Advances in CXL

Increased efficiency may be achieved by simply accelerating the treatment or turning the UV-A beam on and off at a specific time intervals.

BY MICHAEL B. RAIZMAN, MD

Corneal collagen crosslinking (CXL) with ultraviolet-A (UV-A) light and riboflavin photosensitizer, as introduced by Wollensak et al,1 has been rapidly adopted as a standard therapy for treatment of progressive keratoconus and postrefractive-surgery ectasia.2-5 Recent scientific and technological advances have highlighted the opportunity to optimize the CXL procedure in order to maximize procedural efficiency and improve outcomes.6-9

TWO ADVANCES

Accelerated CXL. One technological improvement is the introduction of UV-A delivery devices with higher irradiance output (9–45 mW/cm²).10-12 The energy delivered by a light source (J/cm²) is the product of the irradiance of the light source (mW/cm²) and the delivery time (seconds). Although the treatment UV-A dose was delivered over 30 minutes in early studies, higher irradiance UV-A delivery devices have been introduced to shorten irradiation time to as little as 160 seconds. Provided equivalent safety and sufficient efficacy are obtained, the advantages of significantly reduced surgical time are clear, with the potential to reduce overhead costs and patient anxiety.

Pulsed illumination. An additional opportunity for increasing the efficiency of CXL procedures may be as simple as turning the UV-A beam on and off at a specific time intervals. Laboratory measurement of real-time oxygen levels in the cornea during CXL demonstrates that irradiation with 365-nm UV-A light causes rapid oxygen depletion in a riboflavin-saturated cornea. However, turning the UV-A beam off allows oxygen to diffuse to the stroma without being depleted by the photochemical mechanisms that occur while the beam is on.13

Measured oxygen concentrations in the corneal stroma reveal that specific pulse intervals (on and off times) lead to rapid replenishment of oxygen to its original level. The increased availability of oxygen is thought to balance the competing photochemical mechanisms that occur in response to riboflavin activation with UV-A. This can amplify the series of chemical events that lead to the production of free radicals that are believed to result in CXL.14

Pulsed illumination has the potential to increase the amount of corneal stiffening obtained without increasing the UV-A energy dose delivered.15 Therefore, using specific pulse intervals of UV-A irradiation has implications for maximizing the efficacy of CXL while maintaining or improving the safety profile of the procedure.

OUR EXPERIENCE

We have treated patients with accelerated CXL and pulsed accelerated CXL as part of two ongoing multicenter prospective randomized controlled clinical trials in the United States, performed under guidelines of the US Food and Drug Administration (FDA) and approved and monitored by an investigational review board. Patients included are age 12 years or older, with distance BCVA of 1 or more letters and 80 or fewer letters on the Early Treatment Diabetic Retinopathy Study chart, and axial topography patterns consistent with keratoconus or corneal ectasia with maximum corneal curvature of at least 47.00 D as measured by Kmax (Pentacam; Oculus Optikgeräte). Patients with a history of corneal surgery or with corneal pachymetry less than 375 µm prior to epithelial debridement at the thinnest point to be treated are excluded from the study, as are patients with a history of corneal disease likely to predispose the eye to future complications (eg, herpes simplex, herpes zoster keratitis, corneal melt, corneal dystrophy), clinically significant corneal scarring, a history of delayed epithelial healing in the eye(s) to be treated, aphakia or pseudophakia without a UV-blocking lens implanted, and pregnancy or lactation during the course of the study.

TAKE-HOME MESSAGE

- UV-A delivery devices with higher irradiance output can shorten irradiation time to as little as 160 seconds.
- Increasing the availability of oxygen in the corneal stroma with pulsed illumination can amplify the series of chemical events that lead to the production of free radicals that are believed to result in CXL.
- There remains room for further optimization of CXL protocols.
In both studies, the corneal epithelium is removed in eyes randomized to the treatment. Five drops of 0.12% riboflavin-5-phosphate in 10% dextran are instilled every 2 minutes for 20 minutes. In the study of accelerated CXL, the 7.2 J/cm² UV-A treatment dose is delivered as determined by the randomization scheme using 15, 30, or 45 mW/cm² of continuous illumination for 8, 4, or 2 minutes and 40 seconds, respectively, with the KXL System (Avedro). In the study of pulsed accelerated illumination, the 7.2 J/cm² UV-A treatment dose is delivered using 30 mW/cm² irradiance with continuous illumination or pulsed illumination with the KXL System at an on/off cycle of 1 second UV-A on/1 second UV-A off.

Although the results of these trials have not been analyzed, it is my impression that the procedures are well tolerated by our patients, with significant adverse events and with initial efficacy that is at least equal to the traditional protocol. These protocols have been used outside the United States, and initial data from the studies support the efficacy and safety of new approaches to crosslinking.

**FUTURE DIRECTIONS**

The introduction of accelerated CXL and pulsed illumination opens the door to a wide range of applications for CXL beyond the stabilization of keratoconus. The procedure has been demonstrated to halt the course of progressive post-LASIK ectasia, but could it prevent the development of ectasia in the first place?

The integration of CXL into LASIK procedures has been proposed in order to stabilize the cornea preoperatively, thereby reducing the risk of post-LASIK ectasia and refractive regression. We are participating in a multicenter, prospective, randomized, controlled clinical trial of this procedure for patients with hyperopia or hyperopic astigmatism in the United States; we have already treated our first patient. Our current protocol requires removal of the corneal epithelium to facilitate riboflavin diffusion. Although advances have been made in the development of transepithelial riboflavin formulations designed for use without epithelial removal, the efficacy of these procedures remains reduced due to attenuation of UV-A light and oxygen penetration by the riboflavin-soaked epithelium. The new understanding of the role of oxygen in CXL procedures provides insight that may be used to develop more effective protocols for transepithelial CXL, such as through the use of pulsed illumination and/or supplemental oxygen delivery.

There remains room for further optimization of CXL protocols. Theoretical modeling has suggested that localized UV-A treatment patterns may provide greater normalization (ie, flattening of steep keratometry or reduction of irregular astigmatism) of the keratoconic corneal shape than is achieved with conventional CXL. Furthermore, zone-specific corneal stiffening has the potential to induce controlled corneal shape, even in nonectatic ametropic eyes. A means of correcting refractive error by stiffening the cornea presents an attractive alternative to traditional refractive surgical options, which weaken the structural integrity of the cornea through lamellar cuts, ablation, or thermal degradation. Early clinical work in this area is promising.

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