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CME ACTIVITY

HEALING THE OCULAR SURFACE

Optimizing the standard of care in the treatment of dry eye disease and ocular allergy.

THE DULANEY FOUNDATION

Supported by an unrestricted educational grant from Allergan, Inc.

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STATEMENT OF NEED

In the past few years, new mechanisms for diagnosing dry eye and tracking its progression have been developed. Notably, a point-of-care test can provide clinicians with a measure of tear osmolarity; in clinical testing of this device, researchers validated that tear osmolarity levels closely correlated with widely used mechanisms for diagnosing and stratifying dry eye disease.[1,2] Likewise, both optical coherence tomography and topography devices are being investigated for their ability to objectively measure tear film breakup time, although further validation studies are needed before these are adopted into regular clinical practice.

Researchers' growing understanding of the pathogenesis of dry eye has led to a number of treatments, including artificial tears, nonpreserved artificial tears, punctal occlusion, topical corticosteroids,[3] and topical cyclosporine.[4,5] Systemic medications such as cholinergic agonists are also used in severe cases, such as those associated with Sjögren Syndrome.[4] Recent evidence has emerged that patients may benefit from dietary changes, the addition of nutritional supplementation, or both.[6] These forms of complementary treatment align with a growing reliance on prevention strategies, patient education, and an overall more holistic approach to treating dry eye disease.

The classic dry eye treatment strategy considered the severity of disease as preeminent in decision making. However, an appreciation of the progressive nature of dry eye disease, the awareness that the disease affects surgical planning and outcomes, and the neurotrophic nature of dry eye disease (thus undermining the ability of some patients to perceive their own symptoms) have caused clinicians to reevaluate this treatment schema. A new model for treating dry eye disease is becoming popular, wherein even patients with mild or moderate disease are treated aggressively, comprehensively, and holistically, with the end point of eventually scaling back patients' medication requirements for continued maintenance therapy.

The emerging trends in preferred practice patterns also suggest a shift in how medications are used in the clinic. Conventional wisdom has been to treat moderate dry eye conservatively with artificial tears. However, Rao's study shows that one-third of patients treated with artificial tears still had measurable progression of dry eye disease after 1 year,[7] which reinforces evidence showing the continued effectiveness of topical cyclosporine in treating moderate dry eye.

One of the challenges involved in recognizing and managing dry eye disease is that symptoms of the disease—including itching, discharge, and irritation—mimic ocular allergies,[8] and the two are often confused. Although allergies and other forms of conjunctivitis are not commonly considered serious illnesses, the conditions have been cited as being among the most frequent causes of patient self-referral, meaning they have a significant impact on patients' quality of life.[9] To effectively treat the ocular surface, ophthalmologists and optometrists will need to be able to differentiate between dry eye and an allergic condition, as well as recognize blepharitis or other causes of ocular surface inflammation. Besides itching, discharge, and irritation, symptoms of allergy include pain, photophobia, and blurred vision. According to *Preferred Practice Patterns* of the American Academy of Ophthalmology, practitioners should be able to recognize the following forms of allergic conjunctivitis: seasonal, vernal, atopic, and giant papillary.[10]

This educational activity will review treatment protocols indicated for ocular allergy. Mast cell stabilizers can be used for frequently recurrent or persistent conditions,[11] and topical corticosteroids are usually reserved for acute exacerbations of vernal/atopic conjunctivitis.[12] Topical cyclosporine 2% can also be used as an adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis.[13-15] A randomized controlled trial of 22 patients who were followed for 4 weeks determined that patients treated with cyclosporine 0.05% had fewer signs and symptoms than patients using artificial tears.[16] However, when using corticosteroids or cyclosporine for repeated short-term therapy, such as for treatment of vernal keratoconjunctivitis, physicians will need to be instructed on potential complications.

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TARGET AUDIENCE

This certified CME activity is designed for all ophthalmologists and general eye care professionals.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Know the role of patient history and tests in diagnosing dry eye disease and ocular allergy
- Distinguish between the signs and symptoms of dry eye disease and ocular allergy
- Know the impact of ocular surface conditions on cataract and refractive surgery
- Manage ocular surface inflammation
- Effectively treat dry eye disease and ocular allergy, including concomitant therapy
- Screen all patients carefully for dry eye disease, particularly candidates for ocular surgery

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses."

Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit.*™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation, *Cataract & Refractive Surgery Today*, and *Advanced Ocular Care.* The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring activity for a maximum of 1 *AMA PRA Category 1 Credit.*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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FACULTY CREDENTIALS

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FACULTY/STAFF DISCLOSURE DECLARATIONS

Neda Shamie, MD, has had a financial agreement or affiliation during the past year with the following commercial interest(s): *Advisory Board/Consultant/Speaker's Bureau:* Allergan, Inc., and Bausch & Lomb Incorporated.

Christopher E. Starr, MD, has had a financial agreement or affiliation during the past year with the following commercial interest(s): *Advisory Board/Consultant/Speaker's Bureau:* Alcon Laboratories, Inc.; Allergan, Inc.; Bausch & Lomb Incorporated; Nicox; and TearLab Corporation. *Grant/Research Support:* Rapid Pathogen Screening, Inc.

Elizabeth Yeu, MD, has had no financial agreements or affiliations during the past year.

Cheryl Cavanaugh, The Dulaney Foundation; Brianna Falcone, *Retina Today*; Michelle Dalton, writer; and David Friess, reviewer have no financial relationships with commercial interests.

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Healing the Ocular Surface

Optimizing the standard of care in the treatment of dry eye disease and ocular allergy.

SUPPORTED BY AN UNRESTRICTED EDUCATIONAL GRANT FROM ALLERGAN, INC.

DRY EYE DISEASE OVERVIEW

Dr. Starr: Let us begin with a basic overview of dry eye disease. How common is this condition?

Dr. Shamie: Dry eye is a very common condition, both as a presenting symptom as well as an incidental finding upon examination. When we look for the condition, we find that we come across signs, even when the patient may not be directly complaining of dry eyes. An example is the cataract patient population. William Trattler, MD, and colleagues presented a multicenter study in which cataract patients were asked to return to their surgeon for reassessment of their ocular surface. In fact, more than 60% of those patients had findings consistent with moderate dry eyes.[1]

Dr. Yeu: Dry eye disease, also known as dysfunctional tear syndrome, does not just affect postmenopausal women, although that may be its largest demographic.[2] It is a multifactorial disease with many causes that relate to environment and lifestyle (Figure 1).[3] One lifestyle influence, for example, is the increasing use of personal computers with electronic screens. Studies have shown that reading on a screen increases the rate of tear deficiency.[4] Factors such as these are contributing to the progressive epidemic.

Dr. Starr: True, baby boomers are entering the health care market in epidemic proportions.[5] We know that the risk of dry eye disease increases with age, but as Dr. Yeu alluded, it is also very important that we look for it in younger patients, especially those aged 30 to 40 who wear contact lenses and/or work in office environments where they may be surrounded by forced-air vents, low humidity, and are likely staring at computers all day long. Prolonged work conditions such as these certainly can exacerbate pre-existing dryness or even induce dry eye disease in some people.

Furthermore, the American diet has been changing over the years to a much more skewed ratio of essential fatty acids. Specifically, the ratio of omega-6 to omega-3 fatty acids was approximately 1:1 50 years ago, whereas today's standard diet is more often 50:1 of omega-6 to omega-3 fatty acids.[6] Such an imbalance is proinflammatory and can decrease the quality of the meibum, contributing to meibomian gland disease (MGD) and evaporative dry eye disease, not to mention the negative systemic and cardiovascular effects of this poor diet.[7]

Dr. Shamie: Yes, and these dietary factors help in part to explain why we see this disease more and more in younger patients, as you said. Although postmenopausal women have traditionally been the stereotypical dry eye patients, we are finding it in men and children more frequently.[8]

Dr. Starr: Right. If we look for ocular surface disorders, we will find them in almost every patient who walks in the door, even if they are asymptomatic. It is rare that I see a completely normal lid margin or tear film in a patient over the age of 25. But, we have to look for it and ask the appropriate historical questions.

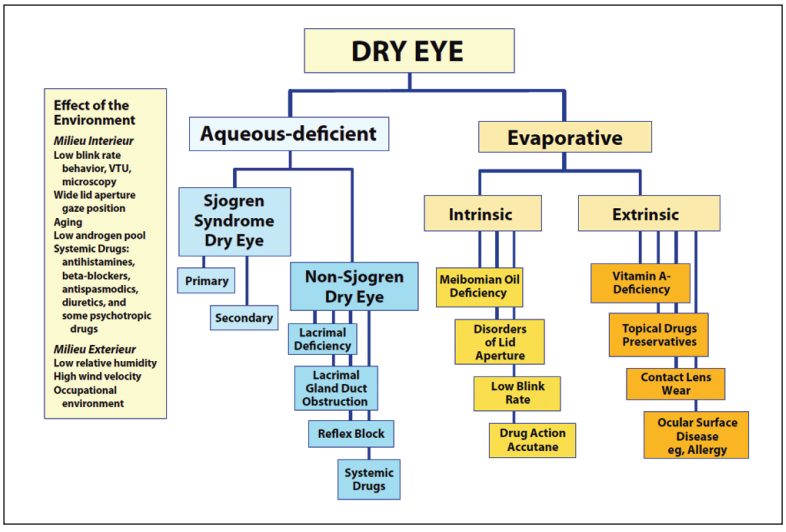

Figure 1. The major etiological causes of dry eye, divided into aqueous-deficient and evaporative categories. The left-hand box lists environmental conditions that may contribute to the presentation of dry eye disease in a person. (Reprinted from: 2007 Report of the International Dry Eye Workshop [DEWS]. *The Ocular Surface*. 2007;5(2):17 with permission from Elsevier.)

TABLE 1. CONTRIBUTORS TO DRY EYE DISEASE

- **Physiological issues:** age and related hormonal changes
- **Environment:** low humidity, wind, forced-air heating and cooling and other sources of air movement, pollution, prolonged staring at a computer screen
- **Ocular issues:** contact lens wear, corneal refractive surgery, poor blink rate, exposure keratopathy/lagophthalmos
- **Health issues:** lack of omega-3 fatty acids in the diet, alcohol consumption, systemic inflammation, systemic medications (eg, antihistamines), topical ocular medications (especially those containing benzalkonium chloride), autoimmune disease, thyroid disease

Dr. Shamie: I talk to my patients about the aging process of the tear film[9] and how we need to catch it and prevent it from progressing rapidly. So, I frame the discussion of ocular surface care to patients in terms of maintaining the youthfulness of their ocular surface by treating it and slowing down the progression of inflammatory dry eye or dysfunctional tear syndrome. Still, we cannot overlook the primary demographic of older women, in whom hormones are the driving component.

Dr. Starr: Absolutely. Another contributing factor we must consider, especially in the older population, is medications that can exacerbate ocular surface dryness, hormonal therapies, antihistamines, some antidepressants and antihypertensives among others (Table 1).[10] On a side note, I've wondered if many cases of advanced dry eye disease in older patients are simply the result of years of missed diagnoses or inadequate treatment rather than simply aging. Perhaps many dry eye sufferers are at International Task Force[11] level 1 or 2 of dry eye in their 30s and 40s, and after 1 or 2 decades of smoldering, low-level inflammation damaging the ocular surface, their severity level creeps up over time. A study that just completed enrollment may help us better understand the long-term natural history of this disease.

Dr. Shamie: I agree that dry eye syndrome exists on a spectrum. Many of our colleagues do not treat the disease in its early stages, but instead wait until the patient shows significant signs and symptoms before offering sufficiently aggressive treatment. I prefer to catch the condition early and begin treating it to prevent the natural progression of disease; I offer artificial tears for mild symptoms of tear dysfunction but do not hesitate at all prescribing cyclosporine A or steroids for symptomatic mild and moderate cases. Once the advanced sequelae of scarring and lacrimal insufficiency has ensued, even aggressive treatment may not offer relief. If we can catch dry eye syndrome early and stop it in its tracks, we can save patients a lifetime of problems.

Dr. Yeu: With all of the good research that has been done on mapping elevated levels of inflammatory cytokines, I think more physicians are recognizing that dry eye truly is an inflammatory disease (Figure 2).[12-15] If left untreated, studies demonstrate that the chronic inflammation damages corneal nerves.[16-18] We have all seen patients in their 80s who present with a huge epithelial defect but only complain about mild irritation. Again, we need to catch these individuals early in the disease process, when they have minimal signs but are more symptomatic.

Also, the public needs to know that if they are using

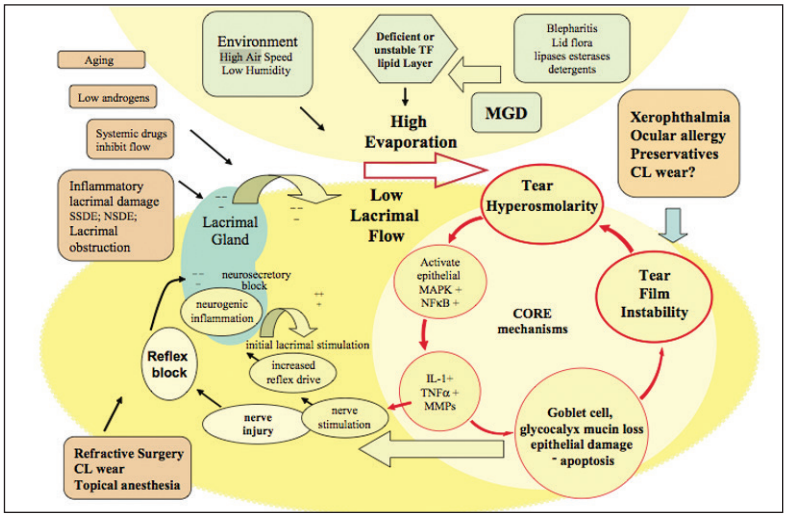

Figure 2. The core mechanisms of dry eye are driven by tear hyperosmolarity and tear film instability. Tear hyperosmolarity damages the surface epithelium by activating a cascade of inflammatory events at the ocular surface and a release of inflammatory mediators into the tears. Epithelial damage involves cell death by apoptosis, a loss of goblet cells, and disturbance of mucin expression that leads to tear film instability. This instability exacerbates ocular surface hyperosmolarity and completes the vicious circle. Tear film instability can be initiated, without the prior occurrence of tear hyperosmolarity, by several etiologies, including xerophthalmia, ocular allergy, topical preservative use, and contact lens wear. (Reprinted from: 2007 Report of the International Dry Eye Workshop [DEWS]. *The Ocular Surface*. 2007;5(2):25 with permission from Elsevier.)

> "In order to achieve optimal results with laser vision correction or premium lens implants after cataract surgery, surgeons need to assess and optimize the cornea."
> —Neda Shamie, MD

artificial tears more than once per day or three times per week, they are already into level two of the International Dry Eye Workshop's (DEWS) categorization.[19]

Dr. Shamie: As Dr. Yeu mentioned, neurotrophic epitheliopathy is one of the signs of end-stage dry eye, and unfortunately, those patients are past the point of treatment with artificial tears and punctal plugs. It is the same for individuals who develop meibomian gland stenosis or lacrimal gland atrophy. Again, catching these conditions early and preventing the neurotrophic pathology that usually accompanies the end stage of advanced disease[20,21] is critically important.

Dr. Starr: Often, the symptoms of dry eye disease are poorly correlated with clinical signs, presumably partly due to inflammatory effects on the corneal and conjunctival nerves: hypersensitive early and neurotrophic later.[16,21] This frequent disconnect between signs and symptoms has led to a general misconception of dry eye disease as being a nuisance for practitioners to diagnose and treat, and thus it is often overlooked or purposely avoided.

Dr. Shamie: I think the advent of premium-level cataract and refractive surgery has uncovered these issues, because surgeons are now motivated to look for corneal pathology, even if the patient is asymptomatic. For example, a patient may present to the clinic because he or she can no longer tolerate contact lenses and wants refractive surgery. That person may not realize his or her symptoms are related to tear dysfunction. However, in order to achieve optimal results with laser vision correction or premium lens implants after cataract surgery, surgeons need to assess and optimize the cornea.

Dr. Yeu: That is a very good point, because we have learned that one inherent problem with multifocal IOLs is decreased contrast sensitivity.[22] If we want to keep multifocal IOL recipients seeing as well as possible, they should really keep using artificial tears for the long term. But, patients tend to get lax with their drops after the first few years. If we can treat their tear dysfunction preoperatively so that they do not need artificial tears after surgery, we can maintain their good postoperative vision for decades.

MANAGEMENT OF POSTSURGICAL DRY EYE

Dr. Starr: Dry eye syndrome gained notoriety as microkeratome-based LASIK became more popular—with some patients complaining of postoperative pain, unsatisfactory vision, and in rare cases, chronically recalcitrant dry eye disease.[23] These cases are multifactorial but primarily related to the transient neurotrophic effect after cutting the corneal nerves during flap creation. Fortunately, with our modern thin femtosecond flaps and a resurgence in surface ablation techniques, the risk of postrefractive surgery dry eye has been significantly reduced, but not entirely eliminated. Conversely, in our modern era of premium cataract surgery with advanced-technology IOLs, we frequently perform limbal relaxing incisions (LRIs) to minimize corneal astigmatism. LRIs, however, especially when long and paired, can have a similar neurotrophic effect as LASIK and can result in postoperative discomfort and unsatisfactory vision, often erroneously attributed to the IOL.[24]

Dr. Shamie: Many of us have seen patients who, 5 years after bilateral cataract surgery with LRIs in one eye, have much more ocular staining in the LRI-treated eye than the other.

Dr. Starr: Exactly, very interesting. Dr. Shamie, what is your treatment regimen in cataract patients who receive premium IOLs? If the individual displays mild MGD and some aqueous deficiency preoperatively, perhaps with some corneal staining, what is your protocol for preparing these patients for surgery and then in the postoperative period?

Dr. Shamie: I think the key to achieving the best postoperative vision is to optimize the ocular surface. If I find that a patient's corneal topography is irregular, with areas of dry spots or even significant irregularity, I will delay surgery. I discuss with the patient my findings, and I explain that if our goal is to get them out of their glasses and give them a premium quality of vision, then we first need to optimize the tear film in order to obtain accurate preoperative measurements (Table 2). We need sequential measurements on both keratometry and topography with the values recorded as close to each other as possible between the sequential visits in order to feel confident about proceeding with surgery. If I find tear-film abnormalities on that initial examination, I treat the eye aggressively. For ocular surface disease and meibomian gland dysfunction that show staining on the cornea, I start with a mild topical steroid. I like loteprednol etabonate ophthalmic gel 0.5% applied at

TABLE 2. PRE- AND POSTOPERATIVE DRY EYE PROTOCOL OF DRs. SHAMIE, STARR, AND YEU

Preoperatively	Postoperatively
1. Delay surgery and preoperative biometry until better measurements are obtained. 2. For corneal staining: begin with topical cyclosporine emulsion 0.05% and preservative-free artifical tears. If there is significant inflammation, follow with a short course of mild topical steroid for 2 to 4 weeks as necessary. 3. For signs of aqueous deficiency or a low tear lake: punctal plugs (avoid using these if significant untreated lid margin inflammation or meibomitis are noted. Surface inflammation should be controlled prior or concurrent to using plugs). 4. For rapid tear breakup time and posterior lid margin disease: oral tetracyclines and/or topical azithromycin in conjunction with lid hygiene, massage, warm compresses, and supplementation with omega-3 essential fatty acids. 5. Delay surgery until anterior blepharitis is addressed with at least 4 weeks of lid hygiene. 6. Proceed with surgery once good keratoscope mires are consistent, sequential keratometric and topographic measurements with closely related values are achieved.	1. Have patients continue preoperative regimen. 2. Taper the topical steroid after 2 to 4 weeks. 3. Preservative-free artificial tears as needed.

bedtime for 2 to 4 weeks, depending on the severity of the condition. Another baseline treatment I often use is cyclosporine ophthalmic emulsion 0.05%. This would be used together with preservative-free artificial tears to try to optimize the topography and keratometric readings. If there were significant meibomian gland disease and very rapid tear breakup time, I may consider adding either oral tetracyclines or topical azithromycin.

Postoperatively, I have patients continue these same treatments for the long term to prevent their dry eye disease from progressing, although I will have them stop the steroids after 2 or 4 weeks, depending on the severity of their underlying problem.

Dr. Yeu: Anything that we add to the corneal surface, including fluorescein drops to check IOP, affects corneal readings. Therefore, my patients receive no drops until after they undergo biometry and corneal mapping. Then, I examine them before and after they receive IOP drops.

I find that scrutinizing the tear film centrally and how well it spreads across the corneal surface is very telling. Bacteria and the toxins they produce fester in the collarettes and cause scarring. So, if I see telangiectasias and subclinical-to-obvious inflammation present, I will also withhold surgery for 4 to 6 weeks and prescribe the same treatment that Dr. Shamie mentioned.

Dr. Starr: Yes, a very good point. When do you use punctal plugs in your regimen, before or after anti-inflammatory medications?

Dr. Shamie: That is the million-dollar question. I have tried both ways successfully. The one scenario in which I avoid the use of punctal occlusion before treating with anti-inflammatories is when I can confirm that the ocular surface disease is driven by lid-margin disease. That is when I see significant signs of ocular rosacea, telangiectasia at the lid margin, and maybe saponification of the tear film. That condition is associated with a lot of inflammation[25] and inflammatory mediators in the tear film, which I do not want to concentrate onto the ocular surface by blocking its drainage with a punctal plug.

Dr. Yeu: I tend to delay punctal occlusion and try to treat the inflammation first. I have found that when I've delayed punctal occlusion in appropriate candidates, half of them respond well enough to the anti-inflammatories and other treatments that they do not need occlusion. However, I consider punctal occlusion early in eyes that have a low, slim tear lake. If there is a suboptimal tear meniscus present, then I will insert punctal plugs concomitantly at the beginning of treatment.

Dr. Starr: I do the same. If we do not treat the inflammation first, punctal occlusion may cause the inflammation on the ocular surface to build up and fester and exacerbate symptoms.

DIAGNOSTIC TOOLS FOR DRY EYE SYNDROME

Dr. Starr: Earlier, we suggested that it can sometimes be challenging to not only make a correct diagnosis of

> "We learned from the DEWS report that our classic tests such as Schirmer, corneal staining, and tear breakup time are fairly insensitive for accurately diagnosing dry eye disease."
> —Christopher Starr, MD

dry eye disease, but also to distinguish between evaporative or aqueous-deficient dry eye. Have either of you embraced any of the newer point-of-care diagnostic tools for identifying dry eye disease or meibomian gland dysfunction?

Dr. Shamie: I think it is very beneficial to have point-of-service diagnostic tools available to not only arm us with diagnostic information, but also to assist with disease management and maintenance. Additionally, patients want objective data. If all dry eye etiologies were the same, and if it all affected the precorneal tear film, then truly all we would need is a topography reading that had some kind of indices of measurement for examining asymmetry. Instead, there is so much variation in dysfunctional tear syndrome that you can have a great precorneal tear film, but inflammation everywhere else. So, we need devices that can measure levels of lactoferrin, matrix metalloproteinase, and osmolarity.

Dr. Starr: Yes, I agree.

Dr. Yeu: I think that at the most basic level, we all need to use topography to screen for tear film deficiency. I am always surprised by how many physicians do not have a topographer in their practices, especially if they are implanting premium IOLs. I rely on the topographer to assess the tear film and the ocular surface; I think it is an important tool. My practice does not yet have the tear osmolarity testing or an ocular surface interferometer (LipiView; TearScience), but I have embraced the value of these devices, and we have plans to add them to our practice. I agree that the most important application of these tools may be to increase patients' compliance with their ocular surface disease treatment. The ability to give patients a report card on their tear film and convince them that there is a progressive condition that requires sustained treatment will be very effective.

Dr. Starr: I agree. Endocrinologists have successfully educated diabetic patients to the point that they almost always know their most recent hemoglobin A1c level. Likewise, glaucoma patients often know their most recent IOP readings. It would be nice to have similar patient familiarity and investment in the dry eye realm. We learned from the DEWS report that our classic tests such as Schirmer, corneal staining, and tear breakup time are fairly insensitive for accurately diagnosing dry eye disease. Hyperosmolarity, on the other hand, has been shown to have a much higher sensitivity.[26] I have embraced the TearLab system in my practice, and I find that it saves me time, facilitates a rapid and accurate diagnosis, and most importantly, by providing a simple number, engages patients and improves compliance with our interventions. Notably, the American Academy of Ophthalmology has included tear osmolarity in the most recent *Preferred Practice Patterns* publication, stating, "Tear osmolarity has been shown to be a more sensitive method of diagnosing and grading the severity of dry eye compared to corneal and conjunctival staining, tear breakup time, Schirmer test, and meibomian gland grading,"[3] which is a fairly strong endorsement of this technology.

> "[Patients] need to know that the medication will control their chronic disease, and that stopping its use means that their symptoms of irritation and decreased vision will return."
> —Elizabeth Yeu, MD

Dr. Yeu: I agree; having objective numbers from point-of-care tests helps to turn a "condition" into a "disease" in patients' minds, and we want people to understand that ocular dryness is a disease. Like diabetes, assigning a number to ocular dryness tells an individual if his or her disease is in tight control or not. Another benefit of these point-of-care tests I foresee is that they will elevate the awareness of dry eye disease to another level for primary care physicians, who can explain it to patients in terms of a degree of severity and then send that kind of information back to us.

TERMS FOR DISCUSSING DRY EYE DISEASE

Dr. Starr: That is a good point. The article published by the Delphi panel in 2006[10] suggested that the term *dysfunctional tear syndrome* is much better for describing dry eye disease, although it has not caught on as readily. How do you two refer to the condition?

Dr. Shamie: I write *dysfunctional tear syndrome* in my patient notes and in my letters that I send to referring physicians. I also use the term with patients, although they do not retain it the same way as they do the term *dry eyes.* I continue to use *dysfunctional tear syndrome,*

CYCLOSPORINE 0.05%, USAGE AND EFFICACY

Cyclosporine 0.05% is a fungus-derived peptide that prevents the activation and nuclear translocation of cytoplasmic transcription factors that are required for T-cell activation and inflammatory cytokine production.[1] This topical medication also inhibits mitochondrial pathways of apoptosis. In one study, topical cyclosporine A 0.05% (CsA) appeared to improve the signs and symptoms of dry eye and inhibit apoptosis and MMP-9 expression in conjunctival epithelial cells in thyroid orbitopathy-related dry eye patients after 2 months of treatment.[2] In another study, where 183 patients were randomized to receive CsA 1%, CsA 0.05%, or a vehicle, active treatment reduced complaints and improved major ocular signs in patients with moderate-to-severe dry eye disease in a dose-dependent fashion.[3] A third study assessed the prognosis of dry eye in patients treated with cyclosporine 0.05% or artificial tears using the International Task Force (ITF) guidelines.[4] It was determined that treatment with cyclosporine 0.05% could possibly slow or even prevent disease progression in patients with dry eye at severity levels 2 or 3. A study of 28 eyes of 14 patients also recently found that cyclosporine 0.05% therapy reduced dry eye signs and improved visual quality after multifocal IOL implantation.[5]

Topical cyclosporine has been found to produce beneficial effects in all categories of dry eye disease. Symptomatic improvement is greatest in the mild group, and the best results in improvement of disease signs are found in patients with severe dry eye disease.[6] In the phase 3 studies of cyclosporine 0.05%, patients demonstrated marked improvement in signs and symptoms after 3 months of therapy, but best results were observed after 6 months of therapy,[7] which highlights the importance of patients' compliance. Additionally, subjects in these studies noted burning and stinging upon instillation of cyclosporine, most likely due to their denervated corneas secondary to dry eye disease rather than being a true safety signal. Thus, it will be important for clinicians to be aware of this potentiality in order to properly counsel patients about the importance of compliance and the possibility of discomfort.

1. Preferred Practice Pattern, Dry Eye Syndrome, San Francisco, CA: American Academy of Ophthalmology; September, 2008.
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however, because it lets me segue into the discussion of evaporative dry eyes versus nonevaporative dry eyes (Figure 2), as well as the different layers in the anatomy of the tear film. The term *dry eyes* does not encompass the spectrum of symptoms and presentations that compose dysfunctional tear syndrome.

Dr. Yeu: When I am educating patients, I will begin by stating, "You do have a form of dry eye syndrome," but then I ask them to let me explain what that term means as it relates to an improper balance of the aqueous-mucous-meibum gel that comprises their tear film. When I summarize the explanation, I conclude by saying, "It really means that your tear film layer is dysfunctional."

STRATEGIES TO PROMOTE PATIENTS' MEDICATION COMPLIANCE

Dr. Starr: When you decide that you want to institute a prescription medication into a patient's dry eye treatment, how do you council him or her on proper usage and the importance of compliance?

Dr. Shamie: Cyclosporine emulsion remains the only prescription medication for tear film deficiency, and I consider it a critical component of my regimen for dry eye treatment. When prescribing cyclosporine, it is important to set patients' expectations for how long they will take it, because its effect is not immediate, and prolonged use is needed.

Dr. Yeu: You will only be able to convince your patients of the efficacy of long-term medications if you believe in them wholeheartedly. There are a couple of things we know about cyclosporine emulsion. First, it is true that the more severe the tear deficiency is, the more the medication will burn upon instillation.[27] This is why many physicians will prescribe a topical steroid for a short course at the onset of cyclosporine usage in order to reduce any stinging associated with the drop and to help bridge the therapeutic time gap that exists for cyclosporine to have its full effect.[28,29] Second, cyclosporine emulsion can have a higher copay than some of the systemic medicines patients are used to. These two issues must be discussed with patients up front. Equally important, however, is to describe the benefits of cyclosporine emulsion so that patients understand its value. They need to know that the medication will control their chronic disease, and that stopping its use means

that their symptoms of irritation and decreased vision will return.

Also, like Dr. Shamie said, there are tips we can offer patients for getting more out of the cyclosporine treatment. They should refrigerate it, both to preserve it and also to enhance the cooling effect, and they can utilize an artificial tear or "smart" steroid at the start of using it in order to have the anti-inflammatory effect immediately.

One other patient management tip I have comes from my experience with electronic medical records (EMRs). One benefit of EMRs is that you can create your own templates for brochures. Thus, I have found it effective to make my own brochure of information about dry eye disease and its treatment options for patients to read after consulting with me. I have seen very high compliance rates with medications using this tool.

Dr. Starr: Yes, improving medication compliance through education is key in attaining treatment success. If you neglect to tell patients that a medication is going to burn, they will assume it is damaging their eyes and will stop using it. If you do not tell them that it may take some time to feel the effects of a medication (I usually tell patients not to expect notable effects for 3 months), then they assume that it is not working and stop using it. Another way I encourage compliance is to prescribe a 90-day supply of topical cyclosporine up front. Not all insurance plans allow it, but if patients can get it, I think the 90-day supply fosters compliance and gets them through that critical first 3 months.

Dr. Shamie: In order for physicians to believe in the efficacy of cyclosporine emulsion, they should familiarize themselves with its data. Topical cyclosporine has been used to treat dry eye for more than 10 years, and there are plenty of data to support its benefits for the right patients.[27] If physicians feel they have not had good success with cyclosporine in the past, perhaps they should reassess it in light of the strategies we discussed. In particular, patients who present when they are using an artificial tear more than once per day are great candidates for more aggressive treatment and should be considered for cyclosporine treatment. I have seen this medication give patients great benefit when it is used correctly.

The second trick to success with cyclosporine emulsion is to use it in the appropriate patients. The Ocular Surface Disease Index questionnaire[30] is really helpful for determining the severity of a patient's condition. And then, as we discussed earlier, tools such as topography and tear osmolarity testing are very useful for both diagnosis and for demonstrating to patients that they have a chronic disease. Finally, I think we practitioners need to use language with patients that compares dry eye syndrome to other chronic diseases like diabetes, so that they understand its severe chronicity.

> "There is now evidence that patients who continue on cyclosporine emulsion beyond 6 months have further improvement in their corneal staining and a greater increase in their tear production."
> *—Neda Shamie, MD*

Dr. Starr: What is your approach to treatment?

Dr. Shamie: I do not delay treatment. In any patient who is even mildly symptomatic, with staining of the cornea, and if he or she has any other abnormality related to it, I start treatment with a mild steroid and topical cyclosporine. My approach is to optimize the ocular surface as quickly as possible so as not to waste the patient's time. If the eye responds very well, I can always taper the treatment. Again, I liken the treatment of dry eye to managing diabetes: treat aggressively, address dietary changes and weight management at the same time, and try to get the patient off the medication by treating the underlying problem at its core. I begin dry eye treatment with a mild steroid such as loteprednol etabonate ophthalmic gel 0.5%, because it is very soothing. I follow that with topical cyclosporine emulsion twice per day, and I reassess the progress of my cyclosporine patients at 6 weeks with topography and other diagnostic tools to show them that it is starting to work. I admonish them not to discontinue using it for at least 3 months. If they are still experiencing tear deficiency symptoms at 3 months, then I start thinking about punctal plugs and other modalities. Most patients who use cyclosporine consistently, however, are doing very well on it by 3 months.

Dr. Starr: Do you still allow patients to use artificial tears while they are on topical cyclosporine?

Dr. Shamie: Absolutely.

Dr. Starr: I do the same, but I like to stress to patients that there is a big difference between artificial tears and cyclosporine, even though they may look similar. Cyclosporine emulsion must be used twice per day—no more, no less—and artificial tears can be used as adjunctive treatment in between those drops. I started to be more vigilant about reminding my patients about these differences after having a few tell me, "Dr. Starr, I'm doing great, my eyes feel better and I'm only using Restasis a couple of times a week now." It is important for patients to understand that they can taper the artificial tears, but not the cyclosporine. In actuality, a reduction in artificial

TABLE 3. PROTOCOL FOR OCULAR ALLERGY

Prophylaxis: bring patients in 1 month prior to start of allergy season, prescribe a mast cell stabilizer with antihistamine drop once daily

Symptomatic:

1. Assess the severity of the patient's symptoms
2. Instruct patients to avoid all allergens as much as possible
3. Moderate-to-severe acute allergies: a short tapering course of topical steroids can be added to anti-inflammatory medication
4. Cyclosporine emulsion for concurrent inflammatory dry eye syndrome
5. Preservative-free artificial tears as needed

tear use is a nice metric for gauging treatment success with Restasis.

Dr. Shamie: There is now evidence that patients who continue on cyclosporine emulsion beyond 6 months have further improvement in their corneal staining and a greater increase in their tear production.[31] Therefore, patients should not expect to be "cured" after 6 months of using the drops, but rather at that point, they should expect further discussion and monitoring with their doctor to evaluate the condition of their eyes. If they first presented when they were farther along in that spectrum of disease, then they would probably require far longer treatment, perhaps even indefinite for some patients. However, if the symptoms were milder and caught early enough, then that patient may be able to have a monitored trial off of cyclosporine after 6 months.

Dr. Yeu: I would also add, to both patients and their physicians—anyone who has some trepidation about starting cyclosporine emulsion earlier in the disease treatment paradigm—that the standard alternative, artificial tears, are not cheap. And the cyclosporine emulsion comes in a vehicle of mineral oil, which is the key ingredient in some of the most effective artificial tear products. So it is almost like a two-in-one product.

I also think it is helpful to inform patients that if they start using the cyclosporine emulsion twice per day as prescribed, it will prevent their symptoms from progressing to a more severe form of dry eye disease down the line.

Dr. Starr: Yes, I agree that that conversation is important. It is a vicious cycle of inflammation, and we should be stressing to our patients the importance of halting that cycle.

Dr. Yeu: Yes, we have to get out of the mindset that artificial tears are only palliative, because they are still an important component to a dry eye regimen. Although they ameliorate the mechanical stressors on the cornea, they also dilute the tear film, which is why, if you look at the osmolarity of a cornea in the area without tear film, it is in the thousands. Creating a healthier tear film, that is less concentrated, is key to creating a better ocular surface. This may include a combination of increasing tear production through cyclosporine, retaining tears with punctal occlusion, and/or adding topical artificial lubricants.

OCULAR ALLERGY

Dr. Starr: Another ocular condition that is closely related to dry eye and falls under the umbrella of ocular surface disorders is ocular allergy. The prevalence of ocular allergy has been increasing significantly over the past few decades.[32] Although there are several types of ocular allergies, the most common by far are seasonal and perennial allergies. The difficulty for the clinician, however, is that the signs and symptoms of ocular allergy often resemble those of tear deficiency syndrome.

Dr. Yeu: Unless you see a very obvious red eye with a significant papillary reaction, the two conditions present very similarly. Younger allergy sufferers, especially, can be very symptomatic. They have epiphora, they experience a burning sensation, and if they live in an area that has heavy pollen, they have other symptoms, too. So, it can be very difficult to distinguish between dry eye and ocular allergy, and often, patients likely have a combination of the two.

Dr. Starr: Exactly. Often, both conditions are multifactorial and often coexist. One recent study of allergy patients showed an overlap with dry eye.[33,34] Many dry eye patients have itching, and many allergy patients have foreign body sensation and dryness. So the traditional thinking for ocular care specialists—that if the eyes itch, it's allergy—simply is not as reliable as previously thought. Incidentally, I find the TearLab osmolarity system very useful when a patient complains of mild itching, redness, and dryness but has normal tear osmolarity. That presentation, in my book, is allergic conjunctivitis until proven otherwise (especially if it's April in the Northeast!).

Dr. Yeu: Also, we cannot undermine the effect of systemic antihistamines and how they decrease the tear film and cause dry eye.

TREATMENT STRATEGIES FOR OCULAR ALLERGY

Dr. Starr: What are your strategies for treating these patients?

Dr. Yeu: First, I assess the severity of the patient's symptoms. For certain patients, we really need to halt the disease process, and only a topical steroid can do the job. I am happily surprised to see, however, that the newer-generation antihistamines, particularly the once-daily products, seem gentler on the eye—increasingly, we are able to manage more of the moderate-to-moderately-severe diseases with a shorter course of steroids, weaker steroids, or none at all, in fact.

Dr. Starr: We know that seasonal allergy symptoms peak in the spring and continue through the summer and into the fall. Many of us will see the same patients year after year around these times, with the same complaints: red, itchy, watery eyes, at which point the ocular surface is flooded with inflammatory mediators. Our goal really should be to prevent this from happening rather than treating it when symptomatic (Table 3). Therefore, I've been asking these patients to come in yearly 1 month before their allergies typically start. Alternatively, I'll give them a standing prescription of a combination mast cell stabilizer/antihistamine drop to take preemptively before the symptoms start. This prophylactic strategy may eliminate or reduce the need for adjunctive steroids when these individuals' eyes become highly inflamed and symptomatic.

What are you each doing with your patients as the calendar moves toward allergy season?

Dr. Yeu: I am taking a similar approach. Additionally, there are now apps on smartphones that can actually measure the local pollen count. So, many patients know when the pollen count is rising. It is up to us, however, to encourage them to come into the clinic for advance treatment, because allergy medications are dose-dependent.

Furthermore, I think there is a misconception among practitioners that only the general antihistamines have a drying effect. In fact, many of the systemic medications—loratadine, fexofenadine, cetirizine—induce aqueous deficiency.[16] This drying effect, combined with the allergic reaction, creates a hyperosmolar tear film. This combination causes tear breakup and a subsequent decrease in Schirmer's testing. It may be helpful to prescribe these patients an anti-inflammatory in addition to an antihistamine, to keep their eyes calmer while the antihistamine takes effect.

Dr. Starr: That is a very good point. An off-label yet effective role for cyclosporine is to use it as a steroid-sparing agent in patients with ocular allergy. Of course, if the patient has exacerbated or concurrent inflammatory dry eye disease, then cyclosporine would be on-label. Either way, it can offer secondary benefits with the allergic response.

"An off-label yet effective role for cyclosporine is to use it as a steroid-sparing agent in patients with ocular allergy. ... If the patient has exacerbated or concurrent inflammatory dry eye disease, then cyclosporine would be on-label."
—Christopher Starr, MD

What kinds of tips do you give your patients about reducing the allergen load on the ocular surface? I usually suggest that they use wraparound sunglasses and brimmed caps, that they wash their clothes frequently, and that they keep the windows closed during peak pollen times. I still think there is a role for artificial tears in these patients. In addition to easing some of the symptoms of allergy, especially when chilled, artificial tears also act as an irrigator to flush some of the allergens out of the eye.

Dr. Yeu: We know that the same receptors that bind temperature also bind pain, and itching can be a very, very mild indicator of pain. I sometimes suffer from allergic conjunctivitis myself, and there can be great relief from a cold artificial tear. Tears are also convenient for active people who just need an adjunctive therapy to the maintenance control of an antihistamine.

Dr. Starr: Absolutely. I, too, suffer from seasonal allergies, and I use refrigerated artificial tears myself and recommend it to my patients. I also use a combination antihistamine/mast cell stabilizer, many of which are conveniently dosed once per day. I put one drop in each eye upon waking, and perhaps once more in the afternoon during the height of the season if I begin to get symptomatic again. Do you tell patients that it is OK to take an extra drop if they become symptomatic, or because it's once-daily dosing, should these medications only be taken once per day?

Dr. Yeu: In my experience, the various once-daily dosing medicines act differently. Some of them allow a recurrence of symptoms sooner in the day than others. If patients have "breakthrough" symptoms, I generally tell them to use an artificial tear, but if they instill another drop of q.d. medication, I think it's OK.

Dr. Starr: I agree.

Dr. Starr: How often do you find yourself referring a patient with allergic conjunctivitis to an allergist?

Dr. Yeu: Like dry eye disease, allergic conjunctivitis, which is frequently accompanied by allergic rhinitis, requires systemic control. Nasal antihistamine sprays can be helpful with ocular symptomatology. I tend to refer patients who are younger, are atopic in nature, have asthma, or have the more severe, chronic forms of allergy that have the potential to threaten their vision. I always make these referrals as a recommendation, however.

Dr. Starr: I do exactly the same thing.

CONCLUSION

Dr. Starr: Well this has been an insightful and fascinating conversation about an equally fascinating topic. I want to thank each of you for participating and sharing your expert wisdom on ocular surface disorders; I have certainly learned a lot from this discussion. ■

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CME QUESTIONS

1. Name two primary reasons why dry eye disease is presenting in younger patients with more frequency.
a. changing hormones and stress
b. increased reading on electronic screens and a dietary imbalance in omega-3 essential fatty acids
c. increased air pollution and use of medications
d. none of the above

2. What has been a driving factor in motivating eye care specialists to look for corneal pathology?
a. premium cataract and refractive surgical procedures
b. increased patient complaints
c. improved treatments
d. none of the above

3. What does Dr. Yeu recommend multifocal IOL recipients use to optimize their postoperative vision?
a. punctal plugs
b. topical steroids
c. artificial tears used long term
d. warm compresses

4. LRIs may contribute to dry eye disease by causing a neurotrophic effect when the corneal nerves are cut.
a. true
b. false

5. For how long should the surgeon delay cataract or refractive surgery for patients who present with dry eye disease?
a. 4 to 6 weeks
b. 3 to 5 weeks
c. 6 to 8 weeks
d. until the eyes show consistent, sequential measurements on keratometry and topography

6. When should the use of punctal plugs be avoided?
a. in aqueous-deficient dry eye
b. in evaporative dry eye
c. when the cause of the ocular surface dryness is confirmed to be lid-margin disease
d. when there are no contraindications for punctal plugs

7. How might point-of-care testing for dry eye disease increase patients' compliance with treatment regimens?
a. by providing a definitive diagnosis
b. by being a tool for disease management and maintenance
c. by assisting in patient education about dry eye disease
d. all of the above

8. What medication will halt the disease process of ocular allergy?
a. cyclosporine emulsion
b. antihistamines
c. topical steroids
d. artificial tears

9. What is Dr. Starr's prescription to prevent seasonal ocular allergies from taking hold?
a. a combination of mast cell stabilizer and antihistamine drops
b. antihistamine drops with a topical steroid
c. a systemic antihistamine with an anti-inflammatory medication
d. all of the above

10. In the presence of concurrent inflammatory dry eye, cyclosporine 0.05% ophthalmic emulsion is used on-label as a steroid-sparing agent in ocular allergy patients.
a. true
b. false

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Distinguish between the signs and symptoms of dry eye disease and ocular allergy	_____	_____	_____
Know the impact of ocular surface conditions on cataract and refractive surgery	_____	_____	_____
Manage inflammation	_____	_____	_____
Effectively treat dry eye disease and ocular allergy, including concomitant therapy	_____	_____	_____
Screen all patients carefully for dry eye disease, particularly candidates for ocular surgery	_____	_____	_____

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