

## CME MONOGRAPH

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# IMPROVING RECOGNITION AND MANAGEMENT OF **DRY EYE DISEASE** IN THE 21ST CENTURY

## THE BURDEN OF DRY EYE DISEASE

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This continuing medical education activity is jointly provided by Wills Eye Hospital and MedEdicus LLC.



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### Purpose and Target Audience

Increasing knowledge about dry eye disease is fueling advances in diagnostic techniques and therapeutic modalities that may help to overcome existing problems with underrecognition and undertreatment of this common disorder. The purpose of this activity is to update ophthalmologists on developments in the understanding of dry eye immunopathology, evaluation, and management to enable optimal patient care based on improved diagnosis and treatment tailored to the individual's disease characteristics.

This activity is intended to educate ophthalmologists.

### Designation Statement

Wills Eye Hospital designates this enduring material for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wills Eye Hospital and MedEdicus LLC. Wills Eye Hospital is accredited by the ACCME to provide continuing medical education for physicians.

### Instructions & Registration

This course takes approximately 2.0 hours. Please read the monograph, consulting any additional references if needed. Once the materials have been reviewed, complete the post test and evaluation found at the end of monograph and fax to 215-825-4732 or go to <http://tinyurl.com/dryeyedisease> to take a post test and course evaluation, after which you will be able to generate your CME certificate.

### Learning Objectives

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

- Evaluate, diagnose, and rate the severity of dry eye disease
- Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches
- Select an appropriate treatment regimen for dry eye disease based on individual patient characteristics

### Hardware & Software Requirements—Digital Edition

High-speed Internet connection  
(Broadband, Cable, or DSL)  
Windows 2000 or higher  
256 MBs or more of RAM  
Internet Explorer 6.0 or higher  
Windows Media Player 10.0 or higher  
Adobe Acrobat 7.0 or higher  
Course content compatible with Mac OS

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2. Describe what they or their spouse/partner received (eg, salary, honorarium).

3. Describe their role.

4. No relevant financial relationships.

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**CME Reviewer: Ralph C. Eagle Jr, MD**, has no relevant financial relationships with any commercial interests.

### Faculty:

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**Dr Edward J. Holland** is a consultant for Alcon; Bausch & Lomb Incorporated; Kala Pharmaceuticals; Mati Therapeutics, Inc; PRN, Inc; Rapid Pathogen Screening, Inc; Senju Pharmaceutical Co, Ltd; Shire; TearLab Corporation; and TearScience; receives fees from Alcon; Bausch & Lomb Incorporated; Senju Pharmaceutical Co, Ltd; and TearScience; a contracted researcher for Alcon; Mati Therapeutics, Inc; PRN, Inc; and Senju Pharmaceutical Co, Ltd; and receives other funding (travel) from Alcon; and Bausch & Lomb Incorporated.

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# IMPROVING RECOGNITION AND MANAGEMENT OF DRY EYE DISEASE IN THE 21ST CENTURY

## THE BURDEN OF DRY EYE DISEASE

Dry eye disease (DED) is a common and important problem. According to estimates of various studies and depending on the criteria used to define the disease and the population, the prevalence of DED may be as high as 33%.<sup>1</sup> Importantly, there is good evidence showing that DED can have a considerable negative effect, adversely affecting visual, social, and physical functioning, along with workplace productivity and quality of life.<sup>1-3</sup>

The market of therapies for dry eye has been exploding. Sales of products for the treatment of DED approached \$3.2 billion in 2015 and are expected to reach \$4.5 billion by 2020, driven in part by advances in diagnosis and treatment that stem from improved understanding of DED types and pathophysiology.<sup>4</sup>

This CME monograph provides an update on DED immunopathology, evaluation, and management. The information on these topics is presented through short narratives, a roundtable discussion, and case-based illustrations and focuses on how basic science and clinical developments may be changing and improving patient care. We hope readers will find the insights of the expert faculty participants useful in their clinical practice.

## DRY EYE DISEASE DIAGNOSIS

ESEN AKPEK, MD

The main goals of evaluating patients with ocular surface disease (OSD) symptoms are to diagnose DED and differentiate it from other OSDs; determine DED severity; and uncover any systemic inflammatory diseases underlying DED. Identification of DED can be challenging for various reasons. First, no single test can be used to establish the diagnosis. Second, multiple tests and expert interpretation are infrequently performed because of time constraints, lack of insurance coverage for some tests, and the clinician's underappreciation of DED prevalence and burden. Furthermore, other common OSDs share signs and symptoms with DED, and DED itself can have multiple underlying causes. Therefore, the initial patient assessment involves differential diagnosis and assessment to ascertain all causative and contributing factors. The evaluation should recognize that other OSDs may coexist with and exacerbate DED. In addition, the evaluation should include investigation of extraocular findings, considering that DED can be associated with a variety of dermatologic, rheumatologic, endocrinologic, and other inflammatory systemic diseases.

Bothersome ocular discomfort symptoms are generally what brings patients with DED to seek care, and therefore symptom assessment should be the first step in the diagnostic evaluation. Patients with DED also commonly report difficulty with visually challenging tasks, including computer use, reading, and driving.<sup>3</sup> Although a variety of validated questionnaires and other surveys designed to assess ocular discomfort-related issues, visual difficulty, and effect on quality of life as an initial screen are available, clinicians can simply ask patients whether or not their eyes feel dry and/or uncomfortable, and if so, what effect it has on their activities.

Conventional clinical tests used for diagnosing DED include the Schirmer test with or without anesthesia, tear film break-up time (TBUT) using fluorescein, conjunctival lissamine green staining, and corneal fluorescein staining. These assessments, however, are most useful for identifying patients with later-stage DED because their results generally become abnormal only after significant damage to the ocular surface.<sup>5</sup>

More recently, a number of instrument-based and biomarker methods have become available as in-office adjunctive tools for DED diagnosis (**Table 1**), some of which directly measure features and abnormalities of the tear film rather than the changes occurring on the ocular surface secondary to these abnormalities. Some of these newer modalities may help identify DED at an earlier stage.<sup>5</sup>

**Table 1. Diagnostic Tests for Dry Eye Disease**

Tear film osmolarity
Tear film matrix metalloproteinase-9 assay
Lipid layer interferometry
Meibography
Orbital B-scan sonography assessment of extraocular muscles and lacrimal glands
Corneal topography assessment of tear film regularity/irregularity
Tear meniscus height (optical coherence tomography)

Tear film osmolarity is often increased in patients with DED because of either decreased aqueous tear production or increased evaporation secondary to a poor lipid layer.<sup>6</sup> I routinely test tear film osmolarity using the commercially available platform when evaluating patients for DED, and I repeat it annually or if there is a significant change in ocular surface staining.

An osmolarity reading > 308 mOsm/L or a > 10-mOsm/L difference between eyes is generally considered diagnostic for DED.<sup>7,8</sup> Values below these thresholds, however, do not rule out DED. I consider anyone with an abnormal tear film osmolarity value to have DED that requires more than artificial tears for management.

Matrix metalloproteinase-9 (MMP-9) degrades collagen and proteins that maintain the epithelial barrier function, and its level is increased in the tear film of patients with DED.<sup>9</sup> An elevated MMP-9 level in the tear film as a sign of significant DED can be assessed using a commercial kit. The test is positive when the MMP-9 concentration in the tear sample is  $\geq 40$  ng/mL, which is indicated by the appearance of a red line in the result zone.<sup>10</sup> I interpret a positive result in the MMP-9 assay as an indication for starting a topical anti-inflammatory medication.

Lipid layer interferometry evaluates the thickness of the tear film lipid layer, and I consider it very useful, especially for evaluating patients who have a lot of visual complaints in the absence of significant ocular surface staining. A thin lipid layer, which is a sign of meibomian gland dysfunction (MGD), causes tear film irregularity and instability, leading to a fast TBUT that explains the patient's visual complaints. Identifying a tear film lipid layer abnormality is also important for guiding treatment decisions because MGD is treated differently than DED due to aqueous deficiency. In fact, most patients with DED have some component of MGD.<sup>11</sup>

A commercially available device for meibography allows noninvasive in vivo imaging of meibomian gland morphology. I believe it is very useful for understanding the presence and severity of MGD, and the images also seem to engage patients' interest in their disease, which can make them better participants in their own care. At our center, however, meibography is performed only in the context of research protocols.

Information on aqueous deficiency can be obtained using optical coherence tomography systems that provide quantitative measurements of tear meniscus parameters.<sup>12</sup> We are using this technology only in clinical research.

Topographic evaluation for corneal surface irregularity provides another readily available method for detecting DED-related tear film abnormalities.<sup>13</sup> This imaging is performed routinely in all of our cataract and refractive surgery candidates.

We find orbital B-scan sonography useful in patients with DED, particularly those with conjunctival chemosis, to detect pathologic changes of the lacrimal glands and/or orbital tissue, which are signs of underlying systemic diseases, such as Sjögren syndrome or inflammatory thyroid disease.<sup>14</sup>

In all patients with dry eye complaints, a review of systems should be conducted to identify potential systemic disease associations with DED. In particular, patients should be asked about dry mouth, joint pain, fatigue, gastrointestinal problems, any skin lesions, and family history of autoimmune or inflammatory diseases. In a study at our center of patients with DED, Sjögren syndrome and inflammatory thyroid disease were the 2 systemic diseases most often associated with DED, and these 2 conditions were often undiagnosed.<sup>14</sup> One in 9 patients with clinically significant dry eye had an underlying primary Sjögren syndrome.<sup>14</sup>

Because of the importance of early diagnosis, anyone who is a suspect for Sjögren syndrome undergoes serologic testing, which at our center includes a panel of conventional assays plus 3 newer antibodies (**Table 2**).<sup>14,15</sup> The 3 newer antibodies, along with Sjögren-specific antibody A, Sjögren-specific antibody B, antinuclear antibodies, and rheumatoid factor, are also measured in a commercially available point-of-care diagnostic kit that can be performed using blood obtained by fingerprick.<sup>16</sup> Further studies, however, are needed to determine the significance of these novel biomarkers.

**Table 2. Serologic Testing for Sjögren Syndrome**

Conventional Biomarkers <sup>14</sup>	Novel Biomarkers <sup>15</sup>
Antinuclear antibodies*	Salivary gland protein-1*
Anti-double-stranded DNA antibodies	Parotid secretory protein*
Anti-Sm/ribonucleoprotein antibodies	Carbonic anhydrase VI*
Sjögren-specific antibody A* and Sjögren-specific antibody B*	
C3 and C4	
Anticyclic citrullinated peptide antibodies	
Rheumatoid factor*	
Antimicrobial antibodies	
Antithyroglobulin antibodies	
C-reactive protein	

\* Included in the point-of-care diagnostic test kit.

## Discussion

**Dr Pflugfelder:** Now let us hear how others on the faculty are using the newer diagnostic techniques for identifying and grading the severity of DED.

**Dr Perez:** I think it is important that we and other experts in OSD use the newer tests and analyze the data we collect, with the aim of determining values that we can apply for clinical decision making, just as we use intraocular pressure for managing glaucoma. Data from large patient populations have provided insight on tear film osmolarity levels that might be used to diagnose DED and grade its severity.<sup>7</sup> When assessing individuals, however, I also look at variability because increased variability of tear film osmolarity is a feature of DED.<sup>7</sup> Variability is the result of tear film instability,<sup>17</sup> and it has been shown to decrease after patients start treatment for DED.<sup>18</sup>

I agree with Dr Akpek that the MMP-9 assay is very useful for identifying inflammation. We are finding that almost all patients with ocular graft-vs-host disease have a positive MMP-9 test, which I think provides a proof of concept that the MMP-9 assay identifies inflammation, and it leads me to be aggressive with anti-inflammatory therapy whenever a patient has a positive MMP-9 assay. It would be nice if the MMP-9 test generated a quantitative result because that would provide a better guide for assessing response to therapy. We expect the test will be modified to do so in the future, but right now, we do not know if a highly elevated MMP-9 level is improving until it falls below the 40-ng/mL threshold when the test turns negative.<sup>10</sup>

I think we need more research to help us understand the value of lipid layer interferometry in patient care. As with osmolarity, I believe variability is informative because it is an indication of lipid layer instability.

I agree that meibography is very helpful for educating patients about their DED, its cause, and the severity. I believe there is nothing like showing patients the extent of their meibomian gland dropout for motivating compliance with aggressive therapy.

**Dr Luchs:** All of the newer tests are very easy for technicians to perform. I believe some can help validate our suspicion of dry eye at an earlier stage when treatment will be more successful.

One of the first suggestions that DED can be present before significant ocular surface signs develop comes from the DED severity classification described in the 2006 International Task Force (ITF) Delphi Panel on Dry Eye guidelines.<sup>19</sup> In defining level 1 dry eye, the ITF recognized the disease could present with only mild-to-moderate symptoms and no clinical signs. I believe that now with tear film osmolarity, we have objective data supporting that presumption. In addition to using tear film osmolarity for diagnosing DED, I use it to monitor patients for a response to DED treatment. What I look for is a trend toward a normal level, with reduced variability in the measurements.

I agree with Dr Akpek that a "normal" tear film osmolarity does not necessarily rule out DED, and I also agree with Dr Perez that variability is important. Tear film osmolarity also needs to be interpreted in the context of the patient's history and other clinical findings.

I order MMP-9 testing fairly routinely when I suspect DED, and I know I need to treat inflammation if the result is positive. I use the intensity of the color of the positive result, whether it appears pinker or deeper red, as a poor man's way to grossly grade the MMP-9 level, and I follow that after patients are started on anti-inflammatory therapy.

I perform meibography if I suspect MGD. Abnormalities, including gland tortuosity, shortening, and drop out, are clear evidence of MGD.

**Dr Holland:** I believe the newer diagnostic tests improve efficiency and accuracy of DED diagnosis, but success with their adoption requires knowing when and how to use them. Our technicians are educated on who should be evaluated with these tests. To maintain efficient patient flow, the technicians are empowered to perform the tests before the patient is seen by the clinician. With this sequence, the results are available at the time of the examination.

I consider osmolarity to be the best measure for diagnosing DED, and so I recommend its routine use as an initial screening test. If osmolarity is abnormal, the technician performs the MMP-9 test, which will indicate if inflammation is a factor in DED.

I agree that meibography is very helpful for identifying MGD, which is one of the most underdiagnosed ocular conditions. Meibography is also useful for grading MGD severity and helping patients understand this condition. I recommend performing meibography after assessment of meibomian gland secretions at the slit lamp.

## DRY EYE MANAGEMENT

JODI LUCHS, MD

A decade ago, DED was generally considered a problem of insufficient tear volume, and so it was predominantly managed with artificial tears. Punctal plugs were also being used to retain tears on the ocular surface, and topical cyclosporine was available, but typically reserved for patients with more severe and even end-stage disease on the basis of safety concerns that were related to knowledge of the risks of cyclosporine used systemically.

Artificial tears are still used today for the management of DED, but as an adjunctive treatment for providing symptomatic relief and tear film stabilization. Now strategies for treating DED integrate understanding of the role of inflammation in disease development and progression; apply the findings from our newer diagnostic tests; and use a severity- and diagnosis-based approach that recognizes how other OSDs, such as blepharitis, MGD, and ocular allergy, may contribute to and exacerbate DED.

Evidence that inflammation drives DED progression and that artificial tears alone do not treat the underlying pathophysiology of DED comes from a prospective study in which patients were randomized to receive anti-inflammatory treatment with topical cyclosporine or its vehicle, which is a commercially available artificial tear.<sup>20,21</sup> After 1 year, dry eye severity rated using ITF guidelines had worsened in 32% of the control patients, but in only 6% of those using cyclosporine.<sup>20</sup> Then, patients in the cyclosporine group were rerandomized to continue cyclosporine or to be switched to the artificial tear, whereas the control patients were started on cyclosporine.<sup>21</sup> Twelve months later, DED severity worsened in half of the patients switched from cyclosporine to artificial tears, but not in any of the patients who continued cyclosporine or who switched to the anti-inflammatory treatment.

### Discussion

**Dr Pflugfelder:** Let us talk some more about how the information provided by the newer diagnostic modalities is influencing management of DED. By allowing me to better classify patients with dry eyes and individualize management, I feel it is enabling me to provide better treatment.

For example, optical coherence tomography measurement of the tear meniscus permits identification of low tear volume and conjunctivochalasis.<sup>12,22</sup> On the basis of this assessment, I can treat conjunctivochalasis and distinguish patients who have MGD with a normal tear volume from those with aqueous deficiency. Furthermore, I can identify patients with very low tear volume, such as those with Sjögren syndrome, who might benefit from punctal occlusion.

**Dr Akpek:** I agree that the new tests are allowing us to tailor our treatment. If a patient has MGD, I know treatment is needed to improve the lipid deficiency in the tear film. In addition, I like to differentiate obstructive MGD from *Demodex*-related disease, which I think is more common than previously realized. I use warm compresses and gland expression for obstructive MGD, whereas when *Demodex* is involved, I treat with antibiotics and aggressive lid hygiene that may incorporate a roughened cleansing pad with tea tree oil cleansers. Tea tree oil has been shown to eradicate the mites and improve the signs and symptoms associated with *Demodex* infestation.<sup>23</sup>

Anti-inflammatory treatment also has a role in managing MGD, and, depending on the severity of inflammation, it may include cyclosporine, a corticosteroid, or perhaps an oral antibiotic, such as a tetracycline derivative or azithromycin.<sup>24,25</sup> A recent report from the American Academy of Ophthalmology, however, highlighted the absence of level 1 evidence to support the efficacy of oral antibiotics in MGD.<sup>25</sup> I do not use punctal plugs or cautery in a patient whose DED is mostly MGD related. However, I would use those modalities earlier if a patient has marked aqueous deficiency, such as DED related to Sjögren syndrome.

**Dr Holland:** I also think these new tests are useful for helping us differentiate the etiology of DED. This is important because the more accurate the diagnosis, the more successful the treatment.

It is my impression that clinicians tend to think about aqueous tear deficiency first and foremost when they diagnose and treat DED. However, MGD is more common, and I believe meibography helps make the correct diagnosis.

Regarding treatment for MGD, I think the recent report from the American Academy of Ophthalmology on the efficacy of oral antibiotics is very misleading.<sup>25</sup> The authors' conclusion that there is no level 1 evidence to support using oral antibiotics is being misinterpreted to mean that oral antibiotics are not effective. My clinical experience using low-dose oral tetracyclines shows otherwise, and I believe other clinicians using this treatment for MGD would agree it is beneficial.

**Dr Perez:** For MGD management, we have a clinic for treating the lid margins with physical therapies. This is because we recognize some patients cannot perform lid massage on their own. Our goal is to provide personalized lid margin expression therapy. Depending on disease severity, the approach may involve manual expression, automated treatment combined with thermal or thermal pulsation devices, or automated treatment combined with meibomian gland probing. Although it is not something we do routinely, intense pulsed light therapy also seems promising for treatment of MGD.<sup>26</sup>

**Dr Pflugfelder:** Dr Perez, has your management of severe DED associated with sight-threatening corneal disease changed over the last decade?

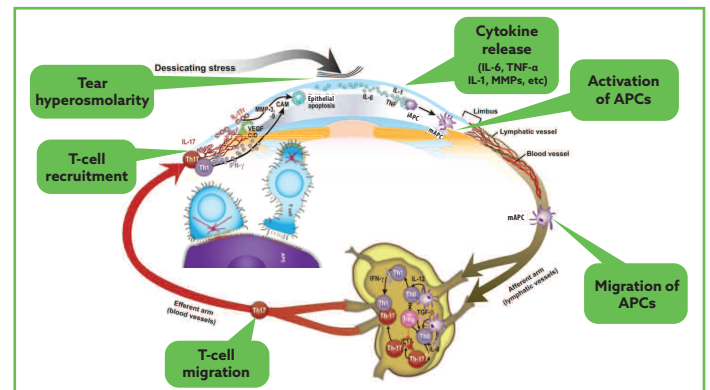
**Dr Perez:** We are still waiting for new medications to control inflammation in these patients. Now we use autologous serum and have a dedicated unit in our clinic for patients who need it. We and others have found autologous serum is safe and improves symptoms and ocular surface health in patients with severe DED, including those with pemphigoid, Sjögren syndrome, or graft-vs-host disease.<sup>27</sup>

We are also using PROSE (prosthetic replacement of the ocular surface ecosystem) for patients with severe DED. PROSE is a customized large-diameter lens that vaults over the cornea and holds a reservoir of saline or another fluid. It protects the ocular surface, reduces symptoms, and improves vision.<sup>28,29</sup> In our experience, both PROSE and autologous serum have also been very helpful for managing patients with a neuropathic disorder who present with a lot of pain, but no stain.

## DRY EYE DISEASE PATHOPHYSIOLOGY AND TREATMENT: IMMUNOINFLAMMATORY PATHWAY

VICTOR L. PEREZ, MD

The efficacy of cyclosporine for treating DED in patients with autoimmune disorders supported the idea that DED is an inflammatory disease and focused attention on the role of T cells and the adaptive immune system in DED pathophysiology (**Figure 1**).<sup>30</sup>



**Figure 1.** Dry eye immunoinflammatory pathway

Abbreviations: APC, antigen-presenting cell; CAM, cell-adhesion molecule; IFN, interferon; IL, interleukin; iAPC, immature antigen-presenting cell; MMP, matrix metalloproteinase; mAPC, mature antigen-presenting cell; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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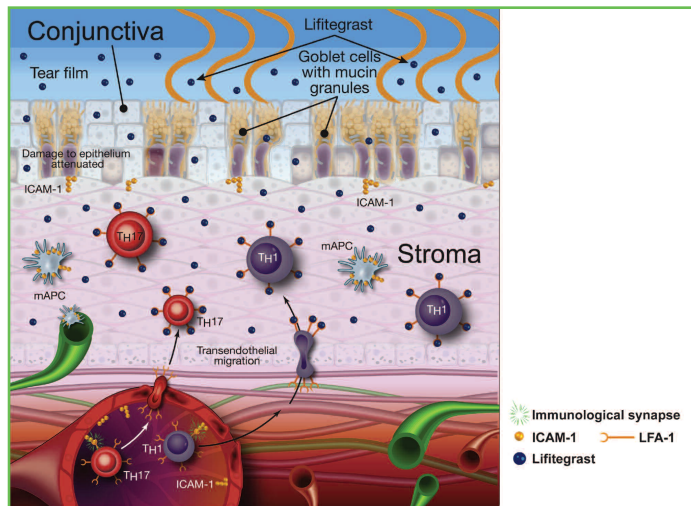
The inflammatory response that causes DED and perpetuates its progression is triggered by exposure of ocular surface tissues to desiccating stress that induces a hyperosmolar tear film.<sup>30,31</sup> Initially, stressed corneal and conjunctival epithelial cells release chemical mediators that activate cells of the innate immune system: macrophages and neutrophils. Soon, however, the process transitions to a T cell-mediated adaptive immune response.

The activated innate immune system cells release cytokines that promote the activation and maturation of antigen presenting cells (APCs) on the ocular surface.<sup>30,31</sup> The activated APCs migrate to the lymph nodes, where T cells become primed against the ocular surface antigens carried by the APCs. The T cells travel to the conjunctiva through the circulation, exit the blood vessels, and become activated after binding with antigens. T-cell activation initiates a cascading release of proinflammatory cytokines and enzymes that destroy ocular surface tissues. The result is worsening of tear film instability and hyperosmolarity, with perpetuation of the inflammatory process.

Understanding of the cellular and molecular pathways involved in the immunoinflammatory process underlying DED explains the efficacy of cyclosporine as a treatment for DED and allows a foundation to develop targeted therapies for blocking inflammation and the tissue damage it causes. Cyclosporine works by blocking the release of proinflammatory cytokines from activated T cells in the conjunctiva. First, however, the T cells that are primed against ocular surface antigens have to

reach the conjunctiva and become activated.<sup>30,31</sup> The latter 2 processes are mediated through binding of T cell-expressed integrin lymphocyte function-associated antigen 1 (LFA-1) to intercellular adhesion molecule 1 (ICAM-1), which is expressed on vascular endothelial cells, epithelial cells, and APCs.<sup>31</sup> Binding of T cells to APCs through the interaction of LFA-1 and ICAM-1 results in formation of the immunologic synapse that is a critical step in T-cell activation.

Lifitegrast is a small molecule integrin antagonist that binds to LFA-1 and prevents its interaction with ICAM-1, thereby blocking the immunologic synapse.<sup>31</sup> In theory, lifitegrast may be more efficient and effective than cyclosporine for quieting and controlling inflammation in DED because lifitegrast works upstream. Lifitegrast prevents the activation of T cells that are already present in ocular surface tissues and the cascade of events that follows T-cell activation, while also blocking the infiltration of new T cells that can sustain the inflammatory process (Figure 2).<sup>31</sup> This profile of actions might also help to explain results of clinical trials showing lifitegrast provided early onset of symptom relief.<sup>32,33</sup>



**Figure 2.** Mechanism of action of lifitegrast at the cellular level

Abbreviations: ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; mAPC, mature antigen-presenting cell; TH, T helper cell.

Disclaimer: This figure illustrates the current understanding of the mechanism of action of lifitegrast based on completed preclinical and clinical studies. Additional studies in the posterior ocular tissues and vascular system are needed to further elucidate the mechanism of action of lifitegrast.

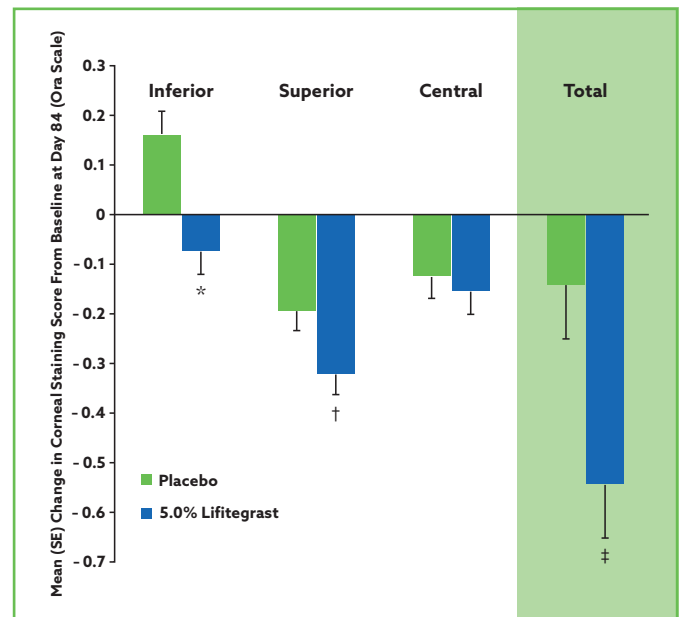
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## NEW AND EMERGING THERAPIES FOR DRY EYE DISEASE

EDWARD J. HOLLAND, MD

Lifitegrast was approved in July 2016 by the US Food and Drug Administration for the treatment of the signs and symptoms of DED. Premarketing studies investigating lifitegrast for the treatment of DED included a phase 2 study that enrolled 230 patients<sup>34</sup> and 3 phase 3 trials—OPUS-1, OPUS-2, and OPUS-3—that together enrolled close to 2000 patients.<sup>32,33,35</sup> In the phase 2 study, lifitegrast, 5.0%, showed a statistically significant benefit ( $P < .05$ ) vs placebo in a prespecified secondary end point analysis of mean change from baseline

to day 84 in inferior corneal staining score (ICSS).<sup>34</sup> Mean change in ICSS was investigated as a coprimary efficacy end point in OPUS-1, and, again, the outcomes analysis showed a significant difference in favor of lifitegrast compared with placebo for improving ICSS ( $P = .0007$ ) (Figure 3).<sup>35</sup>



**Figure 3.** Change from baseline to day 84 in corneal fluorescein staining scores in OPUS-1

Abbreviation: SE, standard error.

\*  $P = .0007$

†  $P = .0392$

‡  $P = .0148$

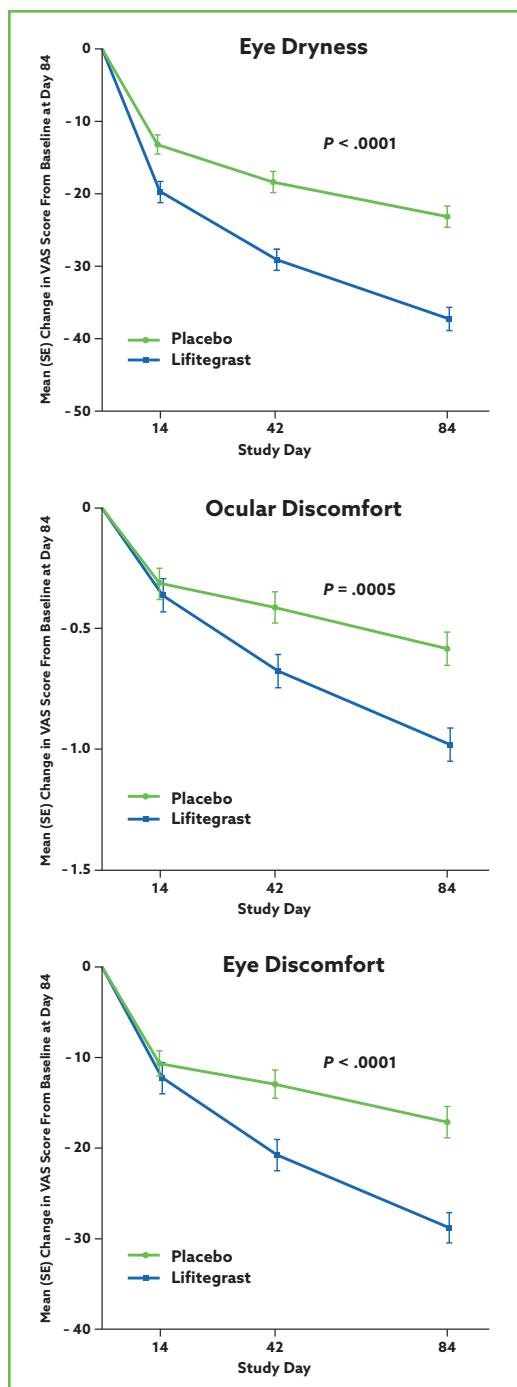
Adapted from Sheppard JD, et al.<sup>35</sup>

Although the phase 2 trial and OPUS-1 enrolled patients with mild-to-moderate symptomatology at baseline,<sup>34,35</sup> participants in OPUS-2 and OPUS-3 were required to have moderate-to-severe symptoms of DED.<sup>32,33</sup> This inclusion criterion afforded increased power for detecting a statistically significant treatment effect for symptom improvement. Eye dryness score (EDS) was a coprimary efficacy end point in OPUS-2 and the primary efficacy end point in OPUS-3, and lifitegrast was significantly superior to placebo for improving EDS in both studies ( $P \leq .0007$ ) (Figure 4).<sup>32,33</sup> In addition, lifitegrast demonstrated an early onset of action in both studies, in which a significant improvement in EDS was achieved by day 14. The sign coprimary end point in OPUS-2, mean change in ICSS, was not met.<sup>32</sup> Lifitegrast was well tolerated in all of the trials, and there were no serious treatment emergent adverse events associated with its use.<sup>32-35</sup>

## Discussion

**Dr Pflugfelder:** Has it been difficult to show that a treatment for DED improves both signs and symptoms?

**Dr Holland:** Depending on what end points are chosen, I think it can be extremely difficult to power a study to achieve statistically significant superiority vs placebo for both a sign and a symptom. The US Food and Drug Administration required that lifitegrast show benefit for improving a sign end point in 2 studies and a symptom end point in 2 studies, but not necessarily to show improvement in both a sign and a symptom in the same trial.<sup>36</sup>



**Figure 4.** Change from baseline to day 84 in symptom scores in the placebo and lifitegrast groups in OPUS-2. Eye dryness was a coprimary end point.

Abbreviations: SE, standard error; VAS, visual analogue scale. Adapted from Tauber J, et al.<sup>32</sup>

**Dr Pflugfelder:** Investigational treatments for DED in late-stage clinical development include tavilermide, 1% (formerly known as MIM-D3). Tavilermide is a tropomyosin receptor kinase A agonist that acts as a nerve growth factor mimetic and seems to stimulate mucin secretion. Pivotal phase 3 trials are now evaluating tavilermide. Published results from

a phase 2, placebo-controlled study enrolling patients with DED showed tavilermide, 1%, protected against the effects of a controlled adverse environment challenge on dry eye signs and symptoms.<sup>37</sup>

Other anti-inflammatory agents that reached phase 2 clinical development include a new nanoparticle formulation of loteprednol in mucus-penetrating particle technology (KPI-121), cyclosporine in a novel nonaqueous vehicle, and dexamethasone in a biodegradable punctal plug for slow-release delivery.<sup>38,39</sup> In a 28-day phase 2 trial enrolling patients with DED, a 0.25% suspension of the loteprednol etabonate nanoparticle technology significantly reduced conjunctival hyperemia and improved dry eye symptoms compared with placebo.<sup>38</sup> In addition, an intranasal lacrimal neurostimulator is being evaluated in phase 3 studies.

## CASE 1: CATARACT SURGERY AND DRY EYE DISEASE

FROM THE FILES OF STEPHEN C. PFLUGFELDER, MD

A 62-year-old woman with cataracts expresses interest in multifocal intraocular lenses (IOLs) because, like a friend who recently had surgery, she would like to be able to see without glasses. The patient is a hyperope and has been in monovision with soft contact lenses for 15 years. She reports that for the past 2 years, her lenses feel uncomfortable after several hours of wear, and she is experiencing burning and fluctuating vision, with blinking that is worse in the morning. Artificial tears provide temporary relief.

**Dr Pflugfelder:** What are your diagnostic considerations for determining whether or not this patient is a candidate for multifocal IOLs?

**Dr Holland:** I believe patients need to have an excellent ocular surface to be satisfied with their vision after multifocal IOL implantation. In fact, when I see patients on referral who are unhappy after multifocal IOL surgery, undiagnosed DED, rather than a suboptimal refractive outcome, is the most common cause.

The history of the woman in this case is consistent with DED, and she should be evaluated to establish the diagnosis, the type of DED, and its severity. I would perform tear film osmolarity testing, the MMP-9 assay, meibomian gland expression, meibography, and ocular surface staining. If there is significant staining, I would recommend against multifocal IOLs. However, if patients with DED truly want a multifocal IOL, I ask them to delay surgery while we treat their OSD. I would consider a multifocal IOL if the ocular surface can be restored to excellent condition.

**Dr Luchs:** I agree with that approach, and I would point out that there are a number of red flags in this patient's history that raise the suspicion for DED. These include a long history of contact lens wear, intolerance after several hours of lens wear, and use of artificial tears. Most importantly, however, is her report of fluctuating vision. Although a fixed problem, such as a cataract, tends to produce fixed visual symptoms, fluctuating vision points to a fluctuating problem, such as DED, on the ocular surface.

**Dr Holland:** Patients who have significant dry eye, especially when it is related to MGD, may not notice fluctuating vision if they also have a significant cataract. The fluctuating vision, however, will manifest after cataract surgery, and then patients often seem to think it is related to the surgery, especially if the diagnosis of MGD was not made preoperatively.

**Dr Perez:** The patient's problem with contact lens intolerance would lead me to target inflammation in choosing management for her OSD. Regardless of how much her ocular surface improves, however, I would try to convince her to have monofocal IOLs implanted for monovision, considering that she is a hyperope who has been successfully using monovision for a long time.

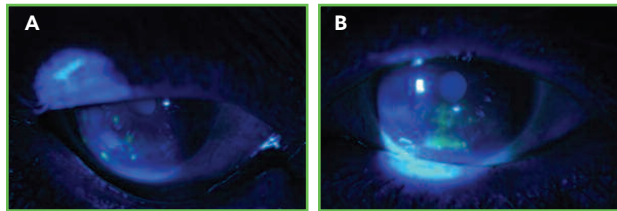
**Dr Pflugfelder:** Would your approach be any different if you saw a younger patient with symptoms of DED who was interested in LASIK because of contact lens intolerance?

**Dr Holland:** Because corneal refractive surgery is more likely than cataract surgery to exacerbate dry eye, I am even more cautious in that situation about proceeding to surgery if a patient has significant DED and corneal staining.

## CASE 2: SJÖGREN SYNDROME-RELATED DRY EYE DISEASE

FROM THE FILES OF STEPHEN C. PFLUGFELDER, MD

A 70-year-old woman presents with dry eye that has been worsening over the past decade. She experiences almost constant foreign body sensation and is bothered by air drafts. She notes that she no longer produces tears when she feels like crying. For the past year, she has had blurred vision and severe photophobia. Artificial tears provide minimal improvement. She has used topical cyclosporine, which provided some relief, but stopped the medication 2 months ago. Her visual acuity is 20/40 OU; TBUT is 1 s OU; and Schirmer 1 score is 3 mm OU. She has confluent central corneal staining with fluorescein dye (**Figure 5**).



**Figure 5.** Bilateral corneal fluorescein staining with microfilaments in the right eye (A) and central involvement in the left eye (B)

Images courtesy of Stephen C. Pflugfelder, MD

**Dr Pflugfelder:** Dr Akpek, how would you approach this patient?

**Dr Akpek:** Any patient with a total ocular surface staining score of 3 or more should be evaluated for Sjögren syndrome.<sup>40</sup> This patient's history, low TBUT, and low Schirmer score are also red flags. I would conduct a review of systems; ask about joint pain, muscle aches, and dry mouth; check for parotid gland swelling; and proceed with serologic testing.

**Dr Pflugfelder:** Do you find there are any advantages for using the newer serology test for Sjögren syndrome?

**Dr Akpek:** More data are needed to determine the diagnostic accuracy of the 3 novel antibodies included in the newer test and their performance for providing earlier identification of patients with Sjögren syndrome. In addition, they are not part of the American College of Rheumatology criteria for diagnosing Sjögren syndrome.<sup>40</sup> However, the kit also includes the 4 traditional antibodies that are needed for diagnosis, and it allows for convenient testing in an outpatient setting.

The diagnosis of Sjögren syndrome is not based on serology alone. The American College of Rheumatology criteria require at least 2 of the following 3 findings: (1) positive serum anti-Sjögren-specific antibody A and/or anti-Sjögren-specific antibody B or positive rheumatoid factor plus antinuclear antibodies ( $\geq 1:320$ ); (2) ocular staining score  $\geq 3$  (cornea and conjunctiva combined together); and (3) presence of focal lymphocytic sialadenitis with focus score  $\geq 1$  focus/4 mm<sup>2</sup> in labial salivary gland biopsy.<sup>40</sup>

**Dr Pflugfelder:** Assuming the patient is diagnosed with Sjögren syndrome and considering she has failed topical cyclosporine, how would you manage her DED?

**Dr Akpek:** I would start a topical corticosteroid to control the inflammation and improve the condition of the ocular surface and tear film. Then, I would insert punctal plugs. I also use serum tears in patients with Sjögren syndrome unless their eyes are severely inflamed and they have bad joint disease. I worry about harmful cytokines in the autologous serum in these patients and would not use it unless the patients are placed on appropriate systemic treatment. I then refer them to be fit with PROSE. I would restart cyclosporine as I wear the patient off the topical steroid because I think it may still benefit the patient unless the patient's Schirmer score is 0. I would use it with a greater dosing frequency than the recommended twice-daily regimen. We found topical cyclosporine was safe and well tolerated when used 3 to 8 times daily by patients with significant OSD.<sup>41</sup> I also use tacrolimus ointment, 0.03%, applied to the lid skin twice daily. We published our experience using the ointment to treat atopic keratoconjunctivitis,<sup>42</sup> and my impression is that it improves the ocular surface.

**Dr Perez:** Published reports also show tacrolimus, 0.03%, drops are effective for treating DED associated with graft-vs-host disease and Sjögren syndrome.<sup>43,44</sup> Tacrolimus, 0.1%, suspension is now available in Japan, and we are using a compounded formulation of tacrolimus, 0.1%, that I think might be very helpful for treating DED related to autoimmune disease.

It is unfortunate this patient had such advanced DED before she was diagnosed with Sjögren syndrome. We hope that ophthalmologists can play a role in improving the prognosis for these patients through early diagnosis, considering that dry eye symptoms precede systemic signs of Sjögren syndrome by a decade.<sup>45</sup> Then, ophthalmologists need to refer patients to a rheumatologist and encourage the rheumatologist to start systemic therapy before the lacrimal gland is damaged irreversibly; once that occurs, there is little ophthalmologists can do to treat the DED other than provide palliative care.

**Dr Akpek:** Even if a patient is suspected to have permanent lacrimal gland damage because of Sjögren syndrome, it is important to uncover the diagnosis. Between 20% and 55% of patients with Sjögren syndrome have extraglandular systemic findings, including pulmonary disease and interstitial kidney or liver disease or vasculitis.<sup>14,45,46</sup> Importantly, 5% to 10% of patients with Sjögren syndrome develop lymphoma, which is the major cause of morbidity and mortality in these patients.<sup>46</sup> Without a formal diagnosis of Sjögren syndrome, these patients may not get the workup they need to detect extraglandular systemic manifestations.

**Dr Luchs:** I suggest this patient could benefit from a course of systemic immunosuppressive therapy, considering she may have some lacrimal gland function to save. With that in mind, I agree with Dr Perez about the importance of partnering with a rheumatologist who will treat these patients in accordance with the understanding that the ophthalmic findings of Sjögren syndrome and other autoimmune diseases are significant and sight-threatening.

From an ophthalmic standpoint, the treatment goal should be to eliminate corneal staining, which I believe is an indicator for risk of corneal scarring and secondary infection. In addition to all of the DED management modalities already mentioned, we should not forget symmetric lateral tarsorrhaphy. It is a very effective but underused technique for promoting ocular surface healing.

## TAKE-HOME POINTS

**Dry eye disease is a common disorder, with potential to negatively affect visual, social, and physical functioning.**

**Evaluation of patients with symptoms of DED should:**

- Consider other OSDs that share overlapping symptoms
- Exclude or establish the diagnosis of DED and determine its severity
- Include assessment for underlying systemic inflammatory diseases

**Newer diagnostic tests for DED are helping clinicians:**

- Distinguish DED type and severity
- Develop a tailored approach to treatment
- Monitor response to therapy

**Treatment regimens for DED should:**

- Consider whether the condition is due to aqueous-deficiency and/or evaporative disease
- Match intensity with DED severity
- Appropriately incorporate anti-inflammatory treatment to mitigate disease progression
- Address coexisting OSDs

**Dry eye disease is an inflammatory disorder that is driven and perpetuated by T cells.**

- Understanding of the immunoinflammatory pathway of DED pathogenesis is supporting the development of targeted therapies and new formulations of existing anti-inflammatory medications

**Identification of DED is critical in the preoperative evaluation of patients who are candidates for cataract and corneal refractive surgery.**

**Early diagnosis of Sjögren syndrome and referral to a rheumatologist are important because these patients are at risk for:**

- Multiple extraglandular complications, including lymphoma
- Lacrimal gland destruction

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# CME POST TEST QUESTIONS

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See detailed instructions under **Instructions & Registration** on page 2.

- Newer DED diagnostic modalities:
  - Are reimbursed by most insurance payers
  - Result in abnormal findings only in patients with moderate-to-severe DED
  - Help quantitate ocular surface damage better than vital dye staining
  - Help with identifying aqueous-deficient vs evaporative DED
- Which of the following diagnostic tests has limited use for distinguishing between mild and severe DED?
  - Meibography
  - MMP-9 assay
  - Ocular surface staining
  - Tear film osmolarity
- A newer point-of-care diagnostic test for Sjögren syndrome:
  - Can establish the diagnosis of Sjögren syndrome 10 years earlier than conventional serology
  - Measures novel biomarkers in a small tear sample
  - Might be considered in the workup of any patient with an ocular surface staining score  $\geq 3$
  - Eliminates the need for further testing to establish the diagnosis of Sjögren syndrome if the result is positive
- Treatment with a topical anti-inflammatory medication for a patient diagnosed with DED may be considered reasonable for anyone with a:
  - Diagnosis of Sjögren syndrome
  - Negative MMP-9 assay
  - Tear film osmolarity of 302 mOsm/L OU
  - All the above
- A recent report from the American Academy of Ophthalmology on oral antibiotics for treatment of MGD concluded:
  - There is no level 1 evidence to support their efficacy
  - There is no level 1 evidence to support their use
  - They are less effective than topical antibiotics
  - They should only be used in subantimicrobial doses for anti-inflammatory activity
- Dessicating stress initiates the pathogenic pathway leading to DED by:
  - Activating phospholipase 2, resulting in prostaglandin synthesis
  - Causing tear film hyperosmolarity
  - Increasing exposure of antigens on ocular surface cells
  - Upregulating MMP-9
- Lifitegrast:
  - Blocks the immunologic synapse by binding to ICAM-1
  - Prevents activation of T cells that are present in ocular surface tissue and the infiltration of new T cells
  - Significantly improved DED-related symptoms (eye dryness score) within 2 weeks after treatment initiation in the 3 phase 3 OPUS trials
  - Significantly improved inferior corneal staining within 2 weeks after treatment initiation in the 3 phase 3 OPUS trials
- Tavilermide:
  - Has the same mechanism of action as cyclosporine, but appears to be better tolerated
  - Improves lipid abnormalities in MGD
  - Is being developed for sustained delivery by formulation in a biodegradable punctal plug
  - Seems to stimulate mucin secretion
- A 62-year-old woman presents with a complaint of blurred vision. She denies burning, dryness, foreign body sensation, or other DED-related symptoms. Examination reveals 2+ NS cataracts OU. She is interested in a multifocal IOL to increase spectacle independence. In her preoperative workup, she has a total ocular surface staining score of 3 OU, tear film osmolarity values of 320 mOsm/L OS and 322 mOsm/L OD, and a positive MMP-9 assay. What would you do?
  - Ask about dry mouth
  - Rule out DED based on the absence of symptoms
  - Schedule surgery because her blurred vision is likely related to her cataract, but recommend against a multifocal IOL because she has DED
  - Start topical cyclosporine, insert punctal plugs, and schedule surgery
- A patient presents in the spring with complaints of fluctuating vision, burning, ocular redness, and tearing. Results from tear film osmolarity testing are 298 mOsm/L OD and 302 mOsm/L OS. What would you do?
  - Prescribe a dual-acting antihistamine/mast cell stabilizer
  - Recommend lid hygiene with tea tree oil cleansers for treatment of DED secondary to *Demodex* infestation
  - Repeat the tear film osmolarity test to check for intervisit variability
  - Rule out DED

## Improving Recognition and Management of Dry Eye Disease in the 21st Century: The Burden of Dry Eye Disease

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### PARTICIPANT INFORMATION (Please Print) Home Office

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 Specialty \_\_\_\_\_ Degree  MD  DO  OD  PharmD  RPh  NP  RN  PA  Other \_\_\_\_\_  
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### POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10

### OVERALL ACTIVITY EVALUATION

Rate the extent to which:	Very High	High	Moderate	Low	Very Low
1. Learning Objectives of this activity were met					
<i>Evaluate, diagnose, and rate the severity of dry eye disease</i>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<i>Describe the implications of inflammation in dry eye disease on diagnosis and treatment approaches</i>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<i>Select an appropriate treatment regimen for dry eye disease based on individual patient characteristics</i>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. You were satisfied with the overall quality of this activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Content was relevant to your practice	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Participation in this activity will change your knowledge/attitudes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. You will make a change in <i>your practice</i> as a result of participation in this activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. The activity presented scientifically rigorous, unbiased, and balanced information	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Individual faculty comments were free of commercial bias	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. In the event that you believe a faculty participant introduced commercial bias, please describe the specifics below:					
9. Topic/Content was appropriate for your needs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Was there a particular discussion that you felt had the most impact?					
What are some of the take-aways/changes that you will implement in your practice as a result of participating in this activity?					
Comments/Suggestions for Future Topics					

