Advances in Antiinflammatory Therapy for Dry Eye

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A critical role for inflammation has become well established in the disease process of dry eye, paving the way for new diagnostic methods and treatment options.

Over the last decade, significant advances have been made in understanding the pathophysiology and symptomatology of dry eye, and clinical interest in the condition has increased. As defined in the International Dry Eye WorkShop (DEWS) report, dry eye is a multifactorial disease of the tears and the ocular surface that results in discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface; it is accompanied by increased tear osmolarity and inflammation of the ocular surface.

The DEWS report, published in 2007, marked the first time that a spotlight was directed at the role of inflammation in dry eye. Today, it is widely recognized that dry eye is an inflammatory condition of the ocular surface and that successful management of dry eye patients requires considering inflammation in clinical evaluation, diagnosis, and treatment.

AN INFLAMMATORY CONDITION

Dry eye can be classified into two major types based on etiology and pathogenesis: aqueous-deficient and evaporative dry eye. Patients with aqueous-deficient dry eye do not produce enough tears, usually as a result of lacrimal gland dysfunction or destruction due to Sjögren’s syndrome or other systemic autoimmune diseases. In evaporative dry eye, changes in quality or composition of the tear film—most commonly caused by inflammatory eyelid or corneal diseases—lead to excessive exposure of the ocular surface and evaporative loss of tears.

Regardless of cause, the common consequences of dry eye are tear film instability and compromised ocular surface homeostasis. With dry eye, the tear film is no longer able to adequately support the health of the corneal epithelium; desiccating or hyperosmotic stress may damage cells and trigger signaling pathways that promote production of inflammatory molecules. The resulting ocular surface inflammation...
disrupts the epithelial and mucin layers, exacerbating tear film breakdown (Figure 1). In the normal eye, tear production and drainage are balanced, with the rate of tear production being greater than the rate of tear drainage. When this balance is disrupted, the accumulation of tears on the ocular surface can cause discomfort and impair vision. This condition is known as dry eye syndrome.

**THE INFLAMMATORY MEDIATORS**

Inflammation in dry eye involves a myriad of proinflammatory mediators including cytokines, chemokines, and matrix metalloproteinases (MMPs). Increased amounts of interleukin (IL)-1α and mature IL-1β, the proinflammatory forms of IL-1, have been found in the tear fluid of dry eye patients. Sjögren’s syndrome-associated dry eye is accompanied by production of IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) on the ocular surface.

Mounting evidence from the past two decades indicates that dry eye-induced ocular surface inflammation is immune-based and driven by the activity of T cells. An up-regulated pattern of intercellular adhesion molecule-1 (ICAM-1) has been identified in the conjunctival epithelial cells and accessory lacrimal tissues of dry eye patients. A ligand of the T-cell-surface receptor lymphocyte function-associated antigen-1 (LFA-1), ICAM-1 promotes lymphocyte activation and migration, predisposing the ocular surface to immune and inflammatory responses.

The inflammatory mediators implicated in dry eye-induced ocular surface inflammation are potential candidates for diagnostic markers. At present, we are able to measure MPP-9 via InflammaDry, a point-of-care test that can be done in 10 minutes in the office. Presence of MPP-9 in tears is a sign of ocular surface inflammation, and a positive result not only helps to diagnosis the presence of dry eye but also implies that the patient may respond to anti-inflammatory therapy.

In our practice, we routinely test for MPP-9 in any patient who has dry eye symptoms. These symptomatic patients are identified at the time of check-in.
using a standardized questionnaire, such as the Ocular Surface Disease Index (OSDI) or the Standard Patient Evaluation of Eye Dryness (SPEED). Aggressively searching for signs of inflammation allows us to proactively address dry eye, which is especially important to the success of contact lens fitting and refractive or cataract surgery. Since dry eye is prevalent in patients scheduled for cataract surgery, we have made screening for dry eye-related inflammation a routine part of our preoperative workup.8

**MANAGING THE OCULAR SURFACE: PALLIATIVE VS. CURATIVE**

The treatment of dry eye has traditionally focused on tear supplementation or preservation, and significant advances have been made on that front over the last 10 years. For example, we have learned that in evaporative dry eye, the inter-blink interval—the period of time during which the ocular surface is exposed between blinks—needs to be shorter than tear film breakup time or else the ocular surface will suffer. This has led up to the development of thicker gel-type artificial tears, which have become a popular tear substitute choice because they increase stability of the tear film as measured by tear breakup time.

Artificial tears, however, provide only palliative therapy for dry eye patients—they do not address inflammation, which, as noted above, is an underlying cause and a common consequence of dry eye. Since ocular surface inflammation can prevent reversal of cellular changes and restoration of the ocular surface, tear supplementation alone may result in treatment failure. In aqueous-deficient dry eye in particular, inflammation of the ocular surface must be treated to subvert the T-cell-mediated processes leading to decreased lacrimal secretion.

**TREATING INFLAMMATION: AVAILABLE THERAPIES**

There are several antiinflammatory modalities that are currently used for the treatment of dry eye. Topical cyclosporine A (CsA) 0.05%, approved by the US Food and Drug Administration (FDA) in 2002, represents a major advance in treating the inflammatory component of dry eye. Topical cyclosporine reduces inflammation by inhibiting T-cell activation and down-regulating inflammatory cytokines in the conjunctiva and lacrimal glands; in treated patients, it increases aqueous tear production (as measured by Schirmer testing) and goblet cell density while reducing corneal staining and the need for artificial tears.10 Achieving the full treatment benefit of CsA, however, often takes months.

Topical corticosteroids, on the other hand, exert rapid antiinflammatory effects that can be appealing to patients. However, the utility of corticosteroids is limited by a significant risk of side effects, including elevated intraocular pressure (IOP), cataract, and risk of infection. Topical corticosteroids for dry eye should only be used carefully and with close observation. Typically, only short courses are employed during acute symptom exacerbation to hasten inflammation control in dry eye.

Oral omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been documented to inhibit the synthesis of lipid mediators of inflammation and block the production of inflammatory cytokines such as IL–1 and TNF-α.11,12 In patients with dry eye, the antiinflammatory properties of omega-3 fatty acids have proved beneficial in increasing aqueous production and improving ocular surface function.11,13

In patients who have meibomitis or ocular rosacea, which are the major causes of eyelid and ocular surface inflammation and resulting tear film instability, oral tetracycline compounds may be an effective treatment. The tetracycline derivatives possess antiinflammatory as well as antibacterial properties. Doxycycline, the best known tetracycline, has been shown to suppress generation of IL-1β and TNF, inhibit MMP-9 activity, and support ocular surface integrity.14,15

**CORE CONCEPTS**

- Ocular surface inflammation, as with tear hyperosmolarity, is a hallmark of dry eye.
- Ocular surface inflammation in dry eye develops as the tear film becomes unstable and the natural equilibrium of the ocular surface is disrupted; inflammation acts to exacerbate the disease by damaging the ocular surface and blocking its communication with the lacrimal glands.
- Management of dry eye should include antiinflammatory therapy. Because the majority of dry eye is associated with MGD, examining and treating the eyelid and meibomian glands are important in managing patients with dry eye.
- Demand for dry eye treatment is increasing due to an aging population, therapeutic and surgical advances, and patients’ desire for a healthier lifestyle.
- Novel therapies targeting inflammatory cascades hold promise for improving our ability to effectively manage dry eye.

**TREATMENT APPROACH: CONSIDERATIONS**

In general, the stratified treatment strategies recommended by the DEWS workshop for managing dry eye still hold up.16 It may not make sense to treat all asymptomatic patients, but there is no doubt that patients with ocular irritation symptoms or blurred vision should be evaluated for dry eye and, if diagnosed, started on treatment with artificial tears or gels.

Examining the eyelid margin and the meibomian glands is critical in uncovering hidden causes of dry eye and associated inflammation. Meibomian gland dysfunction (MGD), in fact, exists in more than 80% of dry eye patients.17 Regular eyelid cleaning alone is often sufficient for controlling inflammation as well as reducing bacterial load to the eyelid margin. Several eyelid hygiene products are commercially available, including baby shampoo, saltwater scrubs, and mild hypofluorous acid; all are easy to apply.

The effect of diet on inflammation is not trivial. Patients should be made aware that a Mediterranean-style diet is...
omega-3 rich and less proinflammatory than the typical American diet. They should know that appropriate omega-3 supplements are a gentle and cost-effective approach to managing inflammation in dry eye. Physicians should also discuss with patients environmental factors and medicinal effects that may exacerbate dry eye, such as sleeping under ceiling fans and use of certain systemic medications (eg, antihistamines, antidepressants, and antihypertensives). Meanwhile, it is important to look for signs of systemic autoimmune or endocrine diseases and, when indicated, refer the patient to a rheumatologist or endocrine specialist.

Usually antiinflammatory therapies are added when patients are not responding to tear substitutes, dietary and environmental modifications, and systemic management. Topical cyclosporine has become a mainstay of treatment for moderate to severe dry eye disease. The approved dose for topical cyclosporine is twice daily, though the dosing frequency is often increased to four times daily to achieve greater efficacy, especially in patients who fail to improve with the initial twice-daily regimen. More aggressive measures, such as punctal plugs, are typically considered after inflammation has been controlled.

NEW THERAPEUTIC OPTIONS

One investigational agent that is anticipated to have approval in the near future as an antiinflammatory therapy for dry eye is lifitegrast, an LFA-1 antagonist that prevents T-cell-mediated release of inflammatory cytokines. In three phase 3 trials, lifitegrast significantly improved clinical signs and symptoms of dry eye. Notably, lifitegrast began to exert its effect in as little as two weeks. Given that many dry eye patients have a delayed response to cyclosporine, the fast onset of lifitegrast’s treatment benefit would be a particular advantage.

Another adjunctive therapy for dry eye that is gaining popularity is the use of autologous serum on the ocular surface. Serum contains several antiinflammatory factors, including IL-1 and TNF antagonists and MMP inhibitors. In dry eye associated with Sjögren’s syndrome, autologous serum drops have shown a remarkable effect in inhibiting ocular surface inflammation and relieving ocular irritation symptoms. Multiple eye banks in the US are now making autologous serum eye drops at 20% to 50% or even higher concentrations. At our practice, we reserve this treatment modality for dry eye patients who have failed more conventional therapies.

Novel cyclosporine formulations, including a 0.1% unpreserved cyclosporine cationic emulsion (Cyclokat) and a non-aqueous preservative-free formulation based on a proprietary drug-delivery technology (CyclASol), are also in clinical development, albeit outside the US. Additionally, a novel dexamethasone intracanalicular depot known as OTX-DP is being investigated in clinical studies for use in the treatment of dry eye. The punctal plug drug-delivery system of OTX-DP provides a two-pronged approach to dry eye management: it decreases the loss of tear through the puncta while releasing a low, steady dose of dexamethasone to the ocular surface.

A CHANGING PATIENT POPULATION

While our understanding and treatment of dry eye has advanced, the patient population of dry eye has undergone tremendous changes. The number of patients with dry eye is expected to increase as the baby boomers age. Furthermore, dry eye is no longer a condition limited to elderly patients with ocular irritation symptoms. It can be encountered in young adults who have contact lens issues or patients who have had refractive surgery. Because macular degeneration and glaucoma can be better managed now, there may be more patients with these once-devastating diseases seeking dry eye treatment in order to enhance the quality of their lives.

One major driving force behind the increasing demand for dry eye treatment is contact lens and surgical advances. Whether it is presbyopic contact lenses, corneal inlays, monovision LASIK, or multifocal intraocular lenses, a good tear film is necessary to achieve the best result.

At the same time, patient expectations have reached an all-time high level. Patients who undergo cataract or corneal refractive surgery expect the highest quality of vision. The LASIK patients of the 1990s and early 2000s are approaching cataract age. With high expectations for quality of vision, they are often adamant that dry eye be addressed early and certainly prior to surgery.

FUTURE DIRECTIONS

The dry eye therapeutic pipeline has not been as robust as we would have thought about 10 years ago. Up until now, topical CsA 0.05% has been the only agent with an approved indication for dry eye. One challenge facing clinical trials of dry eye is the lack of consensus on what is the best way to measure treatment response. In the future, tests such as InflammaDry may have a place in evaluating new drugs or reassessing therapies that have fallen out of favor, such as topical testosterone gels.

The great bulk of dry eye— evaporative or aqueous deficient—has a significant inflammatory component and can be successfully managed with a treatment regimen addressing inflammation. However, there are patients who do not respond well to antiinflammatory treatment modalities such as dietary changes, omega-3 supplementation, and the use of topical cyclosporine and corticosteroids. Currently, we do not understand why these treatments fail in some cases. Most recently, researchers at the Bascom Palmer Eye Institute reported findings that linked dry eye to chronic pain syndromes. This suggests that there could be yet another form of dry eye that is not inflammatory only, and those affected might require more than just tear supplementation and inflammation control.

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Inflammation Control Before and After Cataract Surgery

SHERI ROWEN, MD Pre-treating ocular surface conditions and minimizing postoperative inflammation are essential for achieving desired patient outcomes in cataract surgery.

Cataract surgery is one of the most commonly performed surgical procedures. In the US, cataract affects more than 20 million people older than 40 years, and that number is projected to rise to 30 million by 2020.1 The rates of cataract surgery have steadily increased over the past three decades, and behind the growing trend are two major driving forces: first, the aging population continues to grow; as baby boomers reach 65 years; second, people with cataract are seeking surgical intervention earlier in hopes of maintaining a more active lifestyle.2,3

Thanks to advances in surgical technologies and techniques, cataract surgery has become increasingly safe and effective. Yet, to produce satisfying results, surgeons still must make a concerted effort throughout the perioperative period to eliminate risks and avoid complications. What has proved to be an important strategy for preventing undesired outcomes of cataract surgery is to reduce inflammation—not just the inevitable inflammation that occurs after surgery but also preexisting inflammation of the ocular surface, which may not be so evident.

IMPACT OF OCULAR SURFACE DISEASE

Patients undergoing cataract surgery show signs and symptoms of ocular surface disease much more often than previously thought. According to a prospective study conducted recently at nine clinical sites across the US, as many as 60% of cataract surgery patients (aged 70 years on average) show signs of dry eye (short tear film breakup time, low Schirmer test scores, and presence of corneal staining) in the absence of symptoms.4 In another study of similar design, 59% of patients scheduled for cataract surgery were found to have blepharitis.5

Inflammatory conditions such as dry eye and blepharitis compromise the integrity and normal function of the tear film and thereby can impact visual and surgical outcomes. The pre-corneal tear film is the most anterior refracting interface of the eye and, with the cornea, accounts for about two-thirds of the eye’s total optical power. In addition, tear film breakup occurring between blinks can create optical aberrations and significantly reduce retinal image quality.6 This explains why it is not uncommon for dry eye patients to have symptoms of blurred and fluctuating vision.

Preexisting dry eye can lead to inaccurate keratometry and intraocular lens (IOL) power calculations in surgical planning.7 Postoperatively, an unhealthy ocular surface is more likely to have slower wound healing and visual recovery. Furthermore, cataract surgery can exacerbate preexisting dry eye,8 which will in turn contribute to reduced quality of vision and patient dissatisfaction after surgery. Tear film instability due to dry eye and other ocular surface conditions is especially problematic for patients implanted with a multifocal IOL.9 The multifocal design magnifies distortion induced by an irregular ocular surface; patients may experience blurred vision and various photic phenomena such as starbursts, glare, and halos.

OPTIMIZING THE OCULAR SURFACE

At my practice, preoperative screening for dry eye and ocular surface disease is mandatory. We ask every patient that comes in to fill out the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire to identify any potential dry eye—even when they have symptoms, many patients don’t know they have dry eye. Patients who are identified as symptomatic are further evaluated with dry eye diagnostic tests, including tear osmolarity and the InflammaDry test, and Lipiview I and II meibomian gland imaging and partial blink analysis.

Since meibomian gland dysfunction (MGD) contributes to more than 80% of all dry eye,10 assessing the meibomian
glands is an important component of the examination. Expression of the glands is telling of the quality and consistency of the meibum, and imaging devices such as LipiView II allow visualization of the gland structure. Additionally, fluorescein and lissamine stains are useful in evaluating the integrity of the cornea and conjunctiva, respectively.

Patients diagnosed with dry eye should be treated prior to any pre-surgical measurements. Because these patients are already having visual symptoms from cataracts, they will be better off if surgery can be done sooner. In most cases this calls for more aggressive dry eye treatment, meaning use of antiinflammatory medications in addition to artificial tears.

Dry eye is fundamentally a disease of inflammation, and treating the inflammation is usually the key to improving the function of the lacrimal glands and restoring the equilibrium of the ocular surface. The mainstay of antiinflammatory therapy for dry eye is topical cyclosporine 0.05% and re-esterified omega-3 fish oil supplements. Patients should return in about four to six weeks for re-evaluation. For more severe cases, short courses of topical corticosteroids can often help bring the ocular surface inflammation under control.

Although current options for treating dry eye-related inflammation are fairly limited, it is anticipated that approval of new antiinflammatory agents such as lifitegrast will increase our therapeutic choices in the near future.

**Surgery and Inflammation**

Cataract surgery is an intrusive intraocular procedure, and in response, the eye produces prostaglandins and other pro-inflammatory molecules. The more mechanical stimulation and surgical trauma there is, the more disruption to the blood-aqueous barrier and release of inflammatory mediators there will be. This natural inflammatory response induced by surgery can cause pain and ocular irritation symptoms. It can sometimes have significant visual consequences as well: excessive aqueous flare may blur vision; and persistent inflammation in the anterior chamber may ultimately lead to development of cystoid macular edema (CME), the major cause of poor visual outcome following uneventful cataract surgery.

Today, many surgeons are using a femtosecond laser to perform certain steps of cataract surgery, such as anterior capsulotomy, lens fragmentation, and creation of clear corneal and arcuate incisions. The adoption of femtosecond laser technology is purported to make the procedure easier and safer, though its clinical benefits are yet to be verified. Recently, a group of German researchers reported that prostaglandin levels in the aqueous humor rise immediately after femtosecond laser treatment in cataract surgery patients. The clinical significance of this finding is not yet clear. From my own experience, femtosecond laser-assisted cataract surgery does not induce more inflammation than traditional surgery does. But then all my patients are covered by the same perioperative antiinflammatory regimens.

**Controlling Postoperative Inflammation**

Keeping surgically induced inflammation at bay is essential to postoperative comfort and visual recovery. There are two types of antiinflammatory agents available for minimizing postoperative inflammation: corticosteroids, and non-steroidal antiinflammatory drugs (NSAIDs). The corticosteroids block phospholipase A2, an upstream enzyme in the inflammatory cascade that converts cell membrane phospholipids into arachidonic acid, the most important prostaglandin precursor; the NSAIDs block the cyclooxygenases (COX) 1 and 2, the enzymes that catalyze the conversion of arachidonic acid into eicosanoids including prostaglandins, thromboxane, and prostacyclin.

Because NSAIDs specifically and potently inhibit prostaglandin synthesis, they are especially effective in alleviating postoperative pain and discomfort. In addition, they have fewer side effects than corticosteroids, which are associated with intraocular pressure (IOP) elevation and increased risk of secondary infection. Most cataract surgeons routinely use both corticosteroids and NSAIDs perioperatively for inflammation and pain control, though some believe that NSAIDs alone may be sufficient. Clinical studies have shown that the concomitant use of an NSAID along with a corticosteroid has a greater effect on reducing the incidence of CME than a corticosteroid alone after uneventful cataract surgery.

I usually place patients on a topical corticosteroid and NSAID along with an antibiotic eye drop two days prior to surgery. During the procedure, I add phenylephrine and ketorolac injection 1%/0.3% (OMIDRIA®, Omeros) to the irrigation solution. As an NSAID, ketorolac acts to lower prostaglandin levels in tissues to reduce postoperative pain; after surgery, patients continue with the treatment regimen for one week before discontinuing the antibiotic drop. If there is no sign of significant inflammation at this point, I begin tapering the corticosteroid so it is withdrawn in one or two weeks. At the same time, patients resume the NSAID therapy for a total of about five weeks from time of surgery to fully stabilize the blood-aqueous barrier. It is important to not taper off the drops too quickly, as rebound iritis may develop in some patients.

**Conclusions**

Untreated ocular surface disease and uncontrolled postoperative inflammation can profoundly impact surgical outcomes and patient satisfaction following otherwise uneventful cataract surgery. Surgeons should be mindful of the strong likelihood of dry eye in cataract patients and be proactive in treating ocular surface inflammation prior to preoperative measurement and surgery. Intraocular inflammation is a natural consequence of cataract surgery. All patients should therefore be managed perioperatively with antiinflammatories to improve surgical results.

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REFERENCES


EXAMINATION QUESTIONS  TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 13

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/toai/.

1. Which of the following is the therapy recommended by Dr. Rowen for controlling postoperative inflammation in cataract surgery patients?
   A. Topical corticosteroids
   B. Topical NSAIDs
   C. Combined topical corticosteroids and NSAIDs
   D. Topical cyclosporine

2. Which of the following therapies is the mainstay treatment for moderate to severe dry eye?
   A. Topical cyclosporine
   B. Topical corticosteroids
   C. Oral doxycycline
   D. Punctal plugs

3. Which of the following statements is NOT true about topical cyclosporine for dry eye?
   A. It inhibits T-cell mediated inflammation
   B. It acts on the conjunctiva and lacrimal gland
   C. It has a rapid onset of effect
   D. It reduces the need for artificial tears

4. What effect does an unhealthy ocular surface NOT have in cataract surgery?
   A. It can increase the risk of secondary infection after surgery
   B. It can lead to errors in IOL power calculation
   C. It can slow wound healing and visual recovery
   D. It can cause photic phenomena in patients with a multifocal IOL

5. Which of the following conditions is found in more than 80% of dry eye patients?
   A. Sjögren’s syndrome
   B. Meibomian gland dysfunction
   C. Ocular rosacea
   D. Blepharitis

6. Which of the following ocular surface conditions can be found in the majority of patients scheduled for cataract surgery?
   A. Dry eye
   B. Conjunctivitis
   C. Blepharitis
   D. Both A and C

7. Which of the following is a major sight-threatening complication of cataract surgery that arises from postoperative inflammation?
   A. Epiretinal membrane
   B. Cystoid macular edema
   C. Central serous chorioretinopathy
   D. Optic neuritis

8. Which of the following inflammatory molecules can be measured in tears using an in-office test?
   A. ICAM-1
   B. LFA-1
   C. TNF-α
   D. MMP

9. What is the benefit of autologous serum in the treatment of dry eye?
   A. It stimulates lacrimal tear secretion
   B. It improves ocular surface integrity
   C. It substitutes tears and lubricates the ocular surface
   D. It suppresses inflammation by inhibiting inflammatory cytokines

10. Which of the following statements is true concerning NSAIDs?
    A. They are potent inhibitors of phospholipase A2
    B. They block the production of arachidonic acid
    C. They are especially effective in reducing postoperative pain
    D. They have more side effects than corticosteroids

EXAMINATION ANSWER SHEET  TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 13

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