Dry-eye syndrome affects millions of Americans, with a particularly high incidence among older women. Dry-eye symptoms are among the most common reasons people visit eye doctors. On the mild end of the dry-eye spectrum symptoms such as occasional burning or stinging may be minor annoyances. But dry-eye syndrome can become severe, with constant ocular pain and discomfort, visual distortion, and may lead to scarring and permanent vision loss. For many patients with dry-eye syndrome the condition adversely affects their quality of life.

New strategies for treating patients with dry-eye syndrome have emerged in recent years. New therapies for managing dry eyes have significantly changed ophthalmologists' approach to dry-eye patients. In this monograph we will present and discuss case studies from our practices that are representative of the spectrum of dry-eye syndrome. Our distinguished panel will offer its insights into the management of dry-eye syndrome in the context of these cases. It is our goal to demonstrate the role of new and emerging therapies in the management of dry-eye syndrome.

CASE 1

Case Presentation: A 56-year-old female complains of foreign body sensation and tearing. The irritation is mild, is worse in the evening, and is most noticeable when she is reading. She has a history of allergies and uses an oral antihistamine. On examination her tear meniscus is normal in appearance, and she has no corneal staining. She does have trace conjunctival staining using rose bengal stain. Her Schirmer's are 8 mm and 9 mm with anesthesia.

Discussion: The allergy issue is important in the setting of dry-eye symptoms. Patients who are on antihistamines have a significant risk of dry eyes and decreased tear production, said Dr. Rapuano. This is due in part to the medication-related decrease in tear production, which makes co-existing dry eye worse. It is also due to the ocular allergy symptoms.

If the systemic allergies are not too severe, it is useful to discontinue use of the antihistamine. This will often improve or resolve mild dry-eye symptoms in these patients.

Dr. Rapuano suggested putting patients on minimally preserved tears after they've stopped the antihistamines. He also said physicians should recommend that their patients use standard environmental interventions such as a humidifier in the bedroom at night.

Because the patient reports that her symptoms are most bothersome when she is reading, she should be cautioned not to sit too close to a heating or air conditioning vent when reading. Forced air can accelerate evaporation of the tear film.

The patient is likely to benefit from tear replacement therapy. Artificial tears are often all that are needed for patients with mild symptoms. The issue of preserved versus non-preserved artificial tears often arises. In general, preservatives should be avoided—or at least minimized—whenever possible, as chronic exposure to preservatives can cause toxicity issues and can limit or negate the benefits of tear replacement therapy.

For this reason we often choose to use Refresh tears (Allergan, Irvine, Calif.), as they are transiently preserved. Purite, the preservative in Refresh, preserves the fluid while in the bottle, but after being instilled onto the ocular surface and exposed to light, the purite converts to water and sodium chloride, which are harmless to the ocular surface and are, in fact, components of natural tears.
Dr. Wittpenn does not like to use preserved tears; instead, he said he opts for transiently preserved tears for every case because of the difficulties associated with toxicity.

Resolution: This patient stopped taking oral antihistamines and began to use Refresh tears as needed. Our panel also recommended she use a humidifier in the bedroom. Three months after the patient first presented she still had trace conjunctival staining with rose bengal, but her symptoms had completely resolved using Refresh an average of two to four times a day.

CASE 2

Case Presentation: A 56-year-old woman presents for evaluation of dry-eye syndrome. She has consulted with three ophthalmologists prior to this visit, each of whom has given her a different brand of artificial tears and told her that they should help relieve her condition. So far, none of the brands has relieved her symptoms, and she is extremely frustrated.

The patient explains that her symptoms are worse in the evening. On examination her tear meniscus is normal, and she has no corneal staining, but she does have 2+ rose bengal staining of the conjunctiva (Figure 2). Her Schirmer’s with anesthesia are 10 mm in the right eye and 5 mm in the left eye.

Discussion: As in the first case, this patient’s symptoms are worse in the evening than they are in the morning. This is an important piece of historical information that aids in the process of diagnosis. Symptoms associated with dry-eye syndrome typically worsen throughout the day and reach their peak in the evening hours. In contrast, complaints of itching, burning, or stinging that are worse in the morning are more suggestive of lid diseases such as blepharitis or meibomianitis.

This patient has been using artificial tears without relief. While it is possible that she may not be compliant with her tear therapy or not instilling the drops correctly, the fact that she has now seen four ophthalmologists to find relief suggests that she is motivated and is likely compliant.

Why are tears not helping her? Based on her rose bengal staining pattern (Figure 2), she has early to moderate ocular surface tissue damage. Artificial tears are highly effective as monotherapy in patients with mild aqueous deficiency and who don’t yet have ocular surface damage. But tears alone usually are not enough once tissue damage has occurred.

This is the typical patient who will respond well to Restasis (cyclosporine, Allergan). Relatively mild to moderate dry eyes, surface tissue damage, and failure to achieve symptomatic relief despite tears at least three times a day are all good reasons to consider Restasis. Our panel agreed that the majority of patients will get symptomatic relief within three to four weeks with Restasis (Allergan).

Restasis is an anti-inflammatory medication that has been shown to increase the production of the patient’s own natural tears. In addition, eyes treated with Restasis experienced a 200% increase in their goblet cell density. Goblet cells are essential to maintaining a healthy ocular surface, as mucin from goblet cells allows aqueous to spread evenly over the ocular surface. Goblet cells are decreased in dry-eye syndrome but can be restored with use of Restasis.

“When you take a patient with mild to moderate dry eye and put him on Restasis, the disease goes away,” said Dr. Wittpenn. “Just like with glaucoma, if you treat it early, you prevent the progression of the disease.”

It is important to emphasize that dry-eye syndrome is a chronic, progressive disease. Too often Restasis is saved for end-stage dry eyes such as those with rheumatoid arthritis, though it certainly works in this population. But it also works—extremely well—in earlier-stage patients. The response to Restasis tends to be faster and more effective if used earlier in the disease process. Dr. Dougherty prefers to use Restasis on patients early on because “they tend to respond quicker and have a better response” to the medication.

In severely dry eyes Restasis combined with other therapies—such as tears and punctal plugs—can help patients become asymptomatic. But the earlier-stage patients benefit from Restasis therapy and can

Figure 2: 2+ rose bengal staining of the conjunctiva.

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achieve a symptomatic cure. We have patients who are using tear drops every one to two hours—these are busy patients trying to go to work, trying to play tennis—who now take Restasis twice a day as maintenance therapy, and they are less dependent on—or even completely off—their artificial tears. That is a significant improvement in quality of life.

In general, a patient like the one presented in this case, with mild to moderate dry eyes and symptoms not relieved with tears, will respond well to Restasis. And with Restasis on board the patient is less likely to experience progressive worsening of her dry-eye symptoms over time.

The initiation of Restasis requires some preparation on the part of both the physician and the patient. The most common side effect of Restasis is burning upon instillation; itching is common, too. In the Phase III data, burning was actually worse in the Restasis group (17%) than in the placebo group (7%) after one month of therapy.1

These symptoms may be related to the raw and irritated ocular surface. The symptoms tend to resolve over the first few weeks of therapy.

There is a valid concern that patients may stop the medication before they move past this initiation phase. For this reason patient education is critically important to therapeutic success.

Patients should understand what to expect during the first few weeks and may benefit from frequent follow-up during this time.

Some of our colleagues often see patients who report that they have tried Restasis without success. When questioned, they report that it made their eyes burn more than they did before they started it.

We believe there’s an easy remedy to that problem. Sometimes patients will misunderstand the purpose of the medication and might use it more than twice a day, as they do with tears when their symptoms worsen. Once these patients understand what to expect, they are usually willing to give Restasis another try and often have successful results the second time around.

One way to minimize the initial burning with Restasis—which typically resolves within four to six weeks after starting therapy—is with a low-dose steroid. Dr. Holland noted that topical steroids are an effective way to alleviate burning caused by Restasis. Some panelists pre-treat the patient for two weeks with a twice-daily mild steroid such as loteprednol etabonate, and then start Restasis, while others prefer to start both medications at the same time.

Dr. Holland also noted that pre-treating with loteprednol etabonate is the key to getting patients to accept the Restasis therapy. "It gets back to education—the patient has to understand what Restasis does, what steroids do, and what tears do," said Dr. Holland. The steroid can be discontinued after several weeks.

Resolution: This patient was started on Restasis twice daily following a two-week pre-treatment with Lotemax. After three months her conjunctival staining was down to trace amounts, her Schirmer’s were 16 mm and 12 mm, and she was free of symptoms without the need for artificial tears.

Case Presentation: A 47-year-old moderately myopic female has become contact lens intolerant and presents for a refractive consultation. She has a history of giant papillary conjunctivitis and a history of asthma, and she takes a topical antihistamine for ocular allergy symptoms.

On examination she has mild atopic lid disease, an intact tear meniscus, no corneal staining, and 2+ lissamine green conjunctival staining (Figure 3). Her Schirmer’s with anesthesia were 8 mm in the right eye and 7 mm in the left eye.

Figure 3: Lissamine green conjunctival staining.

“Patients who are on antihistamines have a significant risk of dry eyes and decreased tear production.”

— Christopher J. Rapuano, M.D.

Christopher J. Rapuano, M.D. is a professor of ophthalmology, Jefferson Medical College of Thomas Jefferson University, co-director, Cornea Service, Wills Eye Hospital, Philadelphia.
Discussion: From a refractive standpoint this patient has several risk factors that limit her probability of a refractive surgical success, including peri-menopausal condition, contact lens intolerance, and ocular allergies. She also has atopic disease.

Lid diseases, including atopy, have been shown to increase the risk of lamellar keratitis after LASIK.\(^4\) This array of ocular surface issues greatly complicates pre-operative counseling for refractive surgery.

The first step in the management of this patient is educating her regarding the status of her ocular surface and controlling her ocular surface diseases. Atopy is the most concerning of her surface issues.

Atopy is an inflammatory condition and is among the most under-diagnosed ocular conditions underlying dry eyes. Atopy is a progressive condition, and over time this lady’s ocular surface will continue to worsen, with progressive conjunctival scarring and severe dry eyes later in life.

Short of an intraocular procedure such as a phakic IOL, she is unlikely to enjoy a good refractive outcome regardless of the procedure performed—unless and until her surface disease is addressed.

An inflammation process with atopic disease is one of the most under-diagnosed ocular conditions, said Dr. Holland. "The combination of steroids and Restasis is a wonderful way to manage these patients," he said. Members of the panel agreed that Restasis should be used as a first-line therapy. Mast-cell stabilizers should be used as a second-line therapy, and steroids and antihistamines should be kept on reserve, they said.

The role of Restasis in lid disorders is evolving. A recent paper in the journal *Cornea* demonstrated that patients with meibomian gland dysfunction experienced significant improvement in the appearance of their eyelid margins after treatment with Restasis compared to a group treated with Refresh tears alone.\(^5\)

Lid margin vascular injection, tarsal telangiectasis, fluorescein staining, and, in particular, the number of meibomian gland inclusions were all improved after a three-month course of Restasis. Patients with dry eyes and lid disease often experience a significant reduction in ocular pain while using Restasis—probably because of the anti-inflammatory action of Restasis.

The patient’s ocular allergies also need to be addressed. The role of antihistamines in allergy patients undergoing refractive surgery is a topic of some debate, but it is not often recognized that Restasis is a potent anti-allergy medicine. It is a T-cell suppressor, and T-cells are involved in both allergy and inflammation processes, so in this case Restasis could kill two birds with one stone, so to speak.

Restasis therapy will likely normalize the ocular surface and control the disease, and a steroid may be used at onset, after which refractive surgery can be considered.

For a severe allergic disease such as that seen with vernal keratoconjunctivitis additional anti-allergy therapy may be needed. Initial pulse therapy with antihistamines may help get the disease under control, followed by maintenance therapy with a mast-cell stabilizer. Many patients with severe allergies and dry eyes benefit from chronic therapy with twice-daily mast-cell stabilizers and Restasis.

As for which refractive procedure to perform on this patient, LASIK is a possibility if the ocular surface normalizes. If the ocular surface improves but does not normalize, photorefractive keratectomy (PRK) might be a better option, our panelists said. They agreed that it is worth noting that once the patient’s surface disease is controlled the patient may find that she is no longer intolerant to her contact lenses and could perhaps resume wearing them.

Resolution: This patient began using Restasis twice daily and artificial tears four times daily. After six weeks she discontinued her topical antihistamine, her Schirmer’s were 8 mm and 11 mm, and her lissamine green conjunctival staining was down to 1+.

She underwent uneventful myopic LASIK six weeks after beginning Restasis. Three months post-operatively, her uncorrected acuity was 20/20 in each eye. After six months she discontinued Restasis, her uncorrected acuity was 20/25 in each eye, and she complained of fluctuating vision. Fluctuating vision is dry-eye patients’ chief complaint after LASIK, said Dr. Holland.
An enhancement was considered, but first the patient's acuity was retested after a drop of non-viscous Refresh Plus (Allergan). Her acuity improved significantly, suggesting an ocular surface issue rather than a refractive issue. After restarting Restasis her acuity stabilized back at 20/20 uncorrected in both eyes (Figure 4).

**CASE 4**

**Case Presentation:** A 37-year-old female has a history of dry eyes and a tear film break-up time of five seconds. She is a +1.25D hyperope, has become contact lens intolerant, and presents for a refractive surgery consultation.

**Discussion:** One option to consider is a phakic intraocular lens (IOL). Hyperopic patients with ocular surface disease often do very well with phakic IOLs. In the Phase III registry trial for the Food and Drug Administration (FDA) the smallest amount of hyperopia accepted into the study was +1.50D, so technically the patient does not meet the eligibility criteria for a phakic IOL.

"If this patient were +1.5 or more, I would absolutely offer her an ICL after controlling her ocular surface disease," said Dr. Dougherty. "When I do ICLs [intraocular contact lenses] on patients with ocular surface disease after I control them, they have fewer symptoms than laser vision correction patients. You get a better quality of vision with phakic IOL."

But there are significant potential side effects to this intraocular procedure, including glaucoma, cataract, endophthalmitis, and retinal detachment, that are not associated with surface procedures such as LASIK, PRK, or conductive keratoplasty (CK). In addition, enhancements are difficult after a phakic IOL.

CK is another option. The procedure has minimal affect on dry-eye syndrome, one of the advantages of using CK, said Dr. Donnenfeld. But he said this procedure does have issues: fluctuating vision, regression, induced astigmatism, and the need for enhancement.

PRK is also an option. PRK is a good choice in patients with dry eyes because physicians can avoid cutting corneal nerves, as with LASIK, which would create a more neurotrophic environment on the ocular surface.

Dry-eye patients tend to recover quicker after PRK than after LASIK, from the standpoint of sensation and tear production. The panel agreed that PRK likely would work best for the patient in this case because it works well with patients with mild hyperopia.

There are some downsides to PRK in the setting of dry eye. Visual rehabilitation can be prolonged, and enhancements can be difficult. Also, contact lens wear is difficult after PRK in dry-eye patients, and there is the possibility of typical PRK side effects such as haze, infectious keratitis, and pain.

LASIK is the fourth option. LASIK in an untreated dry eye can be unsatisfying, but the literature supports that pre-treating dry eyes with Restasis can improve LASIK outcomes, with fewer post-operative dry-eye problems and the need for fewer enhancements.

The advantages of LASIK include fast visual rehabilitation, a speedier return to work, minimal pain, and ease of enhancements, if necessary. But in patients with dry eyes the ocular surface needs pre-treatment with Restasis in order to ensure an uncomplicated procedure.

**Resolution:** The patient used Restasis twice daily in both eyes for one month. Her dry-eye symptoms resolved, and she underwent uncomplicated bilateral LASIK.

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"You get a better quality of vision with a phakic IOL."

— Paul J. Dougherty, M.D.
Restasis and Punctal Plugs

The Food and Drug Administration (FDA) labeling for Restasis (Allergan, Irvine, Calif.) states that increased tear production was not seen in patients with punctal plugs. This conclusion was based on the subset of patients in the Phase III trial of Restasis who also had punctal plugs in place at the time of entry into the study.

In that subset of patients there was no statistically significant improvement compared to the group treated with Restasis that did not have plugs. There was only a small number of plugged patients in the trial, and the FDA’s label means that there is not enough data to determine whether plugs provide additional benefit in dry eyes treated with Restasis.

A study was recently conducted to evaluate the possible additive effects of Restasis and punctal plugs in patients with dry-eye syndrome. The study included three treatment groups: plugs alone, Restasis alone, and both plugs and Restasis.

The combination group had statistically better outcomes than either of the two monotherapy groups. Interestingly, the Restasis alone group did better than the plugs alone group.

In general, punctal plugs are a logical second-line treatment in patients whose treatment goals are not met on Restasis alone. A plug alone increases the quantity of tears on the surface but does nothing to improve the quality of tears.

In fact, tears of dry-eye patients contain inflammatory mediators, and placing plugs might only increase the contact time of those inflammatory mediators with the already damaged ocular surface. A better idea is to improve the quality of tears first—using Restasis—then add plugs, if needed, to improve the retention of the improved tears.

References


8. Salib GM, McDonald MB, Smolek M. Results of a prospective randomized clinical trial to investigate the safety and efficacy of cyclosporine 0.05% drops vs. unpreserved artificial tears in dry eye patients undergoing LASIK. J Cat Refr Surg in press, 2006.

Educational Objectives

Ophthalmologists reviewing this material will:

• Review the results of multi-centered studies and develop a better understanding of the implications of their results;

• Review and evaluate current surgical treatment for glaucoma; and

• Determine and develop the appropriate treatment plan for each patient.

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Which of the following environmental adaptations can improve dry eyes?

- A humidifier
- Sitting away from forced air ventilation ducts
- Both a and b

Which of the following are common symptoms of dry eye syndrome?

- Burning
- Floaters
- Both a and b

Which of the following is true regarding dry eye syndrome?

- Tears may be abnormal in quality, quantity, or both
- Mucin-producing goblet cells are lost in the disease process
- Both a and b

Which of the following is true about topical cyclosporine for dry eye syndrome?

- Common side effects include glaucoma and retinal detachment
- Goblet cell populations increase with treatment
- Both a and b

Which of the following is true regarding ocular burning upon initiating therapy with topical cyclosporine?

- It usually resolves within 4-6 weeks after starting therapy
- Pre-treatment or co-treatment with a low-dose anti-inflammatory drug
- Both a and b are true

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