

NEW FRONTIERS IN CXL



Research points to ways to broaden the pool of candidates.

BY JILLIAN K. CHONG, MD, AND A. JAMES KHODABAKSH, MD

INDIVIDUALIZED CORNEAL CROSS-LINKING WITH RIBOFLAVIN AND UV-A IN ULTRATHIN CORNEAS: THE SUB400 PROTOCOL

Hafezi F, Kling S, Gilardoni F, et al¹

Industry support: None

ABSTRACT SUMMARY

Hafezi et al developed a novel, customizable CXL protocol for patients with corneas too thin to receive treatment with the standard Dresden protocol. The sub400 protocol uses the classic 3 mW/cm² UV-A irradiance, but fluence is reduced by decreasing the duration of exposure based on corneal pachymetry after hypotonic (0.1%) riboflavin treatment.

Investigators performed CXL using the sub400 protocol on 39 eyes with progressive keratoconus and corneas that were 214 to 398 μm thick. One year after treatment, tomography was stable in 90% of the eyes, and no eye had experienced endothelial decompensation.

DISCUSSION

CXL remains the only form of treatment proven to halt keratoconus

STUDY IN BRIEF

► The sub400 protocol is a novel approach to CXL that maintains a fixed riboflavin dose and irradiance but customizes the duration of UV-A treatment based on corneal thickness. CXL using this protocol was effective for corneas as thin as 214 μm.

WHY IT MATTERS

Various methods have been proposed for CXL on thin corneas, but the sub400 protocol is the first to apply a verified algorithm for the rate of CXL, allowing a standardized approach to the treatment of thin corneas and expanding the pool of candidates eligible for this procedure.

progression.^{2,3} The Dresden protocol defines the lower limit of safety as a corneal thickness of 400 μm after epithelial debridement. Many people with advanced keratoconus are therefore beyond the reach of preventive care.² Several mechanisms for expanding the range of conventional treatment have been proposed in the literature, but each has been associated with an unacceptable degree of unpredictability, a reduction in efficacy, or both.⁴⁻⁶

Hafezi et al proposed a mechanism based on a rigorously tested and verified algorithm to determine the availability of riboflavin, oxygen, and UV-A radiation in corneal tissue.¹ By modifying fluence by

the duration of UV-A exposure only, the sub400 protocol remains simple without appearing to sacrifice efficacy. An efficacy rate of 90% in 39 eyes of 32 patients may not seem to merit a change in practice patterns, but it is worth noting that, in this population of patients with extremely thin corneas experiencing active progression, disease severity would have been expected to worsen in 100% of untreated eyes.

Advantages of the sub400 protocol included a broader range of candidates for treatment than with the Dresden protocol and greater personalization for improved safety and efficacy for each of the corneas treated.

LONG-TERM FOLLOW-UP OF COMBINED PHOTOREFRACTIVE KERATECTOMY AND CORNEAL CROSSLINKING IN KERATOCONUS SUSPECTS

Kymionis G, Kontadakis G, Grentzelos M, Petrelli M⁷

Industry support: None

ABSTRACT SUMMARY

In this case series, 10 eyes of five individuals with suspected keratoconus

underwent conventional PRK followed by CXL with an accelerated protocol. Preoperatively, each patient had low to moderate myopia and exhibited suspicious findings on tomography, all of them at a risk score of 3 using the Ectasia Risk Score System. The choice to combine PRK with accelerated CXL was based on evidence of a reduced flattening effect with this protocol compared to with the traditional Dresden protocol.⁸

Patients' spherical equivalent, uncorrected distance visual acuity (UDVA), and corrected distance visual acuity were monitored for 5 years. Excellent visual outcomes and refractive stability were demonstrated throughout the follow-up. Corrected distance visual acuity was stable or improved in all eyes. UDVA was 20/20 in all but one eye, which achieved and maintained 20/25 UDVA.

STUDY IN BRIEF

- Five-year data from a small case series indicated that combining PRK and prophylactic CXL is safe in individuals with findings suspicious for keratoconus.

WHY IT MATTERS

This study presents the longest-term data supporting the safety of simultaneous PRK and CXL for the treatment of myopia in patients with suspected keratoconus.

DISCUSSION

In terms of corneal biomechanics, PRK is a relatively benign refractive procedure, but it carries a risk of ectasia for patients in whom keratoconus is suspected.^{9,10} It has been suggested that performing a limited PRK procedure and CXL simultaneously or sequentially is safe and effective in patients with early keratoconus, but the published literature on the full myopic treatment of individuals with suspected keratoconus is limited.¹¹⁻¹⁵

The case series by Kymionis et al suggests that combining PRK and CXL can safely and effectively be used to treat patients with borderline findings of keratoconus.⁷ More robust evidence is required before practice patterns change. ■

1. Hafezi F, Kling S, Gilardoni F, et al. Individualized corneal cross-linking with riboflavin and UV-A in ultrathin corneas: the sub400 protocol. *Am J Ophthalmol*. 2021;224:133-142.
2. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen cross-linking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620-627.
3. Raskup F, Theuring A, Pillunar LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41(1):41-46.
4. Hafezi F, Mrochen M, Iseli HP, Seiler T. Collagen crosslinking with ultraviolet-A and hypotonic riboflavin solution in thin corneas. *J Cataract Refract Surg*. 2009;35(4):621-624.
5. Jacob S, Kumar DA, Agarwal A, Basu S, Sinha P, Agarwal A. Contact lens-assisted collagen cross-linking (CACXL): a new technique for cross-linking thin corneas. *J Refract Surg*. 2014;30(6):366-372.
6. Mazzotta C, Ramovecchi V. Customized epithelial debridement for thin ectatic corneas undergo-ing corneal crosslinking: epithelial island cross-linking technique. *Clin Ophthalmol*. 2014;8:1337-1343.
7. Kymionis G, Kontadakis G, Grentzelos M, Petrelli M. Long-term follow-up of combined photorefractive keratectomy and corneal crosslinking in keratoconus suspects. *Clin Ophthalmol*. 2021;15:2403-2410.
8. Kymionis GD, Kontadakis GA, Hashemi KK. Accelerated versus conventional corneal cross-linking for refractive instability: an update. *Curr Opin Ophthalmol*. 2017;28(4):343-347.
9. Randleman JB, Caster AI, Banning CS, Stulting RD. Corneal ectasia after photorefractive keratectomy. *J Cataract Refract Surg*. 2006;32(8):1395-1398.
10. Malecaze F, Couillet J, Calvas P, Fournié P, Arné JL, Brodaty C. Corneal ectasia after photorefractive keratectomy for low myopia. *Ophthalmology*. 2006;113(5):742-746.

11. Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high-fluence CXL stabilization (the Athens protocol). *J Refract Surg*. 2014;30(2):88-93.
12. Nattis AS, Rosenberg ED, Donnerfeld ED. One-year visual and astigmatic outcomes of keratoconus patients following sequential crosslinking and topography-guided surface ablation: the TOPOLINK study. *J Cataract Refract Surg*. 2020;46(4):507-516.
13. Lee H, Yong Kang DS, Ha BJ, et al. Comparison of outcomes between combined transepithelial photorefractive keratectomy with and without accelerated corneal collagen cross-linking: a 1-year study. *Cornea*. 2017;36(10):1213-1220.
14. Sachdev GS, Ramamurthy S, Dandapani R. Comparative analysis of safety and efficacy of photorefractive keratectomy versus photorefractive keratectomy combined with crosslinking. *Clin Ophthalmol*. 2018;12:783-790.
15. Ohana O, Kaiserman I, Dominiz Y, et al. Outcomes of simultaneous photorefractive keratectomy and collagen crosslinking. *Can J Ophthalmol*. 2018;53(5):523-528.

SECTION EDITOR EDWARD MANCHE, MD

- Director of Cornea and Refractive Surgery, Stanford Laser Eye Center, California
- Professor of Ophthalmology, Stanford University School of Medicine, California
- edward.manche@stanford.edu
- Financial disclosure: Consultant and research support (Avedro)

JILLIAN K. CHONG, MD

- Cornea and refractive surgeon, Beverly Hills Institute of Ophthalmology, California
- drchong@90210eyes.com
- Financial disclosure: None

A. JAMES KHODABAKSH, MD

- Chief, Department of Ophthalmology, Cedars-Sinai Medical Center, Los Angeles
- Medical Director, Beverly Hills Institute of Ophthalmology, California
- lasereyedoc@aol.com
- Financial disclosure: None