CHAPTER 15

Corneal Cross-Linking With Riboflavin and Ultraviolet Irradiation in Unstable Corneas With Progressive Irregular Astigmatism

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Irregular astigmatism can occur naturally or be surgically induced. The alternatives for correction of irregular astigmatism are few, expectations are limited, and consequences may be unpredictable, anatomically and functionally.[1] In the recent years, advancements in laser vision correction have begun to offer us better tools for managing irregular astigmatism.[2-5] These vision-correcting methods, however, attempt to regularize the front surface of the cornea, while assuming stabilty of biomechanical stability within the underlying stroma. In cases where the irregular astigmatism is progressive, such as keratoconus, pellucid marginal degeneration, or post–laser-induced iatrogenic ectasia, the corneal stroma is structurally weakened, and most certainly will worsen over time following tissue ablation procedures. Hence, a primary intervention, such as collagen cross-linking, would first be required, ensuring stabilization of the cornea, before any attempt could be considered to modify the surface curvature.

Principle of Action

Collagen cross-linking is a new technique of corneal tissue strengthening by the photosensitzer riboflavin and ultraviolet A (UVA), similar to photopolymerization in polymers.[6] Collagen cross-linking induces an increase in the formation of intra- and interfibrillar covalent bonds by photosensitized oxidation, which, in turn, leads to a biomechanical stabilization of the cornea.[6-8] Extensive experimental studies in rabbit and porcine eyes, including biomechanical stress–strain measurements, have shown a significant increase in corneal rigidity by approximately 70% in corneas following riboflavin/UVA treatment. The stiffening effect of the riboflavin/UVA treatment is similar to formaldehyde-induced tissue stiffening and fixation in pathologic specimens, also caused by collagen cross-linking.[9]

Histopathologically, corneal cross-liniking leads to a significant increase in collagen fiber diameter, which indirectly confirms the change in its structure and function (rigidity). Interestingly, a naturally occurring increase in both corneal collagen fiber diameter and corneal rigidity have also been described in diabetes mellitus and with aging.[10] In these conditions, keratoconus rarely occurs.

Safety Considerations

With riboflavin as a photosensitizer, the cornea absorbs a great amount of the irradiation intensity. Without riboflavin, the UVA light would be reduced in the cornea only by approximately 30%, with approximately 50% UVA absorption in the lens.[11] This never happens because with 3 mW/cm^2 of UVA irradiance at the surface of the cornea and a riboflavin concentration of 0.1%, there is a considerable reduction of the UVA light by 95%, resulting in a noncytotoxic irradiance of 0.15 mW/cm^2 at the endothelial level.[12] Anteriorly, in the corneal stroma, keratocyte apoptosis leads to a repopulation that has been shown by confocal microscopy to start after 1 month, reaching its preoperative morphology and number by six months after the treatment.[13]

In experiments with rabbit eyes, the cytotoxic threshold irradiance for the endothelial cells after combined riboflavin/UVA treatment is 0.36 mW/cm^2 (~0.65 J/cm^2), which may be reached with a corneal thickness of less than 400

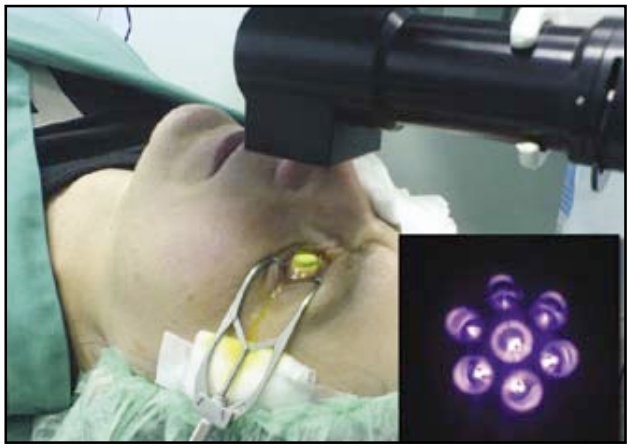

Figure 15-1. Treatment in progress with the cornea soaked with riboflavin and irradiated by the UV lamp. In the lower right corner, one can appreciate the patient's perspective of the UV lamp.

Figure 15-2. Fluorescence of the riboflavin under the UV light indicates active treatment application.

µm using 3 mW/cm^2 irradiance (~5.4 J/cm^2) at the corneal front surface.[14] Therefore, preoperative pachymetry is essential and must be measured in all cases. Usually, the central corneal thickness in keratoconus is not reduced to less than 400 µm. In corneas with less then 400 µm, the cross-linking treatment should be avoided using these dosage parameters, and a hypotonic solution of riboflavin in physiological solution (without Dextran T-500) should be applied in order to swell the cornea before and during the irradiation.

Considering the crystalline lens, the UVA dose of 0.65 J/cm^2 (0.36 mW/cm^2) is far below a cataractogenous level of 70 J/cm^2.[15] In addition, lens damage is usually induced by UVB light (wavelength range of 290 to 320 nm), which has a higher energy than UVA. Regarding retinal phototoxicity, UVA levels in the posterior segment are negligible and comparable to ambient sun exposure.

Surgical Technique

The procedure should be conducted under sterile conditions in the operating room. Topical anesthetic is applied and the central 7 mm of the corneal epithelium is removed using a blunt knife, or 30 s of application of 20% alcohol. As a photosensitizer, riboflavin 0.1% solution in Dextran T-500 20% solution is applied 15 minutes before the irradiation and every 2 to 3 minutes during the irradiation. Alternatively, a smaller area of epithelium may be removed, provided that the time of application of riboflavin is increased, and the presence of riboflavin in the anterior chamber is confirmed by the presence of a yellow flare under the slit-lamp examination prior to the application of UVA light.

After allowing riboflavin to permeate through the cornea into the anterior chamber, the irradiation is started using a UV lamp (370 nm; Peschkemed, Huenenberg, Switzerland) at a 1-cm working distance for 30 minutes using a 3 mW/cm^2 irradiance (~5.4 J/cm^2) (Figures 15-1 and 15-2). After the treatment, an antibiotic eyedrop is applied, and a bandage contact lens is fitted to the corneal surface until reepithelialization.

Indications and Clinical Results

The principle indication for the use of the collagen cross-linking of the cornea is to halt the procession of ectasia in diseases of the cornea, such as keratoconus and pellucid marginal degeneration. Collagen cross-linking may also be effective in the treatment and prophylaxis of iatrogenic keratectasia, resulting from laser in situ keratomileusis (LASIK). Beyond keratoectasia, the new technique can also be used in treating corneal melting conditions or infectious keratitis, as the cross-linking strengthens a collagenolytic cornea and UVA irradiation sterilizes the infectious agent.

The first prospectively controlled clinical study that included 23 eyes with moderate or advanced progressive keratoconus showed collagen cross-linking as effective in halting the progression of keratoconus over a period of up to 4 years.[15] In the study, a mean preoperative progression of keratometry (max K) by 1.42 diopters (D) in 52% of eyes over a 6-month period was followed by a postoperative decrease in 70% of eyes, revealing a reduction of mean keratometry by 2.01 D. Moreover, the postoperative spherical equivalent (SEQ) was reduced by an average of 1.14 D, whereas at the same time, 22% of the untreated fellow control eyes had a postoperative progression of keratectasia by 1.48 D.

Clinical studies carried out elsewhere and presented at the 1st and 2nd International Congress of Corneal

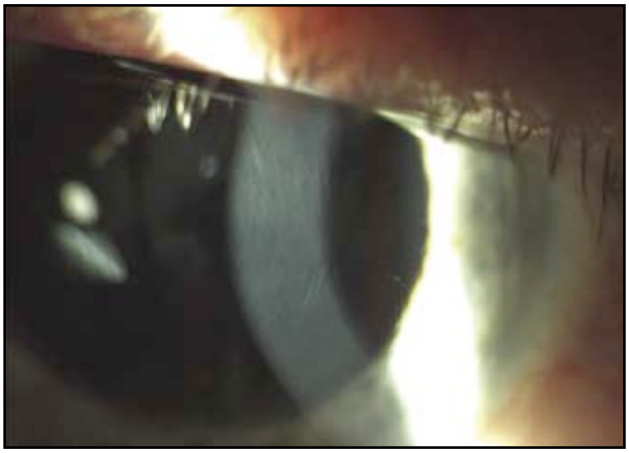

Figure 15-3. Third postoperative day: right after the removal of the contact lens one can observe transient stromal and epithelial edema with a mild cotton-like hazy appearance within the corneal stroma. (Courtesy of T. Seiler, MD PhD.)

Cross Linking in 2005 and 2006 showed similar findings. The prospective results from our group in Serbia for 38 keratoconic eyes of 19 patients, where the more advanced eye was treated and the fellow eye served as a control, showed a 6-month postoperative statistically significant mean decrease in max K by 1.75 ± 1.24 D, SEQ by 1.94 ± 3.30 D, and refractive cylinder by 1.31 ± 1.96 in the treated eyes, whereas the fellow eyes had a mean increase in max K by 0.24 ± 0.97 D, SEQ by 0.13 ± 1.00 D, and cylinder by 0.06 ± 0.83 ($P < 0.01$). Both the uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) increased by 0.01 ± 0.12 and 0.04 ± 0.22, respectively, in the treated eyes, whereas the fellow eyes decreased by 0.03 ± 0.23 and 0.02 ± 0.17, respectively, but without statistically significant difference. Regarding safety, the endothelial cell counts decreased by 64 ± 158 c/mm^2 in the treated eyes and 20 ± 44 c/mm^2 in the fellow eyes without reaching statistical significance. Meanwhile the IOP increased by 1.92 ± 2.22 mm Hg in the treated eyes and 0.08 ± 2.25 mm Hg in the fellow eyes with a high statistically significant difference (P <0.01). This latter finding was not a safety concern, but rather demonstrated the efficacy of cross-linking, because a stiffer, more elastic cornea measures at a higher IOP,[16] similar to the observed IOP measurement differences between thicker and thinner corneas.[17]

An illustrative example is a 36-year-old female patient, rigid gas-permeable contact lens wearer for 18 years, who reported herself to our service because of an unstable contact lens in her left eye. Visual acuity with her contact lens was 20/20, whereas BSCVA with Sph −2.50 D Cyl −1.50 D × 90 was 20/50. Her pachymetry was 484 µm and topography showed typical shape of keratoconus on both eyes, with the worse picture in her left eye. Her left eye was first treated, resulting in a more regular cornea and BSCVA of 20/32, with Sph −3.50 D cyl −1.50 D × 90. Three months after the corneal cross-linking, topography-guided photorefractive keratectomy (PRK) has been performed, increasing the patient's UVA to 20/25 and her BSCVA to 20/20 partial with Sph −0.75 D Cyl −0.50 D × 90 (Figure 15-3).

Corneal cross-linking has also be used successfully in stopping the advancement of iatrogenic ectasia in eyes with aggressive excimer laser ablation. In a published German study of collagen cross-linking following post-LASIK ectasia, the biomechanical status of the cornea was stabilized with a halting of the refractive and topographic progression of ectasia over a period of 18 months.[18] The surgical technique is the same as cross-linking for keratoconus since riboflavin penetrates freely from the flap to the stromal bed.

In managing nonectatic forms of progressive irregular astigmatism, UV radiation with riboflavin has been shown to stop the keratolytic process in eyes with progressive corneal ulceration. In 4 patients suffering from various melting ulcerations of the cornea, collagen cross-linking, using a similar protocol, led to a halting of the progression in 3 of the 4 patients.[19]

Clinical Side Effects

To date, there have been no remarkable clinical side effects or complications noted during clinical trials and studies performed at multiple centers. Mild transient edema is usual in eyes, with a mild cotton-like hazy appearance within the corneal stroma, which usually resolves after 4 to 6 weeks with the usual treatment (Figures 15-4 and 15-5). One case has been reported with focal corneal edema over a small area that had a reduced endothelial cell count and focal endothelial haziness. Retrospectively, this eye was found to be below the minimal thickness range and probably developed localized endothelial damage. However, a week later, the cornea returned to its usual appearance with no sign of endothelial damage visible during the slit lamp examination, which was likely due to a compensatory migration of surrounding endothelial cells.

A delay in reepithelization had been noted in an eye receiving corticosteroid medication during the period of epithelization and bandage soft contact lens wear. With withdrawal of the corticosteroid medication, reepithelization was complete within 24 hours, and the eye suffered no adverse consequences afterwards.

A few anecdotal reports have been made of small sterile corneal infiltrates developing under the contact lens, all of which are believed to be related with the use of non-steroid anti-inflammatory eye drops. The infiltrates did not progress after the contact lens removal, and disappeared with intense topical steroid therapy within 1 to 2 weeks, leaving only a faint visually insignificant opacity.

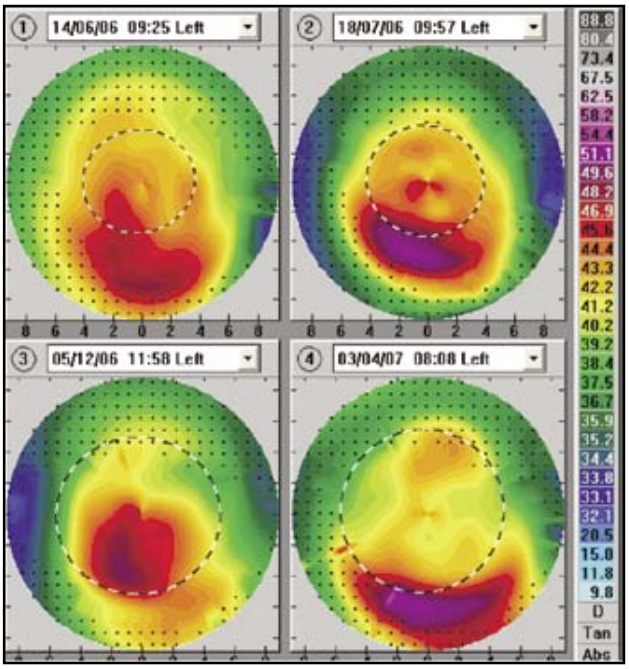

Figure 15-4. Tangential topographic maps illustrate improvements in corneal topography: (1) immediately after the removal of the contact lens (upper left); 2) 1 month after the removal of the contact lens (upper right), corneal cross-linking was performed; (3) 5 months after corneal cross-linking (lower left), topography-guided photorefractive keratectomy (PRK) with T-CAT WaveLight Allegretto Wave was performed; and 4) 4 months after topography-guided PRK (lower right).

Figure 15-5. Under the slit lamp a faint demarcation line between the swollen anterior and normal posterior cornea can be seen on the third day (left). This line can hardly be seen after 3 months (right). (Courtesy of T. Seiler, MD PhD.)

Conclusions

Riboflavin/UVA corneal cross-linking appears to be a safe and efficacious procedure in halting the progression of the keratoconus, and reducing the corneal curvature, spherical equivalent refraction and refractive cylinder in eyes with corneal instability and progressive irregular astigmatism due to keratoconus.

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