rosacea patients, a pooled analysis of isotretinoin in ocular rosacea showed that the majority of patients had no response (60%) with only 40% achieving a partial response (**Figure 1**).¹⁰ Thus, isotretinoin has limited benefit and may even aggravate ocular rosacea by exacerbation of dry eye symptoms and MGD.

Intense pulsed light

The use of IPL for dry eye and ocular symptoms has garnered increased attention in recent years. Treatment protocols generally involve a total of four treatment sessions 2-3 weeks apart using a double-pass protocol developed by Toyos and colleagues.²⁹ The treatment areas include the malar region (from tragus to tragus, including the nose) and the periocular area up to the eye protection positioned along the lower eyelid margin.²⁹ A recent systematic review

and meta-analysis showed that IPL treatment led to an improvement in OSDI scores post-treatment.³⁰ Adjunctive treatments, such as meibomian gland expression; sodium hyaluronate eye drops; heated eye mask; warm compress; lid hygiene; antibiotic drops; cyclosporine drops; omega-3 supplements; and warm compresses, were shown to increase IPL effectiveness.³⁰

Another systematic review showed that patients with ocular rosacea treated with IPL had a >90% rate of treatment response (**Figure 1**).¹⁰ While the treatment protocol varies across published studies, overall, IPL therapy has been shown to be safe and may have a positive impact on the signs and symptoms of ocular rosacea and MGD-related dry eye disease.³⁰ It is likely that patients in the early stages of disease can benefit more from IPL therapy.

Although the mechanism of action of IPL in ocular rosacea remains to be elucidated, one proposed mechanism involves the warming effect produced by IPL on increasing the outflow of viscous meibum.³¹ The increased outflow of meibum may reduce the bacterial proliferation typically seen in meibum stasis, therefore decreasing ocular inflammation and irritation.³¹

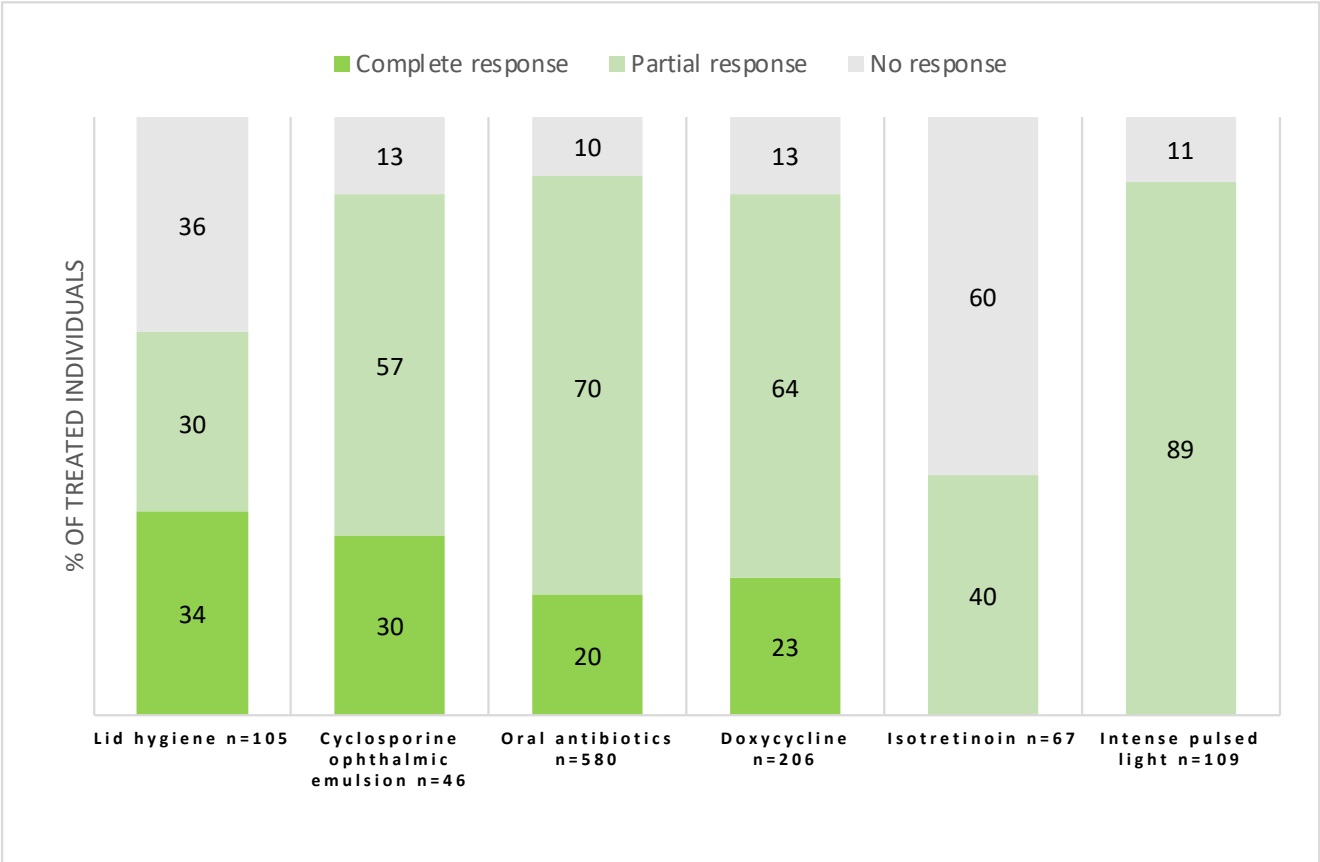


Figure 1. Treatment responses in ocular rosacea by treatment modality.¹⁰

Conclusion

Ocular rosacea presents a significant diagnostic challenge due to its varied clinical manifestations and the absence of specific diagnostic tests. Despite its potential to lead to serious complications, diagnosis and treatment of ocular rosacea are often delayed.⁵

A systematic and stepwise approach to diagnosis, including a thorough history, questionnaire assessments like the OSDI, and careful clinical examination, is crucial for early identification of ocular rosacea. Importantly, ocular symptoms may precede cutaneous manifestations, further complicating diagnosis.

Various treatment modalities have been employed to manage ocular rosacea, ranging from lid hygiene and topical antimicrobials to oral medications like doxycycline and isotretinoin, and therapies such as cyclosporine ophthalmic emulsion and IPL therapy. Lid hygiene and topical antimicrobials have shown promising results, particularly in mild cases, while more severe cases may require oral medications. Topical ivermectin 1% cream and IPL have demonstrated efficacy in many patients with ocular rosacea as both adjunctive and standalone treatments.^{10,27,31}

Overall, early diagnosis and management are essential to prevent complications and improve outcomes in patients with ocular rosacea. As rosacea is a clinical diagnosis, the entire clinical picture must be taken into consideration including family history, dermatologic changes and ocular findings. Further research into diagnostic techniques and treatment modalities is warranted to better understand and address this challenging condition.

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