From Dry Eye to Lid Margin Diseases:

Promoting Quality Healing Through Evidence-Based Therapies

During a recent industry meeting, four corneal specialists came together to discuss how innovative corneal wound-healing and hygiene solutions have changed the way they approach a wide range of ocular surface and eyelid margin diseases and disorders, including dry eye, epithelial defects, conjunctivochalasis, blepharitis and demodex. They shared their experiences with Bio-Tissue Inc.'s PROKERA® biologic corneal bandage, AmnioGraft® biologic ocular transplantation graft and Cliradex® lid, lash and facial cleanser. Highlights from their discussion follow.

HEALING EPITHELIAL DEFECTS

Eric Donnenfeld, MD

To obtain and sustain the best possible outcomes for patients, cornea specialists strive to achieve quality healing of the ocular surface. What is quality healing of the ocular surface? It's the reproduction of quality cells on the ocular surface, or the regeneration of healthy tissue, rather than the need for repair with granulation tissue to restore normal tissue function. Visual acuity, quality of life, comfort and cosmetic appearance all depend on quality healing; needless to say, it is quite important.

Inflammation is the first step in wound healing, but uncontrolled inflammation can cause delayed healing of the ocular surface, more tissue damage, chronic pain and discomfort/irritation, as well as vision-threatening complications such as scarring and haze. Thus, effective control of inflammation is an important strategy for promoting quality healing and minimizing the risk of scar and haze.

Biologic corneal bandages can promote quality healing because they modulate inflammation (*see Figure 1*) and in my experience, they have made a big difference—in both easy and recalcitrant cases. In fact, PROKERA® products provide

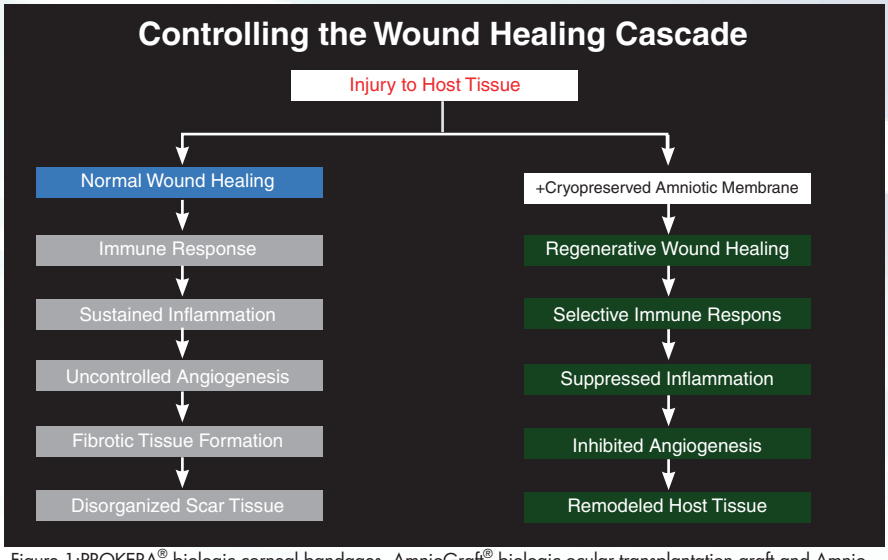

Figure 1 :PROKERA® biologic corneal bandages, AmnioGraft® biologic ocular transplantation graft and AmnioGuard® biologic glaucoma shunt tube graft are the only amniotic membrane tissue products cleared by the FDA for reducing inflammation and promoting regenerative healing of the ocular surface.

faster and more effective healing of the cornea with less pain, scarring and inflammation, leading to clear corneas and improved clinical outcomes. That's because cryopreserved amniotic membrane tissue retains important biologic components that reduce inflammation and simultaneously promote regenerative healing of the ocular surface.

The proprietary method by which cryopreserved amniotic membrane tissue is processed and stored contributes to its effectiveness. Cryopreservation has been shown to be the method that best retains the native architecture of the amniotic membrane extracellular matrix and the quantity and activity of key biological signals present including HC-HA/PTX3 complex—that modulate the inflammatory immune response and promote regenerative healing.[1,2] In dehydrated amniotic membrane, the crucial HC-HA/PTX3 complex is degraded or completely absent.[2]

PROKERA® is designed to be self-retaining in the eye. This cryopreserved amniotic membrane is fastened to an ophthalmic conformer, which is placed between the eyeball and the eyelid. This delivery system is revolutionary and has made it possible for amniotic membrane therapy to be used in-office for many applications. In our practice, cryopreserved amniotic tissue is now considered an option in the full spectrum of ocular surface and corneal conditions. Cryopreserved amniotic tissue has made a substantial difference in our ability to reduce inflammation and promote healing in difficult, recalcitrant cases. It has also allowed us to elevate outcomes in routine cases by improving the health of the ocular surface and reducing the risk of scarring, haze and irregular healing.

Figure 2. Placement of PROKERA® Slim to promote healing of epithelial defect following corneal collagen crosslinking.

"Cryopreserved amniotic tissue has made a substantial difference in our ability to reduce inflammation and promote healing…"

Persistent epithelial defects, recurrent corneal erosion, filamentary keratitis, herpetic ulcers, neurotrophic corneas are several of the clinical situations in which a biologic corneal bandage has been very helpful for us and our patients, as illustrated by the following three cases.

Case 1: Epithelial Defect Caused by Corneal Collagen Cross-Linking

Following epithelium-off collagen crosslinking to treat keratoconus, this 25-year-old male had a 6-mm epithelial defect that did not resolve after use of a bandage contact lens for three days and one day of pressure patching. When he presented to our practice, we placed a PROKERA® biologic corneal bandage to promote healing and prevent development of haze (*see Figure 2*). The cornea healed completely within 48 hours.

Case 2: Epithelial Defect Caused by Lamellar Keratectomy

A 55-year-old male underwent chelation to address a dense corneal scar and band keratopathy, but both recurred. We performed a lamellar keratectomy with a femtosecond laser to remove the scar tissue, leaving an 8-mm epithelial defect. Three days after placement of the PROKERA® biologic corneal bandage, the defect healed. The corneal surface was smooth, and visual acuity was markedly improved.

For this case, we chose PROKERA® Plus due to the severity of the inflammation and the resistance to healing. The PROKERA® Plus contains a thicker membrane that remains present in the eye to enhance the durability of the treatment.

Case 3: Non-healing Superficial Punctate Keratitis and Dry Eye Prior to Cataract Surgery

It is common for cataract surgery patients, such as this 55-year-old female (*see Figure 3a*), to have superficial punctate keratitis and the dry eye that accompanies it preoperatively.

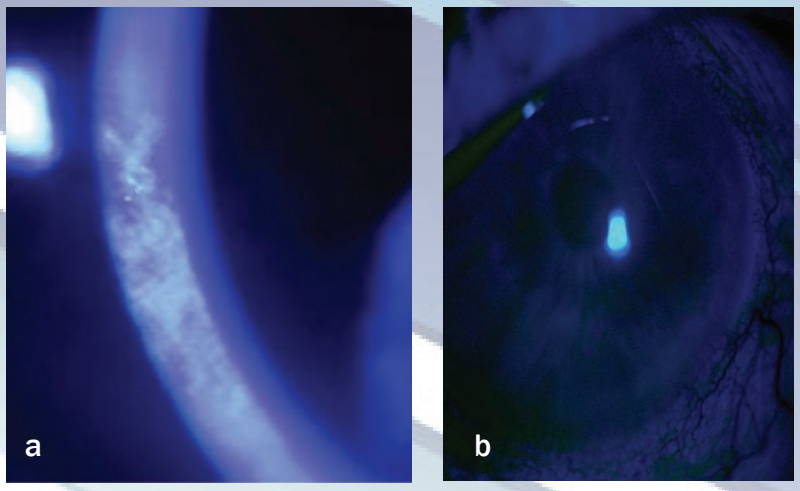

Figure 3. Non-healing SPK and dry eye prior to cataract surgery (a). Placement of PROKERA® Slim to promote healing of epithelial defect following corneal collagen crosslinking (b).

This interferes with keratometry and therefore predictable IOL power calculation and accurate astigmatism management. Often, as in this case, even if the areas of SPK are not large they do not resolve with conservative treatments such as drops, ointments or cyclosporine ophthalmic emulsion 0.05% (Restasis®, Allergan). Therefore, to expedite the healing process for this patient and smooth the ocular surface, we placed a PROKERA® Slim in the affected eye. As we have come to expect, this led to rapid healing (*see Figure 3b*).

Importantly, the cornea resumed normal shape in 24 hours, allowing us to perform accurate preoperative measurements and ensuring that the patient had an uneventful postoperative healing course. If we had used a dehydrated membrane with a BCL, we would likely have needed to wait for up to four weeks for the cornea to stabilize for biometry.

Cryopreserved amniotic membrane tissue provides anterior segment surgeons with a welcome additional resource for managing the ocular surface in a variety of clinical situations. It fits nicely with my approach to any corneal condition that involves inflammation, which is to treat aggressively from the start and taper rapidly rather than settle for incremental improvement. For non-healing epithelial defects in particular, I follow these three primary principles:

1. Discontinue topical drops that may be impeding the healing process, such as those that have a thick vehicle capable of causing problems, especially under a contact lens, and replace with milder options if necessary.
2. Prescribe oral doxycycline, starting at 100 mg bid for the anti-collagenolytic effect.
3. Place a PROKERA® cryopreserved biologic corneal bandage, which, unlike pressure patching, reduces inflammation quickly and allows simultaneous use of topical antibiotics and steroids if needed.

MANAGING CORNEAL INFLAMMATION AND DRY EYE

Brandon D. Ayres, MD

As the Dry Eye WorkShop dry eye severity grading scheme indicates, patients categorized as having Level 3 or Level 4 disease can be profoundly affected by their symptoms. Their daily activities may be curtailed, sometimes to the point of reduced work capacity or a psychological condition such as depression. To provide them with the relief they seek, we must restore the ocular surface to a normal homeostatic stage so that tissue healing can ensue and further damage can be prevented. This requires diminishing factors that incite or promote inflammation or other pathologies. When that is accomplished, regenerative healing can take place. I have seen a clear difference in the efficacy of cryopreserved tissue over autologous serum eye drops for delivering quality healing of the ocular surface.

Bio-Tissue recently conducted a survey of multiple physicians and 295 patients to assess the effectiveness of the PROKERA® Slim biologic corneal bandage in treating dry eye.[4] The survey focused on qualitative feedback, such as patient lifestyle factors and satisfaction with

"...we must restore the ocular surface to a normal homeostatic stage so that tissue healing can ensue..."

treatment results, after one week of use. Of the patients surveyed, 95 percent reported that based on their doctor's feedback, the biologic corneal bandage healed their eye.[3] When asked how their eye felt after treatment compared with before, 93 percent reported the eye felt better. In addition, 75 percent of patients responded that the biologic corneal bandage alleviated the pain associated with dry eye, and 92 percent responded that they would request the same treatment if their symptoms returned.[3]

I participated in the survey, and the overall results match my personal experience using this treatment option. With its ability to quiet the ocular surface disease process, I have seen patients improve from Level 3 or 4 dry eye to Level 1, which is manageable with more mild treatments such as punctal plugs, Restasis® or pulsed topical steroids. If symptoms recur beyond that level, I do not hesitate to use a biologic corneal bandage again. Unlike other treatments for dry eye, which can take substantial time to work or may not work at all, this biologic treatment option allows me to achieve excellent results for dry eye patients quickly.

SUTURELESS RESERVOIR RESTORATION FOR CONJUNCTIVOCHALASIS DRY EYE

Neel R. Desai, MD

Among the misconceptions that exist about the condition known as conjunctivochalasis are that it is a disease of the conjunctiva that only affects the tear meniscus and can be managed in the same way as aqueous tear deficiency. The truth is, CCh is a Tenon's disease stemming from chronic exposure to elevated levels of matrix metalloproteinases, a chronic inflammatory process. Dissolution of the Tenon's fascia occurs over time, which causes the overlying conjunctiva to become loose and redundant. Furthermore, CCh not only obstructs the tear meniscus, it leads to foreshortening of the inferior fornix thereby obliterating the tear reservoir. Once the anatomy of the reservoir is altered, the problems cannot be fixed by topical therapies or punctal occlusion. Surgery is the only solution.

> "...the biologic ocular transplantation graft can be precisely placed and tucked where it is needed during surgery."

Several techniques for surgically treating CCh, such as cautery or "paste, pinch and snip," have been tried and tend to worsen the condition rather than cure it. Dr. Scheffer C. G. Tseng developed a successful technique called reservoir restoration, which restores the function of the anatomical tear reservoir (fornix) by:

1. removing deteriorated Tenon's capsule
2. rearranging conjunctiva and/or removing conjunctiva if necessary
3. deepening the fornix
4. using multiple-layer cryopreserved amniotic membrane to replace the Tenon's and conjunctiva to help prevent recurrence and expedite recovery.

While Dr. Tseng prefers to suture the AmnioGraft® down as part of his procedure, I have developed a version of reservoir restoration that is sutureless. This approach evolved from my sutureless pterygium technique in which I reconstruct the semilunar fold and seal the potential space between the conjunctiva and Tenon's fascia. For sutureless reservoir restoration for CCh, AmnioGraft®serves as an ideal Tenon's replacement. Preserved through Bio-Tissue's CryoTek® process, the AmnioGraft® biologic ocular transplantation graft maintains the high molecular weight proteins and HC-HA/PTX3 complexes that are present in the fetal wound-healing environment. These crucial growth factors, cytokines and proteins are rendered ineffective when membrane is preserved by dehydration. In addition to the benefits of its mechanism of action and anti-inflammatory effects, AmnioGraft® maintains the structural integrity of the tissue histologically, giving it intraoperative workability. This means, in contrast to the more brittle dehydrated tissue, the biologic ocular transplantation graft can be precisely placed and tucked where it is needed during surgery. It also, of course, eliminates the need for an autograft.

The key steps in sutureless reservoir restoration are:

- inject 2% lidocaine infiltrated with epinephrine (for hemostasis and to separate tissue planes)
- resect redundant conjunctiva
- remove unhealthy Tenon's capsule from scleral bed
- cauterize any prolapsed fat so it shrinks back behind the fornix and the edge of remaining Tenon's
- with a small amount of fibrin glue, secure a small piece of AmnioGraft® biologic ocular transplantation graft to cover the inferior rectus muscle insertion (to replace Tenon's in that area and to prevent restriction and potential diplopia)
- using minimal glue, secure a second piece of AmnioGraft® (cut larger than the defect) over the entire defect (overshoot the edges when pulling the graft into place), tucking the edges a minimum of 1 mm under the conjunctiva on the sides (as if tucking a bed sheet under a pillow).
- "squeegee" excess glue (anteriorly or laterally, never posteriorly) and excise excess tissue.

Most of my patients who have had sutureless reservoir restoration with an AmnioGraft® biologic ocular transplantation graft begin to feel relief within 24 hours of the procedure. They are among the most satisfied patients in my practice. They come in miserable from their symptoms, desperate for a solution, and leave thrilled with the results of this procedure, which takes 10 to 12 minutes on average to perform.

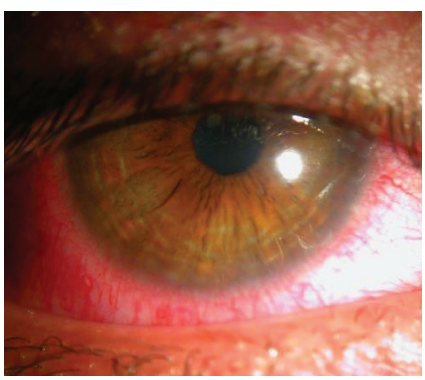

Figure 4. Chronically red eye prior to diagnosis of demodex blepharitis.

> "…chronic lid margin disease and inflammation lead to ocular surface inflammation."

DEALING WITH LID MARGIN AND OCULAR SURFACE DISEASE ISSUES

Preeya K. Gupta, MD

As knowledge about ocular surface disease has advanced, it has become clear that chronic lid margin disease and inflammation lead to ocular surface inflammation. Without proper management of the inflammation, patients are at increased risk for impaired vision, infection and suboptimal cataract and refractive surgical outcomes.

Demodex blepharitis is a common, but frequently overlooked cause of lid margin disease. It can exacerbate pre-existing conditions such as dry eye and pterygium, and it has been implicated as a contributor to rosacea. It can also make patients quite uncomfortable, as it did for a 49-year-old patient who recently presented in my practice. His chief complaint was bilateral ocular irritation, and he had been experiencing redness and recurrent chalazia for approximately a year (*see Figure 4*). He had been diagnosed with chronic blepharoconjunctivitis, but his condition had limited response to hot compresses, lid scrubs, topical antibiotics/steroids, lubricants and oral doxycycline.

Examining this type of patient, with chronic symptoms and no relief from the usual therapies, it's important to consider the full range of potential causes, such as meibomian gland dysfunction associated with rosacea, chronic conjunctivitis, toxicity issues, mucous fishing syndromes, lid apposition problems and, in this particular case, based on the chronic chalazia, sebaceous cell carcinoma. It is also important

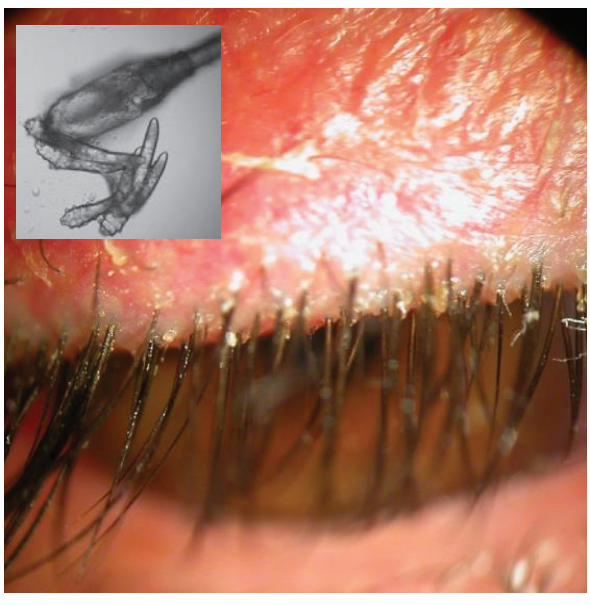

Figure 5. Cylindrical dandruff at the eyelash bases is a strong indication that demodex mites are the cause of lid margin and ocular surface inflammation. Inset: Demodex mites found on a patient's eyelashes.

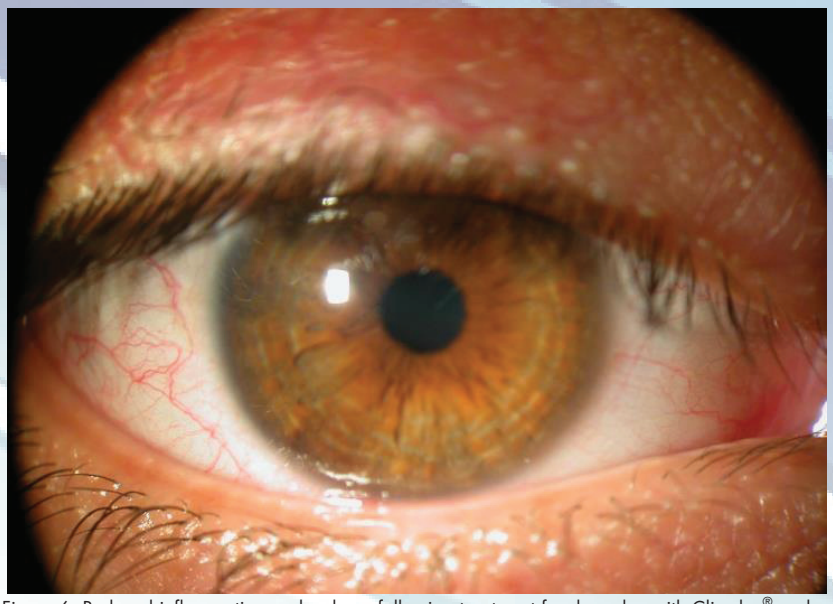

Figure 6. Reduced inflammation and redness following treatment for demodex with Cliradex® and Cliradex® Complete.

to examine the base of the eyelashes for cylindrical dandruff (*see Figure 5*), which is pathognomonic for demodex. When this is observed, a few eyelashes should be plucked and closely examined for the presence of the demodex mites (*see Figure 5 inset*). The mites, which are present on everyone's skin but usually do not cause problems, live in the glands and feed on meibum. When they become a source of inflammation, they require treatment.

In this case, we treated the patient in-office with the Cliradex® Complete Advanced Lid Hygiene Kit, which includes a gel solution and an applicator brush that is used to loosen debris at the eyelash base and lid margin so it can be cleaned away. The lashes and lid margin should be "combed" and cleaned for no more than one to two minutes. The gel is all natural and preservative-free. It contains 4-Terpineol, the component of antimicrobial and anti-inflammatory tea tree oil[4,5] that has been shown to be the most effective component for killing demodex mites.[6] It is effective at low concentrations, which is important in terms of patient comfort and tolerability.

The kit also includes 24 Cliradex® lid, lash and facial cleanser towelettes for patients to use at home. Like the gel, the towelettes are preservative-free and contain 4-Terpineol. My patients find them easy to use, which improves compliance. The gel contains approximately double the concentration of the towelettes and therefore serves as a loading dose when applied in-office.

The demodex patient discussed here used the towelettes as directed for six weeks after his initial advanced treatment, which significantly reduced his eyelid inflammation, ocular surface inflammation and redness and discomfort (*see Figure 6*).

In addition to demodex, Cliradex® is also indicated for managing symptoms associated with meibomian gland dysfunction, rosacea blepharitis, dry eye, chalazia and other lid margin diseases, making it a very useful addition to the treatment options I can offer my lid margin/ocular surface disease patients.

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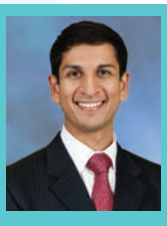
Eric Donnenfeld, MD, is founding partner of Ophthalmic Consultants of Long Island and clinical professor of Ophthalmology at New York University.

Brandon D. Ayres, MD, is part of the Cornea Service at Wills Eye Institute, where he serves as an assistant surgeon. He is also an instructor at Jefferson Medical College, Thomas Jefferson University.



Neel R. Desai, MD, specializes in cornea, cataract and refractive surgery and is the medical director of the International Sight Restoration Eye Bank.

Preeya K. Gupta, MD, is a corneal specialist at Duke Eye Center in North Carolina. Her clinical interests include corneal transplantation as well as cataract and refractive surgery.

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