

THE EVOLUTION OF TREATMENT OF DRY EYE DISEASE

BY JOHN D. SHEPPARD, MD, MMSc

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DED—DISRUPTION OF THE HOMEOSTATIC TEAR FILM

In 1995, the National Eye Institute, together with industry, organized a workshop with the intent to solidify a definition for dry eye disease (DED). The definition they generated stated, “Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.” Since that time, understanding of the etiology, pathology, and treatment has increased considerably.

We now know that while multifactorial, DED is a chronic, immune-mediated inflammatory disease.¹ When the delicate homeostatic balance of the ocular surface system is disturbed, it triggers the activation of a stress response that progresses from mitogen-activated protein kinases to transcription factors, and then production of proinflammatory cytokines and matrix metalloproteinases.² This leads to the activation of T-cells that infiltrate the ocular surface and secrete additional proinflammatory cytokines.^{3,4} Thus begins a self-perpetuating cycle of inflammation and epithelial damage across the entire ocular surface, regardless of the origin of the disruption.

UNDERSTANDING THE TEAR FILM: T-CELLS ARE INTEGRAL TO TEAR FILM HOMEOSTASIS

It is important to understand the composition of the tear film and its interplay with the entire lacrimal functional unit. The innermost layer of the tear film is the mucin layer. The soluble mucin 5AC is produced by goblet cells in the conjunctiva and is essential for viscosity and stability during the blink cycle.⁵ Immediately external to the mucin is the aqueous layer produced by the lacrimal glands. While it is mostly a very diluted saltwater, it also contains a complex mixture of proteins, immunoglobulins, mucins, electrolytes, cytokines, lysozymes, lactoferrin, and growth factors, including T-cells.⁶ While we often speak of T-cells negatively, regulatory T-cells help inhibit a wide variety of autoimmune and inflammatory diseases,⁷ and their surface antigen, LFA-1, may play a critical role in regulatory T-cell homeostasis and function.⁸ The most abundant proteins, lysozyme and lactoferrin, possess antimicrobial functions.



Figure 1. Patient with nonobvious MGD. Although the glands look healthy, they are plugged.



Figure 2. Eye with healthy meibomian glands (A); eye with meibomian gland dropout (B).

(Courtesy of P. Mile Bužić, OD, FAAO, and David L. Kadings, OD, FAAO)

Immunoglobulins such as IgA, IgG, and IgM also have protective functions. Growth factors help regulate the processing of epithelial cell replacement and are necessary for wound healing. Electrolyte concentrations in healthy tears are carefully maintained within a certain range to ensure correct osmolarity, which is important for many aspects of epithelial and nerve cell function. The outermost lipid layer, produced primarily by the meibomian glands, restricts evaporation of the aqueous and lubricates the eye (Figures 1 and 2).

Tears in chronic DED are abnormal in many ways.⁵ A profound loss of goblet cells results in a less soluble and plentiful mucin 5AC, negatively impacting viscosity and

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adherence of the tear film. Tear protein concentrations, including those with antimicrobial functions, are reduced, along with growth factor concentrations. At the same time, proteases like matrix metalloproteinase 9 (MMP-9) that are normally present in healthy tears in a constitutive low concentration in a latent, inactivated form become activated. They can degrade the extracellular matrix and the tight junctions between adjacent cells of the corneal epithelium. Activated proteases are also responsible for cleavage of many cytokines into an activated, proinflammatory form. Elevated tear electrolyte concentrations in DED parallel increased tear film osmolarity.

WHO HAS DED?

The triggers for DED are varied, but essentially fit into three categories. The first is physical irritation, such as environmental irritants, medications, contact lenses, lid abnormalities, or surgical trauma. The second category is systemic inflammation, including rheumatoid arthritis, lupus, or Sjogren syndrome. A third category of DED triggers is tear deficiency or instability arising from postmenopausal hormonal changes, or meibomian gland dysfunction.

Whatever the trigger, 26.4 million Americans reported suffering from DED⁹ in 2012, and many more are believed to suffer from DED yet do not report it or seek medical attention. The PHACO Study found that 87% of patients scheduled for cataract surgery had corneal staining, and 63% had a tear break-up time less than 5 seconds.¹⁰ This is alarming, as untreated DED can negatively impact preoperative measurements, healing, and comfort as well as visual outcomes.

Aside from the deleterious effect upon surgical outcomes, DED can have a significant negative impact on the quality of life of affected individuals. Severe DED is ranked similarly to severe angina and dialysis in validated patient surveys, and it impacts work performance, ability to drive at night, and enjoyment of outdoor activities.^{11,12} Furthermore, it is a common cause of contact lens intolerance.¹³



Figure 3. Lissamine green is used to identify DED and meibomian gland dysfunction.

(courtesy of P. Dee S. Stephenson, MD)

DIAGNOSING DED

DED pathogenesis is multifarious, presentation notoriously idiosyncratic, while signs and symptoms are commonly inconsistent, ruling out the possibility of a single diagnostic criteria. Most practitioners find it essential to deploy a variety of diagnostic tools to better define each patient's disease state. Patient symptoms are generally documented by careful history, but can be measured according to functional visual quality with several standardized questionnaires such as the Ocular Surface Disease Index (OSDI) or the Symptom Assessment in Dry Eye (SANDE).

A proper examination must include careful evaluation of the ocular surface. Epithelial integrity is assessed with corneal and conjunctival staining, using fluorescein, rose Bengal or lissamine green (Figure 3). Impression cytology in a research setting is useful for measuring goblet cell density, inflammatory cell surface markers, and squamous metaplasia.

Tear-based, point-of-service diagnostics currently available include tear secretion (Schirmer), tear osmolarity (TearLab), tear meniscus height (Oculus Keratograph 5M), tear film stability (tear break-up time), and MMP-9 protein elevation (InflammaDry, RPS). Meibomian gland function can be evaluated by lipid layer interferometry (Tear Science) and meibomian gland morphology readily documented by eyelid confocal microscopy or by DMI (dynamic meibomian imaging) (Tear Science, Oculus, Topcon). DMI is easily understood by patients who become far more engaged in their own treatment plan upon clear cut demonstration of their own anatomical changes. Corneal topography indices quantify the recognized effect of corneal irregularity

upon visual quality and subsequent therapeutic response. The Sjogren syndrome test¹⁴ (Sjo, Bausch + Lomb, Immco Laboratories) detects early serum markers permitting much earlier identification of this syndrome that predisposes patients to lymphoma, pulmonary fibrosis, xerostomia, fatigue, and arthritis as well as severe DED.¹⁵

TREATING DED

Numerous extrinsic and intrinsic trigger factors for DED, combined with inconsistency in signs and symptoms, render effective therapy elusive. In 2003, the American Academy of Ophthalmology provided general guidelines for DED treatment that only briefly mention anti-inflammatory treatment.¹⁶ This treatment included cyclosporine and corticosteroids. By 2006, an international task force recommended specific treatments for each severity level that included a recommendation to consider topical cyclosporine for moderate to severe disease.¹⁷ In 2007, the International Dry Eye Workshop (DEWS) expanded on these guidelines and recommended topical cyclosporine for moderate or Level II disease.¹⁸ It was not until 2013 that the American Academy of Ophthalmology formally adopted the DEWS guidelines.¹⁹

It is now well understood that inflammation is one of the most important aspects of DED pathogenesis,^{20,21} and no matter the trigger, untreated or undertreated, established disease can lead to severe refractory disease.²² At this time, there are three topical prescription therapies available to treat inflammation in DED: corticosteroids, topical cyclosporine A (CsA), and lifitegrast. Oral essential fatty acid supplementation²³ and tetracycline-class antibiotics²⁴ are also commonly prescribed for inflammatory ocular conditions, including DED.

CORTICOSTEROIDS

While topical corticosteroids are not yet approved by the FDA specifically for the treatment of DED, they are potent anti-inflammatory drugs that are frequently prescribed off-label by eye care providers for induction²⁵ and pulse therapy.²⁶

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex, and its synthetic counterpart was first approved by the FDA in 1952 for the treatment of irritable bowel syndrome.²⁷ The indication now includes more than 12 categories of use. The most widely used anti-inflammatory agents, corticosteroids suppress the molecular response to desiccating stress, which stimulates expression of MMP-9 and inflammatory cytokines while

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activating mitogen-activated protein kinase (MAPK) signaling pathways in the corneal epithelium.²⁸ Essentially, steroids decrease inflammation by inhibiting T-cells on the ocular surface. Ocular and systemic corticosteroids also function by inducing phospholipase A2 inhibitory proteins that control the biosynthesis of inflammatory mediators, such as prostaglandins, ICAM, and leukotrienes, blunting diapedesis, and by inhibiting the release of their common precursor, arachidonic acid.

Difluprednate is a synthetic prednisolone derivate that was discovered in 1970. It was initially marketed in Japan by Senju Pharmaceuticals as a topical dermatologic formulation starting in 1979, and based on its binding affinity, it is considered a very strong steroid. Difluprednate 0.05% ophthalmic emulsion (Durezol; Alcon) was approved by the FDA for the treatment of inflammation and pain with ocular surgery in 2008 and anterior uveitis in 2009.²⁹

CYCLOSPORINE A

Cyclosporine is a fungal-derived peptide that was first approved by the FDA in 1983 to suppress the immune system in all organ transplant patients (Sandimmune, Sandoz Pharmaceuticals).³⁰ The FDA approved a microemulsion formulation of cyclosporine (Neoral, Novartis) in 1995 and Gengraf (AbbVie) in 2000. Cyclosporine A was first used topically in ophthalmology in the early 1980s to inhibit experimental corneal allograft rejection, and was later found useful for various ocular inflammatory disorders. It was first tested in conjunction with keratoconjunctivitis sicca in canines in 1989,³¹ prior to studies by Leibovitz showing efficacy in humans.³² Restasis (cyclosporine A 0.05% ophthalmic emulsion; Allergan) was approved by the FDA in 2002 to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with dry eye.

Cyclosporine was the first immunosuppressive drug that allowed for selective regulation of T-cells while preserving ocular resident epithelial cells from inflammatory apoptosis through differential modulation of MPTP activity.³³

The next device to come to the market will be an alternative to pharmacotherapy or surgery: neurostimulation.

Cyclosporine also attenuates responses of immune as well as nonimmune cells to inflammatory stimuli via suppression of nuclear factor kB (NF-kB) transcriptional signaling. It has been well documented that cyclosporine selectively inhibits T-cell activation through blocking Ca2p-activated, calcineurin-dependent nuclear factor of activated T-cells (NFAT), and subsequently blocks cytokine (such as IL-2) and chemokine production.³⁴ NF-kB upregulates the production of inflammatory mediators, and is one of the most important factors in proinflammatory gene expression,³⁵ as well as plays a key role in apoptosis, stress response, corneal wound healing, angiogenesis, and lymph-angiogenesis.³⁶

Creation of an appropriate vehicle for ophthalmic delivery of insoluble and hydrophobic cyclosporine was necessary, so accordingly Allergan developed an emulsion formulation in castor oil that also includes glycerin, polysorbate 80, and sodium hydroxide.³⁷ The phase 3 studies of this topical emulsion (Restasis) showed a demonstrated treatment effect after the first month that increased over 6 months with improvements in corneal staining, Schirmer values, blurred vision, and physician evaluation.³⁸

Importantly, topical administration of cyclosporine A 0.05% or 0.1% ophthalmic emulsions resulted in undetectable or very low plasma levels of cyclosporine. Following topical administration of cyclosporine A 0.05% ophthalmic emulsion twice daily for up to 12 months, blood concentrations of cyclosporine remained below the quantitation limit of 0.1 ng/mL. Serum concentrations detected were several orders of magnitude less than those found during systemic immunosuppressive applications.³⁹

LFA-1 INHIBITORS

Leukocytes migrate to sites of inflammation by engaging their ligands on endothelial cells, and many immune-mediated chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease, are characterized by this unregulated migration.⁴⁰ Targeting integrins and ligands of the immunoglobulin superfamily, which are responsible for leukocyte migration, is thought to modulate inflammation and has successfully been used to treat inflammatory bowel diseases.⁴¹

The integrin lymphocyte function-associated antigen 1 (LFA-1) and its interaction with the ligand ICAM-1 is necessary for the trafficking of inflammatory cells.⁴² A humanized monoclonal antibody that targeted the integrin L, was previously on the market (efalizumab, Raptiva) to treat plaque psoriasis. It prevented LFA-1 expressing lymphocytes from interacting with ICAM-1 ligands, thus preventing activation of T-cells and their migration to the skin. Efalizumab was approved in 2003 for treatment of plaque psoriasis and a subsequent safety study showed that patients could receive 1 mg/kg subcutaneously for 24 weeks with no evidence of cumulative toxic effects.⁴³ However, in April 2009 efalizumab was voluntarily withdrawn from the US market due to the report of three cases of progressive multifocal leukoencephalopathy (PML) in patients with psoriasis. PML is a rare central neurological disease caused by the JC polyomavirus (JCV) that has been associated with several monoclonal antibodies intended to treat chronic inflammatory diseases, including Rituxan (Genentech) and other biologics.⁴⁴ JCV is carried by approximately 58% of the population,⁴⁵ but it is kept in check by T-cells, which are the most important component of the immune response against established intracellular viruses.⁴⁶ Untreated PML has a 50% mortality rate⁴⁷ and occurs when the cellular immunity is repressed, thereby markedly decreasing CD4+ T-cell counts.

In 2010, a novel series of small molecules derived from tetrahydroisoquinoline (THIQ) were discovered that could disrupt binding of LFA-1 to its receptor ICAM-1, which demonstrated good bioavailability with either oral or IV administration.⁴⁸ Lifitegrast was identified from this series of THIQ-derived small molecules and engineered as a room temperature stable, pH neutral, highly soluble topical ophthalmic solution.^{49,50} Lifitegrast inhibits the interaction of LFA-1 and ICAM-1, and thus the subsequent cycle of T-cell-mediated inflammation. This includes inhibiting neutrophil recruitment to the corneal stroma⁵¹ and inhibiting cytokine release from activated lymphocytes.⁵²

The safety and efficacy of lifitegrast 5% solution (Xiidra, Shire Pharmaceuticals) has been assessed in a total of 1,181 patients in four, 12-week, randomized, multicenter, double-masked, vehicle-controlled studies.⁵³ The studies found that individuals treated with Xiidra demonstrated greater improvement in signs and symptoms of DED than in groups treated with phosphate buffered saline.^{54,55} On July 12, 2016, Xiidra was approved for treatment of the signs and symptoms of DED under the lymphocyte function-associated antigen 1 antagonist category. The most common side effects of lifitegrast 5% solution include eye

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irritation, blurred vision, and dysgeusia. In a subset of DED patients enrolled in phase 3 trials for lifitegrast 5% solution, 19% (9/47) had plasma lifitegrast trough concentrations above the lower limit of assay quantitation (0.5 ng/mL), ranging from 0.55 ng/mL to 3.74 ng/mL.⁵⁶

NEUROSTIMULATION AND DED

While lifitegrast 5% solution broke ground with a class of drug new to DED treatment, the dry eye market continues to expand and gaps in care remain. The next device to come to market will be an alternative to pharmacotherapy or surgery: neurostimulation.

Neurostimulation is an established, yet highly innovative field that provides an alternative to pharmacotherapy or surgical procedures in a wide variety of conditions. This unique approach to therapy involves applying stimulation techniques to the affected region of the nervous system to alter neurophysiological signals affecting target tissues and organs.⁵⁷ The first implantable neurostimulator for relief of chronic pain was approved in 1967,⁵⁸ and subsequent devices have treated millions of patients for myriad conditions including tremors,⁵⁹ epilepsy,⁶⁰ obsessive-compulsive disorder,⁶¹ Parkinson disease,⁶² obesity,⁶³ overactive bladder,⁶⁴ and retinitis pigmentosa.⁶⁵ Neurostimulators today are either surgically implanted, usually near a central or peripheral nerve, or employ portable technologies that conduct the stimulation transcutaneously or percutaneously.⁶⁶

The lacrimal functional unit (LFU) consists of the lacrimal glands, ocular surface, and lids, regulated by sensory and motor innervation. This is an integrated system whose interdependent components act together, and not in isolation.⁶⁷ Abnormality in any of the extensive neural connections can result in an altered tear film, which no longer supports the normal functioning of the ocular surface. Damage to lacrimal gland innervation can result from diseases such as Sjogren syndrome, refractive surgery, chronic use of contact lens, ocular herpes simplex or zoster infection, adenovirus keratoconjunctivitis, or simply aging; the result is decreased tear secretion.⁶⁸

Upon stimulation, the LFU communicates with the afferent trigeminal nerve via sensory neurons carrying information from the ocular surface, glands, and tissues to the central nervous system, while efferent parasympathetic and sympathetic neurons carry information from the central nervous system to the LFU.⁶⁹ The trigeminal nerve is the largest cranial nerve and has three branches, the ophthalmic nerve, the maxillary nerve, and the mandibular nerve. The ophthalmic nerve is responsible for innervation of the LFU, including the lacrimal gland, the meibomian glands, and the goblet cells.^{70,71}

An intranasal tear neurostimulator, TrueTear (Allergan) is currently awaiting FDA review and approval for treatment of DED. The noninvasive device has two disposable prongs that are inserted into the nose to contact nasal mucosal fibers of the nasociliary branch of the trigeminal nerve. A highly refined low level electrical pulse stimulates the afferent cranial nerve Vii, which then communicates through the brainstem to efferent trigeminal fibers controlling the lacrimal gland, ocular surface goblet cells, and tarsal meibomian glands, thereby increasing truly natural, not reflex, tear production.

CLINICAL APPROACH TO THE DRY EYE PATIENT

Eye care providers who recognize and treat dry eye generally encounter three typical scenarios. Those who do not should at least refer to an interested colleague within their practice or community.

(1) *A new patient, often referred, presenting for the treatment of dry eye, usually having seen one or more previous clinicians and failed several different treatments.* This patient requires a careful diagnostic evaluation with step wise, logical, scientific introduction of one therapy at a time. Adequate time must be allowed for full treatment effect: at least 6 weeks. It is wise to introduce one rapid onset therapy, such as topical steroids or punctal plugs, plus one slower onset therapy, such as nutritionals, lid scrubs, or thermal pulsation, thereby allowing both patient and clinician to differentiate between the two interventions.

(2) *An existing patient with another primary diagnosis who is identified with dry eye.* Careful introduction of new treatments is again warranted, with careful attention to minimizing excessive drop use, particularly in glaucoma patients. These clinic visits may require more than the usual visit time due to their complexity, so the temptation to shrug off significant punctate keratopathy or increased discomfort until the next visit should be suppressed. Some elderly or

neurotrophic patients with obvious ocular surface damage experience minimal discomfort and require more thorough explanations and intensive encouragement.

(3) *A new or current patient preparing for ophthalmic surgery.* Meticulous attention must always be paid to the condition of the refractive surface in order to optimize biometry, healing, and surgical outcomes. In this situation, accelerated ocular surface normalization is preferred, and multiple complementary therapies may be simultaneously initiated. Many cataract, corneal refractive, glaucoma, retina, oculoplastic, and corneal transplant patients may receive expeditious recommendations for all or most of the following in order to hasten response time: oral nutritional, preservative-free tears, lid scrubs containing hypochlorous acid (Avenova, Hypochlor), punctal plugs, oral doxycycline, thermal pulsation, and topical loteprednol, cyclosporine, or lifitegrast.

Patient-centered recommendations reflect the urgency, etiology, clinical context, and severity of each patient presentation. Treatment paradigms are directed by each unique set of signs and symptoms, history and review of systems, point-of-service testing and then intelligent treatment prioritization. It is only through complete efforts to collect all relevant data that the best possible treatment can be selected.

CONCLUSION

DED affects millions of Americans,⁷² and the symptoms range from occasional mild discomfort to debilitating.⁷³ Science has come a long way in understanding the underlying etiology of this disease, creating novel interventions and adapting systemic therapeutics to topical formulations specifically targeting the underlying DED process. ■

John D. Sheppard, MD, MMSc

- professor of ophthalmology, microbiology & immunology, clinical director of the Thomas R. Lee Center for Ocular Pharmacology, and ophthalmology residency research director at the Eastern Virginia Medical School in Norfolk, Virginia
- president of Virginia Eye Consultants and the medical director of the Lions Eye Bank of Eastern Virginia
- (757) 622-2200; docshep@hotmail.com
- financial disclosure: AbbVie; Alcon; Allergan; Bausch + Lomb; Novartis; RPS; Shire; TearLab; Tear Science; and Topcon

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