How to Take the "Recurrent" Out of Recurrent Corneal Erosion Syndrome

Using a combination approach to treatment can help prevent ocular morbidity and drastically reduce recurrences in patients with this frustrating condition.

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Recurrent corneal erosion (RCE) syndrome is a chronic relapsing disease characterized by a disturbance of the epithelial basement membrane. Patients experience repeated episodes of a sudden onset of pain (usually upon wakening) accompanied by redness, photophobia, and watering of the eyes. Management of RCE can be frustrating for both the patient and doctor. The patient becomes upset due to the recurrent episodes of pain and decreased vision, and the doctor is discouraged due to his or her inability to cure the patient's disease.

In 2012, Watson et al updated the Cochrane Collaboration on "Interventions for recurrent corneal erosions."[1] Although RCE has been recognized as a disease entity for more than 100 years (first reported by Hansen in 1872 and Von Arlt in 1874[2-4]), there have been no long-term studies that define a specific treatment protocol.[1] Of the few trials that have been performed in patients with RCE, the greatest successes have been seen when multiple treatments were used together.[5-7] We therefore recommend foregoing the normal stepwise treatment pyramid and instead initiating a combination treatment modality at the first encounter. This approach capitalizes on recent advances in the understanding of the underlying pathological anatomy and greatly increases the chance of successfully managing RCE patients.

ANATOMY

The basement membrane is 300-nm thick and is composed of three layers: the lamina lucida, lamina densa, and lamina reticularis, which are made up of laminin, type IV collagen, and fibronectin, respectively. Along with anchoring fibrils and hemidesmosomes, these components make up the normal "adhesion complexes" that allow the epithelium to properly adhere to the basement membrane.[8,9] In eyes with RCE, the reattachment of the corneal epithelium following an abrasion appears faulty due to a variety of defects of the adhesion complex. There can be a reduplication of the basement membrane, loculation of connective tissue, or a complete absence of the basement membrane and hemidesmosomes.[8] The corneal epithelium then develops pale, swollen basal cells, along with pseudocystic collections of cellular and amorphous debris. This leads to an elevation of the epithelium and an accumulation of underlying debris, with the further formation of abnormal basement membrane in a self-perpetuating cycle.[9]

MATRIX METALLOPROTEINASE

Matrix metalloproteinases (MMP) are enzymes that break down the structure of the extracellular matrix (collagenase). Gelatinase is a specific MMP composed of MMP-9 and MMP-2, which degrades collagen type IV and VII, and laminin, which are major components of the basement membrane.[10,11] Elevated levels of gelatinase have been observed in the tears of patients with RCE, and their expression has been implicated in the pathogenesis of RCE. This upregulation leads to basement membrane degradation and poor epithelial basement membrane adhesion, and the higher-than-required levels of MMP dissolve the old and newly forming basement membrane.[9,7,11]

TREATMENT AND MANAGEMENT

The main goals of the treatment and management of RCE are to control inflammation, promote epithelial regeneration, and to allow the basement membrane complexes to form properly. There are several individual strategies that can be used, and each has shown to have a success rate somewhere between 60% and 80%. The difficulty with performing a single focused treatment strategy is that it will create unneeded frustration for both the doctor and patient if and when it fails. We therefore recommend an initial combination approach that utilizes a minimum of four different treatments that work synergistically to greatly improve the chance of reducing and preventing RCE outbreaks.

Listed are several individual treatment strategies that should be combined together to create a treatment plan.

Medical Management

Artificial tears. One of the main goals of medical management is to promote epithelial health and regeneration. Therefore, initial treatment routinely starts with increasing lubrication and optimizing the health of the tear film.[8,10] This allows a reduction in friction and decreases the adherence of the eyelids to the epithelium. Improving lubrication and moisture is especially critical upon patients' awakening. FreshKote (Focus Laboratories), now available as an over-the-counter option, helps reduce microcystic edema and reestablish the integrity of the corneal epithelium due to its high oncotic pressure.[8]

Hyperosmotics. Sodium chloride solutions and ointments create an osmotic gradient that is useful in reducing corneal edema. These hypertonic agents also promote epithelial adherence.[8]

Tetracyclines. The tetracycline family of antibiotics, specifically doxycycline, plays an important role in the management of RCE. As a known inhibitor of MMP, low-dose doxycycline reduces the level of these inflammatory enzymes and reduces recurrences. Typically prescribed at 20 to 50 mg twice a day for a minimum of 2 months, doxycycline also improves meibomian gland dysfunction by regulating lipases from colonizing bacteria that create an abnormal tear composition.[6,8,9,12] This abnormal tear film, rich in toxic free fatty acids, affects epithelial membrane integrity and healing.[6,8,9,12]

Topical azithromycin. AzaSite (topical azithromycin solution 1%; Akorn), a topical macrolide indicated for the treatment of bacterial conjunctivitis, has also been shown to reduce levels of MMP-9.[13,14] It may also help to control blepharitis and meibomian gland dysfunction, both of which have been correlated with RCE.[9,13]

Corticosteroids. Topical corticosteroids such as loteprednol etabonate 0.5% (Lotemax; Bausch + Lomb) have been shown to be effective in reducing MMP activity.[6] As with all corticosteroids, use may delay epithelial healing and should be used with caution.

Figure 1. An autologous serum vial. Autologous serum affects both early- and late-stage healing of the epithelium.

Cyclosporine ophthalmic emulsion. This topical immunomodulator with antiinflammatory activity has been available topically for 10 years (Restasis; Allergan). It works by reducing inflammation and producing a more stable tear film to help epithelial cells to anchor properly.

Autologous serum. Its use was first described in 1984 by Fox et al for keratoconjunctivitis sicca.[15] Autologous serum replaces the individual's antibodies and gives an extra supply of necessary glucose, proteins, and calcium for the epithelium to migrate rapidly (Figure 1). Autologous serum formulations contain vitamin A and fibronectin, which help speed up the first phase of wound healing. They also affect the final phases of wound healing by supplying growth factors that activate keratocytes to produce extracellular matrix components.[16]

Umbilical cord serum. Compared with autologous serum, umbilical cord serum has a much higher concentration of essential tear components, along with epidermal growth factor, transforming growth factor-b, neurotrophic factors, insulin-like growth factor-1, and nerve growth factor. All of these components promote reepithelialization.[5]

Substance-P-derived peptide. Confocal microscopy of eyes with RCE shows alterations in corneal nerves similar to that seen in neurotrophic corneas. Compounded eye drops containing substance-P-derived peptide, a sensory

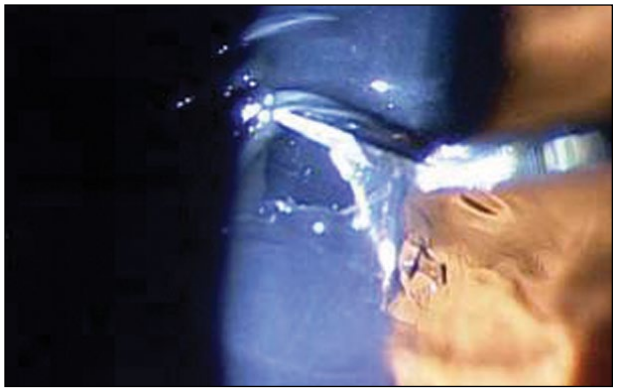

Figure 2. Corneal debridement removed damaged tissue to allow for reepithelialization.

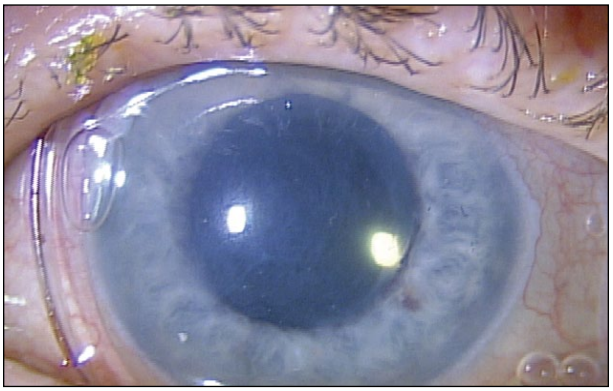

Figure 3. Eye with a sutureless amniotic membrane (Prokera; Bio-Tissue).

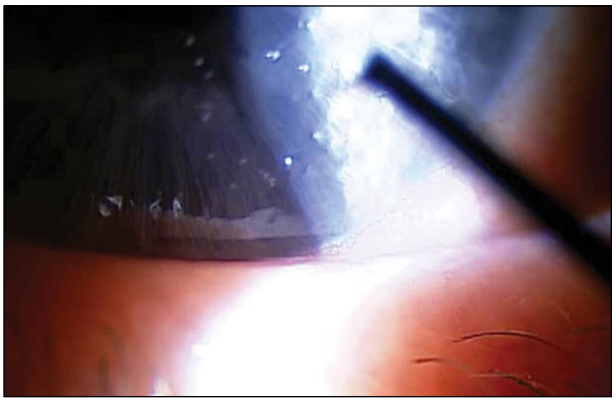

Figure 4. Anterior stromal puncture.

neurotransmitter released from the trigeminal nerve during healing, promote epithelial migration and healing.[17]

N-acetylcysteine. N-acetylcysteine (NAC) is a derivative of cysteine, which inhibits collagenase irreversibly. It is believed that NAC inhibits MMP-9 in a similar fashion. A study in 2012 showed that NAC reduced MMP-9 production in human corneal epithelial cells and inhibited cell migration, making it a viable therapeutic option for RCE.[11]

Mechanical Management

Bandage contact lens. Bandage contact lenses are a useful adjunct for treatment, especially when coupled with other modalities. A study by Fraunfelder and Cabezas showed that extended use of bandage contact lenses (worn for 3 months, replaced every 2 weeks) offered immediate relief of symptoms and long-term resolution for most of their recalcitrant RCE patients.[1,18]

Punctal plugs. These help thicken the tear film and help prevent tear evaporation at night and epithelial avulsion.

Epithelial debridement. Debridement is a means of removing the dystrophic epithelium and basement membrane working from the limbus to the central cornea (Figure 2). The goal is to create a smooth Bowman layer, and a clean, more regular surface for new basement membrane to form with stronger adhesions of the basal epithelial cells to the basement membrane.[1,9,19,20]

Sutureless amniotic membrane. Composed of the innermost of the three membranes surrounding the fetus, the sutureless amniotic membrane is an avascular and acellular tissue that promotes epithelialization, suppresses inflammation, inhibits scarring, inhibits angiogenesis, and has neurotrophic factors.[21] They are easy to insert in the office and allow for easy monitoring of healing, and the clinician can still check intraocular pressure without removal. They do not interfere with antibiotic penetration (Figure 3).

Anterior stromal puncture. With anterior stromal puncture, first described by McLean et al in 1986,[22] a 20- to 25-gauge disposable hypodermic needle is used under the slit lamp to make multiple punctures through loose epithelium and Bowman layer into the anterior half of the stroma (Figure 4). It is believed that the breaching of the Bowman membrane stimulates a more secure bonding of the epithelium to the underlying basement membrane, Bowman, and stroma.[1,9,10,20,22-24]

Surgical Management

Nd:YAG puncture. Nd:YAG puncture is similar in concept to anterior stromal puncture, but employs a Nd:YAG

TABLE. SUGGESTED COMBINATIONS FOR TREATMENT OF RCE.

Option No. 1
- Restasis ophthalmic emulsion (Allergan) b.i.d.
- Punctal plugs
- Hyperosmotic ophthalmic ointment q.h.s.
- FreshKote (Focus Laboratories) q.i.d.

Option No. 2
- Epithelial debridement
- ProKera (Bio-Tissue) slim amniotic membrane
- Doxycycline 20-50 mg b.i.d. x 3 mos
- Autologous serum 4-6x/day

Option No. 3
- Anterior stromal puncture
- Bandage contact lens x 12 wks
- Doxycycline 20-50 mg b.i.d. x 3 mos
- Azasite (Akorn) b.i.d. x 6 wks

Option No. 4
- Alcohol delamination
- Amniotic membrane
- Doxycycline 20-50 mg b.i.d. x 3 mos
- Lotemax ophthalmic gel (Bausch + Lomb) q.i.d. x 2wks, then b.i.d. x 4 wks

laser. Several 0.4- to 0.5-mJ pulses are applied to Bowman layer. The benefits are that it creates shallow, reproducible, translucent spots, but most cases require removal of the epithelium for a full breach into the stroma.[8,20]

Phototherapeutic keratectomy. Phototherapeutic keratectomy involves the use of an excimer laser after the epithelium is removed to help smooth Bowman layer and permit the formation of a new basement membrane with adhesion complexes.[9,20]

Alcohol delamination. A solution of 20% ethanol placed on the cornea for 30 seconds splits the basement membrane epithelium from the stroma at the level of lamina lucida (which is removed) and densa (which stays behind). This results in elimination of the proteinaceous and cellular debris, but leaves behind collagen IV and VII to allow new anchoring fibril formation.[10,20,25]

Superficial keratectomy. Can be performed with a blade, diamond knife, or an Amoils scrubber. The benefit with this technique is that the dystrophic epithelium and basement membrane are peeled off in one continuous sheet, leaving an undisturbed Bowman membrane and a clean surface for new basement membrane to form.[1,10,20]

Combination Approach

Although there is no one straightforward combination treatment that works for every RCE patient, several options to consider are shown in the table.

CONCLUSION

The treatment goal in a patient with RCE patient is to restore the normal ocular surface anatomy, control inflammation, and prevent epithelial avulsion. With today's understanding of RCE, and utilizing a combined treatment modality, it is possible to maintain vision and prevent recurrences in the large majority of these patients. ■

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