Pediatric corneal collagen cross-linking for keratoconus: not an experimental procedure

Vaitheeswaran G. Lalgudi, MBBS,[a,b] and Ken K. Nischal, MD, FRCOphth[a,c]

Corneal collagen cross linking (CXL), first introduced by Wollensak and colleauges[1] in 2003 for adults, is the only treatment modality for arresting progression of keratoconus. Prior to its availability, the only treatment options were contact lens or keratoplasty (penetrating or deep anterior lamellar). The original Dresden protocol consists of manual epithelial debridement followed by riboflavin 0.146% with dextran instillation every 2 minutes for 30 minutes followed by UV-A irradiation, 3 mW/cm2 for 30 minutes, with continuing riboflavin instillation (see Figure 1).[1]

CXL induces and enhances cross-linking between collagen fibrils. Riboflavin causes photosensitization and UV-A creates cross-linking by generating oxidative products.[2] This improves the corneal biomechanical strength, thereby arresting the progression of ectasia, which is basically due to biomechanical weakening.

While several groups around the world have been using the procedure since 2003, Food and Drug Administration approval in the United States was obtained only in April 2016 for progressive keratoconus in adults 14-65 years of age. They approved use of the Dresden protocol with minimum epithelium-off pachymetry of 400 μm. Two forms of riboflavin (riboflavin 5-phosphate in 20% dextran and riboflavin 5'-phosphate) are approved with the Avedro system (Avedro Inc, Waltham, MA) for UV-A delivery at continuous mode.[3,4] Although adults usually can cope with local anesthesia, children often need general anesthesia.

The evidence for CXL is abundant and includes prospective studies[5-9] that have longitudinally evaluated corneal topographic and visual parameters following CXL with follow-up ranging from 1 to 10 years in both adults and children. A study of children 9-19 years of age by Chatzis and Hafezi[10] reported a progression rate of 88% at 1 year in 59 eyes of 42 children with keratoconus who were awaiting CXL. Of the 59 eyes, 46 were then treated and showed stabilization up to 2 years. The authors proposed CXL in this age group without awaiting disease progression. If not cross-linked, children have a sevenfold risk of requiring a keratoplasty compared to adults.[11]

Zotta and colleagues[5] have used the Dresden protocol in 20 eyes of 10 patients 10-17 years of age with documented progressive keratoconus and followed them for a mean of 7.6 years. These patients had no allergic eye disease. At final follow-up, all 20 eyes had keratometric stabilization, and 65% gained more than 1 line of corrected vision. None of them required any further intervention.

In the largest study[7] to date, 194 eyes of 153 children 8-18 years of age with documented progressive keratoconus underwent CXL (142, standard CXL; 52, with hypoosmolar riboflavin) and were followed for up to 6.7 years. They reported flattening and stabilization of pachymetry after CXL. Of 59 eyes with a follow-up >4 years, 14 (24%) showed reversal of keratometric flattening; however, this did not correlate to significant vision or pachymetric change. In the study with the longest follow-up, Mazzotta and colleagues[6] found that in 62 eyes of 47 children 8-18 years of age 80% of eyes remained stable at 10 years after CXL; 4 eyes of 2 patients showed a 2 D increase in mean keratometry and underwent repeat CXL, following which they stabilized. These patients had severe eye allergy with associated eye rubbing. Apart from these 2, no other patient required any repeat treatment owing to CXL failure.

Looking at these long-term studies[5-7] and the rate of progression reported in pediatric keratoconus,[10] it is likely that a much larger percentage of study patients would have required major surgeries, such as keratoplasty, had CXL not been performed. These studies[5-10] have all demonstrated both statistically and clinically that CXL with the Dresden protocol arrests the progression of keratoconus while effecting corneal flattening and variable visual improvement and significantly decreasing the requirement of keratoplasty due to keratoconus.

Pediatric keratoplasty is associated with multiple operative issues and postoperative complications, including frequent need for general anesthesia for suture-related problems, infections, and stronger immune system in children (increasing the risk of rejection). These all contribute to a much higher rate of graft rejection compared to keratoplasty in adults.[12]

The earlier a child with progressive keratoconus undergoes CXL, the earlier the possibility of visual rehabilitation. In patients with keratoconus older than 15 years, an objective study of quality of life using the State Trait anxiety inventory (STAI) and the NEI-VFQ 25 questionnaire has shown better quality of life and decreased anxiety related traits 1 year following CXL.[13]

Author affiliations: [a]UPMC Eye Center, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [b]Narayana Nethralaya, Bangalore, India; [c]University of Pittsburgh, School of Medicine.

Submitted November 4, 2018.
Revision accepted December 15, 2018.
Published online December 30, 2018.

Correspondence: Ken K. Nischal, MD, FAAP, FRCOphth, Suite 5000, Faculty Pavilion, UPMC Children's Hospital of Pittsburgh, 4401 Penn Ave, Pittsburgh, PA, 15224 (email: nischalkk@upmc.edu).

J AAPOS 2019;23:63-65.

1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2018.12.001

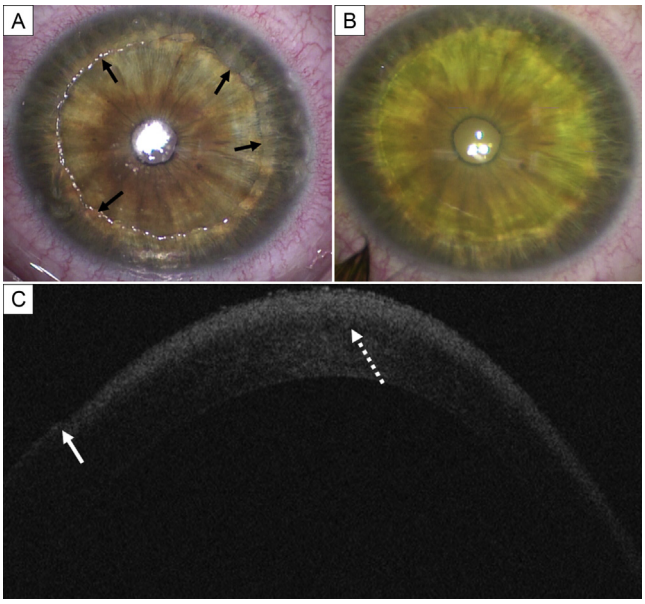

FIG 1. A 21-year-old developmentally delayed patient with Down syndrome undergoing collagen cross-linking under general anesthetic for keratoconus. A, Edge of epithelial defect (arrows) after removal of epithelium using topical alcohol. B, Yellow tint of cornea after soaking for over 30 minutes with 0.146% riboflavin with dextran. C, Spectral domain optical coherence tomography after riboflavin soak showing the edge of the epithelial defect (solid arrow) and the soak depth of the riboflavin (dashed arrow). Studies show that on OCT there is approximately a 150 μm depth of soak, consistent with this image.

Proof of alteration or improvement in biomechanics of the cross-linked corneal tissue is dependent on the technique used to study the biomechanics.[14,15] While ex vivo techniques have shown improvement,[16] the in vivo tools for assessing biomechanical change show variable results.[14] The recently introduced dynamic corneal response curve parameters of Corvis-ST are suggestive of an early biomechanical strengthening of the cornea,[15] but long-term studies are required. Nevertheless, it is clear that CXL definitively helps in arresting progression and also leads to mild-to-moderate visual gain.

CXL has a very low rate of sight-threatening complications, which include infectious keratitis (0.0017%) or sterile infiltrates.[17] Most patients in the early postoperative period develop an anterior stromal haze that does not affect vision.[18] It gradually resolves over a year's time in most of cases. Long-term studies in children have shown a regression of CXL effect or failure of up to 25% beyond 3-4 years.[6,7] If the procedure is performed on very thin corneas there is a danger that the UV phototherapy may damage the endothelium and cause persistent corneal edema,[19] hence the 400 μm epithelium-off pachymetry criteria for treatment. After induction with photrexa viscous, if the stroma is thinner than 400 μm, then photrexa should be used to swell the cornea. Currently, there is no study in children using epithelium-on CXL or accelerated CXL with follow-up of more than 24 months.[20] Hence, the long-term safety is not known with other modalities other than standard CXL.

Studies have shown significant progression of the disease in non-cross-linked eyes.[10,21] Progression is higher and more rapid especially in pediatric keratoconus eyes.[11] As keratoconus progresses, irregular astigmatism worsens, affecting vision significantly. Contact lens fitting becomes more difficult, leading to intolerance. Progressive thinning can lead to acute hydrops, a potentially blinding condition that results in blisters in the cornea, with scarring and significant diminution in vision.[22]

Other options in moderate-to-severe keratoconus management include intracorneal ring segments (Intacs; Addition Technology Inc SA, Lombard, IL) and keratoplasty. Intacs, although their use can partially rehabilitate vision and delay keratoplasty, is associated with poor outcomes with higher grades of keratoconus. Intracorneal ring segments have also been associated with risk of extrusion or need for removal,[23,24] which increases the number of procedures, especially in children. Use of intracorneal ring segments is usually combined with CXL and not used as a stand-alone intervention. Pediatric keratoplasty, as mentioned, has higher risk of infections, graft rejection, and difficult visual rehabilitation compared to adult keratoplasties.[12]

If ever there was a group of patients that we as pediatric ophthalmologists get asked again and again to manage, it is the developmentally delayed adolescent or young adult. Many of these patients have keratoconus because of eye rubbing. Studies have shown that failure to deliver CXL to this group results in marked progression of keratoconus.[25,26]

Pediatric ophthalmologists must manage vernal keratoconjunctivitis (VKC) appropriately, because it is one of the most important predisposing factor for eye rubbing and development of keratoconus.[27] Apart from steroids and antihistamines, cyclosporine or tacrolimus are proven to be beneficial.[28,29] Active VKC predisposes to keratitis following CXL.[17,30] Hence, adequate control before CXL is required. Children who regress following CXL often have more ocular allergy and eye rubbing,[6] and it is essential to manage allergy long term. This subgroup progresses rapidly when left untreated, and for this reason many groups[5,10,31] strongly recommend CXL in children at first diagnosis of keratoconus without waiting for progression.

Crosslinking in adults is beyond doubt the most necessary procedure to prevent progression of keratoconus. Compared to adult keratoconus, pediatric keratoconus has been proven to be more aggressive and more rapidly progressive. Hence, it is of utmost significance to understand the long-term role timely CXL and management of allergy play in pediatric keratoconus, the delay of which can cause irreversible long-term visual impairment. It has also been proven to be cost effective for patients and health-care providers compared to not cross-linking and eventually requiring keratoplasty.[32,33]

CXL clearly has a role in prevention of progression of keratoconus in children, and worldwide experience with the technique has demonstrated that it is *not* an experimental procedure. CXL, as an option must therefore be offered to every child presenting with proven keratoconus so that an attempt at early treatment can be made.

References

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620-27.
2. Meek KM, Hayes S. Corneal cross-linking—a review. Ophthalmic Physiol Opt 2013;33:78-93.
3. Jeng BH, Farid M, Patel SV, Schwab IR. Corneal cross-linking for keratoconus: a look at the data, the food and drug administration, and the future. Ophthalmology 2016;123:2270-72.
4. Belin MW, Lim L, Rajpal RK, Hafezi F, Gomes JAP, Cochener B. Corneal cross-linking: current usa status: report from the Cornea Society. Cornea 2018;37:1218-25.
5. Zotta PG, Diakonis VF, Kymionis GD, Grentzelos M, Moschou KA. Long-term outcomes of corneal cross-linking for keratoconus in pediatric patients. J AAPOS 2017;21:397-401.
6. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal collagen cross-linking with riboflavin and ultraviolet a light for pediatric keratoconus: ten-year results. Cornea 2018;37:560-66.
7. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal collagen cross-linking for keratoconus in pediatric patients-long-term results. Cornea 2017;36:138-43.
8. Raiskup F, Theuring A, Pillunat LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. J Cataract Refract Surg 2015;41:41-6.
9. Nicula C, Nicula D, Pop RN. Results at 7 years after cross-linking procedure in keratoconic patients. J Fr Ophtalmol 2017;40:535-41.
10. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents. J Refract Surg 2012;28:753-8.
11. Leoni-Mesplie S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. Am J Ophthalmol 2012;154:56-62.e1.
12. Vanathi M, Panda A, Vengayil S, Chaudhuri Z, Dada T. Pediatric keratoplasty. Surv Ophthalmol 2009;54:245-71.
13. Cingu AK, Bez Y, Cinar Y, et al. Impact of collagen cross-linking on psychological distress and vision and health-related quality of life in patients with keratoconus. Eye Contact Lens 2015;41:349-53.
14. Gkika M, Labiris G, Giarmoukakis A, Koutsogianni A, Kozobolis V. Evaluation of corneal hysteresis and corneal resistance factor after corneal cross-linking for keratoconus. Graefes Arch Clin Exp Ophthalmol 2012;250:565-73.
15. Vinciguerra R, Romano V, Arbabi EM, et al. In vivo early corneal biomechanical changes after corneal cross-linking in patients with progressive keratoconus. J Refract Surg 2017;33:840-46.
16. Beshtawi IM, Akhtar R, Hillarby MC, et al. Biomechanical properties of human corneas following low- and high-intensity collagen cross-linking determined with scanning acoustic microscopy. Invest Ophthalmol Vis Sci 2013;54:5273-80.
17. Shetty R, Kaweri L, Nuijts RM, Nagaraja H, Arora V, Kumar RS. Profile of microbial keratitis after corneal collagen cross-linking. Biomed Res Int 2014;2014:340509.
18. Evangelista CB, Hatch KM. Corneal collagen cross-linking complications. Semin Ophthalmol 2018;33:29-35.
19. Sharma A, Nottage JM, Mirchia K, Sharma R, Mohan K, Nirankari VS. Persistent corneal edema after collagen cross-linking for keratoconus. Am J Ophthalmol 2012;154:922-926.e1.
20. Perez-Straziota C, Gaster RN, Rabinowitz YS. Corneal cross-linking for pediatric keratcoconus review. Cornea 2018;37:802-9.
21. Romano V, Vinciguerra R, Arbabi EM, et al. Progression of keratoconus in patients while awaiting corneal cross-linking: a prospective clinical study. J Refract Surg 2018;34:177-80.
22. Tuft SJ, Gregory WM, Buckley RJ. Acute corneal hydrops in keratoconus. Ophthalmology 1994;101:1738-44.
23. Alio JL, Shabayek MH, Artola A. Intracorneal ring segments for keratoconus correction: long-term follow-up. J Cataract Refract Surg 2006;32:978-85.
24. Colin J, Malet FJ. Intacs for the correction of keratoconus: two-year follow-up. J Cataract Refract Surg 2007;33:69-74.
25. Koppen C, Leysen I, Tassignon MJ. Riboflavin/UVA cross-linking for keratoconus in Down syndrome. J Refract Surg 2010;26:623-4.
26. Sabti S, Tappeiner C, Frueh BE. Corneal cross-linking in a 4-year-old child with keratoconus and Down syndrome. Cornea 2015;34:1157-60.
27. Sharma N, Rao K, Maharana PK, Vajpayee RB. Ocular allergy and keratoconus. Indian J Ophthalmol 2013;61:407-9.
28. Yucel OE, Ulus ND. Efficacy and safety of topical cyclosporine A 0.05% in vernal keratoconjunctivitis. Singapore Med J 2016;57:507-10.
29. Barot RK, Shitole SC, Bhagat N, Patil D, Sawant P, Patil K. Therapeutic effect of 0.1% tacrolimus eye ointment in allergic ocular diseases. J Clin Diagn Res 2016;10:Nc05-9.
30. Maharana PK, Sahay P, Sujeeth M, et al. Microbial Keratitis after accelerated corneal collagen cross-linking in keratoconus. Cornea 2018;37:162-7.
31. Shetty R, Kaweri L, Pahuja N, et al. Current review and a simplified "five-point management algorithm" for keratoconus. Indian J Ophthalmol 2015;63:46-53.
32. Leung VC, Pechlivanoglou P, Chew HF, Hatch W. Corneal collagen cross-linking in the management of keratoconus in canada: a cost-effectiveness analysis. Ophthalmology 2017;124:1108-19.
33. Godefrooij DA, Mangen MJ, Chan E, et al. Cost-effectiveness analysis of corneal collagen crosslinking for progressive keratoconus. Ophthalmology 2017;124:1485-95.