

Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING
MEDICAL EDUCATION
PUBLICATION



ISSUE 16

Inflammation Control Following Refractive Surgery

STEPHEN LANE, MD As we become increasingly adept at manipulating the cornea for refractive error correction, our ability to achieve precision inflammation control is more important than ever and should continue to evolve.

Refractive surgery—including LASIK, PRK, and now SMILE and newly developed surgery for corneal inlays—inevitably involves some level of corneal trauma (Figure 1). While the use of lasers has reduced surgery-related inflammation compared with using a blade, invading the cornea always results in the generation of free radicals and the induction of inflammation, regardless of the type and source of energy. In addition to the amount of energy applied, inflammation increases in correlation to the amount of tissue cut and, to some extent, the location of the cuts to the cornea. In general, the closer a cut is to the limbus the greater the inflammation, and of course the greater the surface area of the epithelium (more corneal nerve endings involved) affected the greater the pain/discomfort.

Among the most common refractive surgeries, LASIK is generally associated with lesser grades of inflammation than PRK and less pain. Acute control of inflammation is also important in placement of corneal inlays, which are new to the market and gaining increasing acceptance as an option for presbyopia correction.¹ Although relatively inert, an inlay is still a foreign body placed in a femtosecond laser-carved corneal pocket; and so inflammation control remains essential to long-term success. Thus far, the KAMRA inlay has demonstrated good long-term biocompatibility and efficacy at 5 years follow up.¹ Compared to the large and long-term

studies on the KAMRA inlay, there is little data on the other two commercially available corneal inlays, the Flexivue MicroLens by Presbia Coöperatief U.A. and the the Raindrop Near Vision Inlay by ReVision Optics.¹

INFLAMMATION CONTROL SERVES PATIENTS

Controlling refractive surgery-associated inflammation is good patient care, as it serves two critical functions. First, inflammation is uncomfortable and intense inflammation can be quite painful. Getting a handle on inflammation minimizes ocular discomfort and is a key factor in improving the patient experience.

Second, inflammation compromises efficient and event-free healing. Delayed or impaired corneal healing may lead to reduced corneal clarity, the potential for scarring, reduced visual

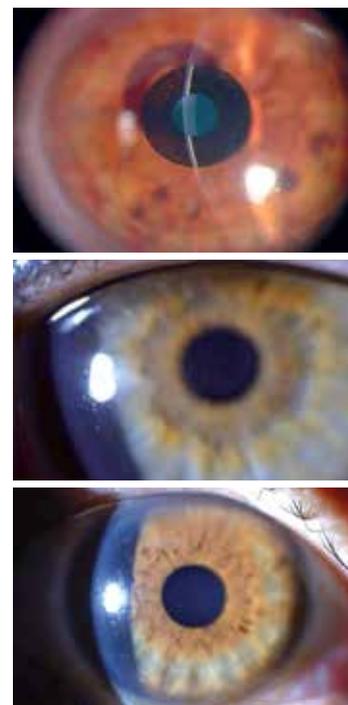


FIGURE 1 Intracorneal inlay images of KAMRA™ Accufocus and Raindrop™ (ReVision Optics) lenses. Intracorneal inlay for presbyopia correction requires antiinflammatory therapy on par with or perhaps greater than LASIK and PRK. (Images courtesy of Dr. Lane.)

See INSIDE for:
Immunity, Inflammation, and Hydration of the Ocular Surface by Stephen C. Pflugfelder, 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. Understand the variables that influence ocular surface inflammation associated with refractive surgery.
2. Reduce ocular surface inflammation in refractive surgery patients.
3. Describe the immunoinflammatory pathway underlying DED.
4. Improve management of DED by focusing treatment strategy on the prevention and treatment of ocular surface inflammation.

EDITORS

Marguerite B. McDonald, MD, FACS, practices at Ophthalmic Consultants of Long Island, and is a clinical professor of ophthalmology at the New York University School of Medicine. She is also an adjunct clinical professor of ophthalmology at Tulane University Health Sciences Center.

Victor L. Perez, MD, is a professor of ophthalmology at the Bascom Palmer Eye Institute and the director of the Ocular Surface Center at Bascom Palmer Eye Institute.

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COURSE DIRECTOR
MATTHEW J. GRAY, MD
University of Florida
Gainesville, FL, USA

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outcome, or an otherwise suboptimal result related to ocular surface irregularities. One can conceive of post-surgical inflammation control as the second stage of the surgery, as it is essential to achieving the desired vision overall and patient experience.

Controlling inflammation will reduce the risk for diffuse lamellar keratitis (DLK), inflammation at the interface between the LASIK flap and

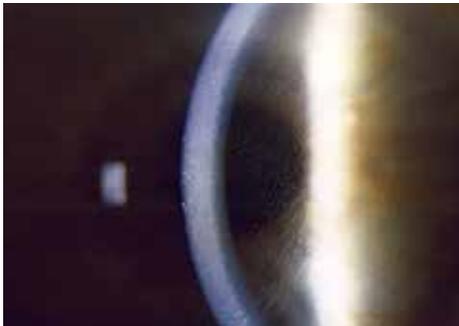


FIGURE 2 Inflammation is thought to play a role in the development of DLK. (Image Courtesy of Dr. Lane.)

the underlying surface. Patients with anterior basement membrane dystrophy, dry eye disease, other ocular surface disease that increases risk for epithelial defects, or staphylococcal lid disease may be at higher risk for DLK than unaffected persons (Figure 2).²

DLK can limit visual outcomes, particularly when severe. While DLK rates dropped markedly with the introduction of laser-related procedures—its exact etiology remains unclear, and it remains a challenge for refractive surgeons. Reports of blades cleaned with toxic substances have previously been reported to be a contributing factor. Keys to reducing risk for DLK include addressing preoperative risk factors and preoperative and intraoperative corticosteroid use.^{3,4}

PRECISION CONTROL

Approaching inflammation control in the refractive surgery patient involves walking a fine line between suppressing inflammation—for all of the reasons mentioned above—while, at the same time, avoiding any untoward effects of antiinflammatory medications. Short-term use of postsurgical antiinflammatory medications places patients at a brief but low risk for ocular surface

TOPICS IN OCULAR ANTIINFLAMMATORIES, ISSUE 16

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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FACULTY AND DISCLOSURE STATEMENTS

Marguerite B. McDonald, MD, FACS (Faculty Advisor), practices at Ophthalmic Consultants of Long Island, and is a clinical professor of ophthalmology at the New York University School of Medicine. She is also an adjunct clinical professor of ophthalmology at Tulane University Health Sciences Center. She's a consultant to Allergan, Alcon, Abbott Medical Optics, Bausch + Lomb, FOCUS Laboratories, Shire, OcuSOFT, and Altaire.

Victor L. Perez, MD (Faculty Advisor), is a professor of ophthalmology at the Bascom Palmer Eye Institute and the director of the Ocular Surface Center at Bascom Palmer Eye Institute. He has received grant/research support from the National Institutes of Health and Shire, and is a consultant for Bausch + Lomb, EyeGate, Allergan, and Alcon. He is also a stock shareholder for EyeGate.

Stephen Lane, MD, is an adjunct clinical professor at the University of Minnesota and medical director of his multisite private practice in Minnesota, Associated Eye Care. He states that he is a consultant for Alcon, AMO, TearLab, VisionCare, Shire, Ivantis, Kala Pharmaceuticals, Bausch + Lomb, PRN, RVO, Omeros, and RPS.

Stephen C. Pflugfelder, MD, is a professor, James and Margaret Elkins Chair and director of the Ocular Surface Center at the Cullen Eye Institute, department of ophthalmology, Baylor College of Medicine, in Houston, TX. Dr. Pflugfelder states that he is a consultant for Allergan and Shire.

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infection, which can damage tissue and compromise visual clarity. Long-term antiinflammatory medication is not typically needed in conjunction with refractive surgery; but if it is, long-term corticosteroid use places patients at increased risk for side effects such as elevated intraocular pressure (IOP) and cataract development.

Each antiinflammatory agent has its characteristic potency, dosing schedule, and side-effect profile; in addition, each patient and surgical case is unique. As new antiinflammatory medications are brought to market, new opportunities for precise patient-specific inflammation control are brought about. For example, it is now possible to use safer, more potent antiinflammatory regimens for shorter periods of time; this improves convenience and compliance compared with longer, more complicated regimens.

SELECTING AGENTS

A well-designed antiinflammatory regimen should succeed on several levels: it should provide the needed level of antiinflammatory potency for patient comfort and proficient corneal healing; it should do so for the shortest duration of time possible and at minimal inconvenience to the patient; and it should present the fewest potential safety and tolerability hurdles.

Currently two classes of agents are generally relied upon to control postoperative ocular inflammation: topical ocular corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs). Corticosteroids block phospholipase A2, an upstream enzyme in the inflammatory cascade that converts cell membrane phospholipids into arachidonic acid, the most important prostaglandin precursor. NSAIDs block the cyclooxygenases (COX) 1 and 2, the enzymes that catalyze the conversion of arachidonic acid into eicosanoids including prostaglandins, thromboxane, and prostacyclin.

When choosing from available ocular corticosteroids, consider the potency, vehicle characteristics, and dosing frequency.

Ocular corticosteroids range from mild (eg, fluorometholone) to strong (eg, difluprednate, dexamethasone). Loteprednol etabonate is intermediate in strength and differs from other topical corticosteroids in being the only one with a 17-chloromethyl ester group (as opposed to a ketone group) at carbon 20 in its chemical structure.⁵ Due to the presence of the ester moiety, unbound drug is metabolized by local esterase enzymes and rapidly deactivated. The deactivation step reduces the amount of drug available to cause side effects; indeed, loteprednol has a lower propensity to induce elevation in IOP in both normals and steroid responders.⁶⁻⁸

Because NSAIDs specifically 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 IOP elevation and increased risk of secondary infection. Topically applied NSAIDs have long been linked to delayed wound healing,⁹ but there is no conclusive evidence of such connection. Although use of NSAIDs was once associated with some severe complications following refractive and cataract surgeries, particularly

CORE CONCEPTS

- ◆ Controlling inflammation before, during, and after refractive surgery improves patient comfort and visual outcomes.
- ◆ Corneal inlay placement adds new demands for inflammation control; current technology is demonstrating good long-term biocompatibility.
- ◆ Topical corticosteroids and NSAIDs remain mainstays of postsurgical antiinflammatory therapy.
- ◆ Correct preexisting dry eye disease and ocular surface inflammation before proceeding with refractive surgery.

keratolysis, it later became clear that the primary culprit was a specific generic NSAID.¹⁰ NSAIDs lack the potency of a corticosteroid; but due to their overall safety, distinct mechanism of action, and powerful analgesic effect, they are often included in antiinflammatory regimens following PRK.

A basic tenet of any antiinflammatory therapy surrounding refractive surgery is to strongly suppress inflammation early (in the first postoperative week), then taper to a mild regimen and on to discontinuation. Patients on any antiinflammatory regimen must be carefully followed to assess wound healing, medication tolerability and adherence, and visual acuity.

BEYOND ANTIINFLAMMATORIES

A gamut of various adjuncts to medical antiinflammatories may be useful in controlling post-surgical inflammation. Bandage contact lenses are often employed to ease discomfort associated with large area surface ablation as is required in PRK. Physically cooling—such as frozen basic salt solution (BSS)-soaked pledget sponge application during surgery (a “popsicle”) and/or refrigerator-chilled artificial tears used after surgery—opposes the heat element of inflammation and can provide relief as well as speed healing. A brief course of oral narcotic, while not helpful for inflammation, may be necessary for pain control following wide area ablation.

Prior to surgery, preexisting inflammatory conditions affecting the ocular surface, such as dry eye, meibomian gland disease, and blepharitis, should be assessed and addressed as they can potentiate postoperative inflammation and delay healing. Currently, the mainstay of anti-inflammatory therapy for dry eye is topical cyclosporine A 0.05%. A new class agent in the treatment of ocular surface inflammation is the LFA-1 antagonist, the first of which, lifitegrast (Xiidra, Shire), was approved in July 2016 for the treatment of dry eye disease. LFA-1 antagonists prevent T-cell-mediated release of inflammatory cytokines, exerting a rapid anti-inflammatory effect.¹¹

LOOKING FORWARD: MEDICATION DELIVERY

A recent direction of development within industry has been improving delivery of current antiinflammatory molecules via more surface-friendly vehicles, such as gel. Medication in gel formulation delivers uniform dosing since it stays in solution without shaking. It provides the benefits of an ointment—good ocular surface retention and feeling comfort-

able on the eye—without the downside of distorting vision.¹² Improved formulations for topical ocular antiinflammatories is a trend that will no doubt continue.

In time, long-term drug delivery via punctal plug, subconjunctival insert, and other depot systems may replace daily drops as the principal means for combatting ocular inflammation.¹³ Such devices would essentially solve the problem of sporadic compliance and lead to far more reliable inflammation control for many.

CONCLUSION

PRK, LASIK, and corneal inlays require careful pre- and postoperative inflammation control for optimal patient comfort and outcomes. Robust initial antiinflammatory use—with corticosteroids with or without NSAIDs—followed by a taper to minimally effective potencies and doses remains fundamental to good control.

Stephen Lane, MD, is an adjunct clinical professor at the University of Minnesota and medical director of his multisite private practice in Minnesota, Associated Eye Care. He states that he is a consultant for Alcon, AMO, TearLab, VisionCare, Shire, Ivantis, Kala Pharmaceuticals, Bausch + Lomb, PRN, RVO, Omeros, and RPS. Medical writer Noelle Lake, MD, assisted in the preparation of this manuscript.

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Immunity, Inflammation, and Hydration of the Ocular Surface

STEPHEN C. PFLUGFELDER, MD Immune responses and chronic inflammation play a major role in the onset and perpetuation of dry eye disease. Early use of antiinflammatory therapy can be key to controlling this ocular surface disorder and preventing its potentially debilitating effects.

Dry eye disease (DED) is a multifactorial disease of the tears and ocular surface characterized by symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.¹ Its estimated prevalence varies widely by study, from less than 1% to more than 30%.² Recent evidence suggests that, unlike conventional thinking, the prevalence of DED in young adults may not differ much from the older population, presumably the result of an increased risk due to the popularity of contact lens wear and earlier onset of chronic inflammatory conditions such as arthritis.³ Many environmental factors, including extended use of computers and electronic devices, may contribute to the tear dysfunction and associated ocular morbidity in DED, but they appear to act through a common pathway in which inflammation of the ocular surface has a key role.¹

Inflammatory responses encompass a constellation of molecular and cellular events triggered by immunity upon the challenge of foreign, noxious stimuli. The ocular surface, like all mucosal surfaces, has its own immune system comprised of a myriad of immune cells and soluble factors produced by the epithelial cells. Distributed throughout the tear film, conjunctiva, corneal epithelium, meibomian glands, and lacrimal gland, these cellular and soluble immunologic elements have important physiologic functions but are also responsible for the underlying inflammatory response in DED.

INNATE AND ADAPTIVE IMMUNITY

Immunity is broadly classified into two categories: innate and adaptive. Innate (ie, natural) immunity is nonspecific and present at birth, whereas adaptive (ie, specific or acquired) immunity reacts to specific microbes or antigens and creates immunological memory after the initial response. The ocular surface has developed a robust innate immune system that functions as the first line of defense against harmful agents. Elements of the system include the physical barrier formed by the tight junctions between corneal epithelial cells, secretory proteins found in tears (eg, immunoglobulins, lactoferrin, lysozyme, and other cytokines), and immune cells such as neutrophils and tissue-resident macrophages.⁴

The mucus layer between the aqueous tear film and the conjunctival and corneal epithelial surface has a unique role in both immune defense and maintenance of hydration at the ocular surface. The mucin family of glycoproteins are highly hydrophilic and bind water molecules. They form a mucous barrier that repels pathogenic organisms, lubricates the ocular surface, and stabilizes the tear film.⁵ Cytokines produced by innate immune cells or T cells, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-13⁶, IL-1, and interferon (IFN)-gamma, are known to alter mucin production on the ocular surface.

Adaptive immune responses, in contrast, are initiated by antigen-presenting cells (APCs), primarily dendritic cells located throughout the conjunctiva in the epithelium and the stroma (immature dendritic cells are found in the cornea). After picking up foreign antigens, usually from microbes but also from damaged cells, the dendritic cells migrate to preauricular and submandibular lymph nodes to present the antigens to T lymphocytes (usually helper T cells). Upon activation, T helper cells then produce cytokines that will either induce antibody secretion by B cells or activate cytotoxic T cells to kill targeted cells.

OCULAR SURFACE IMMUNITY IN DED

The pathogenesis of DED is not fully understood. However, it is increasingly recognized that immune responses and inflammation have a central role. The theory holds that changes in the composition of the tear fluid and tear film stability in DED promote inflammation on the ocular surface, and the inflammatory processes contribute to exacerbation and perpetuation of the disease.^{7,8}

Initially, exposure of surface epithelial cells to hyperosmolar stress triggers the release of inflammatory cytokines and activates innate immunity.⁸ There is evidence that neutrophils are present on the ocular surface of DED patients and contribute to the development of inflammation.⁹ These cells produce free radicals and proteolytic enzymes that can damage the surface cells and break down the innate epithelial barrier, leading to loss of ocular surface integrity. Patients with DED have also been found to have altered expression and distribution of mucins.⁵ Alterations of mucins in DED are likely a result of the production of inflammatory mediators and are thought to contribute to ocular surface damage.^{7,8}

Depending on disease severity and type of DED, cell-mediated adaptive immunity is triggered at a certain point, initiating a sequence of immunopathologic events that has been well characterized: antigen presentation, T cell activation, and release of inflammatory cytokines (Figure 1).^{7,10,11} Specifically, inflammatory mediators released from ocular surface epithelial cells promote the activation and maturation of APCs on the ocular surface. After acquiring and processing antigens from the ocular tissue, the activated APCs travel to the lymph nodes, where they prime naïve T cells against the autoantigens they carry. Subsequently, the activated T cells migrate via the circulation and infiltrate the ocular surface, where they produce additional inflammatory cytokines that further promote epithelial damage.

CORE CONCEPTS

- ◆ DED is an inflammatory ocular surface disease that involves both innate and adaptive immune responses.
- ◆ Activation of T cell-mediated immune response is critical to the perpetuation of ocular surface inflammation and disease progression in DED.
- ◆ Chronic inflammation of the ocular surface is present in all types of DED. Aqueous-deficient types of DED, such as Sjögren syndrome, have a more prominent T cell component.
- ◆ DED patients have increased levels of inflammatory mediators in tears. Much of DED symptomatology results from inflammation and its damaging effects on the ocular surface.
- ◆ Timely initiation of appropriate antiinflammatory treatment is important in mitigating DED symptoms and preventing disease progression.

Currently available evidence indicates that, on the ocular surface of DED patients, there are mainly two subtypes of T helper cells present: 1 (TH1) and 17 (TH17).^{7,10,11} The TH1 and TH17 cells produce IFN-gamma and IL-17, respectively.^{12,13} IFN-gamma can cause loss of goblet cells and apoptosis of

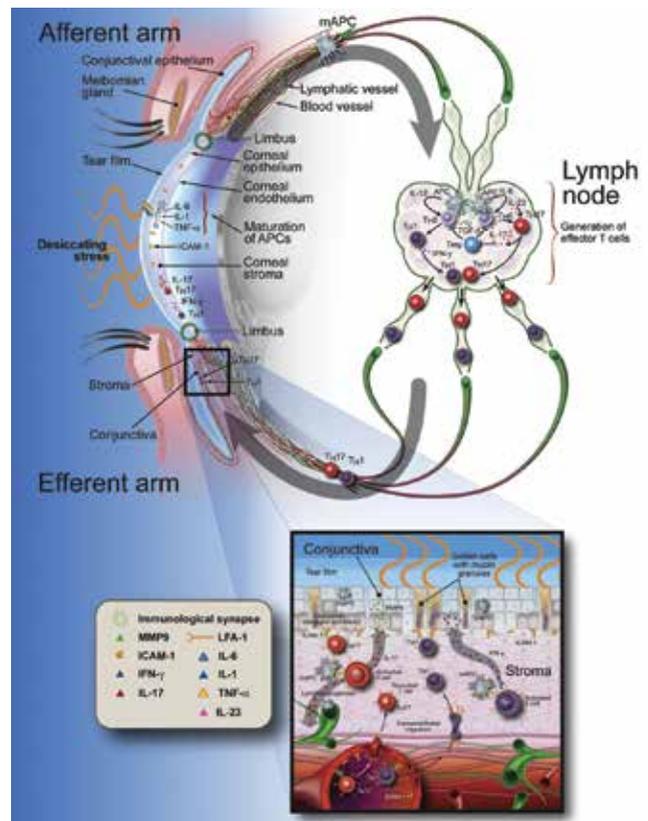


FIGURE 1 The immunoinflammatory pathway in DED. (Reprinted from *The Ocular Surface*, 14(2), Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R, Lifitegrast, a Novel Integrin Antagonist for Treatment of Dry Eye Disease, 207-15, Copyright 2016, with permission from Elsevier.)

ocular surface epithelial cells, whereas IL-17 has been shown to disrupt corneal epithelial barrier function through production of matrix metalloproteinases (MMPs). Immune-mediated damages as such sustain ocular surface irregularity and tear instability, leading to disease exacerbation and the development of a vicious, self-perpetuating cycle of inflammation that is central to the pathogenesis of DED.

INFLAMMATION AND DED: CLINICAL LINKS

While more severe forms of aqueous-deficient DED such as Sjögren syndrome have a more prominent T cell and autoimmune component, evaporative DED with meibomian gland dysfunction (MGD) mainly involves innate immunity. It is important to distinguish between the different types of DED; however, regardless of the underlying etiology, DED is associated with inflammation of the ocular surface.

Inflammation and the resulting pathologies of the ocular surface contribute to both signs and symptoms of DED. Punctate epithelial erosions, a hallmark of the disease, is a corneal epitheliopathy resulting in part from immune mediators that either directly affect the epithelial cells or stimulate production of proteolytic enzymes (eg, MMPs) that break down the corneal epithelial barrier (Figure 2). Patients with DED often complain of irritation or ocular pain, symptoms that arise from the effects of inflammation on sensory nerves. They can be highly sensitive to normal environmental stimuli such as a cool breeze, because exposure to inflammatory insults causes corneal nerves to fire more.

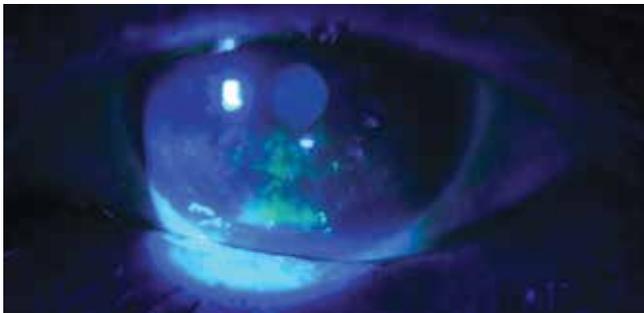


FIGURE 2 Severe punctate fluorescein staining in a woman with Sjögren syndrome-associated aqueous tear deficiency. (Image courtesy of Dr. Pflugfelder.)

One problem with DED evaluation is the disconnect between the symptoms patients report and the clinical signs they demonstrate, especially in early and late stages. In early DED, when the inflammation is at the cellular level, symptoms tend to outweigh signs. Patients may complain of irritation and even ocular pain even though there are no obvious ocular manifestations. In more severe DED, pathologies of inflammation such as epitheliopathy are more evident, but patients may not complain much of irritation or pain because the nerves have been damaged.

For lack of the typical signs of inflammation, DED in an early or mild form often does not strike one as an inflammatory disease. From the molecular perspective, however, there is always an inflammatory component to DED. In the early stages, the eye may not appear inflamed, but increased levels

of inflammatory mediators can be detected if molecular assays are performed using samples of ocular surface epithelial cells or tear fluid.¹⁴

At present, we are limited in our ability to measure different inflammatory mediators on the ocular surface in routine clinical practice. Molecular assays of inflammatory markers are mainly used in research, with the exception of InflammDry, a test for MMP-9 in tears that has been approved by the US Food and Drug Administration (FDA) for the diagnosis of DED. The in-office test does not measure the level of MMP-9; rather, it is a threshold test that detects the inflammatory marker at a certain level. While a positive test result provides a valuable diagnostic clue, a negative result cannot be equated with absence of inflammation. As more experimental methods are refined and incorporated into practice, our ability to identify inflammatory markers for DED should improve in the future.

THERAPEUTIC OPTIONS

Currently, a variety of antiinflammatory therapies are used to treat DED. Until recently, topical cyclosporine A (CsA) 0.05% has been the only FDA-approved pharmaceutical agent for the treatment of dry eye. An immunomodulatory agent, CsA specifically inhibits the proliferation of T cells and prevents production of inflammatory cytokines.¹⁵ Its efficacy as a topical antiinflammatory treatment for dry eye disease supports the pathogenic role of T cell-mediated inflammation. Topical corticosteroids have immediate antiinflammatory effects and potently inhibit some of the innate mediators produced by the epithelial and the resident immune cells,¹⁶ but they also have many side effects and therefore must be used judiciously.

Oral tetracycline antibiotics such as doxycycline exhibit antiinflammatory effects by inhibiting the activity of MMP-9 and production of other cytokines such as IL-1 and TNF.^{16,17} Macrolide antibiotics, especially azithromycin, also have antiinflammatory properties and may be more effective than tetracycline derivatives in treating MGD.^{18,19} Many physicians now recommend oral supplementation of omega-3 fatty acids to their patients. These essential fatty acids (EFAs) are thought to benefit DED patients by blocking the production of proinflammatory eicosanoids (eg, prostaglandin E2 and leukotriene B4) and cytokines (eg, IL-1 and TNF).^{20,21}

Most recently, lifitegrast 5.0% was approved by the FDA and became the first new DED therapy in 13 years. An integrin antagonist, lifitegrast binds to lymphocyte function-associated antigen 1 (LFA-1; an integrin found on leukocytes) and blocks its pairing with intercellular adhesion molecule 1 (ICAM-1; an adhesion protein expressed on APCs and endothelial cells) to form immunological synapse, a key step in T cell-mediated inflammation (Figure 3).¹¹ It is thought that lifitegrast produces antiinflammatory effects by inhibiting T cell activation, T cell migration, and cytokine release.¹¹ Working more upstream in the inflammatory pathway via a novel mechanism of action, the new drug has the potential to work more efficiently and effectively than CsA. In clinical studies, lifitegrast provided rapid and sustained symptomatic relief and also improvement of epitheliopathy in patients with DED.²²⁻²⁴

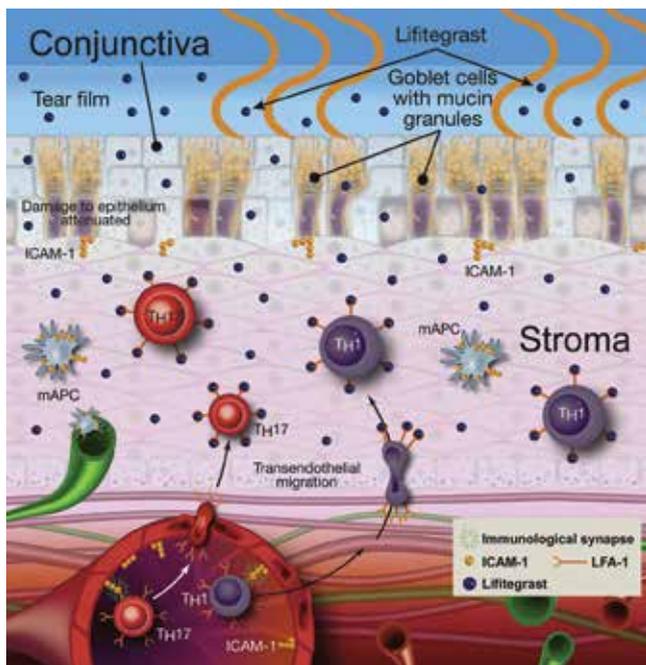


FIGURE 3 Mechanism of action of lifitegrast. (Reprinted from *The Ocular Surface*, 14(2), Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R, Lifitegrast, a Novel Integrin Antagonist for Treatment of Dry Eye Disease, 207-15, Copyright 2016, with permission from Elsevier.)

TREAT EARLY

For patients with DED, reducing the inflammatory response and levels of inflammatory mediators is crucial for adequate treatment and symptom resolution. Physicians managing the disease should have a heightened awareness of ocular surface inflammation and the different types of antiinflammatory therapies that are available now. There is a lack of real-world data on the outcomes of antiinflammatory treatment in DED, but surveys of physicians suggest that about 80% of patients achieve relief of their symptoms with topical CsA.²⁵ Potentially, the success rate of antiinflammatory treatment can be further improved with the introduction of therapies such as lifitegrast.

Presumably, inflammatory treatment is more effective when initiated during the earliest stages. When the self-perpetuating inflammatory process becomes established and the symptoms or signs worsen, the disease may be too advanced to reverse. Currently, the importance of inflammation is under-recognized in the clinical management of DED, especially in cases that are considered early or mild from a clinical perspective. If we can more accurately identify the particular type of DED and more promptly institute appropriate antiinflammatory therapy, we may be better able to lessen symptoms, preserve ocular surface health, and improve patients' quality of life.

Stephen C. Pflugfelder, MD, is a professor, James and Margaret Elkins Chair and director of the Ocular Surface Center at the Cullen Eye Institute, department of ophthalmology, Baylor College of Medicine, in Houston, TX. Dr. Pflugfelder states that he is a consultant for Allergan and Shire. Medical writer

Ying Guo, MBBS, assisted in the preparation of this manuscript.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 16

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 one of the following antiinflammatory agents works by blocking cyclooxygenase 1 and 2?
 - Corticosteroid
 - NSAID
 - Cyclosporine A
 - LFA-1 antagonists
- Which one of the following statements is NOT correct about the ocular surface inflammation in DED?
 - It is primarily mediated by innate immunity
 - It contributes to symptoms and signs of DED
 - It is present in all forms of DED
 - It is a self-perpetuating process
- Significant postoperative inflammation may affect:
 - Visual outcome
 - Ocular surface health
 - Patient comfort
 - Any or all of the above
- Which one of the following pathological changes may be found on the ocular surface of patients with DED?
 - Disrupted barrier function of the corneal epithelium
 - Reduced mucin production
 - Reduced density of conjunctival goblet cells
 - All of the above
- Which one of the following statements is NOT correct about MMP-9?
 - It is a proteolytic enzyme produced by immune cells
 - It disrupts the tight junctions between corneal epithelial cells
 - It is the only inflammatory mediator that can be measured in tears using an in-office test
 - A negative MMP-9 assay indicates absence of ocular surface inflammation
- Which one of the following surgical variables does NOT correlate with the amount of inflammation generated?
 - Energy exerted by laser
 - Age of laser
 - Surface area of incision or ablation
 - Refractive surgery type
- Which one of the following will NOT help reduce postoperative ocular inflammation among patients?
 - Chilled eye drops
 - Oral narcotics
 - Frozen “popsicle” sponge administered intrasurgically
 - Bandage contact lens
- Preexisting ocular surface disease may increase risk for DLK because:
 - The corneal epithelium is vulnerable
 - Inflammation may recur postoperatively
 - Both A and B
 - Neither A nor B
- Which of the following antiinflammatory therapies is approved by the FDA for the treatment of DED?
 - Oral doxycycline
 - Topical CsA
 - Topical lifitegrast
 - Both B and C
- Adaptive immune response is primarily mediated by:
 - Dendritic cells
 - T cells
 - Neutrophils
 - Macrophages

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 16

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 November 30, 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.

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