

ARTICLE COVER SHEET

LWW—ITO

FLA, SF, LTE and Case Study & Review

Article : ITO20090

Creator : cq16

Date : 2/20/2008

Time : 20:14

Article Title :

Number of Pages (including this page) : 7

Template Version : 1.0

01/11/08

Scripts:

1. sc_Extract_Xml
2. sc_Multifig_Marker
3. Autopagination compliant
4. run_on

Corneal Collagen Cross-linking Induced by UVA and Riboflavin (X-linking)

Juan Carlos Abad, MD

Universidad de Antioquia

Medellin, Colombia, and

Clinica Oftalmológica de Medellín (COM)

Medellin, Colombia

José Luis Panesso, MD

Clinica Oftalmológica de Medellín (COM)

Medellin, Colombia

HISTORICAL BACKGROUND

AQ1 Corneal ectasia after laser-assisted in situ keratomileusis
AQ2 ([LASIK] or even photorefractive keratectomy [PRK]) has become one of the most vexing complications of these widely performed refractive procedures. Since the first reports of ectasia by Seiler and colleagues^{1,2} multiple reports have appeared in the literature.³ It is now thought that if an adequate residual stromal bed is left during the LASIK surgery, and the patient later develops ectasia, a form of keratoconus was probably present before the operation,^{4,5} even in patients with hyperopic refractions.⁶ Researchers at Dresden Technical University headed by Seiler noted that diabetic patients do not develop keratoconus because of nonenzymatic cross-linking induced by advanced glycation end-products (Maillard reaction).⁷ They started looking at several methods to induce corneal cross-linking such as sugars, glutaraldehyde, and several light wavelengths combined with riboflavin.⁸ Eventually, they settled in using corneal cross-linking induced by 365-nm UVA enhanced by riboflavin (X-linking) as a parasurgical treatment of keratoconus and corneal ectasia.

When riboflavin (vitamin B2) interacts with UVA, it liberates a free oxygen radical into the surrounding corneal stroma. The oxygen radical causes oxidative desamination and hydrogen bond formation between the amino acids of the collagen chains at the intrahelical, interhelical, and intermicrofibrillar level. At the same time, riboflavin helps to limit the penetration of UVA into the eye, avoiding damage to the corneal endothelium and other intraocular structures.

Riboflavin has several advantages: has an easy and safe handling, does not change the transparency of the cornea, is widely available in the vitamin and food coloring industries, is nontoxic, water soluble, and has a good stromal penetration.

The addition of 20% Dextran T500 prevents the cornea from swelling during the operation to have a more controlled environment and to maximize the penetration of the UVA light, increasing the cross-linked collagen volume.

Studies in porcine and human corneas have demonstrated that X-linking increases collagen fiber diameter,⁹ the stress-strain relationship,¹⁰ their resistance against enzymatic degradation,¹¹ and that it decreases the swelling pressure or edema potential of the cross-linked cornea.¹²

The liberation of free oxygen radicals also produces a cytotoxic and apoptotic effect on stromal keratocytes (threshold, 0.5–0.7 mW/cm²) with depopulation of the cornea for the extent of the penetration of the UVA (300 μm)^{13,14}; the keratocytes repopulate the cornea in a 3- to 6-month period.¹⁵ Riboflavin limits the penetration of UVA into the eye, the radiant dose drops from 3 mW/cm² at the corneal surface to 0.35 mW/cm² (toxic dose for the corneal endothelium¹⁶) 300 μm from the surface; if a 400-μm lower limit of corneal stroma is used as a prerequisite for performing X-linking, there would be a 100-μm buffer zone that limits any endothelial toxicity. The amount of UVA light that penetrates the anterior chamber is minimal, thus avoiding crystalline and retinal toxicity.

TECHNIQUE

The preoperative evaluation consists of a complete eye examination plus a careful refraction, keratometry, topography, regional pachymetry, and an endothelial

Address correspondence and reprint requests to Juan Carlos Abad, MD, Clínica Oftalmológica de Medellín (COM), Cra. 30 no. 7^a-300, Medellín, Colombia (e-mail: jcabad@gmail.com).

The authors state that they do not have any financial interest in any of the products mentioned here.

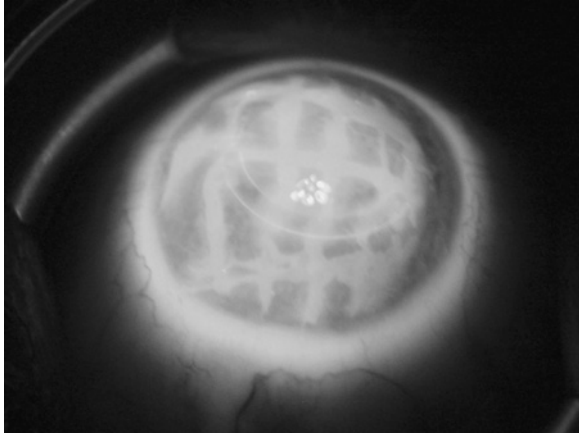


FIGURE 1. The corneal epithelium is removed in strips from limbus to limbus in a cross-hatched pattern with a blunt and narrow instrument taking care not to dislodge a LASIK flap if present. In this case, note the inferotemporal intracorneal ring segment (Intacs).

cell count (optional). Contact lenses should be discontinued before the operation to ensure a corneal contour that is not warped.

We use the 365-nm UV-X Illumination system provided by the Institut für Refraktive und Ophthalmologie (Zurich, Switzerland). It consists of an AC-powered LED UV light source. It produces a homogeneous beam of UVA in 3 spot sizes: large (11.5 mm), medium (9.5 mm), and small (7.5 mm). The light intensity should be calibrated before application with a special UV detector, and the adequate range should be $3.0 \pm 0.3 \text{ mW/cm}^2$, and if it deviates from that value, an intensity switch could be used to make the proper adjustment. The UV-X light source is then mounted and placed 5 cm from the

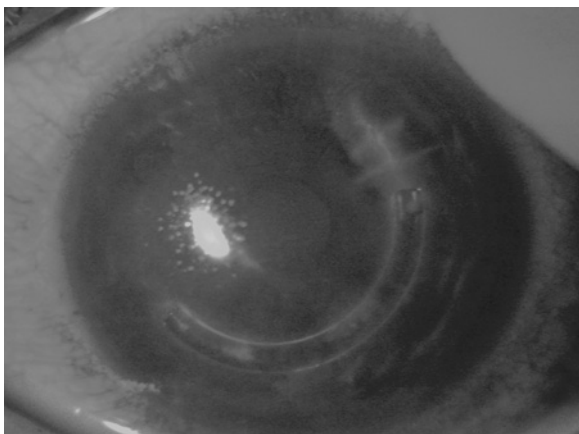


FIGURE 2. Postoperative day 1 in a patient who had the epithelium removed in a cross-hatched pattern. The central cornea has healed completely, and there is only a residual epithelial defect over the intracorneal ring segment.

patient's eye. It is swung out temporarily, and attention is directed to the eye. It is important to measure the ultrasonic corneal thickness at several points at this stage, and it should be greater than $450 \mu\text{m}$ in all points, if less than that, a hypotonic solution (see below) should be at hand. The corneal epithelium is removed in 8- to 9-mm diameter either with a blunt spatula or with 20% alcohol. An alternative is to remove the epithelium in strips creating a cross-hatched pattern from limbus to limbus as suggested by Seiler to speed up the recovery from the surgery (Figs. **F1** and **2**). Penetration studies are being carried out to support this form of epithelium removal. Others apply the riboflavin/Dextran solution to the intact epithelium just loosening it with heavy topical anesthetic use,¹⁷ but this method has not been replicated by most. A solution of 0.1% riboflavin in 20% Dextran T-500 is applied every 2 minutes for 30 minutes. The use of a saturated circular 7.0-mm cellulose sponge acts as a reservoir, maximizing riboflavin delivery to the stroma and minimizing dripping and wasting of the solution (Fig. 3). The sponge should be **F3** lifted with forceps as it is moved from place to place around the cornea to minimize abrasive trauma to the epithelial islands. In the past, fewer riboflavin drops were instilled before UVA application, as the end point was a yellow flare in the anterior chamber detected with a slit lamp's blue light; because flare could appear after only 5 minutes of riboflavin application,¹⁴ the protocol mentioned above seems safer. Check corneal thickness again, and it should be greater than $400 \mu\text{m}$ at all spots, otherwise, use hypotonic 0.1% riboflavin solution (Medio-Cross hypotonic, Peschke Meditrade GmbH, Switzerland) 2 drops every 10 seconds to swell the cornea above $400 \mu\text{m}$ (it usually takes 3 minutes to get from $350 \mu\text{m}$ to $400 \mu\text{m}$). The UV-X light source is swung back over the eye, and it is turned on. Adjust the spot size to irradiate only clear cornea, minimizing any potential limbal toxicity. The UVA



FIGURE 3. The use of a saturated circular sponge maximizes penetration of the riboflavin/Dextran solution and diminishes spillover.

light is applied using a radiant energy of 3 mW/cm² for 30 minutes (5.4 J/cm²). Continue to apply riboflavin drops every 2 minutes. It is important to apply anesthetic drops and lubricants as needed to the cul-de-sac, especially during the laser application where the eye tends to dry out some. The apparatus turns itself off after 30 minutes of constant application.

At the end, a therapeutic soft contact lens with good oxygen transmissibility is recommended to decrease pain without decreasing the quality of the regrowing epithelium. The postoperative management is similar to PRK, where the most important aspects are pain control and promoting the healing of the corneal epithelium.

AQ3

Regarding pain control, the use of oral γ -aminobutyric acid (GABA) analogues starting before the surgery seems to increase pain threshold and improve comfort; there are 2 analogues in the market: gabapentin (Neurontin) and pregabalin (Lyrica); the first is used at a dosage of 300 mg BID starting 1 to 2 days before surgery and continuing 1 or 2 days afterward; the latter is used in a similar manner, but the dosage is 150 mg BID. Strong opioid oral analgesics such as meperidine, tramadol, or codeine are usually needed; the use of an antiemetic such as phenergan might be needed to counteract the opioid-induced nausea. Topical nonsteroidal anti-inflammatory drugs could be used judiciously for no more than 2 or 3 days to dampen the pain; if used in excess, they could hinder corneal reepithelialization.¹⁸ The use of preservative-free topical anesthetics has been used before in PRK.¹⁹ We use them diluted by taking a 3-mL sample bottle of lubricant drops with disappearing preservatives (Refresh Tears or Genteal) and add 10 drops of 0.5% of proparacaine to dilute it down to 0.125%. We have the patients use it liberally (even every 5 minutes) to break the pain cycle. After they are more comfortable, they use it every 30 to 60 minutes. Another aspect sometimes forgotten is sleep induction to promote epithelial healing and to make the patient unaware of the pain; we use either midazolam or clonazepam as needed, taking into account that the GABA analogues and the strong opioids already make most patients sleepy. The pain seems to be worse the first 24 to 48 hours, and it gradually subsides; the patient will usually be pain-free after day 5 to 7 when the contact lens is removed.

AQ4

Topical antibiotics are needed to prevent infection, we prefer one of the fourth-generation quinolones because they have a wide spectrum of coverage and do not seem to retard epithelial healing; they are used 4 times a day starting 1 to 3 days before surgery and for 1 week after the operation. The use of a mild steroid such as fluorometholone is optional. If used, it is prescribed in a manner similar to the topical antibiotics.

■ DISCUSSION

The indications for X-linking are: (1) progressive steepening of the cornea either in keratoconus (or its variants) or iatrogenic keratectasia; (2) to potentiate the effect of intracorneal rings¹⁷ (this indication needs more studies to be confirmed); (3) corneal melting in corneas thicker than 450 μ m (counting the epithelium) at the thinnest spot; and (4) allowing surface ablation in thin or suspicious corneas (this indication needs further long-term studies to be proven).

The contraindications for X-linking are: (1) corneas thinner than 400 μ m (after removing the epithelium)—if the thickness of the stroma could be increased to 400 μ m with partially hypotonic solutions, the procedure could be performed; (2) prior incisional refractive surgery, especially transverse incisions because they tend to gape with contraction of the corneal lamella; although if temporary corneal suturing if performed, a good result could be obtained after corneal cicatrization (Fig. 4); (3) pregnancy or nursing; (4) central corneal opacities, relative to the improvement in visual acuity; (5) severe dry eye that might hinder corneal reepithelialization; and (6) systemic collagen disease, until more information is gathered about X-linking in these conditions.

After the epithelium heals 1 week after surgery, there might be some transient corneal edema. One way to ascertain that the treatment penetrated the cornea adequately is to observe a demarcation line between the cross-linked anterior stroma and the untouched posterior stroma that becomes evident 2 weeks after the

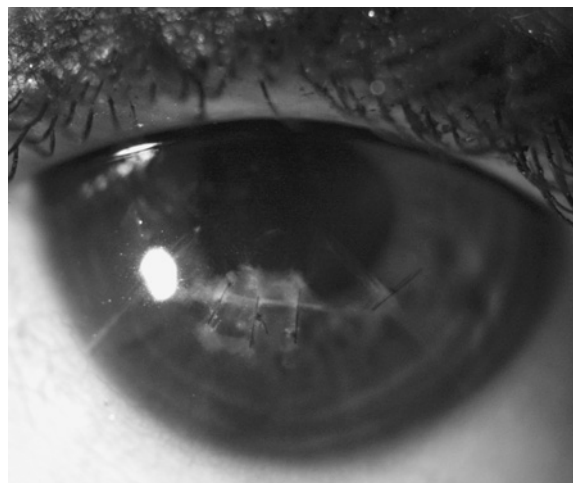


FIGURE 4. Right eye of a patient with underlying keratoconus that underwent radial and transverse incisions many years prior; after X-linking treatment, the inferior incisions gaped and had to be sutured. Six months later, after suture removal, there was a significant decrease in the amount of astigmatism and coma.

surgery in most patients.²⁰ The cornea is gradually repopulated by stromal keratocytes during the next 3 to 6 months. According to the first published human study in progressive keratoconus (23 eyes of 22 patients), all eyes except one achieved stabilization of the corneal steepening, and up to 70% had an average reduction of their steepest keratometric reading of 2.01 diopters 6 months after the surgery; this effect was mirrored in an improvement in the refraction and best spectacle-corrected visual acuity.²¹ The longest follow-up so far has been from this same group of patients where stability of the results has been reported up to 5 years.²² In a pilot study of 10 patients done in Italy, the reduction of the mean keratometry value was 2.1 ± 0.13 diopters, with improvements in the refraction, visual acuity, and corneal regularity as well.²³ Because the corneal collagen has a turnover rate of 3 to 7 years, it might be that the procedure has to be repeated in some patients. On the other hand, environmental cross-linking forces (UV light, blood glucose) might have acted enough in a particular patient to obviate the need for a repeat UVA/riboflavin cross-linking treatment.

X-linking was developed as a parasurgical tool to halt progressive steepening/weakening of keratoconic and postexcimer surgery ectatic corneas. It also might have the potential to help in some corneal melting cases. Further studies in a broader range of patients will help to nail down the indications of this new and exciting therapeutic modality.

Clinical Pearls During the X-linking Surgery

- Removing the corneal epithelium in intersecting strips (cross-hatched pattern) markedly speeds up the recovery time.
- The use of a saturated sponge acts as a reservoir, improving the penetration of riboflavin into the corneal stroma, and it also prevents spillover and wasting of the medication.
- During UVA application, avoid excessive dehydration of the conjunctiva by wetting it with balanced salt solution or artificial tears.

Clinical Pearls During the Postoperative Period

- Pain control should be similar to a PRK case, where the use of GABA analogues such as gabapentin and pregabalin increase the pain threshold and make the patient more comfortable.
- If a patient has transverse incisions, they might have to be sutured at least for 6 months to avoid gaping and promote healing with adequate scar tissue.
- Expect a temporary worsening in vision because of corneal edema during the first month.

■ REFERENCES

1. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. *J Refract Surg.* 1998;14: 312–317.
2. Seiler T, Quurke AW. Iatrogenic keratectasia after LASIK in a case of forme fruste keratoconus. *J Cataract Refract Surg.* 1998;24:1007–1009.
3. Randleman JB, Russell B, Ward MA, et al. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology.* 2003;110: 267–275.
4. Binder PS, Lindstrom RL, Stulting RD, et al. Keratoconus and corneal ectasia after LASIK. *J Refract Surg.* 2005; 21:749–752.
5. Abad JC, Rubinfeld RS, Del VM, et al. Vertical D: a novel topographic pattern in some keratoconus suspects. *Ophthalmology.* 2007;114:1020–1026.
6. Abad JC, Awad A, Kurstin JM. Hyperopic keratoconus. *J Refract Surg.* 2007;23:520–523.
7. Seiler T, Huhle S, Spoerl E, et al. Manifest diabetes and keratoconus: a retrospective case-control study. *Graefes Arch Clin Exp Ophthalmol.* 2000;238:822–825.
8. Spoerl E, Seiler T. Techniques for stiffening the cornea. *J Refract Surg.* 1999;15:711–713.
9. Wollensak G, Wilsch M, Spoerl E, et al. Collagen fiber diameter in the rabbit cornea after collagen crosslinking by riboflavin/UVA. *Cornea.* 2004;23:503–507.
10. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg.* 2003;29:1780–1785.
11. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. *Curr Eye Res.* 2004;29:35–40.
12. Wollensak G, Aurich H, Pham DT, et al. Hydration behavior of porcine cornea crosslinked with riboflavin and ultraviolet A. *J Cataract Refract Surg.* 2007;33:516–521.
13. Wollensak G, Spoerl E, Reber F, et al. Keratocyte cytotoxicity of riboflavin/UVA-treatment in vitro. *Eye.* 2004;18:718–722.
14. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea.* 2007;26: 385–389.
15. Mazzotta C, Balestrazzi A, Traversi C, et al. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg retinal tomograph II. In vivo confocal microscopy in humans. *Cornea.* 2007;26:390–397.
16. Wollensak G, Spoerl E, Wilsch M, et al. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. *J Cataract Refract Surg.* 2003; 29: 1786–1790.
17. Chan CC, Sharma M, Wachler BS. Effect of inferior-segment Intacs with and without C3-R on keratoconus. *J Cataract Refract Surg.* 2007;33:75–80.

18. Mian SI, Gupta A, Pineda R. Corneal ulceration and perforation with ketorolac tromethamine (Acular) use after PRK. *Cornea*. 2006;25:232–234.
19. Verma S, Corbett MC, Marshall J. A prospective, randomized, double-masked trial to evaluate the role of topical anesthetics in controlling pain after photorefractive keratectomy. *Ophthalmology*. 1995;102:1918–1924.
20. Seiler T, Hafezi F. Corneal cross-linking–induced stromal demarcation line. *Cornea*. 2006;25:1057–1059.
21. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
22. Wollensak 2G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol*. 2006;17:356–360.
23. Caporossi A, Baiocchi S, Mazzotta C, et al. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg*. 2006;32:837–845.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

AQ1 = Please provide an abstract for this article.

AQ2 = Please check if the expanded forms of LASIK and PRK are correct.

AQ3 = Please check if the expanded form of GABA is correct.

AQ4 = Please check if the expanded form of NSAID is correct.

AQ5 = Please check if proposed running title is ok.

AQ6 = Please check if the expanded form of BSCVA is correct.

AQ7 = Please check if the expanded form of BSS is correct.

END OF AUTHOR QUERIES

Author Reprints

For **Rapid Ordering** go to: www.lww.com/periodicals/author-reprints

Techniques in Ophthalmology

 Lippincott
Williams & Wilkins
a Wolters Kluwer business

Order

Author(s) Name _____

Title of Article _____

*Article # _____

*Publication Mo/Yr _____

*Fields may be left blank if order is placed before article number and publication month are assigned.

Quantity of Reprints _____ \$ _____

Covers (Optional) _____ \$ _____

Shipping Cost _____ \$ _____

Reprint Color Cost _____ \$ _____

Tax _____ \$ _____

Total _____ \$ _____

Reprint Pricing

100 copies = \$208.00

200 copies = \$257.00

300 copies = \$303.00

400 copies = \$360.00

500 copies = \$405.00

Covers

\$108.00 for first 100 copies

\$18.00 each add'l 100 copies

Reprint Color

(\$70.00/100 reprints)

Shipping

\$5.00 per 100 for orders shipping within the U.S.

\$20.00 per 100 for orders shipping outside the U.S.

Tax

U.S. and Canadian residents add the appropriate tax or submit a tax exempt form.

Use this form to order reprints. Publication fees, including color separation charges and page charges will be billed separately, if applicable.

Payment must be received before reprints can be shipped. Payment is accepted in the form of a check or credit card; purchase orders are accepted for orders billed to a U.S. address.

You may have included color figures in your article. The costs to publish those will be invoiced separately. If your article contains color figures, use Rapid Ordering www.lww.com/periodicals/author-reprints.

Prices are subject to change without notice.

Payment

MC VISA Discover American Express

Account # _____ / _____ / _____ Exp. Date _____

Name _____

Address _____ Dept/Rm _____

City _____ State _____ Zip _____ Country _____

Telephone _____

Signature _____

Quantities over 500 copies: contact our Pharma Solutions Department at **410.528.4077**

Outside the U.S. call **4420.7981.0700**

MAIL your order to:
Lippincott Williams & Wilkins
Author Reprints Dept.
351 W. Camden St.
Baltimore, MD 21201

FAX:
410.528.4434

For questions regarding reprints or publication fees,

E-MAIL:
reprints@lww.com

OR **PHONE:**
1.800.341.2258

Ship to

Name _____

Address _____ Dept/Rm _____

City _____ State _____ Zip _____ Country _____

Telephone _____

For **Rapid Ordering** go to: www.lww.com/periodicals/author-reprints