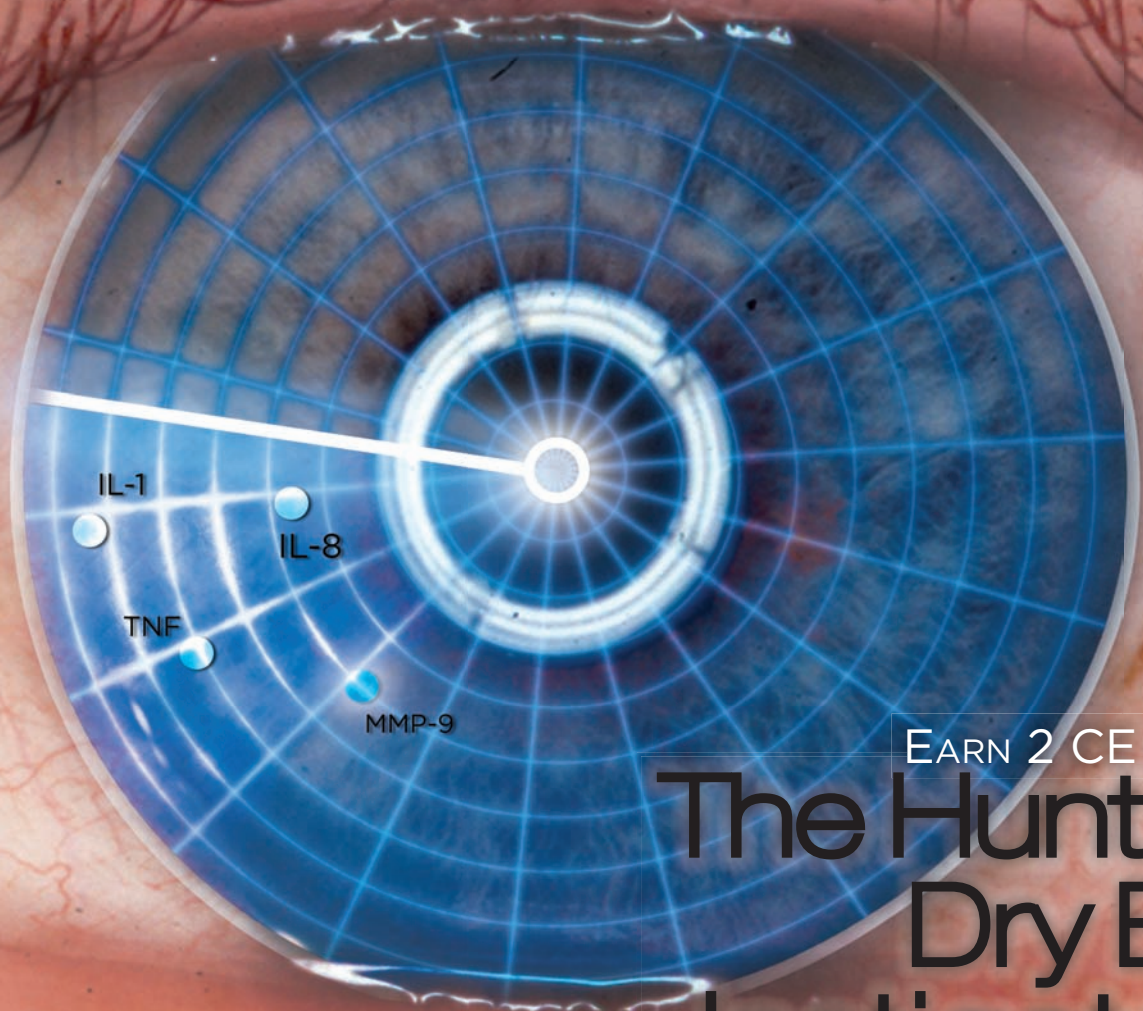
RCCL®
REVIEW OF CORNEA & CONTACT LENSES

MAY 2014



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The Hunt for Dry Eye Instigators

Treatment options that target inflammatory mediators in the tear film may help clinicians achieve victory over this often difficult to manage condition.

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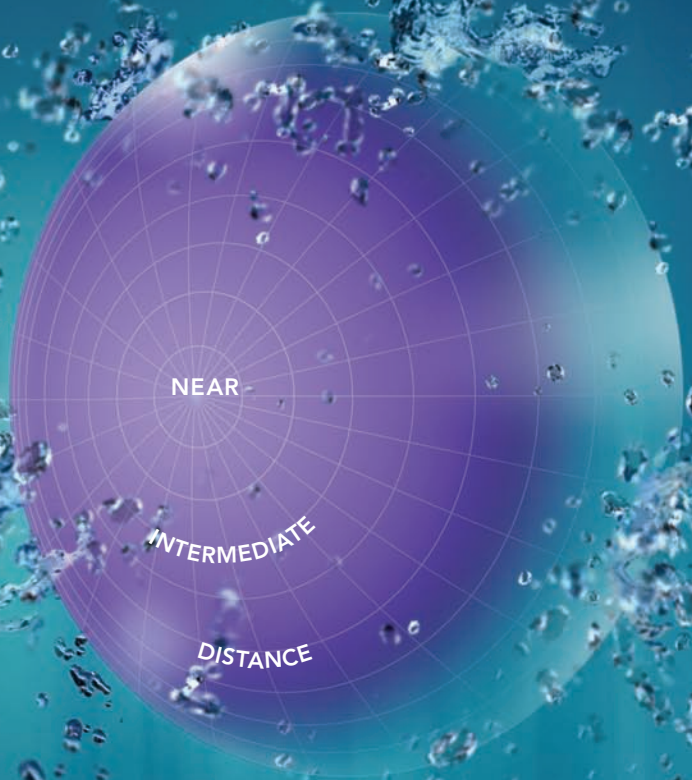

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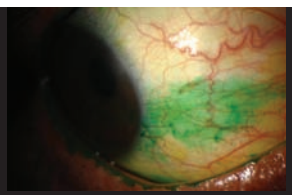

CE — The Hunt for Dry Eye Instigators

Treatment options that target inflammatory mediators in the tear film may help clinicians achieve victory over this often difficult to manage condition.

By Michelle M. Hessen, OD

Clinical image on the cover courtesy of Mark Abelson, MD/Ora, Inc.

IN BRIEF

• **Google** has applied for a patent to fit a **camera** into a **contact lens**. According to the application, inserting the camera into the lens will not dramatically increase the thickness of the lens. The addition of cameras will allow the lenses to process images and collect a variety of data, such as motion, colors, face, etc. Additionally, the contact lenses may include sensors that would be used to track blinking, which could be used to control or trigger devices remotely via blinks.

• **Johnson & Johnson** announced that the company is now **accepting research proposals** related to **meibography and tear film stability** with contact lens wear. Specifically, J&J is looking for research proposals in the areas of correlating clinical findings to meibomian gland image analysis and tear film stability, and categorizing the magnitude of meibomian gland changes to contact lens type or length of wear. **To inquire** about proposal submission, contact the Clinical Research Administrator at RA-VISUSIISRequests@its.jnj.com.

• **Smoking tobacco** has a negative impact on the **healing process of corneal insults**. In a study published in the May 2014 *Cornea*, researchers reviewed the charts of 87 patients with corneal abrasions and 52 patients with keratitis between 1990 and 2010. The study demonstrated that **epithelial healing is delayed** 1.1 days on average in smokers vs. non-smokers, and 23.9 days on average in smokers with keratitis. Additionally, neurotrophic corneas and fungal infections also exhibited a prolonged healing period in smokers.

Jetton JA, et al. Effects of tobacco smoking on human corneal wound healing. Cornea. 2014 May;33(5):453-6.

A New Treatment for Allergic Conjunctivitis?

Use of tacrolimus 0.1% eye drops is highly effective in treating refractory allergic conjunctivitis, according to a study published in the April 2 online *British Journal of Ophthalmology*.

The prospective observational study evaluated the eyes of 1,436 patients with refractory allergic conjunctivitis who did not respond favorably to prior treatment with conventional allergy drugs, topical steroids and/or topical cyclosporine.

During the trial, tacrolimus 0.1% drops were administered twice daily to each patient. The researchers rated 10 clinical signs (palpebral conjunctiva hyperemia, diffuse edema, follicles, papillae, giant papillae, bulbar conjunctiva hyperemia, bullous edema, limbal trantas' dot, swelling and corneal epithelial signs) and six clinical symptoms (itching, discharge, lacrimation, photophobia, foreign body sensation and eye pain) on a four-grade scale (0=none, 1=mild, 2=moderate and 3=severe).

Patients were graded at baseline, one month, two months, three months and six months. The total score of both the 10 clinical signs (range 0-30) and six clinical symptoms (range 0-18) decreased significantly from baseline to the one-month evaluation ($p<0.001$), indicating the agent's ability to provide rapid relief.

At baseline, the mean total score of clinical signs was 15.3; at final observation, the mean total score decreased to 5.9. The mean total score of clinical symptoms decreased from 8.1 at baseline to 1.8 at final observation. Additionally, both giant papillae and corneal lesions were reduced significantly ($p<0.001$) following use of tacrolimus 0.1%.

Prior to initiating tacrolimus therapy, 239 patients were treated with cyclosporine 0.1% eye drops for at least one month; these patients exhibited giant papillae or corneal epithelial disorder scores greater than two at initiation of treatment. Following one month of tacrolimus use their clinical signs score decreased from 16.8 to 6.7, and their clinical symptoms score decreased from 9.1 to 1.9.

The researchers noted adverse reactions in 117 patients, with the only major reaction being a burning sensation (45 cases).

Additionally, two cases of bacterial keratitis, two cases of herpetic keratitis and one case of bacterial corneal ulceration were observed. Atopic dermatitis or asthma was noted as an underlying condition in these cases.

Initially developed as an immunosuppressant for use following organ transplantation, tacrolimus is now used clinically for multiple immune-mediated conditions. The researchers suggest that the use of topical tacrolimus is both safe and effective in treating patients with severe allergic conjunctivitis.

Fukushima A, et al. Therapeutic effects of 0.1% tacrolimus eye drops for refractory allergic ocular diseases with proliferative lesion or corneal involvement. Br J Ophthalmol. 2014 Apr 2. [Epub ahead of print]

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A Balanced Dry Eye Diet

A Mediterranean diet may actually have a negative effect on dry eye symptoms, while increased intake of vitamin D may have a small but positive effect, according to a study published in the May 2014 *Cornea*.

Two hundred forty-seven male patients between 55 and 95 years old (mean age 69) at the Miami Veteran's Affairs eye clinic with normal eyelid, corneal and conjunctival anatomy were recruited to undergo dry eye testing following dietary changes.

The subjects adhered to the Mediterranean diet, which includes a relatively high intake of fruits, vegetables, monounsaturated fat, fish, whole grains, legumes and nuts, as well as moderate alcohol consumption. In addition, the overall intake of red meat, saturated fat and refined grains is significantly decreased.

Previous studies have demonstrated that the Mediterranean diet may be a protective factor against all-cause mortality, coronary heart disease and diabetes. Because the diet is linked to a decrease in inflammatory markers, there is plausibility that it may have an effect on dry eye disease.

Additionally, the researchers examined the effects of increased vitamin D intake on dry eye disease, as 25-hydroxy vitamin D was inversely correlated with the inflammatory marker soluble interleukin-2 receptor.

Each patient was asked to fill out a 2005 Block Food Frequency Questionnaire and the 5-item Dry Eye Questionnaire. Additionally, an ocular surface examination consisting of tear osmolarity evaluation, tear break-up time, corneal staining, Schirmer's test was conducted on each patient.

Patients who adhered to the Mediterranean diet were actually found to have an *increased* risk of dry eye ($p=0.007$). Patients who reported a higher Mediterranean diet score on the food frequency questionnaire (i.e., those who adhered to the plan) demonstrated abnormal meibum quality, abnormal staining and higher Schirmer's test scores. Vitamin D levels exhibited no significant association with dry eye parameters; however, increased levels of vitamin D were significantly associated with a decreased presence of dry eye symptoms ($p<0.01$).

While the Mediterranean diet has been shown to improve systemic health, there was no beneficial effect on dry eye symptoms. However, higher levels of vitamin D exhibited a small but favorable effect on dry eye disease.

Galor A, Gardener H, Pouyeh B, et al. Effect of a Mediterranean dietary pattern and vitamin D levels on dry eye syndrome. 2014 May;33(5):437-41.

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LSCD—It May Be the Lenses

We must be on the lookout for limbal stem cell deficiency early in its course, especially in contact lens wearers, to avoid the need for surgical intervention.

Every year we see a handful of soft contact lens wearers who present with significant stem cell deficiency (LSCD). Unlike acute stem cell changes associated with chemical injury, surgery, radiation, trauma or congenital deficiencies caused by aniridia, stem cell deficiencies associated with lens wear have features that include chronicity.[1-3] And that distinction gives us a window of opportunity to control its course.

The cause is most likely multifactorial and seems to be driven by an underlying inflammation and hypoxia, toxicity from the use of multipurpose solutions, and a mechanical component from overwear of soft lenses.

Many of the patients I've seen with this condition also have an accompanying ocular surface disease such as rosacea, meibomian gland dysfunction, dry eye or other additional drivers of inflammation. Of great interest, a disproportionate number of female wearers are affected, perhaps due to additional confounding factors (e.g., number of hours of lens wear, make-up, dry eye, etc.).[3]

As eye care practitioners who fit contact lenses and manage their complications, it's important to first recognize the problem, and second to be able to manage the complication in a timely and appropriate fashion.

In this month's Corneal Consult column (page 30), Jim Thimons highlights the many facets of early recognition of limbal stem cell deficiency, with a special focus on treatment options.

LOOK FOR THE SIGNS

Early signals of stem cell deficiency (exhaustion) can encompass a multitude of signs. A few examples include a whorl keratopathy and a confluent staining in a saw-tooth pattern, representing a difficulty in repopulating the epithelium in that region of the cornea.[1]

All of this ultimately leads to a non-healing defect and extensive irregularity of the corneal surface; conjunctivalization of the cornea can also occur wherein the conjunctiva grows past the limbus because there is no intact barrier.[1-3] A marked drop in acuity (increase in with-the-rule astigmatism), tearing, foreign body sensation and pain may occur.

One method of identifying LSCD, impression cytology, is done by pressing filter paper to the limbus. This simple procedure can detect a deficiency by confirming the presence and density of goblet cells from the cornea and conjunctiva. Confocal microscopy and even OCT imaging can help detect early changes of stem cell deficiency by characterizing the stem cell niche or palisades of Vogt.[1]

Holland and Schwartz have proposed a grading system whereby >50% clock-hour involvement and/or visual axis incursion constitutes severe disease.3 Unfortunately, when left unchecked and untreated, progression may require surgical intervention.

Stem cell autografts, although negating the need for immunosuppression, often are not an option because both eyes are generally involved (though the fellow eye may be subclinical). This requires allograft surgery with immunosuppression, using either cadaver or living relative limbal stem cell donors.[2,3]

There are several options for immunosuppression, including medications such as cyclosporine, tacrolimus, mycophenolate mofetil and corticosteroids.[1] Also, patients will require very close monitoring for possible side effects.[1]

Practitioners should continue to pay close attention to the limbus and peripheral corneal epithelium, as well as any accompanying ocular surface disease in every soft lens wearer. Ongoing surveillance for mild forms of the disease is critical! Remember the hallmarks—LSCD is insidious and recalcitrant, and I suspect it's an under-recognized complication of lens wear.[3]

It's important to stress that early recognition and intervention may prevent the need for surgical intervention.[3] Additionally, a lens wear holiday or hiatus with a modification in wearing time, a change in solution or a switch to GP lenses may help ward off potentially serious complications associated with this disease. RCCL

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Wash Away Your Old Hygiene Strategy

Early impressions of a new eyelid cleansing option to help keep your patients' eyes clean and microbe-free.

It really is no secret that clean eyelids promote healthy contact lens wear. As we've all seen clinically, patients who have blepharitis exhibit significant differences in tear physiology than those without blepharitis.[1] Tear lipids are oxidatively stable in their native environment because meibomian glands predominantly secrete only saturated and monounsaturated lipids.[2] Stable lipids don't degrade and don't cause discomfort or blur.

Blepharitis and meibomian gland dysfunction (MGD) patients typically experience heavy deposits of lipids on their lenses. This phenomenon is not limited to these patients, however. These lipid deposits may also be seen in those with no apparent MGD due to the individual composition of the meibum. Over time, lipids associated with the contact lens will become unstable and degrade. Once formed, these deposits impair optical quality and the wettability of the lens surface (with the latter resulting in a quick break-up of the tear film), which can eventually lead to intolerance to contact lens wear.[3]

In addition to affecting the tear film, vision and comfort, the lids play host to myriad microorganisms. Bacterial contamination of soft lenses is associated with microbial keratitis and corneal inflammatory events. Normal ocular organisms include coagulase-negative *Staphylococci*, *Corynebacterium* species, *Micrococcus* species, *Bacillus* species and *Propionibacterium* species.[4] The lid margin, commonly colonized by microbes, is found to harbor organisms up to 70% of the time.[5] Additionally, substantial lid bioburden is associated with a 2.5-fold greater risk of substantial lens bioburden, and is likely the major route of lens contamination.[5]

A NEW OPTION

Keeping the lids clean, which in turn keeps the lens clean, directly benefits patient comfort, safety and quality of vision. The "old-school" lid hygiene method included the use of diluted baby shampoo to remove debris and contaminants. While it remains convenient and inexpensive, this is not as safe or simple as it may sound.

Baby shampoos—as well as some eyelid cleansers—contain cocamidopropyl betaine, a surfactant and lathering agent that may cause an eyelid dermatitis.[6] Surfactants, the key ingredient in most lid scrub products, are also known to dry the skin and strip the area of oil—ironically, inducing increased production of oil in the glands.

A novel product, i-Lid Cleanser (NovaBay Pharmaceuticals), which contains pure hypochlorous acid 0.01%, offers practitioners a new option for lid hygiene. Hypochlorous acid is a naturally occurring chemical released by neutrophils to kill microorganisms and neutralize toxins released from pathogens and inflammatory mediators. As it is neutralized quickly, it's nontoxic to the ocular surface. Other hypochlorous acid products (e.g., Dakin) contain impurities (such as bleach), which are toxic to the ocular surface. In my experience, i-Lid Cleanser offers excellent lid cleansing capability without extraneous ingredients such as surfactants.

Pure hypochlorous acid 0.01% has shown to be fast acting against the five major bacterial pathogens associated with blepharitis during in-vitro laboratory tests. Although some conventional lid scrubs may lack antimicrobial activity even after prolonged exposure, efficacy of pure hypochlorous acid 0.01% was documented after just seconds of exposure, according to NovaBay Pharmaceuticals. In direct comparisons, the company says, pure hypochlorous acid 0.01% demonstrated a similar antibacterial spectrum of activity to Betadine—with 1,000 times less toxicity.

Its antibacterial properties make i-Lid Cleanser a welcome addition to any blepharitis or MGD-related dry eye treatment regimen. Additionally, the product can be useful in make-up removal and as an adjunct to contact lens wear. RCCL

1. McCann LC, et al. Tear and meibomian gland function in blepharitis and normals.. Eye Contact Lens. 2009 Jul;35(4):203-8.

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By Elyse L. Chaglasian, OD, and Tammy Than, MS, OD

The Source of the Irritation

Updated information from SCUT and a new in-office diagnostic test may help us provide better treatment options for many patients.

Ocular inflammation contributes to a number of patient symptoms and, in some cases, can even result in a loss of visual acuity. This month's column will review recently released information that may provide guidance to manage the often-devastating effects of corneal inflammation associated with microbial keratitis. Additionally, we will cover a new, in-office test that can aid practitioners in diagnosing ocular surface inflammation and selecting an appropriate treatment regimen.

REVISITING SCUT

We're all aware of what causes a corneal ulcer: the infectious agent adheres to the corneal epithelium and penetrates into the stroma. The response to the infection is inflammation, degradation of corneal structural proteins, ulceration and scarring.[1] Because steroid use to manage infectious keratitis is controversial, many were hopeful that the NEI's Steroids for Corneal Ulcers Trial (SCUT) would provide insight on this topic when it was published. To some extent, it did.

SCUT enrolled 500 patients with culture-confirmed bacterial ulcers and randomized them to either prednisolone or a vehicle with a tapering dose over a three-week period; all patients first received moxifloxacin for two days. As we learned in 2012, the study found that a majority of subjects did not demonstrate an improved outcome in best spectacle-corrected visual acuity (BSCVA) at three months, nor did they experience an increased incidence of side effects.[2]

Those who presented with the most central, severe corneal ulcers—which resulted in visual acuity of count fingers or worse—did appear to benefit from steroid use at the three-month evaulation.[2] While this study may not have had a radical impact on clinical practice, it did provide some reassurance to those who opt to use steroids in corneal ulcer management.

Additionally, this trial exemplifies why it is often important to read more than just the abstract to understand the nuances of a study. For example, just 3% of the patients were recruited from the US, while the remaining 97% were from India (of which 44% were agricultural workers).[3] As such, the organisms causing the ulcers were different than those expected in a study population primarily from the US.

Another factor to consider: only eight of the 500 subjects were CL wearers—a statistic atypical of a population presenting in the US with corneal ulcers. Also, the steroid used was prednisolone *phosphate* rather than *acetate*; ocular penetration is much poorer in the former once the cornea has re-epithelialized.[4] This choice of steroid prompts the question: Had the acetate formulation been used, would the outcome have been different?

Now, with new 12-month SCUT data published on BSCVA and corneal scar size in 399 cases from the original sample, we've learned:[5,6]

- Myofibroblasts and fibroblasts—active during wound healing—may help restore corneal transparency.
- There is some thought that the steroid benefit may be delayed.
- Immune-mediated tissue damage may be reduced, corneal remodeling may occur and the scar density may be reduced well after steroid use has been discontinued.

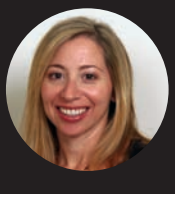
Following this 12-month analysis (note that steroid use had been discontinued for over 11 months), the researchers concluded that adjunctive topical steroid therapy might be associated with long-term clinical improvement in corneal ulcers not caused by *Nocardia* organisms.

In a small case series that examined five patients from SCUT, McClintic et al. published dramatic images at presentation, three months and 12 months. Over the course of the study, the density of the opacity in each patient was dramatically reduced by the 12-month evaluation. Additionally, when compared to the three-month visits, these patients also exhibited improved BCVA (when fitted with rigid contact lenses) at the 12-month follow up.[7] This case series demonstrates that corneal scars may continue to improve for many months after the ulcer has healed and the topical steroid has been discontinued.

EXAMINE THE TEARS

Matrix metalloproteinases (MMP), a family of proteolytic enzymes involved in remodeling of normal and pathological tissue, have the ability to degrade all components of the extracellular matrix.[8]

While the number of distinct MMP enzymes continues to grow, one is of particular interest to eye care professionals. MMP-9,




produced by stressed epithelial cells on the ocular surface, is detected in higher levels as a non-specific inflammatory marker of ocular surface disease. Elevated MMP-9 levels are found in a number of conditions, including ocular rosacea, meibomitis, Sjögren's syndrome and recurrent corneal erosions.[9]

Studies have shown that the range of MMP-9 in normal tears is between 3ng/mL and 40ng/mL.[10] A level greater than 40ng/mL is indicative of inflammation. Additionally, there is a direct correlation between MMP-9 concentration and the severity of dry eye. (*Table 1*).[11]

Solomon et al. showed that MMP-9 levels increased 66-fold in patients with meibomian gland dysfunction and 90-fold in patients with Sjögren's syndrome when compared to normal controls.[9]

In February 2014, Rapid Plasma Screening (RPS) received FDA CLIA-waived approval for a new in-office test called InflammaDry. It uses a process in which two antigen-specific antibodies capture the MMP-9 antigens. The test is confirmatory for inflammation if MMP-9 levels are 40ng/mL or higher.

Those familiar with the AdenoPlus detection test from the same manufacturer will note that the sample collector and test cassette look identical. However, the way samples are collected is different. With AdenoPlus, the collector should be dabbed and dragged along the inferior palpebral conjunctiva to rupture the follicles (freeing adenoviral hexon proteins). When collecting a sample with InflammaDry, the dragging motion is omitted.

Table 1. Severity Levels of Tear Dysfunction and Corresponding Average MMP-9 Levels[11]

Severity Level	Average MMP-9 Level
One	35.57ng/mL
Two	66.16ng/mL
Three	101.42ng/mL
Four	381.24ng/mL

The collector should be dabbed six to eight times, moving from temporal to nasal, allowing the patient to blink after each two dabs. A final five-second press on the nasal palpebral conjunctiva is recommended to ensure adequate saturation of the sampling pad. The collector is then snapped into the test cassette and placed in buffer for 20 seconds.

The results are available in 10 minutes. A single blue line indicates a good test and a normal MMP-9 level, while an additional red line of any intensity confirms the MMP-9 is at least 40ng/mL. The line intensity provides a semi-quantitative indicator of the concentration of MMP-9s; a lighter shade of red indicates lower MMP-9 levels, while a darker line signifies higher levels.

A multi-center trial noted a sensitivity of 85% and a specificity of 94% for InflammaDry. In the clinical setting, we may be able to use this test to identify dry eye patients who have an inflammatory component. These patients would benefit from anti-inflammatory therapy, such as corticosteroids, cyclosporine and doxycycline—all of which have been shown to inhibit MMP-9 activity. Conversely, we could also use the test to determine when to avoid therapies in patients with normal levels of MMP-9; this might help to avoid treatment failures.

Overall, the test may help to better determine appropriate treatments for our dry eye patients. The company also suggests it may be of benefit to identify elevated MMP-9 levels in patients prior to surgery (e.g., refractive surgery). Pre-surgical intervention with anti-inflammatory therapy for patients with elevated MMP-9 levels could then improve post-surgical outcomes and reduce potential complications.[12] RCCL

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12. www.rpsdetectors.com/in/products/about/product-information accessed 4/12/2014·

Surveyor of the Surface

Corneal topographers are great diagnostic tools for contact lens specialists —if you know how to use them. Here are several key points.

Imagine trying to steer your car while looking through a ship's porthole—and then suddenly one day being able to use a luxuriously large windshield instead. That's akin to the impact that corneal topography had on contact lens fitting when it became commercially available in the 1990s.[1]

Topographers offer practitioners a more comprehensive evaluation of the cornea than traditional manual keratometers, which measure only about 3mm to 4mm of the central cornea, whereas topographers measure the entire corneal surface. As such, they often reveal critical information that manual keratometers may miss. Corneal curvature in diopters or millimeters can be assessed on any portion of the cornea, a virtue that's especially useful when designing larger diameter GP lenses.

Topographers display a number of corneal maps, which can be used to analyze various types of valuable information. Different topographers have unique functions and features, but all are extremely helpful in GP lens design and evaluation. You do not need to be an expert on topography or spend hours learning how to manipulate the equipment or interpret the report to find success with these powerful tools. This month, I'll discuss some easy ways to understand topography—and use it to its full potential.

FOLLOW THE MAPS

The following maps can be essential in GP lens fitting:

• ***Axial power maps*** are very important and very useful diagnostic tools, as they are capable of distinguishing between regular astigmatism and irregular astigmatism. If a patient presents with a high amount of astigmatism and does not reach 20/20 through best-corrected acuity, it is necessary to use topography to rule out irregular astigmatism. If the astigmatism has an hourglass shape with symmetry (e.g., the superior half of the cornea is almost a mirror reflection of the inferior half), you're most likely dealing with regular astigmatism (*Figure 1*). Conversely, if the topography printout does *not* reveal symmetry, it's reasonable to consider it irregular astigmatism (*Figure 2*).

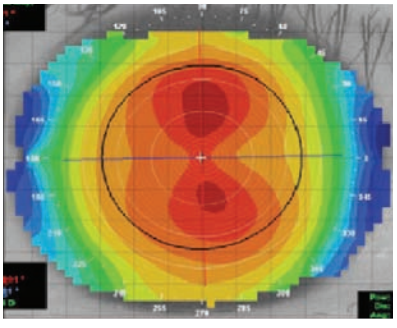


Fig. 1. An axial map of regular astigmatism.

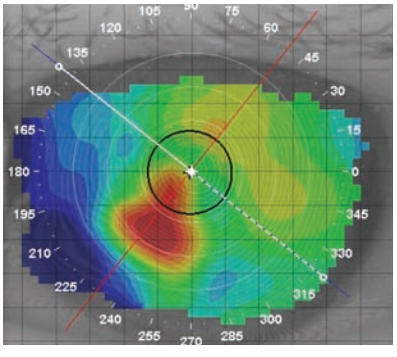


Fig. 2. An axial map showing irregular astigmatism.

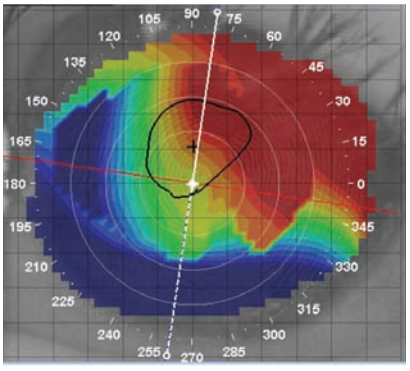
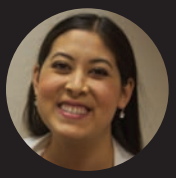


Fig. 3. Elevation maps reveal the cornea's highest and lowest points.

The ability to map the entire surface of the cornea has given practitioners the ability to diagnose and manage corneal surface abnormalities such as keratoconus and pellucid marginal degeneration. Additionally, this technology helps us to spot many other causes of irregular astigmatism. Post-transplant and post-refractive surgery patients have also greatly benefited from this technology.

• ***Elevation maps*** are incredibly useful resources that, curiously, many practitioners do not take full advantage of. This map highlights "high" and "low" areas of the cornea. Higher areas of the cornea will appear as warm colors (e.g., red and yellow), while the lower areas appear as cooler colors (e.g., green and blue) (*Figure 3*).

This map is particularly useful for scleral lens design—it can determine areas where corneal touch may occur, so that the lens can be designed to vault it. Once a scleral lens has been placed on the eye, it is necessary to examine the highest area of the cornea, as shown by the elevation map—this area will likely have



the thinnest amount of clearance underneath the lens and should be monitored very carefully.

An important point to remember: the steepest point of the cornea is not always the tallest point on the cornea; I repeat, *the steepest part of the cornea is not always the tallest point on the cornea!* This misconception is common among practitioners. I encourage you to quickly compare the axial map and elevation map on every patient—you may be surprised by where the highest point of the cornea is on some patients.

• ***Tangential maps*** are used to define points of curvature change. This map is particularly useful for your keratoconus patients, as it will allow you to measure the exact size and shape of the cone, which can help to determine an ideal GP lens design and optic zone size.[2]

For example, if topography reveals the patient has an oval cone that is decentered inferiorly, perhaps a nipple cone lens design would not be the best choice. Tangential curvature is also very helpful for corneal reshaping (i.e., orthokeratology). The tangential curve comparison map can be used to track progression of the reshaping process from visit to visit (*Figure 4*).

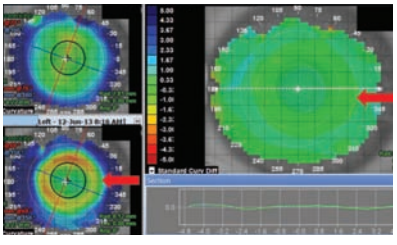


Fig. 4. Tangential maps can help to determine an ideal GP lens design.

The comparison map allows you to assess the effectiveness of treatment, as it shows a dioptric power change induced in the cornea.

OTHER MEASUREMENTS

These can be handy, too:

• ***Ruler***. Most topography software includes a ruler feature, which measures the precise corneal diameter. This can assist practitioners in determining appropriate lens diameters in both GP designs and soft custom toric lenses as well.

Measuring the overall corneal diameter is as simple as dragging the ruler from one edge of the cornea to another (*Figure 5*). It is often advantageous to measure at a 45° angle since the upper and lower lids/lashes can sometimes overlap the limbus/peripheral cornea, potentially resulting in an inaccurate measurement. Because it is estimated that one out of four patients fall outside the range of normal corneal diameters (11.6mm to 12.0mm), measuring corneal diameter can be very important to success of your contact lens wearers.[3,5]

• The ***sagittal height*** feature is especially useful when fitting scleral contact lenses. To begin, simply set the chord length to 10.0mm and find the height of the cornea. Next, take the sagittal height measurement and add 2,000.[4] For example, if we used a sagittal height measurement of 1,759 and added 2,000 to it, we would have a total of 3,759. This tells us the approximate height of the cornea at a set chord length, which in this example is 3,759 microns.

For a scleral lens fitting set that uses sag or sagittal height, simply choose the first diagnostic lens closest to this measurement. For this example, that would mean selecting a lens that is close to 3.759 sag, which would likely be approximately 3.8 sag. Taking advantage of the sagittal height feature will help reduce the amount of lenses needed during a trial lens fitting.

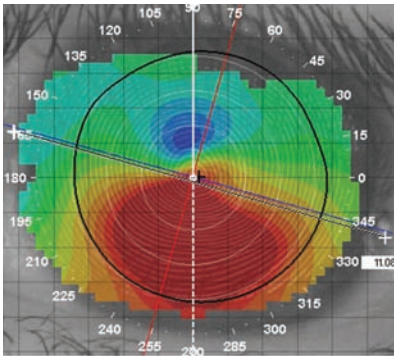


Fig. 5. The ruler can measure the entire corneal diameter.

Topographers are a great diagnostic tool for contact lens practitioners, and can help tremendously GP lens design. Spending a few extra moments with your topographer's software can reduce chair time by selecting appropriate lenses right off the bat and help monitor patient conditions more effectively. RCCL

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CONTROLLING THE OCULAR

We must strive to limit its untoward effects without undermining its essential role in protection and healing.

In eye care, there is a tendency to characterize ocular inflammation as something inherently negative that needs to be combated at all costs. In reality, however, the inflammatory response is part of the body's natural self-defense and tissue repair system, and is required to ensure normal functioning of the eye. When ocular tissue is exposed to an irritant or a perceived threat, the body responds by sending chemical mediators and inflammatory cells to clear the antigen, remove compromised tissue and assist in tissue reconstruction. There are many times indeed when we should be grateful rather than fearful.

These complex processes involve immune cells (e.g., lymphocytes, granulocytes, antigen-presenting cells) chemical mediators of ongoing inflammation (e.g., cytokines, prostaglandins, chemokines) and immune tissue (e.g., regional lymph nodes, secondary lymph tissue and primary lymph tissue such as the thymus).[1] Potential catalysts are many, but the reaction most commonly follows injury, allergy, infection or autoimmunity.

The subsequent effect could be mild and self-contained or severe and destructive; the outcome depends on the trigger and host events. In cases when the inflammatory response is excessive—with potential for permanent damage to ocular tissue—or the patient is symptomatic, treatment becomes indicated. Fortunately, clinicians have myriad ophthalmic anti-inflammatories to consider, of which the two broad classes are of course the steroids and the NSAIDs.

This article will provide an overview of the available options and my clinical impressions of the decision-making process. Given the many inherent differences in practitioners' comfort level and patients' circumstances, individualization is a necessity and practice patterns will vary.

Corticosteroids

The most important class of topical anti-inflammatory medications, corticosteroids have been a staple of medical care since the early 1950s.[2,3,6] Despite this long tenure, their exact anti-inflammatory mechanism is still not fully understood.[3] What we do know is that nearly all cells of the body express a receptor for these chemicals (the glucocorticoid receptor, or GR), which helps explain the wide-ranging effects—and side effects—of this class of medications. [3,5-7]

The primary anti-inflammatory mechanism of corticosteroids is likely their role in inhibiting cytokines and chemokines.[2,3,5,7] Though these chemical mediators are a cellular byproduct of inflammation, they are also probably among the primary mediators of the entire inflammatory cascade. They promote activation, migration, proliferation and recruitment of immune cells.

Secondarily, steroids inhibit production of inflammatory molecules such as prostaglandins (PGs), promote stability of granulocytes such as mast cells and basophils, reduce permeability of vascular beds, and reduce both angiogenesis and fibrogenesis.[2,5]

While systemic steroids have a direct impact on the development and differentiation of immune-competent cells, topical steroids probably exert their effect by reducing local tissue permeability and decreasing production of cytokines and chemokines within local immune cells.[2] Due to their broad range of target cells, corticosteroids have the widest (though least specific) anti-inflammatory effect of any topically used agent.

Mitigating to some extent the dramatically positive anti-inflammatory effect of glucocorticoids are their side effects. Though topically administered corticosteroids are better tolerated than systemic formulations, they have the well-known side effects within the eye of accelerating

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By Aaron Bronner, OD

IMMUNE REPSONSE

cataract formation, increasing intraocular pressure, increasing risk of infection or prolonging pre-existing infectious processes and may very rarely cause systemic effects such as increased blood sugar or psychological effects such as anxiety and insomnia. Therefore, use of topical ophthalmic steroids is a decision in which the balance of benefit and risk should be carefully assessed, as cavalier use may lead to substantial worsening of ocular health.

Complicating things further, penetration of glucocorticoids is impeded by the corneal epithelium. Lipophilic bases such as alcohols and acetates, and higher viscosity delivery vehicles that increase contact time generally increase intraocular penetration of most topical corticosteroids, and therefore increase aqueous concentrations. However, in many cases of anterior segment use, it's worth asking whether or not you want anterior chamber penetration of a steroid.[3-6] After all, the weaker the steroid penetration, the less potential for IOP response and cataract development there is.

Lastly, each commercially available ophthalmic steroid has its own pharmacokinetic properties, strength of anti-inflammatory effect and propensity for steroid-induced side effects. Therefore, selection of an appropriate corticosteroid should derive from the full clinical picture, including:

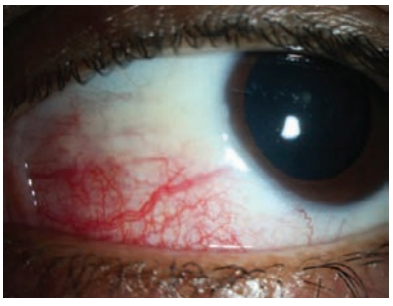
- *the site of inflammation (for example, intraocular penetration is unnecessary and ultimately unwanted in cases of inflammatory conjunctivitis or superficial keratitis)*
- *the magnitude of the inflammatory response*
- *the likelihood of inducing steroidal side effects within a patient, the possible magnitude of that side effect for a given agent and the patient-specific consequences of those effects*

Below are broad overviews of several available preparations, in descending order of efficacy.

- ***Difluprednate emulsion (Durezol, Alcon).*** The newest ophthalmic corticosteroid on the market, difluprednate has the greatest theoretical anti-inflammatory effect and highest in vivo potency of available options.[10] Anecdotally, I have used Durezol to good effect on eyes that have had inflammation recalcitrant to prednislone acetate 1%, including my own eye during flare-ups of uveitis. It also has the benefit of a more uniform distribution, with dosing based on the emulsion vehicle, and doesn't require shaking prior to use, unlike the suspension-based steroids.

Does this increased potency affect the propensity for IOP response? Reports vary based upon treatment populations and study design. A large study showed only transient differences in IOP between prednisolone and difluprednate, while a smaller retrospective analysis of their use in iritis showed an IOP increase of 20mm Hg or more in 19% of patients recalcitrant to prednislone who were switched to difluprednate.[14,15] The study design, treatment duration (as long as 16 weeks in some eyes) and population (7% of whom were on no steroid prior to beginning diflurprednate) limit broad application of these findings to other populations, but it highlights the importance of IOP monitoring when considering difluprednate for long periods.

Regardless, given its potency, there is no doubt Durezol is a useful part of the clinical armament, particularly in cases of moderate to severe intraocular inflammation or when only a short course of treatment is expected and with careful monitoring for IOP spikes when treatment duration is extended.



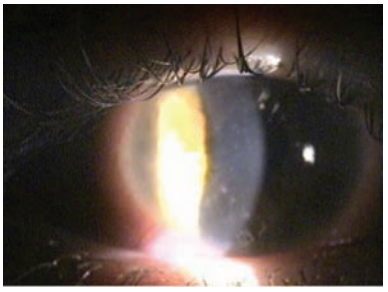
Sectoral episcleritis: Frontline treatment is an oral NSAID or topical steroid. With scleritis, topical steroids should generally be avoided—in some subtypes, their use may accelerate scleral thinning by potentiating collagenase activity.

• ***Prednisolone acetate 1% (Pred Forte, Allergan or generic).*** This is a good general purpose, cortisone-based anti-inflammatory that most eye care providers are quite familiar with. Though increasing the concentration from 0.25% to 1% increases its efficacy, any further increase in concentration would yield no benefit; therefore, 1% is the highest concentration available commercially.[4,5]

It is well described in eye care that the branded version of the medication exhibits superior distribution and dose uniformity within the suspension than the generic, although both require re-suspension with shaking.[16] Both branded and generic prednisolone acetate are good steroid choices for many forms of anterior segment inflammation, though severe cases may occasionally require a greater potency medication.

• ***Dexamethasone.*** The steroidal king of the combination drugs, dexamethasone is also one of the most potent anti-inflammatories of all corticosteroids. Though the molecule of dexamethasone has roughly six times the anti-inflammatory effect of prednisolone, its topical formulation is 10 times more dilute (prednisolone acetate 1% vs. dexamethasone 0.1%) and does not penetrate into the anterior chamber as readily.[3-5] Thus, topical prednisolone acetate 1% is a slightly more potent corticosteroid as dosed.[4,5] The tendency of IOP response with dexamethasone is thought to be similar to that of prednisolone acetate.

• ***Fluorometholone.*** Unlike prednisolone's cortisol base, fluorometholone is progesterone derived. The 0.1% version of the drug is roughly equivalent in efficacy to and better in safety than the 0.25% version. As a result, there is limited rationale for choosing FML in its higher-concentration form.[5]



Infiltrative keratitis responds well to treatment with corticosteroids. Loteprednol or FML are great choices in an eye like this.

Fluorometholone is reported to be somewhat weaker than prednisolone acetate both in vitro and within the anterior chamber.[3] It does not penetrate as readily into the chamber, although in certain ocular surface scenarios it is generally reported to be equivalent.[4] Fluorometholone has a lower incidence of IOP spike than prednisolone acetate.[5,9] Because of its enhanced safety profile over prednisolone acetate and roughly equivalent anti-inflammatory effect when used at the ocular surface, it is a good alternative to prednisolone acetate or (when cost is an issue) loteprednol for ocular surface disease. Currently, availability of fluorometholone has been limited in some (but not all) areas of the country, as a handful of its manufacturers have ceased producing it.

• ***Loteprednol etabonate (Lotemax, Alrex, Bausch + Lomb).*** This ester-based steroid was developed in the early 1990s as an alternative to prednisolone acetate with a better safety profile.[5,11] Excess unbound loteprednol molecules undergo metabolic transformation after a relatively short time, resulting in fewer unwanted side effects such as increased IOP and cataract development. Theoretical and clinical efficacy of the original loteprednol products has been shown to be quite good, lagging only slightly behind that of prednisolone acetate.[5,10,11] Its safety profile has also been clinically shown to be good, with a lower degree of IOP spikes in the setting of known steroid responders.[5,11,13]

The recent change of Lotemax from a suspension to a gel delivery increases uniformity between drops and increases maximum tissue concentrations within the cornea and conjunctiva compared to the suspension form.[11] Given its safety and anti-inflammatory profile, loteprednol is a terrific option in most forms of ocular surface and moderate forms of deeper inflammation. Out-of-pocket cost to the patient in some circumstances may need to be addressed.

Non Steroidal Anti-Inflammatories

Where can you turn when you want the benefit of an anti-inflammatory without the steroid-associated eye effects? NSAIDs, of course.

As mentioned above, one effect of corticosteroids is inhibition of pro-inflammatory molecules such as prostaglandins, a group of eicosanoids derived from arachidonic acid via the cyclo-oxygenase enzymes COX-1 and COX-2.[5,12]

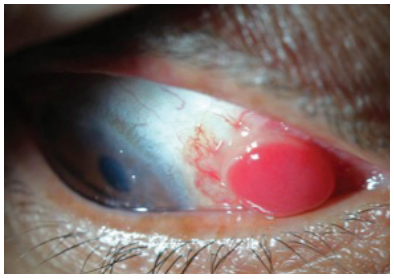
COX-1 is an enzyme that plays a role in mediation of physiologic function. Therefore, the PGs that it produces are created under normal circumstances. COX-2, on the other hand, mediates production of pro-inflammatory PGs. The exact mechanism that PGs play in the inflammatory cascade is not fully understood, but it appears they primarily enhance vascular permeability and also sensitize pain receptors.[5,12]

As NSAIDs are inhibitors of COX enzymes, they reduce their inflammatory product —prostaglandins. Given that inhibition of PGs is only one of the many anti-inflammatory effects of steroids, it's no surprise that they have a broader effect in suppressing inflammation than NSAIDs. That's not to say that steroids are superior in all ways, however. A number of studies show NSAIDs are objectively more effective in helping reestablish the blood-aqueous barrier than glucocorticoids, and pairing the two drugs may yield even greater benefit.[12]

Excess PG production has been strongly implicated in a number of retinal disorders, such as diabetic macular edema and the development of choroidal neovascular membranes.[12] Given the role PGs seem to play in enhancing vascular permeability, perhaps it's no surprise that NSAIDs are widely used in the prevention and treatment of cystoid macular edema. For anterior segment use, NSAIDs are useful for their analgesic effect—which is not paired with an anesthetic effect, unlike proparacaine and similar drugs.[17] This makes NSAIDs useful for managing pain with corneal trauma, as the analgesia provides some pain relief without compromising healing of the cornea.[5,12]

At my clinic, we use topical NSAIDs with our PRK patients in the postoperative period to help alleviate pain, as well as in other painful presentations. Of course, some eyes are more sensitive than others, so NSAIDs may not be sufficient for pain control in some cases of corneal abrasion.

While the different commercial preparations of corticosteroids have quite different properties given their varied anti-inflammatory effects, permeability and side effect profiles, NSAIDs as a class seem to be a bit more uniform. Permeability and half-life are both enhanced with nepafenac (a prodrug) and bromfenac, and only ketorolac is approved for allergic conjunctivitis, but all perform somewhat comparably at their recommended dosages. Of the group, only flurbiprofen 0.03% has been shown to be less effective than others in the treatment of cataract surgery-induced inflammation.[12]



A pyogenic granuloma. These capillary-based, reactionary growths often respond well to treatment with topical corticosteroids.

As stated, the primary benefit of NSAIDs is to offer some of the anti-inflammatory effects of cortiocosteroids without their side effects. Interestingly, despite PG analogs being widely employed for glaucoma therapy, there is no apparent net effect on IOP with the ophthalmic use of NSAIDs, whose chief mechanism is to reduce PG, and they have not been linked to cataract formation. NSAIDs are generally quite safe, though reports of corneal melts have rarely been reported. Most typically these events have been attributed to generic diclofenac, but the event has been reported with all members of the ophthalmic NSAID class except flurbiprofen.[12]

Conclusion

Though not all ophthalmic inflammatory events require pharmaceutical intervention, you will be frequently required to prescribe an anti-inflammatory. Thankfully, the number and diversity of medications at our disposal should allow clinicians to prescribe case-specific anti-inflammatories, where extent and location of inflammation are taken into account. As a result, the patient is subsequently offered the safest available option. RCCL

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IT'S TIME TO BRING SJÖGREN'S

This autoimmune disease can go undiagnosed for years. By working closely with other health care providers, we may be able to detect it in its earliest stages.

Sjögren's syndrome has a bit of a Dr. Jekyll/Mr. Hyde duality in eye care. On the one hand, we are all well aware of the condition and understand its ophthalmic association. On the other, the prevalence of Sjögren's is grossly underestimated and infrequently mentioned to patients. It is estimated that Sjögren's syndrome affects four million people in the United States alone, yet three million of those who suffer from this disease have not yet been diagnosed.[1] Clinicians routinely fail to recognize and diagnose Sjögren's patients at an early enough stage to have an impact on their quality of life.

As with many autoimmune diseases, the presentation of Sjögren's syndrome can be highly variable. In some patients, Sjögren's can present as a fairly aggressive, rapidly advancing, severe disease; in others, it can present in a relatively mild state. Because the presentation of Sjögren's can vary so much between patients, it can easily be mistaken for typical dry eye or age-related dryness in its earlier stages.

We must start to discuss Sjögren's syndrome—with our peers and our patients—to fully understand the disease and its systemic manifestations, as well as the most effective way of managing patients who suffer from it.

HOW TO SPOT SJÖGREN'S

When most of us think of Sjögren's syndrome, an archetypal patient readily comes to mind: the post-menopausal woman presenting with a classic aqueous-deficient dry eye. Beyond the characteristic findings of dry eye and often—but not always—dry mouth, Sjögren's syndrome is a chronic and systemic disease with the potential to affect many body systems.

Lack of salivary production in the advanced stages of the disease leads to a number of additional complications, including dental decay, difficulty swallowing, bleeding cracks in the gums and severely chapped lips. The autoimmune component of Sjögren's, which is more often the secondary form of the disease, has a deleterious effect on the organs. For example, it can cause pneumonia, interstitial lung disease and recurrent bronchitis in the lungs; acid reflux, esophagitis and difficulty swallowing in the gastrointestinal system; and primary biliary cirrhosis as well as autoimmune hepatitis in the liver. There are also neurological symptoms, such as memory loss and "brain fog."

Additionally, because Sjögren's affects all the body's mucous membranes, patients often experience recurrent sinusitis, nosebleeds, acid reflux, breathing problems, bronchitis, dry skin, Raynaud's phenomenon, abnormal liver function and peripheral neuropathy. All of these complications worsen quality of life, so it is important that we make the diagnosis early. We must realize that we are treating more than just the *eyes* of our Sjögren's patients.

DIAGNOSIS

Staining is a hallmark sign of Sjögren's syndrome. In a 2010 study, researchers compared 231 patients with primary Sjögren's syndrome to 89 patients with aqueous-deficient dry eye to determine the objective signs that best differentiated the two conditions. They found that rose bengal staining of the temporal conjunctiva was the most important variable that separated the two groups. This staining and the severity of dry mouth symptoms were the major factors in distinguishing Sjögren's syndrome patients from those with aqueous-deficient dry eye.[2]

Another telltale sign of Sjögren's syndrome is an elevated tear osmolarity score. Typically, patients

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By Arthur B. Epstein, OD, and Paul M. Karpecki, OD

OUT OF THE SHADOWS

with Sjögren's exhibit scores of 330 and above—with some variance between the two eyes. Due to the absence of reflex tearing, non-anaesthetized Schirmer's testing tends to be an accurate diagnostic measure in this group. This is unusual because Schirmer's testing is often inaccurate in the general dry eye population.

The disease is most likely to initiate in women in their 30s and 40s. Additionally, it is typically more prevalent in patients with an existing autoimmune disease, such as lupus or rheumatoid arthritis. While there is no cure for Sjögren's, the morbidity of the disease can be lessened thanks to new therapies.

Most patients are diagnosed with Sjögren's syndrome late in its course. Unfortunately, due to the progressive nature of the disease, it is significantly more difficult to manage at that point. However, the future of diagnosing Sjögren's looks bright. As technology continues to advance, new options for the early diagnosis of Sjögren's are becoming available.

For example, an in-office panel test for early detection of Sjögren's (Sjö, Nicox) was recently launched in the United States. The test combines traditional Sjögren's biomarkers (e.g., SSA (Ro), SSB (La), anti-nuclear antibody and rheumatoid factor) with additional biomarkers (e.g., salivary protein 1, carbonic anhydrase 6 and parotid secretory protein) that have also been associated with Sjögren's at an earlier stage of disease progression. The eye care professional takes blood samples (where allowed) from potential Sjögren's patients in the clinic and receives accurate lab results in days.

Sjögren's often accompanies other autoimmune diseases. As such, when a patient presents with complaints of dry eye, as well as an autoimmune disease such as lupus or rheumatoid arthritis, it is important to consider Sjögren's immediately. While there is a possible association between rheumatoid arthritis and dry eye, it is important to be mindful that a significant number of these patients may have Sjögren's syndrome in addition to an autoimmune disease.[3] We must find ways to differentiate between the two.

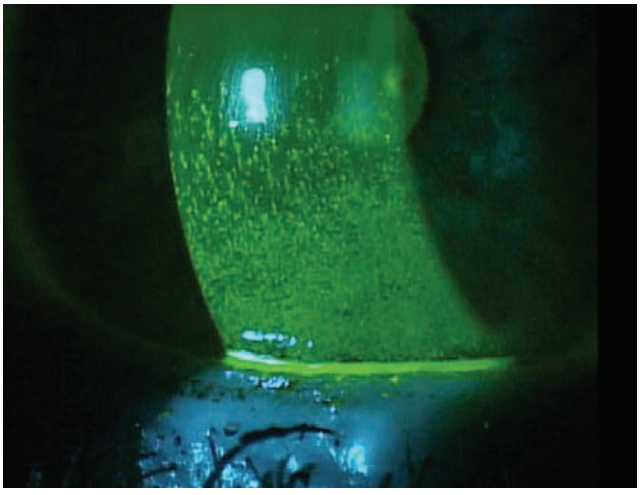

Photo: Mile Brujic, OD

Fluorescein staining revealing dry eye. Staining is a hallmark sign of Sjögren's syndrome and can be used to assist diagnosis of the disease in its early stages.

THOUGHTS ON MANAGING SJÖGREN'S SYNDROME

Due to a lack of available topical options for treating late-stage Sjögren's patients, steroids are a mainstay for the condition. However, proceed with caution with the use of steroids if the patient has a poorly controlled autoimmune disease. If there's a systemic component that is not well controlled, such as arthritis, there is a risk of a corneal melt or secondary infection when using corticosteroids.

Oral secretagogues have been shown to be worthy alternative to steroids. These agents have a favorable safety profile, and research shows that cevimeline is safe and effective in improving symptoms of dry eye.[4] Additionally, Sjögren's patients respond well to preservative-free artificial tears because of the hyper-osmolarity associated with the condition—particularly

artificial tears that can significantly lower hyper-osmolarity levels (e.g., TheraTears, Blink and FreshKote).[5]

Once a Sjögren's syndrome patient is well controlled, he or she can often be maintained on topical cyclosporine (Restasis, Allergan). This must be done early, however, because once the scarring of the lacrimal gland occurs, Restasis will no longer be a viable option—Restasis can stimulate tear production and reduce inflammation, but it cannot repair or restore tissue that is destroyed. Nutritional supplements, such as HydroEye (Science Based Health), may also be useful for maintaining Sjögren's patients on a long-term basis.

A recent study demonstrated that GLA (e.g., black currant seed oil) in the presence of DHA/EPA (i.e., fish oil) appears to stimulate PGE1 significantly in the tears, which improved both signs (corneal staining) and symptoms (OSDI).[6] Other options that have worked well include moisture chamber goggles, autologous serum, warm compresses, humidifiers, amniotic membrane rings, punctal occlusion and scleral lenses. Some success has been achieved using bandage contact lenses made of newer hydrophilic materials.

symptoms while involving other physicians to assist in controlling the systemic component of the disease.

BUILDING RELATIONSHIPS

Optometry is increasingly the first point of contact for many systemic conditions, Sjögren's syndrome included. If we diagnose Sjögren's early, we can track the progression of the disease more precisely and work with primary care physicians and other specialists to ensure patients are followed, accruing benefits along the entire path of the disease course, and its care, will follow for the patient.

While optometrists commonly manage patients with Sjögren's syndrome, ophthalmologists may be less interested in doing so—managing Sjögren's patients can be very time consuming, and dry eye work-ups are rather extensive and sometimes unpleasant for the patient.

The average time it takes for a patient with Sjögren's to receive a diagnosis is 4.7 years.[7] The idea that these patients are floating around undiagnosed for almost five years is a significant cost to the health care system and to the morbidity these patient endure.

"**SJÖGREN'S** OFTEN ACCOMPANIES OTHER **AUTOIMMUNE DISEASES**."

As is the case with treatment options for any condition, risks and benefits should be carefully weighed before making any decisions. Until advanced medications are developed for Sjögren's patients, we must try our best to manage and control the ocular

Optometrists and other health professionals tend to underestimate the potential for mutual cooperation. As such, communication is vital. The key to success is the patient's rheumatologist controlling the systemic disease, as this will greatly help with the accompanying keratoconjunctivis sicca. Additionally, because of the high correlation between lymphoma and Sjögren's, it is also important that the rheumatologist monitor for lymphoma. Because we are more likely to diagnose Sjögren's in our severe dry eye patients, it is our responsibility to communicate this closely with rheumatologists.

When thinking of patients with Sjögren's it is also important to consider the old adage, "when you hear hoof beats you think of horses—not zebras." We too often think we are dealing with a case of typical dry eye before we consider Sjögren's syndrome. This wastes valuable health care resources and, more importantly, can cause a patient to suffer unnecessarily.

Beginning discussions about Sjögren's syndrome in the eye care community is an important and long overdue step in the right direction. By working closely with other health care providers, we will create opportunities to improve quality of life for our Sjögren's patients in sustainable ways. RCCL

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THE HUNT FOR DRY EYE INSTIGATORS

In the seven years since the International Dry Eye Workshop (DEWS) noted that keratoconjunctivitis sicca "is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface," researchers and clinicians alike have worked diligently to update our understanding of its causes and consequences.[1] The identification of inflammation as a major component represented a tremendous step forward in both the description and treatment of a growing public health concern that affects as many as 17% of women and 11.1% of men in the United States alone.[2] (Actual prevalence numbers are likely even higher, given the omission of unreported self-treating patients and mild/periodic cases with intermittent symptomology.)

DEWS also sought to bring greater precision to the loosely-termed condition "dry eye" by recognizing two subgroups based on pathogenesis: aqueous deficient and evaporative. The former can be further subcategorized based on Sjögren's syndrome (SS) involvement (see, *"In Search of Sjogren's, p. 23*).

While it is not known whether the local inflammation is causative or simply occurs as a consequence of ocular dryness, dry eye seems to be invariably associated with chronic inflammation of the ocular surface. As such, it is important to recognize the role of inflammation in dry eye, as it has been a crucial factor in directing the proper course of treatment for the condition.

PATHOPHYSIOLOGY

Evidence gathered in the past decade indicates that dry eye-related ocular surface inflammation is mediated by lymphocytes.[11] Based on earlier immunohistopathological evaluations, patients with both SS-related and non-SS dry eye demonstrated identical conjunctival inflammation manifested by T-cell infiltrates and upregulation of CD3, CD4 and CD8.[12] Such patients also exhibited identical lymphocyte activation markers CD11a and HLA-DR.[12] These results suggest that the clinical symptoms of dry eye may be dependent on T-cell activation and resultant autoimmune inflammation.

Several additional studies demonstrated the role of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) in the pathogenesis of dry eye. Interleukin (IL)-1 is one of the most widely studied cytokines accompanying this condition. Dry eye patients have exhibited an increase in the proinflammatory forms of IL-1 (IL-1α and mature IL-1β) and a decrease in the biologically inactive precursor IL-1β in the tear film.[13] Based on a number of immunohistochemical studies, the conjunctival epithelium was originally thought to be the source of the increased levels of IL-1.[13] However, more recently, reactive nitrogen species expressed by conjunctival epithelium have been recognized in the pathogenesis or self-propagation of SS-related dry eye.[14] In the same study, the researchers determined that IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α play a significant role in SS-related dry eye.

The response of cells to extracellular stimuli such as ocular surface stress (e.g., changes in tear film composition, hyperosmolarity and ultraviolet light exposure) is mediated in part by a number of intracellular kinase and phosphatase enzymes.[15] Mitogen-activated protein (MAP) kinases are integral

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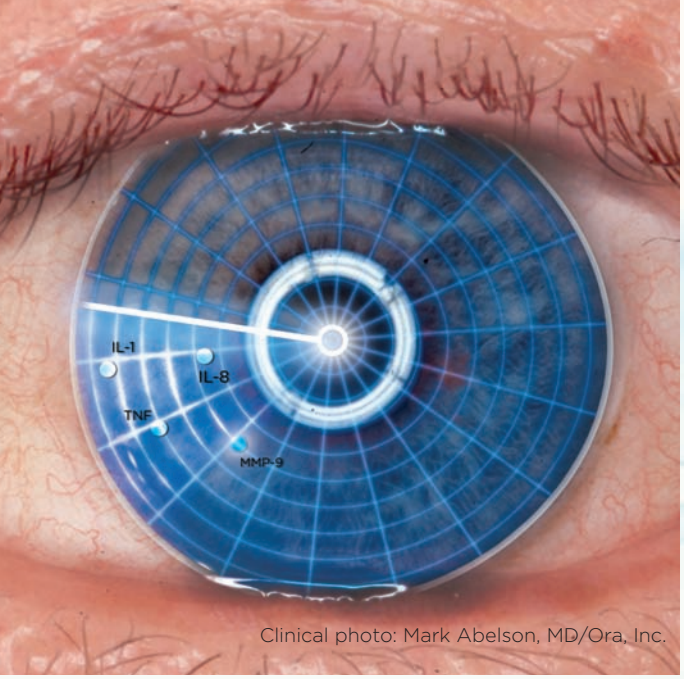

Clinical photo: Mark Abelson, MD/Ora, Inc.

Treatment options that target inflammatory mediators in the tear film may help clinicians achieve victory over this often difficult to manage condition. ***By Michelle M. Hessen, OD***

components of parallel MAP kinase cascades, which are activated in response to a number of cellular stresses, including inflammatory cytokines (e.g., Il-1 and TNF-alpha), heat shock, bacterial endotoxin and ischemia.

Activation of these MAP kinase homologues mediates the transduction of extracellular signals to the nucleus; this activation is pivotal in regulation of the transcription events that determine functional outcome in response to such stresses.

These stress-activated protein kinases have been identified in the tear film of patients with dry eye. Activation of these stress pathways results in transcription of stress-related genes, including MMPs—specifically MMP-9.[16] Another study found that MAP kinases stimulate the production of inflammatory cytokines, including IL-β, TNF-α and MMP-9, resulting in ocular surface damage.[17]

As previously mentioned, hyperosmolarity contributes to ocular surface inflammation; in human limbal epithelial cells, it increases the expression and production of pro-inflammatory cytokines and chemokines, such as IL-1β, TNF-α and the C-X-C chemokine, IL-8.[18] It appears this process is mediated through activation of the c-Jun N-terminal kinases and MAPK signalling pathways.

All of the previously discussed inflammatory mediators and pathways are not only important to the pathogenesis of dry eye, but also to the treatment strategies of the condition.

TREATING DRY EYE

It is widely recognized that inflammation plays a significant role in the etiopathogenesis of dry eye, as it promotes ocular surface disruption and creates symptoms of irritation. As such, a number of anti-inflammatory treatments are currently in use for its management, and many more are either in development or undergoing clinical trials to test their efficacy. These agents inhibit the expression of inflammatory mediators on the ocular surface, thereby restoring the secretion of a healthy tear film and reducing the signs and symptoms of afflicted patients.

• ***Cyclosporin A*** is commercially available as a topical agent in two forms: 0.05% (Restasis, Allergan) and a 1% compounded preparation. These agents are frequently used to treat various inflammatory ocular surface disorders.[19] It is recommended to dose topical cyclosporine twice daily, but for patients with severe dry eye who do not demonstrate any improvement, a dosing frequency greater than twice per day may be beneficial.[6,20] The immunomodulating effects of cyclosporin A are achieved through binding with a group of proteins known as cyclophilins. Cyclophilin A is found in the cytosol. The cyclophilin-cyclosporin A complex inhibits calcineurin, a calcium/calmodulin-dependent phosphatase.[21] It is believed that this inhibition halts the production of the

Release Date: May 2014
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transcription of T-cell activation by inhibiting IL-2.[21]

Cyclophilin D is located in the matrix of the mitochondria. The cyclosporin A-cyclophilin D complex modulates the mitochondrial permeability transition pore, which induces mitochondrial dysfunction and cell death.[22] The reduction in inflammation—achieved via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland—is thought to allow enhanced tear production.[23-27] Additionally, topical cyclosporine increases goblet cell density and decreases epithelial cell apoptosis, which is particularly good for dryness in rosacea patients.[28]

• ***Corticosteroids.*** Topical steroids can help to reduce ocular inflammation by suppressing cellular infiltration, capillary dilation, proliferation of fibroblasts and collagen deposition. Additionally, they stabilize intracellular and extracellular membranes. Corticosteroids increase the synthesis of lipocortins that block phospholipase A2 and inhibit histamine synthesis in the mast cells.[29] Inhibition of phospholipase A2, an essential step in the inflammatory cascade, prevents the conversion of phospholipids to arachidonic acid. Corticosteroids also interfere with transcription factor NF-kB, which regulates synthesis of numerous pro-inflammatory molecules, thereby stimulating lymphocyte apoptosis.

Corticosteroids mediate their anti-inflammatory effects primarily through the modulation of the cytosolic glucocorticoid receptor at the genomic level.[30,31] After corticosteroids bind to the glucocorticoid receptor in the cytoplasm, the activated corticosteroid-glucocorticoid receptor complex migrates to the nucleus, where it upregulates the expression of anti-inflammatory proteins and represses the expression of pro-inflammatory proteins. However, recent work suggests that the activated corticosteroid-glucocorticoid receptor complex also elicits nongenomic effects, such as inhibition of vasodilation, vascular permeability and migration of leukocytes.[30,32]

Several clinical studies have demonstrated the effectiveness of topical steroids in treating dry eye. In a retrospective series, topical administration of non-preserved methylprednisolone 1% solution, dosed three to four times daily for several weeks to patients with SS-related dry eye, provided moderate to complete relief of symptoms in all patients.[33] In addition to symptom relief, there was a decrease in corneal fluorescein staining score and complete resolution of filamentary keratitis. This therapy was effective even for patients suffering from severe dry eye who exhibited no improvement from maximum aqueous tear enhancement/replacement therapies.

A pilot study consisting of 64 patients evaluated the efficacy of loteprednol etabonate 0.5% (LE) ophthalmic suspension for the treatment of the inflammatory component of dry eye associated with aqueous tear deficiency and delayed tear clearance.[34] The LE-treated group was dosed four times daily and compared to a placebo group. Following two weeks of therapy, the subset of patients with moderate to severe clinical inflammation showed a significant difference between the LE-treated group and vehicle-treated group in central corneal staining, nasal bulbar conjunctival hyperemia and lid margin injection.

None of the patients experienced a clinically significant increase in intraocular pressure following one month of therapy. Patients treated with topical corticosteroids should be monitored closely for known risks of cataract formation, glaucoma, corneal thinning and infectious keratitis.[35]

• ***Topical NSAIDs*** treat inflammation by inhibiting the production of prostaglandins via the cyclooxygenase enzyme.[36] In addition, a number of NSAIDs—specifically diclofenac—have been shown to reduce corneal sensitivity.[37] This reduction in sensitivity may lead to an adjunctive insult to disrupted epithelium in patients with dry eye. Several cases of corneal melt have been described in the literature associated with topical NSAIDs, including diclofenac, ketorolac, nepafenac and bronfenac.[38-44] In each of these cases, preexisting epitheliopathy was identified.

While we do not currently know the exact relationship between corneal melt and the use of topical NSAIDs, a number of mechanisms have been suggested: activation of MMPs, impairment of wound healing and neurotrophic effect resulting from analgesic action of these drugs.[38] Short-term use of NSAIDs can be useful in ameliorating symptoms of ocular discomfort in dry eye; however, these agents should be used with caution and patients should be monitored closely. If the corneal epithelium shows any sign of damage, NSAIDs should be discontinued immediately.

• ***Tetracycline derivatives.*** Various dosages of oral doxycycline and minocycline, typically used for 12 weeks or more, are commonly used to treat dry eye. Tetracycline derivatives uniquely possess both antibacterial and anti-inflammatory properties. Doxycycline has been shown to inhibit c-Jun N-terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase signaling in epithelial cells of the ocular surface exposed to hyperosmolar stress, downregu-

In Search of Sjogren's

The aqueous-deficient subgroup of dry eye is further divided into two major subgroups: Sjögren's syndrome (SS)-dry eye and non-SS dry eye. Typically, the American-European Consensus Group 2002 revised classification criteria is used to diagnose SS. Either four out of the six criteria or three out of the four objective criteria are required for diagnosis. The six criteria include:[3]

- Subjective ocular dryness
- Objective ocular dryness
- Subjective oral dryness
- Objective oral dryness
- Presence of Sjögren-specific antibody A (SSA)/Ro, and/or Sjögren-specific antibody B (SSB)/La
- Positive minor salivary gland biopsy

However, a new classification criteria for SS was endorsed in 2012 by the American College of Rheumatology. The new assessment requires at least two of the following three criteria to diagnose SS:[4]

- Positive serum anti-SSA, and/or anti-SSB or rheumatoid factor or antinuclear antibody (titer>1:320)
- A total ocular surface staining score greater than three
- Presence of focal lymphocytic sialadenitis (inflammation of the salivary gland) with a focus score greater than 1/4mm^2 in labial salivary gland biopsy samples

According to the classification criteria from the American-European collaboration, secondary SS consists of the features of primary SS in addition to the features of an overt autoimmune connective tissues disease (e.g., rheumatoid arthritis). Several systemic diseases have a well-known association with dry eye syndrome, including rheumatoid arthritis, scleroderma, polymyositis, lymphoma, amyloidosis, hemochromatosis, sarcoidosis and systemic lupus erythematosus.[5] Autoimmune thyroid disease should also be considered when evaluating patients with dry eye, as it has been shown to be a cause of inflammatory ocular surface disease with dry eye symptomology.[6]

Based on numerous epidemiological studies, women and older individuals are commonly at risk for developing dry eye.[7,8] As such, both perimenopausal and postmenopausal women appear to be at a particularly higher risk. Additionally, hormonal studies have demonstrated that sex hormones influence ocular surface conditions through their effects on aqueous tear secretion, meibomian gland function and conjunctival goblet cell density.[9,10] Thus, an altered hormonal state (e.g., following menopause) may be a potential cause of dry eye.

lating the expression of CXCL8 and pro-inflammatory cytokines IL-1β and TNF.[45]

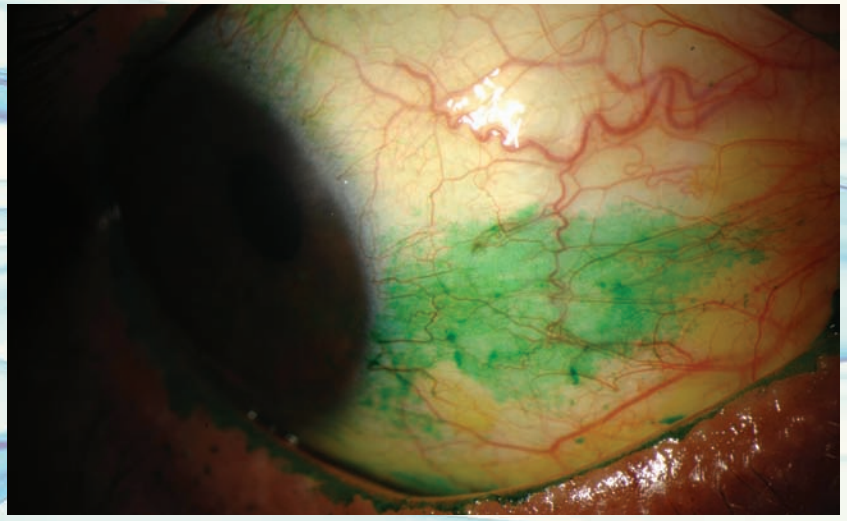
Doxycycline also inhibits MMP-9 activity and supports ocular surface integrity.[46,47] Additionally, studies demonstrated that minocycline inhibits expression of cell-associated pro-inflammatory molecules, including major histocompatibility complex class II.[48] Patients with ocular rosacea have benefited from the use of doxycycline—it has been reported to reduce irritation symptoms, improve tear film stability and decrease the severity of ocular surface disease.[49-51] In addition, when used in tandem with topical corticosteroids, doxycycline has been useful in the treatment of corneal erosions.[52,53]

- ***Autologous serum*** contains several anti-inflammatory factors that have the capability to inhibit soluble mediators of the ocular surface inflammatory cascade of dry eye. These include inhibitors of inflammatory cytokines (e.g., IL-1 RA and soluble TNF-receptors) and MMP inhibitors (e.g., TIMPs).[54-56] Clinical trials have shown autologous serum drops to improve ocular irritation symptoms and conjunctival and corneal dye staining in SS-related dry eye.[57-59] Conversely, there is greater risk of microbial growth—in addition to antimicrobial agents, autologous serum drops contain high protein content and are generally non-preserved.[60]

Recent studies have investigated cord serum drops (prepared from donor umbilical cord serum) and allogenic serum drops (from a relative donor).[61,62] A recent clinical trial, which enrolled 17 patients with graft-versus-host-disease (GVHD)-associated dry eye and 13 patients with SS-associated dry eye, treated each patient with cord blood serum for a duration of one month. Patients received cord blood containing 0.15ng epithelial growth factor per drop once a day. Patients reported a decrease in discomfort symptoms, as measured with Ocular Surface Disease Index score (OSDI). In addition, clinical findings such as impression cytology score, tear osmolarity and corneal sensation (measured with Cochet-Bonnet esthesiometer) improved significantly.[62]

Allogenic serum drops, prepared using the blood from a family member, were also shown to be effective in treating patients with GVHD. Following four weeks of continuous use, patients exhibited a reduction in OSDI symptom scores, tear osmolarity and corneal staining. Additionally, both goblet cell density and tear film break-up time increased.[63]

• ***Topical tacrolimus***, available in 0.03% and 0.1% concentrations as both an ointment and compounded eye drops, is a promising dry eye treatment option for patients with chronic GVHD and SS.[64-66] Systemic tacrolimus has been reported to be effective for improving GVHD-associated dry eye; however, there are potential adverse reactions to be aware of when administering long-term systemic therapy.[67] These risks include an increased risk of nephrotoxicity, neurotoxicity and malignancy—especially lymphomas and skin malignancies. This topical anti-inflammatory agent (previously known as FK506) is a macrolide antibiotic isolated from *Streptomyces tsukubaensis* fermentation.[68]



Conjunctival staining with lissamine green in a dry eye patient.

Although the mechanism of tacrolimus is similar to cyclosporin A, the potency in vitro has been shown to be significantly greater. Tacrolimus demonstrated effects similar to cyclosporin A, but at concentrations 100 times lower.[69] Only when bound to immunophilin does it become biologically active, thus effectively inhibiting calcineurin, as well as T- and B-lymphocyte activation via reduction in IL-2 synthesis.[70-76] Additionally, tacrolimus suppresses the immune response by inhibiting the release of other inflammatory cytokines (e.g., IL-3, IL-4, IL-5, IL-8, interferon-gamma and TNF-alpha).[77-80]

EXPERIMENTAL TREATMENTS

Although clinicians today have many viable treatment options for inflammatory-mediated dry eye, investigators are actively exploring new options to augment our efforts.

• ***Interleukin-1 receptor antagonist*** (IL-1Ra) is an endogenous IL-1 receptor blocker produced primarily by activated monocytes and tissue macrophages.[81] It inhibits the activities of the pro-inflammatory forms of IL-1 (IL-1α and IL-1β) by competitively binding to the IL-1 receptor-I.[81] A murine model with environmentally induced dry eye was treated with 3µl of topical IL-Ra three times daily for nine days. Following treatment, a significant decrease in corneal fluorescein staining was observed with slit-lamp biomicroscopy. Comparison treatments (methylprednisolone 1% and cyclosporin A 0.05%) were equally effective in this model.[82]

Additionally, confocal microscopy revealed a significant decrease in the numbers of central corneal CD11b+ cells, lymphatic growth and interleukin-1β expression after treatment with IL-1Ra 5% and methylprednisolone 1%, but not cyclosporin A. This suggests that IL-1Ra is comparable to topical methylprednisolone in reducing inflammation and improving clinical signs of dry eye.

• ***Resolvin E1*** (RvE1) is a new class of endogenous immune response mediators derived from the lipoxygenation of the essential dietary omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid.[83] In animal models, a treatment regimen of topical 100µg/mL (0.01%) omega-3 derivatives QID for one week has been shown to reverse corneal epithelial damage associated with dry eye. In this study, a specialized corneal module of a tomographer was used to study the corneas in vivo. The researchers noted increased tear flow (promoting a healthy epithelium), decreased cyclooxygenase-2 expression by Western Blot analysis and a decreased macrophage infiltration.[84]

A murine model of dry eye demonstrated that 300µg/ml topical RvE1 QID improved both corneal staining and goblet cell density.[85] The synthetic analog of RvE1, RX-10045, is being tested in a Phase II clinical trial for the treatment of chronic dry eye. Preliminary data of a 28-day, randomized, placebo-controlled, 232-patient trial showed dose-dependent and statistically significant improvements using RX-10045; however, final data has not been published.[86]

• ***Chemokine receptor antagonist.*** Monocyte chemotactic protein 1 (MCP-1) is secreted by monocytes, memory T-cells, macrophages, fibroblasts, endothelial cells and mast cells. It stimulates

the movement of leukocytes along a chemotactic gradient after binding to its cell surface receptor, chemokine receptor antagonist.[87] The critical role of the coupled MCP-1/chemokine receptor antagonist in inflammation has been demonstrated using MCP-1 and chemokine receptor antagonist knockout mice, suggesting that inhibiting the migration of chemokine receptor antagonist-bearing mononuclear cells may be an effective mechanism to modulate disease progression in chronic inflammation.[88]

A study of dry eye disease examined a murine model treated with topical chemokine receptor antagonist 5.0mg/ml BID for seven days. The model exhibited a significant decrease in corneal fluorescein staining following treatment. Real-time polymerase chain reaction revealed decreased infiltration of corneal CD11b(+) cells and conjunctival T-cells vs. both the vehicle treated and untreated dry eye groups.[89] The chemokine receptor antagonist also significantly decreased messenger RNA expression levels of IL-1α and IL-1β in the cornea, and TNF-α and IL-1β in the conjunctiva.

• ***Tofacitinib*** (CP-690,550) is a selective inhibitor of the janus kinase (JAK) used orally to treat rheumatoid arthritis. JAK signaling is essential for immune cell activation, pro-inflammatory cytokine production and cytokine signalling.[90] Tofacitinib inhibits JAK1, JAK2 and JAK3 in vitro, with functional cellular selectivity for JAK1 and JAK3 over JAK2.[91] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common γ-chain containing receptors for several cytokines, including IL-2, IL-4, IL-7, IL-9, IL-1, and IL-21. Additionally, inhibition of JAK1 results in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon γ. Tofacitinib subsequently modulates adaptive and innate immunity, with limited effects on hematopoiesis.[92]

In Phase I and Phase II clinical trials, topical tofacitinib 0.0003% to 0.005% was used to treat 327 patients with clinically significant aqueous deficient dry eye for eight weeks. Using Schrimer's test without anesthesia and corneal fluorescein staining, a trend for improving both signs and symptoms of dry eye was observed.[93] The topical agent also demonstrated a reasonable safety profile.[93] A sub-study of the Phase I/II trials showed a reduction in inflammation assessed by change from baseline in conjunctival cell surface expression of human leukocyte antigen DR-1.[94] This was accomplished by studying flow cytometry and tear level of several cytokines and inflammation markers by microsphere-based immunoassays.[94]

• ***Lifitegrast*** (previously known as SAR 1118) is a novel, investigational, small-molecule lymphocyte function-associated antigen-1 antagonist engineered for topical ophthalmic delivery.[95,96] The binding of lymphocyte function-associated antigen-1 on the surface of T-cells to intercellular adhesion molecule-1 on endothelial, epithelial and antigen presenting cells is a critical step in T-cell activation (normal immune response and inflammation). Thus, it has been proposed that a blockade of lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction may provide a therapeutic benefit to patients with dry eye, breaking the chronic cycle of T-cell-mediated inflammation and aiding in the recovery of the ocular surface.

Lifitegrast is an effective inhibitor of T-cell activation, adhesion, migration, proliferation and cytokine release.[95] In a multicenter, prospective, double-masked, placebo-controlled trial of 230 patients with dry eye, subjects were randomized to lifitegrast (0.1, 1.0, 5.0%) or placebo eye drops twice daily for 84 days. Lifitegrast showed dose-dependent and statistically significant improvements in corneal staining scores and symptoms measured with OSDI (both total ocular surface disease index and visual related function questions) vs. placebo. Improvements in both tear production and symptoms were noted as early as day 14. In addition, lifitegrast was well tolerated; no serious ocular adverse events were reported.[96]

OPUS-1, a recent Phase III clinical trial, compared lifitegrast 5% BID for 84 days to placebo in 588 adult subjects with dry eye.[97] The results of the study revealed that lifitegrast significantly reduced corneal fluorescein and conjunctival lissamine staining, and also improved symptoms of ocular discomfort and eye dryness compared with placebo.

• ***Mapracorat*** (formerly ZK-245186 and subsequently BOL-303242-X) is a novel, selective glucocorticoid receptor agonist currently under investigation. The anti-inflammatory effects of mapracorat were assessed in an in vitro osmotic stress model, which simulates some of the pathophysiological changes seen in dry eye.[98] Incubation of cells with mapracorat 0.1-1.0% applied three times a day for seven to eight days inhibited hyperosmolar-induced cytokine release. The activity and potency of mapracorat was comparable to the commonly used steroid, dexamethasone. In a study using a rabbit model, mapracorat was effective in maintaining tear volume and tear break-up time, with no increase in intraocular pressure.[99]

Regardless of whether or not an underlying systemic inflammatory condition can be identified, dry

eye is associated with chronic and sometimes subclinical inflammation. If left unchecked, this inflammation may cause ocular surface damage. Novel treatments, which target specific mediators in inflammatory reactions associated with dry eye, are constantly evolving. It's important that we continue to look for the underlying causes of dry eye, and manage the condition based on the clinical signs and symptoms with all currently available options. RCCL

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THE HUNT FOR DRY EYE INSTIGATORS

CE TEST

1. The International Dry eye Worskshop (DEWS) definition of dry eye includes all of the following, except:
a. Increased tear film osmolarity
b. Potential damage to the ocular surface
c. Decreased tear film osmolarity
d. Symptoms of discomfort

2. Based on the 2012 classification criteria for Sjogren's syndrome, endorsed by The American College of Rheumatology, requires 2 of the 3 criteria. The following are identified as possible criteria, except:
a. Positive anti-DNA antibody
b. Positive anti-SSA and/or SSB
c. Presence of lymphocytic sialadenitis with a focus score >1/4mm2 in labial salivary gland biopsy
d. Total ocular surface staining score greater than 3

3. Dry eye has a well-known association with the following systemic disease:
a. Rheumatoid arthritis
b. Systemic lupus erythematosus
c. Thyroid disease
d. All of the above

4. The following have been identified as risk factors for dry eye, except:
a. Older age
b. Refractive laser surgery
c. Male sex
d. Smoking

5. Which of the following systemic medications may exacerbate dry eye:
a. Antihistamines
b. Tetracyclines
c. Diuretics
d. A and C

6. The following inflammatory mediators have been found to play a role in dry eye, except:
a. Interleukin (IL)-1
b. Matrix metallopeptidase (MMP)-9
c. Tumor necrosis factor (TNF)-α
d. Interleukin (IL)-7

7. Mitogen activated protein (MAP) kinase cascades may be activated in response to:
a. Heat shock
b. Ischemia
c. Inflammatory cytokines
d. All of the above

8. Cyclosporine has been shown to be effective in improving dry eye through:
a. Decreasing goblet cell density
b. Increasing epithelial cell apoptosis
c. Enhancing tear production
d. None of the above

9. Which of the following is true when prescribing topical cyclosporine A:
a. It should always be dosed once daily
b. It should only be used for patients with mild dry eye
c. A frequency of greater than twice daily may be more effective in improving severe dry eye when no improvement is noted with twice daily dosage
d. Compounded concentrations greater than 0.05% should never be prescribed as they have been shown to be toxic to the corneal epithelium

10. Topical corticosteroids, for treatment of dry eye, have been correlated with all of the following risks, except:
a. Cataract formation
b. Corneal thinning
c. Infectious keratitis
d. Reduction of intraocular pressure

11. The mechanism by which topical NSAIDs reduce inflammation for the treatment of dry eye is via:
a. Inhibition of prostaglandins via the cyclooxygenase (COX) enzyme
b. Increasing the synthesis of lipocortins that block phospholipase A2 to prevent the conversion of phospholipids to arachidonic acid
c. Inhibition of c-Jun N-terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase
d. All of the above

12. When treating a patient with significant punctate epithelial erosions due to severe dry eye:
a. Topical NSAIDs should be prescribed at a frequent dosage
b. Topical NSAIDs may cause corneal melt therefore should not be used until improvement of the epithelium is noted
c. Topical NSAIDs should be prescribed prn to relieve the patient's symptoms of discomfort
d. Topical NSAIDs have been shown to improve corneal sensitivity in patients with severe ocular surface disease

13. Doxycycline has been reported to be effective in the treatment of:
a. Fuchs' corneal dystrophy
b. Dry eye at the setting of ocular rosacea
c. Recurrent corneal erosions
d. B and C

14. Serum eye drops, for the treatment of dry eye, have been shown to:
a. Reduce tear osmolarity
b. Decrease discomfort symptoms as measured with OSDI
c. Reduce corneal staining
d. All of the above

15. For the treatment of dry eye, topical tacrolimus was shown to have a mechanism of action similar to:
a. Tetracyclines
b. NSAIDs
c. Cyclosporine A

CE TEST

d. Autologous serum

16. Tofacitinib (CP-690,550) is a novel treatment for dry eye, which acts as a selective inhibitor of:
a. Janus kinase (JAK)
b. Tumor necrosis factor (TNF) α
c. Transcription factor NF-kB
d. Cyclooxygenase (COX) enzyme

17. The following are treatments being studied for the treatment of inflammatory-mediated dry eye, except:
a. Interleukin-1 receptor antagonist (IL-1Ra)
b. Resolvin E1 (Rx-10001)
c. Ocriplasmin
d. Chemokine receptor antagonist

18. Lifitegrast is an effective inhibitor of:
a. T-cell mediated inflammation
b. Cyclooxygenase (COX) enzyme
c. Janus kinase (JAK)
d. All of the above

19. A controlled clinical trial evaluating lifitegrast (0.1, 1.0, 5.0%), for the treatment of dry eye, found a dose-dependent and statistically significant improvements in:
a. Corneal staining scores
b. Symptoms measured with OSDI
c. Corneal sensitivity
d. A and B

20. Mapracorat, currently being investigated for anti-inflammatory effects as it pertains to dry eye, acts as a(n):
a. Interleukin-1 receptor antagonist
b. Selective glucocorticoid receptor agonist
c. T-cell activator
d. Selective inhibitor of janus kinase (JAK)

Examination Answer Sheet

Valid for credit through May 1, 2017

This exam can be taken online at www.reviewofcontactlenses.com. Upon passing the exam, you can view your results immediately. You can also view your test history at any time from the website.

The Hunt for Dry Eye Instigators, by Michelle M. Hessen, OD

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit.

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20. Ⓐ Ⓑ Ⓒ Ⓓ

1 = Excellent 2 = Very Good 3 = Good 4 = Fair 5 = Poor

Rate the effectiveness of how well the activity:

21. Met the goal statement: ① ② ③ ④ ⑤
22. Related to your practice needs: ① ② ③ ④ ⑤
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Lesson 110123 RO-RCCL-0514

Stemming the Tide

Much can be done to keep conjunctival tissue from breaching the cornea in patients with limbal stem cell disease. Here's the latest thinking.

The diagnosis and treatment of limbal stem cell disease (LSCD) can be a complex and challenging situation at the primary care level. We have known for decades of abnormal stem cell physiology, and its subsequent impact on the corneal surface. But only recently have definitive treatments for more advanced patients become a reality. Once you have a good sense of the condition and its severity, you will be able to target your response appropriately.

WHAT YOU'LL SEE

Patients who experience LSCD can have a variety of symptoms and signs. For example, these patients may present with complications as simple as decreased vision, tearing, photophobia and hyperemia (which is usually accompanied by inflammation). In more severe cases, patients will present with pain and significant loss of visual function. These cases are typically accompanied by clinical signs indicative of severe cell damage, including intense hyperemia at the limbal junction and the development of a unique, whorl-like pattern of corneal staining, which produces a dimensional change in the quality of the corneal epithelium.

In less severe cases, such as those caused by contact lens overwear, this is typically observed as an abnormality of surface quality. This corneal irregularity can be seen beginning at approximately the 10 o'clock location and extending over to two o'clock, with a triangular-like, saw-toothed shape that leads towards the apex of the cornea.

This clinical abnormality occurs because the absence of normal limbal stem cells causes the regeneration of corneal epithelial cells to be irregular; therefore, the section that is abnormal will produce an atypical regenerative pattern that extends towards the apex. Because the remaining limbal cells are normal, their natural contribution will account for the remaining aspect of the cornea. The clinical appearance will be such that 75% to 80% of the cornea is relatively normal while the remaining 20% to 25% demonstrates the atypical regenerative pattern.

In more severe cases, patients may experience non-healing epithelial defects. Also, it is possible for the cornea to become conjunctivalized—a condition in which the natural limbal barrier is disrupted, allowing cells from the conjunctiva to invade the corneal surface and produce an abnormal pattern and stratification of epithelial cells.

Patients with partial limbal stem cell deficiency make up less than one half of the afflicted population, while greater than one half of the population has the condition known as sub-total LSCD; the differentiation is by magnitude of tissue damage.

There are numerous etiologies for LSCD, which can range from a condition as simple as contact lens overwear syndrome or adverse solution reaction to a more severe presentation, such as an ocular cicatricial surface disease (e.g., Stevens-Johnson syndrome or cicatricial pemphigoid). Other causes of LSCD are typically related to toxicity from medications, chemical burns or radiation exposure. Additionally, a number of surgical interventions have been cited as etiologic factors, and patients who have experienced cases of severe microbial keratitis are sometimes left with LSCD presentations.

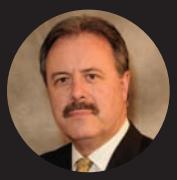
In addition to visual identification, LSCD can be diagnosed using impression cytology—a process that identifies and reviews the presence of goblet cells on the corneal surface. Impression cytology can be used to determine if the limbal stem cell barrier has been breached, indicating that LSCD is present.

Other diagnostic technologies include the use of ocular computed tomography to identify corneal epithelial characteristics unique to the disease and confocal microscopy to assess specific cellular morphology and identify the underlying disease state.

WHAT TO DO

Appropriate treatment of LSCD will derive from the severity of the presentation. The vast majority of cases seen at the primary care level are related to toxicity, overwear of contact lenses, previous surgical intervention or infectious disease tissue trauma. For cases such as these, traditional therapies using a bandage contact lens (BCL) with non-preserved lubricant drops and ointments can be extremely effective in reversing the damage.

Typically, I will add a topical steroid (e.g., loteprednol etabonate) on a QID basis for several weeks to one month to decrease the inflam-



matory response at the limbal junction, which is in part responsible for the abnormal cellular proliferation.

As previously mentioned, a number of interventional therapies have proven to be efficacious in the lesser stages of the deficiency, and in many cases, can rejuvenate the corneal epithelium. These options include lubrication, cessation of contact lens wear, non-preserved lubrication, ointments and topical applications, removal of the offending agents (e.g., chemical and/or mechanical) and the introduction of a topical anti-inflammatory in the initial phase of therapy.

I would recommend extending the duration of therapy for patients who present with cases of LSCD that take weeks or months to resolve. In such cases, it is important that the clinician be vigilant, as chronic therapy may lead to additional complications, such as toxicity or IOP issues. In more severe cases, I tend to implement additional intervention, such as oral doxycycline 100mg PO for four to six weeks. This provides inhibition of MMP9-induced inflammation and improves meibomian function.

Occasionally, you will encounter patients resistant to topical therapy. In such cases, I will debride the affected area and place a BCL (along with a topical anti-infective) over it while maintaining the previous regimen. Because LSCD eyes that are debrided can heal more slowly than typical epithelial defects, I will usually leave the BCL on for several days to a week to enhance the corneal healing. In my experience, patients presenting with recalcitrant healing may benefit from pressure patching and, in some cases, an amniotic membrane placement.

Patients who present with significant LSCD as a result of more traumatic concerns (e.g., chemical or thermal burns, surgical complications or severe microbial infectious disease), which leave the limbal region damaged, typically require more aggressive intervention. Over the last several decades, significant work has been done examining the use of tissue replacement, such as stem cell transplants, conjunctival limbal autografts (CLAU), living-related conjunctival limbal allografts and amniotic membrane transplantation. These techniques have been shown to have a greater level of success than previously used therapies.

In patients with advanced LSCD, treatment protocols are based in part on whether the disease is a unilateral or bilateral condition. For example, in unilateral disease presentations, the use of stem cell transplantation from the unaffected eye can be an effective therapy. Additionally, once the original abnormal cellular zone has been removed, amniotic membrane transplantation has been shown to be successful, and new cell growth can be enhanced by stem cell transplantation.

When both eyes are involved, or a significant segment of the limbal architecture is damaged, limbal tissue can be grafted into the arcade. Once the tissue is successfully grafted in place, those cells will expand and repopulate the corneal surface.

Another option for surgical intervention beyond amniotic membrane and limbal stem cell transplantation is the use of conjunctival limbal allografts. This procedure involves harvesting healthy limbal tissue with a conjunctival carrier from a living relative and then transplanting it into the patient. One significant concern with this intervention is the need for extended—if not lifelong—immunosuppression therapy. As such, this technique should be only be selected in patients who have been unresponsive to traditional interventions.

Patients with unilateral LSCD may benefit from CLAU surgery, as the harvesting is done from the fellow eye. This technique involves the acquisition of two trapezoid-shaped segments, each of which must contain approximately 6mm of tissue.
(Continued on page 33)

Corneoscleral Junction, What's Your Function?

Limbal stem cells—composed of non-keratinized, stratified squamous epithelium—are located at the basal level of the epithelium, in the zone between the cornea and conjunctival epithelial cells. The primary role of limbal stem cells is to barricade or protect the cornea from the invasion of conjunctival epithelium, which typically occurs as a result of trauma—creating and subsequently maintaining a clear, distinct boundary between two critical tissues in the anterior segment. It is also responsible for the regeneration of new epithelial cells during normal physiology and following trauma.

By Mile Brujic, OD, and Jason Miller, OD, MBA

Patch It Up

Providing specialized care to patients presenting with corneal insults can hasten their return to comfortable contact lens care.

Are we providing the best contact lens care for our medical patients? A number of contact lens wearers suffer from various conditions that may hinder their ability to wear contacts, including dry eye, ocular allergies and even glaucoma. But with these so ubiquitous in eye care practices, it is often difficult to separate such patients from our "healthy" contact lens wearers. When we do, we tend to sideline their contact lens-wearing goals, thinking that's an acceptable sacrifice for the greater good of restoring ocular health. Sometimes, perhaps. But not universally.

We also have patients we like to call "silent sufferers." These are our contact lens wearers who don't want to admit to having any type of medical condition. Oftentimes, they perceive this as an issue that may even prevent them from wearing contact lenses in the future. Take the time to identify any chronic or urgent underlying condition that will impact their corneal health—and, in so doing, you'll keep them in their contact lenses long term.

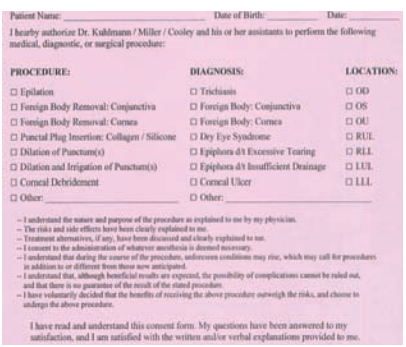
DO YOU PROMOTE URGENT CARE?

Too many times a patient visits their local urgent care facility to receive eye care, only to be given nothing more than an eye patch for a corneal insult. Of course, these patients are best cared for by their eye care professional, who can treat the issue using a bandage—be it a contact lens or a biologically active substance.

These patients are often very loyal to our practices, just typically unaware that they are supposed to see us for their urgent conditions.

Most patients know to come to us for vision exams, contact lens evaluations and medical treatment for various conditions. But, most do not know that we provide urgent care as well—and it's our job to let them know that we do. Giving your patients this urgent medical care can serve to both distinguish your practice and further strengthen patient loyalty. This area of our practices may prove to offer the most growth potential in the near future.

While developing a medical model and offering this service may take some internal changes (e.g., understanding medical billing and educating your staff), it can be extremely rewarding. The medical treatment and procedures you will perform will provide the patient with the highest quality of care. Prior to conducting any medical procedure, it is important to have the patient sign an informed consent form. *Figure 1* shows an example of one used in Dr. Miller's office.



Patient Name: _____ Date of Birth: _____ Date: _____

I hearby authorize Dr. Kuhlmann / Miller / Cooley and his or her assistants to perform the following medical, diagnostic, or surgical procedure:

PROCEDURE:	DIAGNOSIS:	LOCATION:
☐ Epilation	☐ Trichiasis	☐ OD
☐ Foreign Body Removal: Conjunctiva	☐ Foreign Body: Conjunctiva	☐ OS
☐ Foreign Body Removal: Cornea	☐ Foreign Body: Cornea	☐ OU
☐ Punctal Plug Insertion: Collagen / Silicone	☐ Dry Eye Syndrome	☐ RUL
☐ Dilation of Punctum(s)	☐ Epiphora d/t Excessive Tearing	☐ RLL
☐ Dilation and Irrigation of Punctum(s)	☐ Epiphora d/t Insufficient Drainage	☐ LUL
☐ Corneal Debridement	☐ Corneal Ulcer	☐ LLL
☐ Other: _____	☐ Other: _____	

-- I understand the nature and purpose of the procedure as explained to me by my physician.
-- The risks and side effects have been clearly explained to me.
-- Treatment alternatives, if any, have been discussed and clearly explained to me.
-- I consent to the administration of whatever anesthesia is deemed necessary.
-- I understand that during the course of the procedure, unforeseen conditions may rise, which may call for procedures in addition to or different from those now anticipated.
-- I understand that, although beneficial results are expected, the possibility of complications cannot be ruled out, and that there is no guarantee of the result of the stated procedure.
-- I have voluntarily decided that the benefits of receiving the above procedure outweigh the risks, and choose to undergo the above procedure.

I have read and understand this consent form. My questions have been answered to my satisfaction, and I am satisfied with the written and/or verbal explanations provided to me.

Fig. 1. Have patients fill out an informed consent before conducting medical procedures.

As eye care professionals, we're no strangers to patients with various types of ocular surface disease. Patients who present with advanced conditions, such as recurrent corneal erosions, are typically treated with the use of bandage soft contact lenses. In some cases, however, they will need special biological therapies to encourage corneal healing. Both of these options can help relieve pain and promote healing in patients with trauma to the cornea.

BANDAGE CONTACT LENSES

Corneal abrasions are one of the most common uses for these lenses in primary eye care. In the presence of an abrasion, bandage contact lenses shield the highly-enervated corneal surface from the constant mechanical irritation of the eyelids. This offers patients a high level of comfort almost immediately upon lens insertion, and allows patients to return to normal function by controlling the pain.[1]

Unfortunately, not every insurance carrier will pay for this care. As such, it is necessary to first contact the patient's insurer to determine which services (e.g., the fitting, the lens, replacement of lost lenses, etc.), if any, are covered. Then, have them sign an ABN before moving forward with any treatment.

AMNIOTIC MEMBRANES

Prokera (Bio-Tissue) is an FDA class II medical device comprised of an amniotic membrane suspended between two plastic rings. The company describes it as a "biologic corneal bandage" that helps reduce inflammation and stimulate healing.

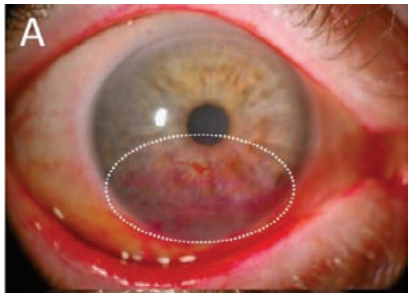


Fig. 2a. Exposure keratopathy before treatment with Prokera.

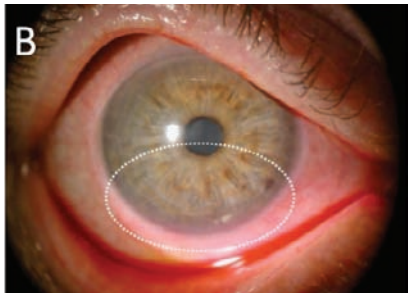


Fig. 2b. The same eye post-treatment.

The therapy uses a cryopreserved amniotic membrane as a novel alternative to traditional bandage treatment options. These devices are capable of treating many common corneal conditions, such as recurrent corneal erosions, corneal ulcers and ocular surface disease. They do so by promoting active healing.

It'll Take More Than a Bandage

A 57-year-old female with history of penetrating kerotaplasty OU and chronic recurrent corneal erosion presented with complaints of another painful red eye. She couldn't remember any recent incident or trauma to her eye, and her only ocular therapy at the time was Pred Forte 1% QD. She had been treated multiple times with a bandage contact lens.

We discussed the use of an amniotic membrane, explaining how it differs from simply putting on a contact lens. She consented and the amniotic membrane was applied. Her recurrent corneal erosions healed in approximately one week, and then the device was removed. She is now six months post-treatment without recurrence.

Amniotic membranes naturally promote epithelialization, suppress inflammation, and inhibit scarring and anti-microbial agents—without the harmful side effects found in topical and oral medications. These devices have been instrumental in the proper healing of many patients.

Patients who suffer from chronic ocular surface disease need our help. Whether you are treating these patients with bandage contact lenses during an acute episode or amniotic membranes when appropriate, taking the initiative to actively diagnose and treat these patients is an important part of the healing process.

Using the aforementioned options to manage these conditions may allow the patient to return to comfortable full-time lens wear sooner and more comfortably. Taking the "extra steps" to improve the health and comfort of these individuals may prove valuable in preventing contact lens dropouts and further enhance patient loyalty. RCCL

A special thank you to Walt Whitley, OD, MBA, and Rachèle M. Rivière, MBA, Associate Brand Director, Prokera, for their assistance with this article.

1.Buglisi JA, Knoop KJ, Levsky ME, Euwema M. Experience with bandage contact lenses for the treatment of corneal abrasions in a combat environment. Mil Med. 2007 Apr;172(4):411-3.

Corneal Consult

(Continued from page 31)

Other surgical techniques, such as kerato-limbal autografts and combined conjunctival and kerato-limbal autografts, have been used in more severe presentations.

There have been significant advances made in stem cell technology in just the last decade—specifically in the ability to differentiate types of stem cell lines that are available for different purposes. Human embryonic stem cells, tissue stem cells and pluripotent stem cells have all evolved as potential interventions for significant limbal stem cell deficiency. Currently, all of these modalities are being inversigated, and hold great promise for the future as a mechanism to improve healing characteristics of LSCD.

Unfortunately, treatments such as penetrating keratoplasty have not been shown to be particularly successful in LSCD. As such, the recent trend has been to replace the abnormal limbal stem cell beds and manage the resulting cell growth to replace the corneal epithelial surface. RCCL

Can't We All Just Get Along?

Understanding who your *real* competitors are—and perhaps even working in cooperation with them—will dramatically improve your contact lens practice.

When you visit most OD Internet forums, blogs or trade show talks, you'll inevitably hear constant tales of woe about the demise of our profession. Many of these doomsayers lament too many doctors graduating from too many schools, all of which are competing for the same patients.

Fortunately, this common belief couldn't be further from the truth in a contact lens practice. Consider this: approximately 80% of the US population requires some form of vision correction, yet only about 15% of the population wears contact lenses. Even if we remove patients who are difficult to fit, there is still obviously a huge opportunity to grow your contact lens practice.

Thanks to a healthy stream of new contact lens options having reached the market in recent months—including toric, multifocal and colored lenses—the number of patients who could successfully wear lenses has increased dramatically. The question is: have you seen this change reflected in your practice? Probably not, and it's likely because you're having trouble overcoming the two biggest obstacles to expanding your practice: competition and inertia.

ASSESSING THE COMPETITION

A good way to determine exactly whom your practice is up against is to use colored contact lenses. Patients have the option of wearing either clear or colored lenses to correct their vision. Those who opt for colored lenses are aware of this fact. So, what motivates them to "add" color to their lenses? And, if they didn't do so, where would that incremental spending take place instead? Once you are able to determine this information, you can then use that intelligence to expand your practice.

Some practitioners describe colored contact lenses as frivolous, time consuming and even nonsensical in some cases. But, it's important to look at colored contact lenses in a different way, as they can increase both self-esteem and self-confidence in many patients. Wearers tend to describe these lenses as life changing, fun, sexy and empowering.

Customers at a hair or nail salon, patients at a plastic surgeon's or cosmetic dentist's office, or clients of a personal trainer may use those very same adjectives to describe the services they receive. In this case, what's really preventing an increase in your colored lens practice isn't another practitioner at all—it's the patients' desire to spend their money on services such as teeth whitening or six months of personal training instead of contact lenses.

The point to consider here: the discretionary dollars the patient has allocated towards physical self-improvement can be spent on either colored contact lenses or nail tips. Taking that into account, you should change your marketing message from, "We can change your eye color from brown to blue," to something that really grabs these patients. Good examples of effectively marketing your colored contact lens practice would be something along the lines of, "Put the finishing touches on your new hairstyle by changing your eye color," or, "Working out to get six-pack abs is hard; changing your eye color is easy."

OVERCOMING INERTIA

Additionally, there is often an opportunity to cross-market your practice with all of the above competitors. Imagine this: a client walks into the nail salon and notices the salon operator's brand new eye color. This will inevitably lead the client to ask, "Where and how did you do that?" When the operator responds and tells the client it was done at your practice, you reap the benefits.

The concept above is easy to understand. The only barrier to executing this marketing mindset is inertia. While not cognitively complex, it does require that you make use of some new marketing techniques. Specifically, you (or a representative from your office) must physically visit the nail salon instead of simply making a Facebook post. But, like most well thought out marketing initiatives, once it's in place, actively tended to, monitored and constantly measured, it works.

Of course, none of these strategies are limited to colored lenses—they can be applied to all of your contact lens wearers. Have a fun and engaging staff meeting and put on your marketing thinking caps to discuss where presbyopes might be spending their discretionary dollars, and use the exact same concept as above. RCCL

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Ask your CooperVision sales representative about current programs and promotions.

*Evaporative Tear Deficiency or Aqueous Tear Deficiency (non-Sjogren's only).

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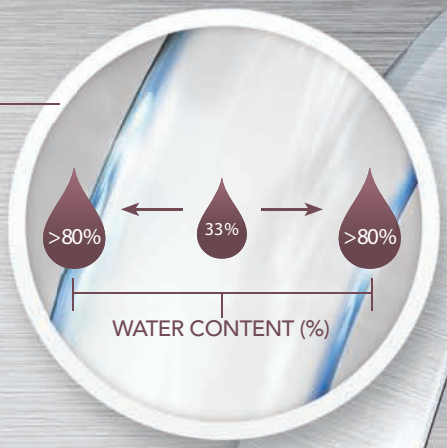
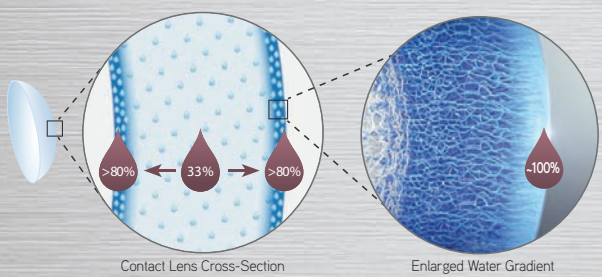


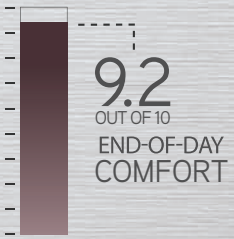
THIS IS WHY contact lenses have reached a new era in comfort.

DAILIES TOTAL1® Water Gradient Contact Lenses feature an increase from 33% to over 80% water content from core to surface[1]* for the highest oxygen transmissibility,[2] and lasting lubricity[3] for exceptional end-of-day comfort.[4]

The First and Only Water Gradient Contact Lens



Contact Lens Cross-Section | Enlarged Water Gradient



9.2
OUT OF 10
END-OF-DAY COMFORT

UNIQUE WATER GRADIENT
Features different surface and core water contents, optimizing both surface and core properties[1]

LASTING LUBRICITY
Ultrasoft, hydrophilic surface gel approaches 100% water at the outermost surface[5] for exceptional lubricity

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Let your patients experience the DAILIES TOTAL1® contact lens difference today.

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*_In vitro_ measurement of unworn lenses

1. Thekveli S, Qiu Y, Kapoor Y, Kumi A, Liang W, Pruitt J. Structure-property relationship of delefilcon A lenses. Cont Lens Anterior Eye. 2012;35(suppl 1):e14.
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3. Alcon data on file, 2011.
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