Improving the Health of the Ocular Surface With Artificial Tears

Ophthalmologists offer their insights into how and when to use drops to improve ocular surface disease.

BY KERRY D. SOLOMON, MD; KARL G. STONECIPHER, MD; RAJESH K. RAJPAL, MD; PAUL KARPECKI, OD; AND DANIEL S. DURRIE, MD

Blink Tears: my go-to treatment.

By Kerry D. Solomon, MD

When choosing an artificial tear to optimize the ocular surface and visual acuity, I look for one that minimizes blur and remains on the eye for a long time. I have a few top choices, but recently, I have favored a hyaluronic acid-based tear (Blink Tears; Abbott Medical Optics Inc., Santa Ana, CA) that is clinically proven to reduce blur and moisturize the cornea for at least 1 hour (data on file with Abbott Medical Optics Inc.). Blink Tears came on the market in 2008. My patients like this product because it treats all types of dry eye, both aqueous-deficient and evaporative dry eye etiologies. The hyaluronic acid, which is found naturally in the eye, performs the main moisturizing and lubricating function.

In my experience, a tear containing hyaluronic acid relieves both the subjective and objective symptoms of patients. Many artificial tears will only treat the subjective symptoms, such as burning and scratchiness, but in my patients, Blink Tears has significantly improved corneal staining with lissamine green. I recommend this product to all of my dry eye patients, but some need supplemental treatment. I instruct these patients to use Blink Tears four-to-five times daily to treat their symptoms and to administer Restasis (Allergan, Inc., Irvine, CA) twice a day, as a means to increase the production of aqueous and treat the underlying problem. Occasionally, a patient may have evaporative dry eye, in which case I will also prescribe oral omega-3s and blepharitis treatment (eg, warm compresses, lid hygiene, and pulsed therapy with topical azithromycin as needed). A tear containing hyaluronic acid, however, is my basic choice for treatment in all dry eye patients.

The clinical benefits of an artificial tear with hyaluronic acid are excellent coating of the ocular surface, relief of symptoms, enhanced visual quality, and a longer duration on the eye than other artificial tears. Studies of Blink Tears have shown that it has a moisture-retention time of more than 60 minutes. The product works by thickening on the ocular surface when the eye opens and thinning with each blink (data on file with Abbott Medical Optics Inc.). This behavior is due to the hyaluronic acid’s ability to retain moisture, which, in my experience, allows the tear to adapt to each patient’s needs.
I find Blink Tears beneficial to cataract and refractive surgery patients as well. Pretreating the ocular surface produces better wavefront measurements for refractive surgery, and optimizing the ocular surface provides cataract surgery patients with better visual results faster. I recommend patients use Blink Tears four or five times daily before surgery. The length of the treatment really depends on how long their symptoms last, and most patients are eventually able to discontinue using the tears.

Blink Tears are an important part of my practice because the hyaluronic acid relieves patients’ dry eye symptoms in the same way it does naturally in the eye.

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Optimizing the ocular surface with Oasis Tears to improve outcomes.

By Karl G. Stonecipher, MD

In a refractive or a refractive cataract surgery practice, I believe the number-one issue is how the patient sees postoperatively. Patients are paying additional money to improve the quality of their life with superior vision. That process starts with surgeons’ attention to detail preoperatively and ends with paying attention to postoperative outcomes. The primary referral I receive in my practice today is the unhappy patient, and the usual problem is a compromised ocular surface.

Ocular surface disease is magnified by presbyopia-correcting IOLs. A healthy preoperative tear film reduces the chance of postoperative infection, enhances ocular comfort, and improves postoperative visual outcomes.

By treating dry eye before working up patients for refractive or multifocal IOL surgery, I can obtain more accurate information about their eyes and thus better predict important parameters, such as the data required to calculate the lens’ power. One of the products I have found helps my patients preoperatively is Oasis Tears (Oasis Medical, Inc., Glendora, CA).

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—Karl G. Stonecipher, MD

The high molecular weight of Oasis Tears combined with the concentration of the delivery system creates a sponge-like matrix through a process called molecular crowding. The glycerin within this matrix captures and holds water with each blink of the eye. The hyaluronan adapts to the eye by thinning when the lids close and thickening upon their opening.

Exactly how hyaluronan works is unknown, but the viscoadaptive formulation stays on the ocular surface for a longer period of time than do other drops. In a study of 30 eyes, 77% of patients increased their tear breakup time by about 50%, which means they saw better for longer and did not need to use drops as frequently (data on file with Oasis Medical, Inc.). Unlike most artificial tears, Oasis Tears do not distort patients’ vision for 30 seconds to 1 minute upon instillation. I find that patients are more compliant with artificial tear therapy when they have visual clarity upon instillation and a long-lasting effect. These qualities make Oasis Tears ideal for patients undergoing refractive and premium IOL surgery. I recommend Oasis Tears as a first-line agent or in conjunction with Restasis (Allergan, Inc., Irvine, CA) when the problem is more severe.

In addition, sodium hyaluronate has been shown to improve both fluorescein and rose bengal staining in patients with dry eye disease,1,2 a finding that suggests that treatment with this agent promotes corneal and conjunctival epithelial healing. In addition, two recent studies demonstrated that artificial tears containing sodium hyaluronate reduced damage to the ocular surface in patients with ocular surface disease and promoted corneal wound healing.3,4

I favor a product that patients find comfortable and that does not induce more visual distortion. Oasis Tears fit these criteria.

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Clinical experience with Optive for managing the ocular surface.

By Rajesh K. Rajpal, MD

As our understanding of dry eye disease has improved, we ophthalmologists have added new treatment options to our practice that have enhanced patients care. Artificial tears continue to be an important component of most treatment regimens. With more brands and types of tears now available over the counter, patients often ask me to recommend a product. I find it useful to educate patients on the types of tears that may be most suitable to their condition and to provide samples so they may choose what helps them most.

After they try multiple sample drops, the majority of my dry eye patients select Optive (Allergan, Inc., Irvine, CA), because they feel it provides the greatest level of ocular comfort and improvement of their symptoms. I believe that their assessment is likely due to Optive’s dual mechanism of action. This product protects the corneal epithelial cells and treats the hypertonicity that is associated with dry eye disease. In addition, it lubricates and hydrates the surface, which improves ocular comfort. Optive Sensitive is a preservative-free formulation and may be a more appropriate choice for patients who instill lubricating drops frequently.

One of the most common concerns that patients face is blurring after the instillation of artificial tears, which is generally worse with highly viscous drops. Patients frequently tell me that they like the consistency of Optive, because it improves their ocular irritation and dryness and lasts longer than many other drops. They also notice less blurring after its instillation. The decrease in blurring is particularly important when considering the use of artificial tears prior to refractive or cataract surgery due to concerns about the healing process and the need for the vision to clear as quickly as possible.

The benefits of treating ocular surface disease prior to refractive surgery are well known. For example, in a randomized, controlled clinical trial of 228 patients undergoing LASIK, preoperative treatment two to four times daily with Optive Sensitive resulted in a statistically significant improvement in the signs and symptoms of dry eye (poster to be presented by Peter Simmons, MD, at the ASCRS/ASOA Symposium on Cataract, IOL and Refractive Surgery in April 2009). I find that the use of artificial tears is just as important in patients undergoing cataract or corneal surgery.

I have patients start using artificial tears 4 to 6 weeks preoperatively at least four times daily. I recommend that they continue administering the drops postoperatively as necessary during the healing process. Most patients taper their use of artificial tears during the postoperative course, although the majority of them will continue to use drops once or twice daily. Some may need tears indefinitely. Patients undergoing refractive surgery or the implantation of a premium IOL during cataract surgery are often more sensitive to visual changes. In my experience, treating the ocular surface improves the visual outcomes of most of my patients and thus enhances their postoperative satisfaction.

As the options for treating ocular surface disease expand, artificial tears will still be helpful, and surgeons will continue to rely on them. I have found Optive to be beneficial, because my patients do, too.

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Advances in the management of dry eye: Soothe XP.

By Paul Karpecki, OD

Clinicians often see advanced ocular surface disease. All artificial tears are not the same; what works for some forms of dry eye does not work for others. A key variable is concurrent lid disease and its effects on the lipid layer of the tear film.

Lid disease, especially posterior blepharitis, is extremely common. Furthermore, due to the fact that meibomian glands contribute to the oil in the tear film, it is likely that disruption of the meibomian gland production could adversely affect the tear film. There are various stages of posterior blepharitis. The disease’s signs range from a frothy tear film to inspissated and even scarred meibomian glands. All levels of posterior blepharitis may disrupt the tear film by affecting the critical oil layer. The oil layer is essential to prevent evaporative dry eye consequences.

Soothe XP (Bausch & Lomb, Rochester, NY) is the only artificial tear that has the highest clinically demonstrated ability to statistically increase the lipid layer thickness of the tears. In one study, one drop actually doubled the lipid layer thickness.1

The lipid layer is essential to quality vision, ocular comfort, and the retention of tears on the ocular surface. Although there are no diagnostic tests to measure the tear film’s components and determine lipid deficiency, it is clear that certain patients are prone to lipid-related problems. They include patients with lid disease such as meibomitis and blepharitis, those with systemic conditions such as rosacea, and individuals whose eyes are unresponsive to aqueous-based artificial tears.

In a clinical study comparing Soothe XP to the most commonly prescribed artificial tear, the former was shown to statistically and substantially increase the thickness of the lipid layer.2 Soothe XP contains mineral oils of varying molecular weight, which contribute to the lipid layer’s improvement and the long-term effect of a single drop.

By thickening the lipid layer, Soothe XP is very effective at preventing the evaporation of tears from the ocular surface. It is a wonderful tool in the management of dry eye disease. The product is also useful in contact lens patients who have mild or moderate meibomitis or blepharitis.

Systane Ultra and refractive surgery.

By Daniel S. Durrie, MD

I am very impressed that several pharmaceutical companies have started to focus on the treatment of dry eye. In addition to developing drops that effectively lubricate the ocular surface, manufacturers are creating agents that are more comfortable for patients to instill as well as trying to treat the underlying disease. As a result, more companies are emphasizing the soothing properties of their artificial tears.

I prescribe Systane Ultra (Alcon Laboratories, Inc., Fort Worth, TX) to all of my refractive surgery patients pre- and postoperatively. Because the drops have soothing properties, they may improve patients’ compliance with their postoperative regimen. Patients who are more comfortable are also more likely to share their positive experiences with friends and family, who may then decide to undergo refractive surgery.

I always try new brands of drops myself before I prescribe them to patients. I also ask my staff and some key patients to try them, and their feedback guides my decision on whether to add the product to my offerings. I have always valued the results of this informal process in addition to scientific evidence when deciding which treatment is best for my patients. Artificial tears often have satisfactory outcomes in a laboratory setting, but the true test of their effectiveness is how they perform in the real world. Because I had a positive experience with Systane Ultra, I did not hesitate to add it to other products in my treatment armamentarium.

I approach all dry eye patients, whether I am treating them pre- or postoperatively, as individuals. Instead of

following a “cookbook” regimen, I prescribe treatments that best fit their symptoms and the underlying cause of their discomfort.

Although all patients benefit from having the best possible tear film, a healthy ocular surface is paramount before refractive surgery. Several studies showed that refractive surgery exacerbates the symptoms of dry eye in patients who suffered from the condition preoperatively. Patients who have dry eyes preoperatively may also experience postoperative dryness longer than those who had healthy ocular surfaces preoperatively.

When I evaluate patients for refractive surgery, I always check the function of their meibomian glands as well as the quality and stability (ie, tear breakup time) of their tear film. Patients who present with blepharitis or other conditions caused by poorly functioning meibomian glands start a regimen of lid hygiene and oral omega-3 fatty supplements. I always follow up with these patients to ensure they are adhering to my instructions before scheduling them for surgery, because the oils produced by the meibomian gland are important for maintaining the tear film’s quality. Any abnormalities in the tear film can affect wound healing. Preliminary research has shown that some patients with blepharitis respond well to Azasite (azithromycin ophthalmic solution 1%; Inspire Pharmaceuticals, Durham, NC), but this agent is still under investigation. In some cases, I prescribe Restasis (cyclosporine 0.05%; Allergan, Inc., Irvine, CA) preoperatively for 1 month if I think it will further improve the quality of the tear film.

For the first 4 to 6 hours postoperatively, I instruct my patients to instill Systane Ultra every 30 minutes to maintain sufficient lubrication as the anesthesia wears off. I also advise patients to blink frequently, since the cornea is numb and this suppresses the normal blink reflex. For the past 15 years, I have been pressuring the pharmaceutical industry to expand its research into treatments for dry eye. I am happy to report that several companies have risen to the challenge and that patients are beginning to benefit from their efforts. I look forward to the results of the companies’ ongoing clinical studies.

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“Because Systane Ultra drops have soothing properties, they may improve patients’ compliance with their postoperative regimen.”
—Daniel S. Durrie, MD

“Ecabet sodium’s unique mechanism of action may improve the quality and quantity of the tear film.”
—Gregg J. Berdy, MD

The aging of the baby boomer generation and the popularity of advanced refractive surgical procedures have made the evaluation and treatment of dry eye syndrome a much more important clinical challenge. Based on the great strides ophthalmologists have made in understanding the underlying pathophysiology of dry eye and the impact of the tear film on the health of the ocular surface, quality of vision, and surgical outcomes, a consensus is emerging that successful dry eye therapy must address both the quantity of tears produced and the quality of the tear film. Our existing therapeutic choices, including the only prescription product currently available (Restasis; Allergan, Inc., Irvine, CA), principally address the quantitative side of the equation. Agents or interventions that stimulate the production of a healthy tear film through the production of mucins and lipids remain the next frontier in dry eye therapy.

A new class of topical mucin secretagogues—agents that increase the quantity of mucin produced by conjunctival goblet cells—is moving through the laboratory and toward FDA review. A healthy tear film is composed of mucin, lipid, and aqueous layers, with mucin forming the lowest layer of the film adjacent to the ocular surface. By smoothing the ocular surface while enhancing the stability of the tear, mucin prolongs the time that the tear lubricates the eye. Generally, mucin secretagogues are thought to work by tar-
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targeting the P2Y2 receptor pathway. These receptors are abundant on the mucosal, conjunctival and palpebral epithelia and activate goblet cell-mediated mucin secretion. One agent currently in development (ecabet sodium; Ista Pharmaceuticals, Inc., Irvine, CA), however, seems to have a different and not yet thoroughly understood mechanism of action that may enable it to improve both the quality and the quantity of the tear film. Ecabet sodium’s capacity to stimulate the production of mucin by goblet cells has already been established in a different part of the anatomy. In Japan, the agent is available as an oral treatment for gastritis and gastric ulcers. In the United States, ecabet sodium, formulated as an eye drop, has recently emerged from phase 2 clinical evaluations for dry eye. Although these three studies have yet to be published, the company has announced intriguing results that point to the agent’s dual action.

The first two studies, conducted in controlled-environment chambers, demonstrated positive trends in the improvement of patients’ symptoms (per the Ocular Surface Disease Index and patients’ worst symptoms) and several key signs of dry eye such as corneal staining in one study and the blink rate in both (data on file with Ista Pharmaceuticals, Inc.). In the latest study, patients whose dry eyes were treated with ecabet sodium achieved an encouraging improvement in the objective signs of the quality of the tear film (measured by tear film breakup time) and the production of
tears (measured by anesthetized and unanesthetized Schirmer tests) compared with the results among patients given placebo drops (data on file with Ista Pharmaceuticals, Inc.). There was no improvement, however, in the Ocular Surface Disease Index. The anesthetized Schirmer results suggest that ecabet sodium may affect basal tear secretion, which is one of the main factors in the etiology of dry eye disease. Test scores began trending positive as early as day 22 of treatment and continued to improve through day 43, when dosing was stopped, per protocol. Furthermore, the percentage of patients who responded to treatment with ecabet sodium was favorable overall by historical standards, and patients with more severe disease tended to have higher response rates. It should be noted that these three studies were not powered to show statistical significance, so confidence intervals were used to evaluate trends in improvement. These findings will guide the design of a phase 3 clinical program for ecabet sodium (data on file with Ista Pharmaceuticals, Inc.).

Given the multifactorial nature of dry eye syndrome, ongoing development and research are necessary. Ista Pharmaceuticals is also evaluating the efficacy of a low concentration of its topical nonsteroidal anti-inflammatory drug bromfenac (Xibrom) in breaking the inflammatory cycle associated with ocular surface disease in a phase 2 trial currently underway.

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Prolacria stimulates the release of all three major components of the tear film.

BY JODI I. LUCHS, MD

Dry eye syndrome is one of the most common conditions encountered by eye care professionals. This multifactorial disease of the tears and ocular surface causes ocular discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is also accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

The tear film is a complex structure composed of three elements: lipids derived from the meibomian glands of the lids, an aqueous component produced by the lacrimal glands and transconjunctival fluid transport, and mucins produced by the epithelial cells of the cornea and conjunctiva as well as the goblet cells of the conjunctiva. These components form a complex gel of mucin and aqueous elements covered by a thin lipid layer that rests on a base of mucins, which form glyocalyx-protecting corneal epithelial cells. This epithelial structure is essential to the creation and maintenance of a stable tear film, which protects the cornea from infectious and environmental assaults.

The medical community recently recognized an important correlation between visual symptoms, postoperative surgical outcomes, and the status of the tear film. Specifically, the tear film is the most important refractive surface of the eye. Its stability is essential for accurate preoperative keratometry, topography, and wavefront measurements; proper corneal wound healing after cataract and refractive surgery; and optimal visual outcomes. An unstable tear film and central corneal staining can translate into degraded visual acuity. In these eyes, the irregular corneal surface impedes vision. Because blinking does not restore an adequate tear film, the visual disturbance remains even immediately after the blink. In this situation, despite successful surgery, the patient may be unhappy postoperatively.

I have been involved in the clinical trials of a promising new drug for the treatment of dry eye. Prolacria (Inspire Pharmaceuticals, Inc., Durham, NC), the proposed brand name for the compound diquafosol tetrasodium, has a novel mechanism of action that targets the release of all three major components of natural tears: mucin, lipids, and fluids. This potent and selective agonist for the P2Y2
receptor (a purinergic receptor on mucosal surfaces that is responsible for regulating fluid transport across cell membranes) on corneal and conjunctival surfaces. The drug stimulates fluid secretion from the conjunctiva, mucin secretion from goblet cells, and lipid production from the meibomian glands. It also enhances epithelial migration.

Prolacria has received two approvable letters from the FDA and is awaiting final approval pending the outcome of additional phase 3 trials, which are underway.

In studies, Prolacria has consistently reduced mean corneal and conjunctival staining compared to placebo, and the effects have been observed within 2 weeks of patients’ starting the drug, with peak effects around 6 weeks. Patients in these studies have achieved higher rates of complete corneal clearing after treatment with Prolacria compared to placebo, with one trial showing a statistically significant difference. The drug has also consistently been shown to reduce mean central corneal staining compared to placebo. In one study, Prolacria produced an improvement in Schirmer scores and some patient-reported symptoms. Finally, the integrated safety database from studies with a combined sample size of 1,645 found Prolacria to be generally well tolerated. The most common ocular adverse event was burning and stinging upon instillation, with a rate of 4% for the drug versus 1% for placebo (data on file with Inspire Pharmaceuticals, Inc.).

Prolacria is a potent new medication that I hope will be available in the near future for the treatment of dry eye. The drug’s novel mechanism of action, which stimulates the release of all three major components of the tear film, may make it an appropriate choice as primary therapy for dry eye resulting from a variety of causes. Furthermore, the agent may complement existing therapies for dry eye such as Restasis (Allergan, Inc., Irvine, CA), by supporting the mucin and lipid components of the tear film, in addition to the aqueous components.

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