Corneal Collagen Cross-Linking in Europe

The technique continues to evolve.

BY AYLIN KILIÇ, MD

In 2003, 22 eyes of 22 patients with moderate or advanced progressive keratoconus underwent corneal collagen cross-linking (CXL; not approved in the United States) in a seminal study performed by Wollensak and colleagues. The central 7 mm of the central corneal epithelium was cautiously removed, and riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 10 mL dextran T-500 20% solution) was applied every 5 minutes before and during irradiation. The patients in this study were treated with ultraviolet A (UVA) light diodes (370 nm) at a distance of 1 cm for 30 minutes using 3 mW/cm^2 irradiance, which corresponds to a dose of 5.4 J/cm^2.[1]

The authors subsequently wrote, "[CXL] may be a new way for stopping the progression of keratectasia in patients with keratoconus. The need for penetrating keratoplasty might then be significantly reduced in keratoconus. Given the simplicity and minimal costs of the treatment, it might also be well-suited for developing countries. Long-term results are necessary to evaluate the duration of the stiffening effect and to exclude long-term side effects."

DEVICES

UV-X 1000 and UV-X 2000

The UV-X illumination system (IROC) for CXL was introduced into practice in 2006. Its specifications are listed in the table.

With its optimized beam profile, the UV-X 2000 is designed to take into account the thickness distribution of the cornea. The high-intensity illumination of this model shortens treatment to 10 minutes.[2] New distance control reliably aligns the patient's eye below the illumination system. Another change is a greater CXL depth in the periphery and thus a higher volume of cross-linked tissue. The optical design, based on a Koehler beam path, ensures that the necessary radiant exposure at the cornea immediately dissipates behind the cornea, which minimizes retinal irradiation (Table).

IROC is also producing riboflavin solution. Innocross-R Isotonic (riboflavin 5-phosphate 0.1% with 20% dextran T-500) in 2-mL syringes is a standard isotonic riboflavin solution. Innocross-R Hypotonic (riboflavin 5-phosphate 0.1%) in 2-mL syringes is the hypo-osmolar solution used to swell thin corneas by an osmotic process.[3]

CCL-Vario

Peschke, the manufacturer of this device, is also providing riboflavin solution: Medio Cross Isotonic solution, packed in 3-mL syringes, and Medio Cross Hypotonic solution for thin corneas, packaged in 0.5-mL syringes (Table).

Vega

CSO constructed the Vega device with solid-state diode-emitting UVA rays peaking at 370 nm. The system has an integrated ¼ camera (Table). The distributor, Sooft Italia, is producing Ricrolin (riboflavin 0.1% solution) in 1-mL syringes for the standard CXL procedure and Ricrolin-TE in 1-mL syringes for the transepithelial CXL procedure.

TABLE. SYSTEM SPECIFICATIONS FOR CXL DEVICES

Manufacturer	System	Wavelength (nm)	Illumination Intensity	Working Distance	Light Emission	Illumination Diameter (mm)	Electric Power (V)	Timer (min)
IROC	UV-X 1000	365 ±10	3 mW/cm^2	50 cm	CW	7, 9, 11	100 to 240	30
	UV-X 2000	365 ±10	9 mW/cm^2	45 cm	CW	7.5, 9.5	100 to 240	10
Peschke	CCL-Vario	365	3 to 9 to 18 mW/cm^2	45 ±5	CW	7 to 11 continuously adjustable	100 to 240	
CSO	Vega	370	3 mW/cm^2	54 cm	CW	4 to 11		
Opto Global	Opto Xlink	365 ±5	< 1 mWc^2	45 ±1 mm	CW	6, 8, 10	90 to 240	
Avedro	KXL	365	Controlled to 5.4 J/cm^2			≤ 11		10 (presoak) + 3 (radiation)

Abbreviation: CW, continuous wave.

Opto Xlink

Opto Global manufactures the Opto Xlink (Table).

KXL System

In 2010, Avedro developed accelerated CXL. During this procedure, the cornea is presoaked with riboflavin solution for 10 minutes to achieve a total loading concentration of at least 0.04% in the top 150 µm of the stroma. The cornea is then exposed to energy at an irradiance (exposure dose rate) of 30 mW/cm^2 for 3 minutes to reach a total radiant exposure of 3.6 J/cm^2.[4] Energy density is controlled to 5.4 J/cm^2. The system features a touch screen monitor and a wireless remote control in the x, y, and z axes (Table).

VibeX is Avedro's proprietary riboflavin isotonic solution (riboflavin 0.1%, dextran 20%) used in conjunction with the company's KXL System. VibeX Rapid is formulated with no dextran, whereas VibeX Xtra (riboflavin 0.25%, saline) is formulated for use during a LASIK Xtra procedure. ParaCel (riboflavin 0.25%, hydroxypropyl methylcellulose, benzalkonium chloride, ethylenediaminetetraacetic acid, trishydroxymethyl aminomethane) is formulated for direct intact epithelium.

LASIK Xtra

Controversy

Perhaps the most controversial topic in CXL is its use to prevent regression or ectasia after refractive surgery. The creation of a LASIK flap weakens the cornea by 14% to 33%, depending on the thickness of the flap.[5] In theory, the LASIK Xtra procedure performed with the KXL System restores the strength of corneas weakened by LASIK. An advantage of this procedure is its direct application of riboflavin to the LASIK flap interface, eliminating the need to remove the epithelium.

Theoretically, the 5-minute LASIK Xtra procedure is integrated into standard LASIK to restore the biomechanical integrity of the cornea after the flap's creation and excimer laser ablation.[6] Early studies using very small cohorts have demonstrated some efficacy for reducing regression after hyperopic LASIK.[7] A pilot study of eight eyes of four patients, however, showed no difference between eyes that underwent simultaneous CXL and LASIK versus fellow eyes that underwent LASIK only.[6]

TREATMENT DURATION

Spoerl et al increased the irradiance from 2 to 3 W/cm^2 to provide 5.4 J/cm^2 of radiant energy in 30 minutes. These parameters became the standard protocol.[8] Recent studies have shown that the irradiance can be further increased three- to tenfold with a proportional decrease in treatment time.[9]

RIBOFLAVIN DOSING

The frequency of riboflavin dosing generally ranges from every 2 to 5 minutes. The riboflavin/dextran formulation used in the standard protocol is viscous and leaves a film on the cornea. The total absorbtion coefficient of human corneas treated with the standard 0.1% riboflavin/dextran solution for 30 minutes was about 50% higher when a film of riboflavin was present on the surface than without the riboflavin film.[10]

THIN CORNEAS

In 2009, Hafezi at al published the first case series of 20 patients with a stromal thickness of lower than 400 µm treated with CXL.[11] Hypo-osmolar riboflavin 0.1% solution was generated by diluting vitamin B2 0.5% with physiological salt solution (sodium chloride 0.9% solution; B. Braun Medical) 310 mOsm/L without the addition of dextran.

PRESOAK TIME

As the riboflavin diffuses into the cornea, the initially steep concentration gradient flattens over time. In practice, presoak times have ranged from 5 to 30 minutes. The presoak time was 5 minutes in a pilot clinical study and 20 minutes in patients treated subsequently in the Dresden clinic.[8,12] None of the studies reported endothelial damage, suggesting that a range of presoak times are well tolerated.

TRANSEPITHELIAL CXL

The main concerns with transepithelial CXL are that riboflavin cannot penetrate an intact epithelium and that the intact epithelium will block approximately 20% of the UVA light from reaching the stroma. The advantages of the epi-on CXL method are less pain, a more comfortable postoperative course, faster recovery, a lower risk of infection, and a faster return to contact lens wear.

Approaches to increase the epithelium's permeability to riboflavin include

- administration of benzalkonium chloride, ethylenediaminetetraacetic acid, chlorobutanol, and channel-forming peptide (NC-1059)
- incomplete abrasion
- iontophorese
- intrastromal application (needles, pocket application)

PEDIATRIC CXL

The literature supports the use of CXL in young patients. At present, experts agree that it is critical to perform the procedure on keratoconic eyes as early as possible.[13]

CONCLUSION

The techniques and applications for CXL continue to evolve. The most meaningful future developments, however, may pertain to riboflavin delivery and the timing of treatment. ■

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