ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Review Article

What's Next for Ultraviolet Corneal Crosslinking?

Philip W Dockery[1], Katelyn P Joubert[1] and Jack S Parker[1,2]*

[1]*Parker Cornea, Birmingham, AL, USA*

[2]*Netherlands Institute for Innovative Ocular Surgery-USA (NIIOS-USA), San Diego, USA*

***Corresponding Author:** Jack S Parker, Parker Cornea, Birmingham, Alabama, USA.

Received: July 17, 2019; **Published:** August 21, 2019

Abstract

Early last decade, ultraviolet corneal crosslinking (CXL) entered the scene of ophthalmology and transformed the way keratoconus (KC) was treated. Traditionally, patients with KC were given contact lenses for visual correction and were monitored for progression until disease advanced to the point of central scarring or uncorrectably-poor visual acuity, necessitating penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK), both of which require long-term postoperative management including anti-rejection medications, suture removal, fluctuation in refractive error, and potentially re-transplantation. CXL was developed to be a minimally invasive procedure used to halt disease progression before the need of PK or DALK. Just as CXL has revolutionized the management of KC, crosslinking protocol continues to evolve, leading to more efficient treatment, improved patient satisfaction, and new clinical indications.

Keywords: *Corneal Crosslinking; CXL; Keratoconus; Athens Protocol; PRK; Photoreactive Intrastromal Crosslinking; PiXL; Presbyopia; Infectious Keratitis*

In the United States, the only method currently approved by the FDA is Dresden protocol: removal of the central corneal epithelium (epi-off), application of a 0.1% riboflavin solution containing 20% dextran for 30 minutes, and exposure to 370 nm ultraviolet A (UVA) light with an irradiance of 3 mW/cm^2 for 30 minutes for a total dose of 5.4 J/cm^2 [1]. Elsewhere in the world, modifications to the protocol have been performed in search for the most effective treatment.

Accelerated protocol

From a logistics perspective, the time spent in the clinic or operating room performing the procedure is a major limiting factor. According to a law of photochemical reciprocity, irradiance and its duration can be manipulated to create the same photochemical effects as long as the total dose, or fluence, remains constant. For example, if UVA light is applied for 6 minutes with an irradiance of 15 mW/cm^2, it should theoretically have the same outcomes as Dresden protocol because the total fluence remains 5.4 J/cm^2. However, many studies demonstrate accelerated protocol with mixed results. While mildly accelerated protocols seem to have similar results, those that are rapidly accelerated seem to have decreased efficacy. When CXL is performed, ultraviolet light interacts with a photosensitizer, such as riboflavin, to form new connections between corneal collagen fibrils, which is a process mediated by oxygen [2]. Introducing supplemental oxygen and using pulsated irradiation may improve the effectiveness of rapidly accelerated protocols; however, more recent studies indicate that maintaining intrastromal riboflavin concentration is the key ingredient to achieving success with accelerated protocol [3]. When accelerated protocols were first developed, no significant changes were made in the application of riboflavin during exposure to UVA light, so the maintenance doses of riboflavin could not replenish the stroma at the rate it was being utilized in the accelerated procedure, thus,

decreasing the concentration and the procedure's effectiveness. Because more rapid application of 0.1% riboflavin drops could decrease the penetration of UVA light due to persistence of a riboflavin solution meniscus on the surface of the cornea, O'Brart., *et al.* stipulates that higher concentration solutions (0.2% or 0.4%) could increase the stromal concentration of riboflavin without the creation of a meniscus, leading to improved efficacy with accelerated protocol [4].

Epithelial obstacles and photosensitizers

If asked, most every patient who underwent CXL will describe the de-epithelialization of the cornea to be the most discomforting part of the experience. In addition to the postoperative pain, epi-off CXL poses a risk of infection and persistent corneal haze, delaying visual recovery [5]. Many attempts have been made at improving patient satisfaction, the first being epithelium-on CXL. Despite patient comfort significantly improving, the outcomes of halting a progressive ectasia using epi-on CXL and 0.1% riboflavin solution with dextran are unfortunately far inferior [6-8]. Although alternative methods of de-epithelialization, such as alcohol or epi-Bowman keratectomy (EBK; Orca, New York City, USA), promise decreased pain, re-epithelialization time, and risk of scar formation, they do not fully resolve the dangers and discomforts surrounding epi-off CXL.

Because riboflavin is a relatively large molecule, it does not make the transit through the corneal epithelium with ease, hence why the original crosslinking protocol required de-epithelialization. One small study has shown that additives to riboflavin, such as D-alpha-tocopheryl polyethylene-glycol 1000 succinate (vitamin E-TPGS), can improve epithelial penetration of riboflavin and even produce similar results to epi-off CXL [9]. Other techniques demonstrate that iontophoresis can stimulate sufficient transepithelial migration to improve the outcomes of epi-on CXL [10]. More recently, a large study (512 eyes on 308 patients) demonstrated halt in keratoconic disease progression following epi-on CXL with the following caveats: dextran-free riboflavin to help with epithelial penetration, a 12 mm specialized soaking sponge designed to increase absorptive surface area, riboflavin rinsing from the surface to reduce light scatter, and pulsating UVA with an irradiance of 4 mW/cm^2 [11]. Development of an effective epi-on protocol for CXL could reduce risk of infection and corneal haze, decrease time to visual recovery, and eliminate postoperative pain, which could expand the use of this procedure to populations that have traditionally not tolerated the procedure well, such as young children or those with Down syndrome.

Treating advanced keratoconus

While current protocol generally reserves CXL for the treatment of corneas thicker than 400 µm [12], changes in fluence or photosensitizers could allow for thinner corneas to be crosslinked without damage to corneal endothelial cells, which could expand its indication to treat moderate to advanced keratoconus. Attempts to artificially thicken the cornea using hypotonic riboflavin solution or through lenticule-assisted or contact lens assisted CXL successfully protect corneal endothelial cells but fail to halt progression of keratoconus in as many as 40 - 50% of cases [13]. However, CXL has been shown to not have notable endothelial damage on corneas that are 320 µm [14]. Improving the safety of crosslinking thin corneas opens the door to expanding its indication to advanced KC. Currently, the only procedure documented to stabilize severely ectatic corneas is Bowman layer transplantation, but the 5-year success rate sits at 84% [15]. While CXL commonly follows other corneal surgeries, such as intracorneal ring segment implantation, incorporation of CXL following Bowman layer transplantation (Figure 1) could potentially provide additional structural reinforcement, which could reduce the rate of disease progression, leading to fewer corneas with advanced KC requiring PK; however, clinical data is needed to prove this benefit.

Combining with keratorefractive surgeries

CXL was originally developed to halt disease progression in individuals with KC, but over the past decade, Kanellopoulos., *et al.* has led the charge to improved visual acuity in conjunction with improved corneal stability by combining CXL with topography-guided refractive surgery [16,17]. Photorefractive keratectomy (PRK) is a surgery to promote spectacle free visual acuity via the removal corneal stroma; however, significant stromal removal in corneas with KC increases instability and further ectasia [18]. Considering the difficulty in visual correction in keratoconic corneas arises from their irregular astigmatism, Athens protocol, or a topography-guided partial PRK combined

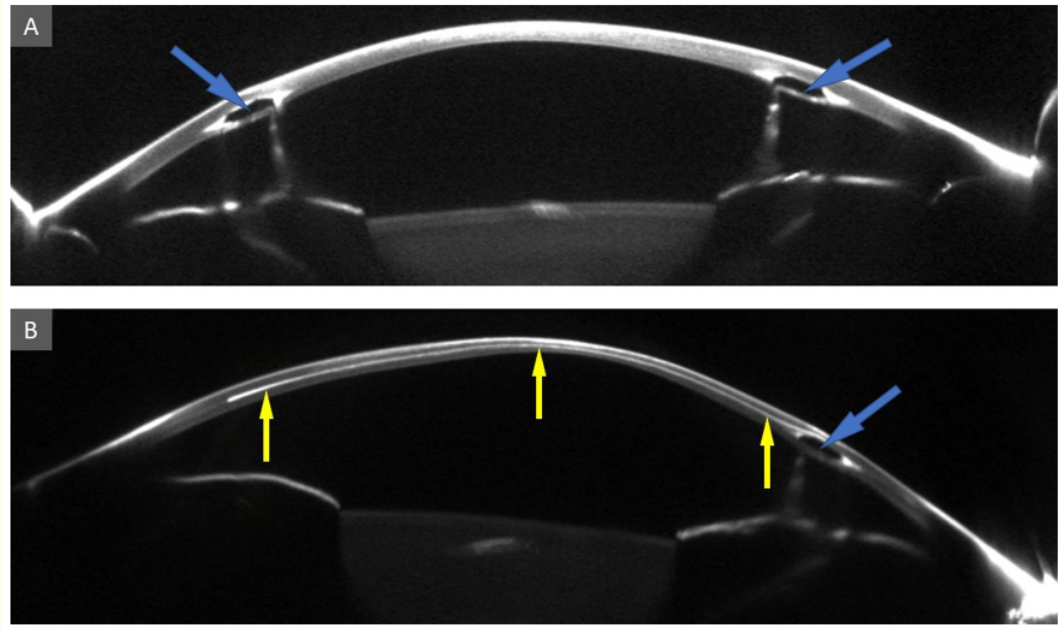

Figure 1: *Two Scheimpflug images that have undergone ultraviolet corneal crosslinking according to Dresden protocol, along with intracorneal ring segment (ICRS) implantation (A) or ICRS implantation and Bowman layer (BL) transplantation (B). ICRS are marked with blue arrows, and the BL graft is marked with yellow arrows.*

with CXL, was developed to reduce irregular shape, enhance best spectacle corrected visual acuity (BSCVA), and halt progressive ectasia [19]. Long-term data show equivocal results for termination of disease progression, but also include improved visual acuity (particularly BSCVA) and psychological well-being [20]. New modifications to Athens protocol have allowed for treatment of thinner, more ectatic corneas by customizing fluence patterns of UVA light based on corneal tomography (Pentacam HR; Oculus, Wetzlar, Germany), with the thinner, more central parts receiving a lower energy dose and the thicker, more peripheral parts receiving a higher energy dose. Additionally, this enhanced protocol restricts PRK to a maximum of 30 μm over the thinnest part of the cone, and initial results seem promising, showing high rates of corneal stability and improved uncorrected visual acuity [21].

Laser *in-situ* keratomileusis (LASIK) sometimes leads to post-LASIK ectasia (PLE), which can be treated similarly to KC with CXL, but combining LASIK or small incision lenticule extraction (SMILE) with same-day CXL can minimize the increase in maximum posterior elevation following the refractive surgery and thus, reduce the incidence in PLE [18,22,23].

Non-surgical refraction correction

While the combination of CXL and keratorefractive surgery can lead to improved BSCVA and corneal stability in patients with KC, UVA crosslinking alone can change corneal shape by altering corneal structure. Topography-guided photoreactive intrastromal crosslinking (PiXL) is a relatively new technique that focuses UVA exposure to specific regions of the cornea, leading to more significant changes in corneal curvature, when compared to traditional CXL. While CXL according to Dresden protocol delivers 5.4 J/cm^2 of UVA uniformly over a 9 mm-diameter circle, PiXL can be used to tailor UVA delivery depending on pathology (Figure 2); for KC, small customized treatment can be focused over the peak of the cone with total fluence ranging from 7.2 - 15.0 J/cm^2, creating increased local rigidity and regional flattening [24]. PiXL may be an option as a non-incisional refractive procedure, potentially eliminating some of the complications seen with stromal

removal in LASIK and SMILE. Early results show that centrally-focused UVA exposure can provoke corneal flattening, reducing the power in corneas with low myopia by 0.72D at 12 months [25]. Conversely, peripherally-focused UVA exposure, sparing the central 6mm of the cornea, can stimulate a mild myopic shift, increasing corneal power by 0.75 - 0.85D, which can be used to treat hyperopia or presbyopia [26]. Apart from correcting treatment-naïve eyes with mild refractive abnormalities, PiXL could potentially be used as a non-invasive way to revise corneal power in patients with hyperopic or myopic surprise following cataract surgery or in patients who are dissatisfied with their LASIK or SMILE results. However, more clinical data is needed to predict an accurate refractive change expected with PiXL.

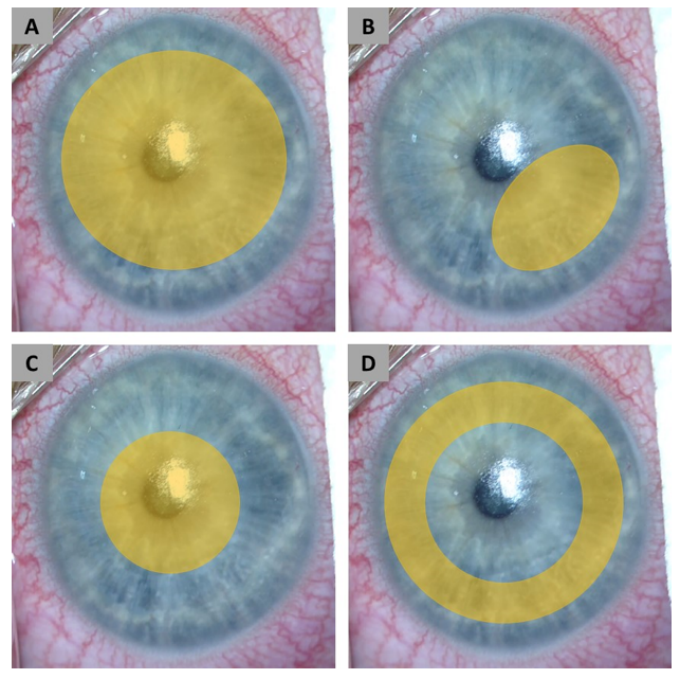

Figure 2: *Diagram of different patterns of ultraviolet light (UV) exposure in corneal crosslinking: Standard Dresden protocol with uniform UV exposure over a 9 mm circle centered on the cornea (A), a small customized area of UV exposure overlying the peak of the cone using topography-guided photoreactive intrastromal crosslinking (PiXL) to treat keratoconus (B), small circular area of UV exposure centered over the cornea using PiXL to treat low myopia (C), and a 9 mm annular UV exposure, sparing the central 6mm of the cornea, using PiXL to treat hyperopia or presbyopia (D).*

Infectious keratitis

Reaching beyond the realm of structural stability and refractive correction, the utility of CXL expands to the treatment of infectious keratitis. Although most corneal infections resolve following appropriate antimicrobial therapy, many reports have demonstrated CXL's effectiveness in treating culture-negative or treatment-resistant bacterial, protozoal, and fungal keratitis [27-31]. However, CXL does not always prove successful, and in certain cases, particularly among corneas with recalcitrant deep stromal fungal keratitis, a higher rate of treatment failure and corneal perforation are observed [32]. More clinical trials are needed to determine which pathogens and what depths of infection are best treated with UVA light exposure. Further, more data is needed to determine at what stage in treatment failure is the most economical for CXL to be adopted, but overall, CXL shows promise in the treatment of many superficial corneal infections.

Conclusions

CXL has transformed the treatment landscape for KC by terminating disease progression at high rates. More recently advances, such as accelerated and transepithelial protocols, have been made to improve the safety and overall experience of CXL. Additionally, expansion of CXL to severely keratoconic corneas could significantly decrease the morbidity seen in people with advanced disease. By combining with refractive surgery and planning with corneal tomography, CXL is becoming a procedure designed to improve visual acuity and structural stability, specifically tailored for each patient with KC. Growing past its use in treating KC, PiXL allows for a non-invasive way to reduce or eliminate suboptimal refractive outcomes following phacoemulsification or keratorefractive surgery. PiXL can also be used to modify corneal shape for people with presbyopia who want to avoid using reading glasses. However, the ophthalmic use of UVA light exposure is reaching beyond stabilization and refraction when it is used to treat infectious keratitis, and although most of the evidence is limited to case series and case reports, CXL shows great potential in the treatment of elusive corneal pathogens.

Overall, CXL is a rapidly advancing procedure that is quickly becoming highly personalized and is consistently being modified for new indications.

Financial Disclosure

No author has a financial or proprietary interest in any material or method mentioned.

Bibliography

1. Wollensak G., *et al*. "Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus". *American Journal of Ophthalmology* 135.5 (2003): 620-627.

2. Hayes S., *et al*. "The effect of riboflavin/UVA collagen cross-linking therapy on the structure and hydrodynamic behaviour of the ungulate and rabbit corneal stroma". *PLoS One* 8.1 (2013): e52860.

3. O'Brart NAL., et al. "An investigation of the effects of riboflavin concentration on the efficacy of corneal cross-linking using an enzymatic resistance model in porcine corneas". *Investigative Ophthalmology and Visual Science* 59 (2018): 1058-1065.

4. O'Brart DPS., *et al*. "Author Response: The Role of Riboflavin Concentration and Oxygen in the Efficacy and Depth of Corneal Crosslinking". *Investigative Ophthalmology and Visual Science* 59.11 (2018): 4451-4452.

5. Lim L and Lim EWL. "A review of corneal collagen cross-linking - current trends in practice applications". *Open Ophthalmology Journal* 12 (2018): 181-213.

6. Rush SW and Rush RB. "Epithelium-off versus transepithelial corneal collagen crosslinking for progressive corneal ectasia: a randomised and controlled trial". *British Journal of Ophthalmology* 101 (2017): 503-508.

7. Cerman E., *et al*. "Transepithelial versus epithelium-off crosslinking in adults with progressive keratoconus". *Journal of Cataract and Refractive Surgery* 41 (2015): 1416-25.

8. Kobashi H., et al. "Transepithelial versus epithelium-off corneal crosslinking for corneal ectasia". *Journal of Cataract and Refractive Surgery* 44.12 (2018): 1507-1516.

9. Caruso C., *et al*. "Transepithelial Corneal Cross-Linking With Vitamin E-Enhanced Riboflavin Solution and Abbreviated, Low-Dose UV-A: 24-Month Clinical Outcomes". *Cornea* 35.2 (2016): 145-150.

10. Vinciguerra P., *et al*. "Transepithelial iontophoresis corneal collagen cross-linking for progressive keratoconus: initial clinical outcomes". *Journal of Refractive Surgery* 30 (2014): 746-753.

11. Stulting RD., *et al*. "Corneal crosslinking without epithelial removal". *Journal of Cataract and Refractive Surgery* 44.1 (2018): 1363-1370.

12. Wollensak G., *et al*. "Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro". *Ophthalmic Research* 35 (2003): 324-8.

13. Chen X., *et al*. "Corneal collagen cross-linking (CXL) in thin corneas". *Eye and Vision* 2 (2015): 15.

14. Deshmukh R., *et al*. "Current concepts in crosslinking thin corneas". *Indian Journal of Ophthalmology* 67.1 (2019): 8-15.

15. Tong CM., *et al*. "Update on Bowman layer transplantation". *Current Opinion in Ophthalmology* 30.4 (2019): 249-255.

16. Kanellopoulos AJ and Binder PS. "Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty". *Cornea* 26.7 (2007): 891-895.

17. Kanellopoulos AJ. "Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconuss". *Journal of Refractive Surgery* 25.9 (2009): 812-818.

18. Seiler T and Quurke AW. "Iatrogenic keratectasia after LASIK in a case of forme fruste keratoconus". *Journal of Cataract and Refractive Surgery* 24.7 (1998): 1007-1009.

19. Kanellopoulos AJ and Binder PS. "Management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK and collagen cross-linking: the Athens protocol". *Journal of Refractive Surgery* 27.5 (2011): 323-331.

20. Kanellopoulos AJ. "The impact of keratoconus treatment with the Athens Protocol (partial topography-guided photorefractive keratectomy combined with higher-fluence corneal collagen cross-linking) on quality of life: a long-term study". *Clinical Ophthalmology* 13 (2019): 795-803.

21. Kanellopoulos AJ. "Management of progressive keratoconus with partial topography-guided PRK combined with refractive, customized CXL - a novel technique: the enhanced Athens protocol". *Clinical Ophthalmology* 13 (2019): 581-588.

22. Tomita M. "Combined laser in-situ keratomileusis and accelerated corneal cross-linking: an update". *Current Opinion in Ophthalmology* 27.4 (2016): 304-310.

23. Konstantopoulos A., *et al*. "Corneal stability of LASIK and SMILE when combined with collagen cross-linking". *Translational Vision Science and Technology* 8.3 (2019): 21.

24. Nordström., *et al*. "Refractive improvements and safety with topography-guided corneal crosslinking for keratoconus: 1-year results". *British Journal of Ophthalmology* 101.7 (2017): 920-925.

25. Lim WK., *et al*. "Epithelium-on photorefractive intrastromal cross-linking (PiXL) for reduction of low myopia". *Clinical Ophthalmology* 1 (2017): 1205-1211.

26. Kanellopoulos AJ and Asimellis G. "Hyperopic correction: clinical validation with epithelium-on and epithelium-off protocols, using variable fluence and topographically customized collagen corneal crosslinking". *Clinical Ophthalmology* 8 (2014): 2425-2433.

27. Morén H., *et al.* "Riboflavin and ultraviolet a collagen crosslinking of the cornea for the treatment of keratitis". *Cornea* 29.1 (2010): 102-104.

28. Kono Y., *et al*. "Two cases of severe infectious keratitis treated with corneal collagen crosslinking". *Nippon Ganka Gakkai Zasshi* 120.12 (2016): 831-836.

29. Shetty R., *et al.* "Collagen crosslinking in the management of advanced non-resolving microbial keratitis". *British Journal of Ophthalmology* 98.8 (2014): 1033-1035.

30. Hager T., *et al*. "Crosslinking and corneal cryotherapy in acanthamoeba keratitis -- a histological study". *Graefe's Archive for Clinical and Experimental Ophthalmology* 254.1 (2016): 149-153.

31. Ramona BI., *et al*. "Collagen crosslinking in the management of microbial keratitis". *Romanian Journal of Ophthalmology* 60.1 (2016): 28-30.

32. Uddaraju M., *et al*. "Corneal Cross-linking as an Adjuvant Therapy in the Management of Recalcitrant Deep Stromal Fungal Keratitis: A Randomized Trial". *American Journal of Ophthalmology* 160.1 (2015): 131-134.

Volume 10 Issue 9 September 2019
©All rights reserved by Jack S Parker.*, et al.*