

Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING
MEDICAL EDUCATION
PUBLICATION



ISSUE 15

Ocular Surface Consequences of Systemic Inflammatory Diseases

LAURA M. PERIMAN, MD Ocular surface problems such as dry eye can herald serious systemic inflammatory conditions. Early diagnosis and multidisciplinary collaboration are critical to long-term management of patients with inflammatory ocular surface disease of systemic origin.

The ocular surface can be involved in a number of systemic inflammatory disorders. These include a closely related group of autoimmune rheumatic diseases such as Sjögren's syndrome (SS), rheumatoid arthritis, scleroderma, and systemic lupus. Other autoimmune conditions with ocular surface involvement include sarcoidosis, graft-versus-host disease, and inflammatory gastrointestinal conditions (eg, ulcerative colitis and Crohn's disease). Dermatological issues such as rosacea, seborrhea, atopic disease, and Demodex infestation often affect the ocular surface as well.

Ocular surface manifestations of these conditions vary in presentation and severity, encompassing dry eye due to aqueous deficiency, primary or secondary meibomian gland dysfunction, conjunctival cicatrization, and, in extreme situations, complete keratinization or ulceration of the ocular surface.

The delicate and highly innervated ocular surface is frequently involved in autoimmune disease;¹ and although many systemic inflammatory disorders are known to have deleterious effects on the ocular surface, solid epidemiologic data on their prevalence, incidence, and comorbidities have largely been lacking. In part, this is due to: (1) the multisystem involvement of the diseases; and (2) the fact that systemic manifestations often remain underrecognized and under-

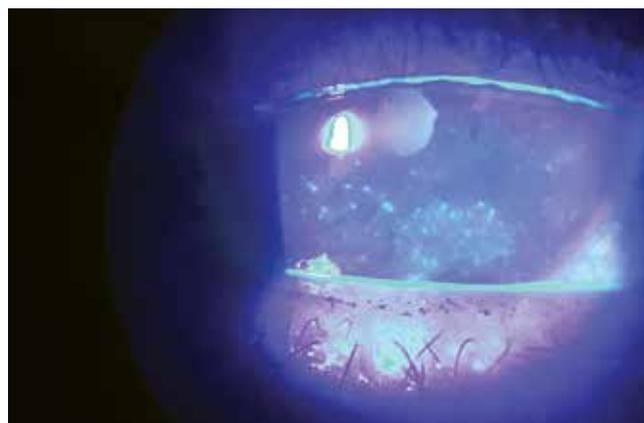


FIGURE 1 Moderate dry eye. (Image courtesy of Dr. Periman.)

diagnosed until later stages of these diseases. Some of my ocular surface disease (OSD) patients with recent autoimmune diagnoses report they have had systemic symptoms for 10 to 30 years. In the case of SS, the interval from symptoms to diagnosis averages 3.9 years.²

OCULAR SURFACE INVOLVEMENT

Systemic autoimmune and inflammatory diseases typically affect multiple organ systems, including but not limited to the skin, lungs, gut, and brain. The initial manifestations, however, are often ocular, and it is incumbent upon ophthal-

See INSIDE for:

Blepharitis and Meibomian Gland Dysfunction
by *Kenneth A. Beckman, MD*

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Make earlier diagnosis of dry eye associated with an underlying systemic inflammatory condition.
2. Engage in a multidisciplinary clinical approach to systemic inflammatory disease with ocular surface consequences.
3. Distinguish anatomic sites of blepharitis.
4. Better manage patients with anterior blepharitis or MGD.

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Topics in Ocular Antiinflammatories is jointly sponsored by Candeo Clinical/Science Communications, LLC, and the University of Florida College of Medicine. This publication is administered by an independent editorial board and supported by an unrestricted educational grant from Shire.

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mologists to be mindful of a potential systemic condition when managing patients with OSD.

The lacrimal functional unit (LFU)—a highly innervated, tightly integrated protective system of the ocular surface—is designed to maintain homeostatic control of the tear film. The LFU is comprised of nociceptor and sensory feedback signals from corneal and conjunctival nerves as well as osmoreceptors of the cornea and nasolacrimal duct. The intact central nervous system integrates the information and then sends efferent impulses to the lacrimal gland, goblet cells, and meibomian glands to increase output in order to maintain homeostasis.³ Once the integrated compensatory mechanisms fail, OSD results.⁴

Dry eye, primarily a result of chronic inflammation of the LFU,⁵ is often the first presenting symptom of systemic autoimmune disease (Figure 1). A retrospective chart review at a referral center for ocular diseases shows that 11% of patients diagnosed with dry eye had primary SS, and almost 12% had rheumatoid arthritis.¹ This finding highlights the fact that systemic autoimmune diseases are undetected in many dry eye patients.

Clinically, my index of suspicion for autoimmune disease is increased if a review of systems, family history, dental history, and past medical history are suggestive of an underlying autoimmune component to the ocular surface disease inflammatory load. When we send for early biomarker testing using the Sjögren test (Bausch + Lomb, Bridgewater, NJ) in suspected cases, approximately one third of patients test positive.

EARLY DIAGNOSIS

Accurate early diagnosis is imperative for patients whose ocular surface is affected by systemic inflammatory disease. Once lacrimal gland epithelial cells die by apoptosis due to inflammatory infiltration from autoimmune disease, there is no way (currently) to restore them.

Patients with dry eye secondary to systemic inflammatory conditions tend to progress more severely and quickly than patients with primary dry

TOPICS IN OCULAR ANTIINFLAMMATORIES, ISSUE 15

STATEMENT OF NEED

The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular surgery, contributing greatly to patient comfort and positive outcomes.

The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market.^{1,2} Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis was viewed with alarm; today, it is accepted practice.

Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular antiinflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.^{3,4}

As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist between these classes and among formulations within each of these classes.^{5,6}

By putting the latest published evidence into the context of current clinical practice, Topics in Ocular Antiinflammatories equips ophthalmologists to maintain competencies and narrow gaps between their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

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DATE OF ORIGINAL RELEASE November 2016. Approved for a period of 12 months.

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COMMERCIAL SUPPORTERS This activity is supported by an unrestricted educational grant from Shire.

eye disease. Increased disease activity in SS, for example, is demonstrated as increased dendritic cell density on confocal microscopy.⁶ Due to the higher inflammatory burden of systemically ill patients, more aggressive topical interventions and systemic interventions are necessary.

When patients present with dry eye, a tip-off for systemic involvement is often a general impression that their disease is way out of proportion to risk factors, such as the patient's age. Furthermore, the family medical history may reveal predisposition to autoimmune disorders, and a review of systems may uncover dermatologic, pulmonary, dental, gastrointestinal, or neurologic symptoms such as dry skin, shortness of breath, excessive dental caries, gut disturbance, mood imbalance, brain fog, or peripheral neuropathies. In all these cases, further testing is warranted to rule out autoimmune disease.

The clinician should pay close attention to the patient's medication list: antidepressants, anxiolytics, and agents for reflux or irritable bowel may be a sign of other organ system involvement.

SJÖGREN'S SYNDROME

One of the most prevalent autoimmune diseases is SS, which affects about 1 to 4 million people in the US.⁷ Characterized by sicca symptoms such as dry eye and dry mouth, SS has two major forms: primary (in absence of other autoimmune connective tissue disease) and secondary (in the setting of another overt autoimmune disorder, most commonly rheumatoid arthritis).⁸ Patients often have excessive cavities due to the inflammation-induced impairment of salivary gland function.⁹

SS is a major cause of aqueous tear-deficient dry eye syndrome.³ An ophthalmic workup for this chronic disease includes OSDI or SPEED questionnaires, tear osmolarity, MMP-9 testing, ocular surface staining, meibomian gland evaluation, and a non-anesthetized Schirmer's test for the reflexive capacity of the lacrimal gland.

DIAGNOSTIC TESTING

When aqueous tear deficiency is established in the presence of typical dry eye symptoms, serologic studies should be considered for a definitive SS diagnosis. Still, a significant proportion of patients with SS dry eye will have negative serology results, because traditional serologic biomarkers for SS (ie, anti-Ro/SSA and anti-La/SSB) appear in the late stages of the disease. If serology studies are negative yet clinical suspicion remains high, a labial salivary gland biopsy should be considered.

Recently, three novel autoantibodies (salivary gland protein-1, carbonic anhydrase-6, and parotid secretory protein) have been identified as earlier biomarkers for SS¹⁰ and can be tested for with the FDA-approved Sjö. Another diagnostic test on the horizon for SS is sonoelastography, an ultrasound imaging technique that measures the pliability and compressibility of salivary glands.¹¹

Though useful in making earlier diagnoses, the new biomarkers likely will not be included in consensus criteria for SS diagnosis anytime soon. The newest criteria, proposed by the American College of Rheumatology,¹² rely on a combina-

CORE CONCEPTS

- ◆ A wide range of systemic autoimmune and inflammatory disorders can have deleterious effects on the ocular surface. Inflammatory damage to the ocular surface is often the first presentation of systemic inflammatory conditions.
- ◆ Dry eye is the most common ocular surface manifestation of systemic inflammatory conditions.
- ◆ Sjögren's syndrome is a major cause of aqueous tear-deficient dry eye. Serologic studies of autoantibodies specific to this chronic autoimmune disease can provide critical diagnostic information, but the traditional serologic biomarkers may fail to detect patients at early stages of disease.
- ◆ Ocular surface involvement in systemic inflammatory conditions requires more aggressive intervention for control of local inflammation and preservation of the lacrimal functional unit.
- ◆ Earlier systemic immunosuppressive therapies may be beneficial to patients with ocular surface manifestations of an underlying systemic inflammatory condition. Close collaboration between ophthalmologists and other specialists is essential to appropriate management of these patients.

tion of objective tests that identify late disease. There is less emphasis on ocular surface changes, which are often the first manifestation of the disease.

MANAGING DRY EYE

Patients with SS should be treated more aggressively than non-SS patients. SS dry eye is associated with more inflammatory activity on the ocular surface,⁶ and it is urgent to control local inflammation to preserve as much of the LFU as possible.

When managing these patients, I follow the International Task Force (ITF) treatment guidelines,¹³ which are similar to and have been incorporated into the DEWS guidelines (Table I).³ For level 2 Sjögren's dry eye, I will often layer on level 3 interventions, which include patient education; environmental modification; discontinuation of aggravating medications (eg, oral antihistamines, tricyclic antidepressants); and the use of preservative-free artificial tears, antiinflammatories (eg, topical cyclosporine, topical loteprednol for induction and flare-ups, tetracyclines or azithromycin, and triglyceride fish oil), moisture chambers, and autologous serum.¹³ Punctal occlusion is considered a level 3 treatment but should only be added after the inflammation is controlled, which can be confirmed with the InflammDry testing. The increased inflammatory load in SS dry eye patients often creates secondary MGD that can be successfully addressed with in-office LipiFlow[®] or eyeXpress[®] therapy and home care.¹⁴

Corticosteroids are an important tool, but they are best reserved for induction therapy¹⁵ and treating acute exacerbations of chronic disease.¹⁶ Systemic corticosteroid therapy may be called for in some severe cases, but I try to control

TABLE I Dry Eye Treatment Recommended Severity Level**LEVEL 1:**

- Education and environmental/dietary modifications
- Elimination of offending systemic medications
- Artificial tear substitutes, gels/ointments
- Eye lid therapy

LEVEL 2:

If Level 1 treatments are inadequate, add:

- Anti-inflammatories
- Tetracyclines (for meibomianitis, rosacea)
- Punctal plugs
- Secretagogues
- Moisture chamber spectacles

LEVEL 3:

If Level 2 treatments are inadequate, add:

- Serum
- Contact lenses
- Permanent punctal occlusion

LEVEL 4:

If Level 3 treatments are inadequate, add:

- Systemic anti-inflammatory agents
- Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

Modified from: International Task Force Guidelines for Dry Eye¹³

local inflammation with a foundation of steroid-sparing and macrophage-function-sparing immunomodulators such as cyclosporine, which has unique properties of preventing goblet cell, lacrimal gland cell, and epithelial cell MPTP-mediated apoptosis while promoting the Fas/Fas ligand cell death of activated T cells.¹⁷

Vitamin A ointment may support goblet cells and epithelial cells; however, the metabolites demonstrate direct upregulation of inflammatory messengers IL-1 and MMP-9 in human meibomian gland cell culture.¹⁸

Patients with SS or other systemic inflammatory diseases are at increased risk for filamentary keratitis. I find amniotic membrane therapy followed by intensive autologous serum eye drop therapy to be a more effective and better-tolerated treatment than acetylcysteine for these patients.

LFA-1 integrin inhibition, a new class of antiinflammatory therapy that has recently become available for dry eye, suppresses inflammation by decreasing localization, extravasation, and cytokine-release signaling of activated T cells. It may be a helpful addition to the current broad-spectrum antiinflammatory treatments for OSD. The inflammatory processes in ocular surface disease are complex, redundant, and chronically progressive;^{19,20} a broad-spectrum approach is key in maintaining adequate control of the inflammatory load. Since OSD results from aberrant activation of important native immunologic defenses designed to protect from bacteria, fungi, and viruses,^{19,20} it appears unlikely we will develop a preventative treatment or cure.

SYSTEMIC TREATMENT

The mainstay of treatment for autoimmune diseases is

topical and systemic immunomodulatory and immunosuppressive therapy. Conventional options include corticosteroids, immunomodulators, antimetabolites, and alkylating agents. Biologic agents are becoming important alternatives, though there are still barriers to their use as first-line treatment: cost, complicated regimens, and side effects.

Despite the variety of currently available therapeutics, none of these are considered the treatment of choice. Even biologic therapy, a promising approach with target-specific treatment, does not always demonstrate evident clinical benefits—perhaps because, in most cases, we still lack the necessary information to specifically define the inflammatory imbalance. Patients with autoimmune diseases usually have heterogeneous cytokine profiles; B-cell targeted therapies may fail in an individual where T cells might be more predominant.

To make the most out of the biologic therapies, we need more individualized diagnosis, analysis, and characterization of a patient's autoimmune cellular profile. Using advanced testing modalities such as tissue histochemistry and flow cytometry, systemic therapies can be strategically employed. The technologies are not widely available at this point, but they may become a more common clinical tool in the future.

IMPROVING MANAGEMENT

Systemic inflammatory and autoimmune diseases affect multiple organ systems and require a multidisciplinary approach to management. Close collaboration with other physicians is necessary. In reality, however, there is a significant disconnect between what we discover and are concerned about as ophthalmologists and what our other MD colleagues see as a call to treat. Many patients that could benefit from systemic immunosuppressive treatment are not treated early enough. In my earlier-stage patients, I often have trouble getting systemic therapeutics prescribed. As a result, I rely heavily on topical immunomodulators and antiinflammatory therapies.

I often advise these patients to switch to the autoimmune protocol (AIP) diet, a restrictive diet that eliminates foods considered to be inflammatory and allergenic. Although the diet has not been scientifically proven to be beneficial, it may allow the patient to regain a sense of control. Clinically, a significant proportion of my patients report that the AIP diet helps their symptoms.

One special project I will be working on this year is to organize a roundtable discussion where a small group of experts from different disciplines will together review the best current SS literature in their respective fields and create a multidisciplinary guideline. I expect that such collaborative work will lead to improved exchange of ideas and enhance patient care.

Laura M. Periman, MD, is a general ophthalmologist and OSD specialist at Redmond Eye Clinic in Redmond, WA. She is a consultant for Allergan and a speaker for Allergan, BioTissue, and the Tear Film & Ocular Surface Society (TFOS). Medical writer Ying Guo, MBBS, assisted in the preparation of this manuscript.

PERIMAN REFERENCES are on page 9

Blepharitis and Meibomian Gland Dysfunction

KENNETH A. BECKMAN, MD Where there's smoke, there's fire; and where there's dry eye, there may be blepharitis. Understanding the connection between blepharitis and dry eye is the first step to relieving symptoms and preventing untoward consequences associated with the disorder.

Blepharitis—inflammation of the eyelid margin—affects millions of individuals; surveys suggest 37% of patients seen in ophthalmology clinics are likely affected.¹ The term “blepharitis” encompasses a range of conditions characterized by infectious and inflammatory mechanisms which may include bacterial overgrowth and enzyme production; inflammation of the lids, the tear film, and potentially the cornea; and abnormal meibomian gland secretions and unstable tear film. As treatment varies according to the cause and the anatomic involvement, it is useful to make a distinction between anterior blepharitis (affecting the anterior lid margin, skin, and eyelashes) and posterior blepharitis (affecting the posterior lid margin and meibomian glands), although both forms may be present at once.^{1,2}

PATHOGENESIS AND PRESENTATION

Anterior blepharitis is generally thought to result from imbalance or overgrowth of commensal bacteria (commonly *Staphylococcus* spp., *Propionibacterium* spp., and corynebacteria) or parasites (eg, Demodex). Patients tend to present with erythema and swelling of the lid margin that is sometimes accompanied by surface symptoms including burning, itching, foreign body sensation, irritation, grittiness, photophobia, and contact lens intolerance. They may complain of excessive crusting or eyelids sticking together, especially in the morning.²

Meibomian gland disease or dysfunction (MGD) is a common subtype of posterior blepharitis. With MGD, meibomian secretions are thick like toothpaste (in contrast to healthy meibum, which is thin and clear like vegetable oil) and only sluggishly expressed from the glands. Inflammation and thickened meibum can cause the glands to plug, which reduces the quality of the tear film lipid layer and contributes to evaporative dry eye. While not usually considered a primary pathogenic factor in posterior blepharitis, bacterial overgrowth may be present and contribute to MGD patients' symptoms. Bacterial lipase can break down the meibum into free fatty acids and other products that can irritate the eye and disrupt the tear film.³

Evaporative dry eye due to MGD may be associated with ocular surface symptoms (eg, irritation, burning, watering, foreign body sensation) that typically fluctuate or worsen over the course of the day. Activities that reduce blink frequency,

CORE CONCEPTS

- ◆ Blepharitis may have infectious and inflammatory elements.
- ◆ Blepharitis involves the lids by definition; it also may affect meibomian glands, tear film, and cornea.
- ◆ MGD, a type of posterior blepharitis, is a common cause of evaporative dry eye.
- ◆ Fluctuating vision is a red flag for evaporative dry eye; posterior blepharitis may also be present.
- ◆ Resolving blepharitis before surgery is critical for preventing postoperative infection, gaining accurate IOL measurements, and ensuring optimal postoperative vision.
- ◆ Like dry eye, lid margin disease may be asymptomatic: examine the face, lids, and lashes during each ophthalmic exam; express the glands to assess meibum.
- ◆ Blepharitis treatment always includes lid hygiene; it may also include antibiotic and antiinflammatory agents.

such as computer use, exacerbate evaporative forms of dry eye, including MGD. In fact, a complaint of fluctuating vision should immediately call to mind tear film-related disorders, the most common of which is evaporative dry eye due to MGD. In my experience, it is not uncommon for patients referred for cataract surgery due to visual difficulty to have lid margin disease instead or in addition to cataract. When questioned, these patients will describe experiencing normal vision at first (eg, normal ability to read) that gets worse over the course of an hour or so. Vision loss from cataracts does not fluctuate, while visual difficulties related to the tear film and lid margins often does.

HISTORY AND PHYSICAL

While the presentations above are common, many patients with blepharitis are asymptomatic; their disease may be found incidentally on presurgical evaluation, at a routine checkup, or in association with another condition. In one survey, ophthalmologists reported that, among blepharitis patients, 41% initially presented with dry eye complaints and 22% initially presented for surgical evaluation, routine evaluation, or with vision complaints unrelated to the ocular surface.¹

In addition to inquiring about signs and symptoms, it is important that history-taking include questions about systemic inflammatory diseases that affect skin and glands (eg, systemic lupus erythematosus, scleroderma), dermatologic conditions that can occur in association with blepharitis (eg, seborrheic dermatitis, rosacea, atopic dermatitis), systemic and topical medications, and contact lens use.² Picking up on rosacea is particularly important as both rosacea and MGD

involve the glands of the face and commonly coexist.

In fact, regardless of the reason for a patient's visit, it is good practice to examine the face, skin, lids, and lashes. Patients with anterior blepharitis may demonstrate lid margin changes or eyelash misdirection, breakage, or loss. Sebaceous matter may accumulate around the lashes and create a sleeve or collarette, a sign of bacterial or Demodex involvement.² An immune reaction on the cornea to the staphylococcal pathogens on the lids can cause staph marginal keratitis.

While signs of anterior blepharitis are usually plain to see, posterior blepharitis requires a more proactive diagnostic approach: express the glands! Evidence of thickened and/or cloudy meibum on expression of the glands is characteristic of MGD; producing no meibum on expression of the glands might indicate an advanced state in which the gland has become obliterated and scarred closed. Other MGD signs may include pouting or plugging of meibomian gland orifices, increased eyelid margin thickness and vascularity, and lash loss.⁴ Obstructed meibomian glands can become acutely infected, resulting in a sty; chronic inflammation and swelling of the glands can form a chalazion.

ADDITIONAL CONSIDERATIONS

In addition to checking vision, taking a history, and performing a physical examination, evaluating the tear film, cornea, and meibomian glands may aid in making the diagnosis. Measuring tear film breakup time (TFBUT) and performing conjunctival and cornea staining may reveal evidence of evaporative dry eye. The discovery of a rapid TFBUT, for example, is a good reason to push on the glands to assess the quality of the meibum, if that has not already been done in the course of a workup. Meibography may provide additional clues, including evidence of meibomian gland dropout.

Occasionally, what seems like MGD or straightforward anterior blepharitis is something else requiring different management. Patients on ocular medication for chronic conditions may have an ocular surface reaction to a component of their medication. Patients who wear eye makeup may have an allergic dermatitis-type reaction on the face that involves the lids and lid margin. Viral infection—including herpes simplex virus, molluscum contagiosum, or varicella zoster (shingles)—may involve the lids.

WHY TREAT

Treating blepharitis and MGD serves to reduce symptoms (eg, irritation, grittiness, mattering, dryness, and red eyes), interrupts the cycle of infection and inflammation, and improves surgical outcomes. Presurgical blepharitis treatment stands to improve patient outcomes in three ways. The first is that it reduces risk for post-operative infection due to organisms on the lid margin.

Secondly, lid margin inflammation and dry eye at the time of presurgical evaluation can skew corneal measurements (keratometry or K readings) and interfere with the accuracy of intraocular lens (IOL) implant calculations (see Case Study).

An improperly calculated IOL leads to poor postoperative visual outcomes and often a very unhappy patient. And the third reason is to avoid postoperative visual aberrations associated with an irregular ocular surface. Even if IOL power is properly calculated and the right IOL selected, abnormal lid margins and tear film associated with untreated blepharitis can complicate patients' ability to form a clear visual image after surgery. Thus, postop management of the lid margin and tear film remains an important aspect of patient care.

MANAGEMENT

The goals of blepharitis management include making the patient comfortable and reducing any risks associated with their condition.

Nonpharmaceutical Rx

First, nearly all patients benefit from mechanical treatment of the lids; the main difference is that removing debris is essential to treating anterior blepharitis, while heat is essential in treating posterior blepharitis. For patients with anterior blepharitis with significant crusting, I recommend lid scrubs. Typically, I only use warm water; but occasionally, if the crusting is significant, it may require the use of dilute baby shampoo (for example, a cup of warm water with a few drops of baby shampoo) initially, to help dissolve the crusts. Once the crusting has improved, I will recommend warm water without shampoo. Commercially available wipes and foams, such as TheraTears® SteriLid® Cleanser (Akorn, Lake Forest, IL), OCuSoft® Lid Scrub® (OCuSoft, Rosenberg, TX), and Avenova® (NovaBay Pharmaceuticals, Emeryville, CA) also work well.

For patients with MGD, I recommend warm water without shampoo for lid scrubs, as shampoo can saponify the lipids in the meibomian glands and cause a detergent-like irritating effect within the tear film. Hot compresses or thermal lid margin treatments such as LipiFlow® (TearScience, Morrisville, NC), and eyeXpress® (Holbar Medical Products, Tyler, Texas) help liquify stuck meibum and can be very helpful.

Antibiotics

Antibiotic ointment at night is soothing to the eye, combats bacterial overgrowth, and, in some instances, reduces lid inflammation. AzaSite® (azithromycin ophthalmic solution) 1% (Akorn, Lake Forest, IL) is commonly used for treating anterior or posterior blepharitis; like the similar agents erythromycin and doxycycline, azithromycin is thought to have both antibiotic and antiinflammatory properties.⁵ AzaSite can be applied daily at bedtime for up to a month, then, following one month off of medication, used at weekly intervals as needed.

Another macrolide antibiotic—erythromycin ophthalmic ointment—works in a similar fashion. Alternatives include bacitracin ophthalmic; or clindamycin, metronidazole, or doxycycline compounded in ophthalmic drop formulation. Metronidazole (compounded especially for the eye) is particularly useful for treating rosacea-associated MGD, as it shares the same active ingredient of the dermatologic formulation

in the treatment of dermatologic rosacea.

Using oral doxycycline once daily at a low dose, for example 20 to 50 milligrams a day, is subtherapeutic as an antiinfective but provides an antiinflammatory effect. A recent study by Foulks and coworkers comparing topical azithromycin with oral doxycycline revealed comparable improvement in signs and symptoms of MGD and restoration of meibum quality.⁶

Antiinflammatories

Inflammation tends to play a significant role in the pathophysiology of blepharitis. When a strong inflammatory response is evident (eg, when the lid is hot and red or there is a sty or chalazion) and contraindications have been ruled out (eg, herpetic keratitis), adding an antiinflammatory agent short-term or using a combination antibiotic and corticosteroid agent such as TobraDex® (tobramycin 0.3% and dexamethasone 0.1%; Alcon, Fort Worth, TX) or Zylet® (loteprednol etabonate 0.5% plus tobramycin 0.3% ophthalmic suspension; Bausch and Lomb, Tampa) may be effective. For patients with staphylococcal marginal keratitis, I will usually start with an antibiotic and then add a topical ocular corticosteroid after seeing that the infectious component is under control.

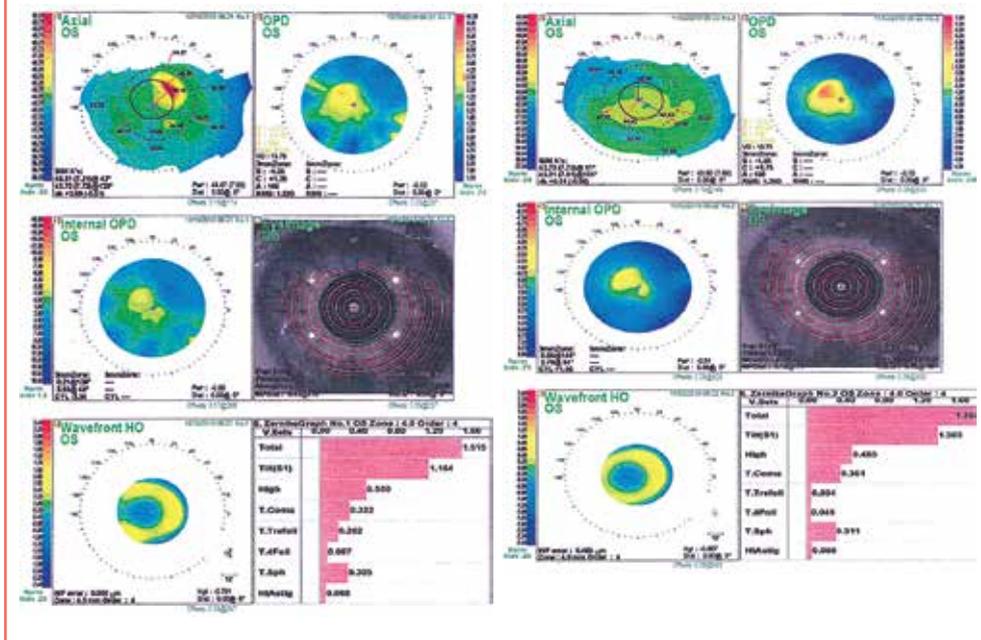
Immune modulator cyclosporine A (Restasis®; Allergan, Irvine, CA) has also been used off-label to reduce inflammation associated with blepharitis. In one study by Rubin and coworkers, treatment of posterior blepharitis with topical ocular cyclosporine A was superior to TobraDex in normalizing TFBUT, Schirmer scores, and meibum quality—as well as several clinical parameters—compared with TobraDex.⁷

Other Considerations

Omega-3-fatty acid deficiency (or a predominance of omega-6-fatty acids) has been associated with decreased fluidity of meibum and plugging of glands. There is some evidence that oral omega-3-fatty acid supplementation may correct that imbalance and improve the health of meibum. Treatment of Demodex infestation of the lids may include Cliradex® (Bio-Tissue, Doral, FL) or TheraTears® SteriLid® Cleanser; both contain tea tree oil.

CASE STUDY: Ocular Surface is the Key to Precision Presurgical Measurements

A patient was sent to my practice by an optometrist for evaluation for a toric IOL. Review of the initial K readings revealed 3D of astigmatism and an irregularity (a divot in the mires) at around one o'clock on the cornea (below left). When I examined the patient, I found signs of dry eye and severe blepharitis. The patient was prescribed hot compresses, lid hygiene, and AzaSite. At 2 weeks followup, the blepharitis was improved and the divot had resolved; notably, the K readings were down from 3D to 0.5D of astigmatism (below right). In this example, an abnormal tear film due to lid margin disease was the cause of the irregular K readings. Had we proceeded with the initial measurements and placed a toric lens, the patient's mild astigmatism would have been markedly overcorrected and his visual outcome would have been poor.⁸ (Images courtesy of Dr. Beckman.)



CONCLUSION

Blepharitis and MGD are prevalent, and identifying and managing these conditions is increasingly important. Examine the tear film and lid margins in all patients, especially those with dry eye or who are preparing for surgery. If there is evidence of lid margin abnormality, attempt to discern whether the primary pathology is anterior or posterior. Be sure to examine the face, skin, and lids as part of a regular ophthalmic exam, and don't be shy about expressing the meibomian glands. Use a multipronged approach to treatment based on the underlying disorder.

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BECKMAN REFERENCES are on page 9

EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 15

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Shire. **Directions:** Select the one best answer to each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at <http://cme.ufl.edu/ed/self-study/taoi/>.

- Which of the following tests are recommended by the American College of Rheumatology as a diagnostic criterion for Sjögren's syndrome?
 - Non-anesthetized Schirmer's test
 - Ocular surface staining
 - MMP9 testing
 - Tear osmolarity
- Which of the following clinical findings may be indicative sign of an underlying systemic inflammatory condition in patients with dry eye?
 - Gastrointestinal disturbances
 - A family history of autoimmune disorder
 - Active use of antidepressants
 - All of the above
- Tea tree oil-containing agents are typically effective against
 - Demodex
 - Inflammation
 - Lipase
 - Endotoxin
- Which of the following statement about the lacrimal glands is true?
 - They are one of two parts of the lacrimal functional unit (the meibomian glands being the other)
 - They are susceptible to inflammatory damage in autoimmune diseases
 - The lacrimal gland epithelium lost to inflammatory damage cannot be recovered
 - Both B and C
- Meibomian gland obstruction can lead to which of the following conditions?
 - Chalazion
 - Stye
 - Evaporative dry eye
 - Any of the above
- According to a recent study, the rate of primary Sjögren's syndrome in dry eye patients is about:
 - 1 in 2
 - 1 in 10
 - 1 in 100
 - 1 in 1,000
- Crusting around the lashes may be an indication of:
 - Anterior blepharitis related to Propionibacterium
 - Posterior blepharitis
 - Posterior blepharitis related to Staphylococcus
 - None of the above
- Which of the following is NOT an antiinflammatory therapy recommended by Dr. Periman for the treatment of dry eye with an associated chronic systemic inflammatory disease?
 - Chronic corticosteroids
 - Azithromycin
 - An autoimmune protocol diet
 - Fish oil
- Which of the following viruses is not a potential cause of blepharitis?
 - Molluscum
 - Herpes Simplex
 - Varicella Zoster
 - Epstein Barr
- Visual difficulties that fluctuate or get worse with prolonged computer use may relate to:
 - Cataracts
 - Glaucoma
 - Tear film disorder
 - All of the above

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 15

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Shire. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires October 31, 2017.

ANSWERS:

- | | |
|------------|-------------|
| 1. A B C D | 6. A B C D |
| 2. A B C D | 7. A B C D |
| 3. A B C D | 8. A B C D |
| 4. A B C D | 9. A B C D |
| 5. A B C D | 10. A B C D |

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

- Extent to which the activity met the identified
 - Objective 1: 1 2 3 4 5
 - Objective 2: 1 2 3 4 5
 - Objective 3: 1 2 3 4 5
 - Objective 4: 1 2 3 4 5
- Rate the overall effectiveness of how the activity:
 - Related to my practice: 1 2 3 4 5
 - Will influence how I practice: 1 2 3 4 5
 - Will help me improve patient care: 1 2 3 4 5
 - Stimulated my intellectual curiosity: 1 2 3 4 5
 - Overall quality of material: 1 2 3 4 5
 - Overall met my expectations: 1 2 3 4 5
 - Avoided commercial bias/influence: 1 2 3 4 5
- Will the information presented cause you to make any changes in your practice? Yes No
- If yes, please describe: _____
- How committed are you to making these changes? 1 2 3 4 5
- Are future activities on this topic important to you? Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

PLEASE PRINT CLEARLY

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