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Corneal Cross-Linking for Keratoconus: Current Knowledge and Practice and Future Trends

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Abstract: Corneal collagen cross-linking (CXL) with riboflavin is an accepted universal standard of care for our keratoconus patients with progressive disease. It has been a game changer in how we manage keratoconus. Early diagnosis and treatment is essential in paediatric patients as younger patients progress more rapidly and have poorer transplant outcomes. There is an ongoing debate around standard, accelerated, and transepithelial protocols of CXL, the role of CXL, and the combination of laser refractive surgery. Future developments will improve CXL safety and efficacy and the scope of utilization, but we must be careful not to leap too far ahead with clinical applications before publication of basic science research and good clinical results with standardized protocols.

Key Words: cornea, cross-linking, keratoconus, riboflavin

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One of the greatest sources of fulfillment as a doctor is to witness the advent and be part of the evolution of a new treatment which profoundly alters the management of a disease for our patients. Such has been the impact of corneal cross-linking (CXL) with riboflavin for the prevention of disease progression in keratoconus (KC). KC used to be one of the leading reasons for corneal transplantation in many nations and transplant rates have dropped in many hospital departments as a result of CXL. An analysis of the Dutch National Organ Transplant Registry found a 25% decrease in the number of corneal transplants in the 3 years after CXL was introduced.[1] In Norway, the reduction reported was even more dramatic with the number of transplants more than halved.[2] A 2019 report on the Canadian graft registry showed that although the number of transplants overall did not decrease, the proportion done for KC significantly dropped, potentially meaning that an additional benefit of CXL is the increased availability of graft tissue for patients with other corneal disease.

CXL means that quality of life has significantly improved for our patients by maintenance of vision, reduced spectacle and contact lens issues, and avoidance of corneal transplants. In 2019, members of the ASCRS Cornea Clinical Committee published a review of the current literature on the corneal cross-linking (CXL) procedure for treating corneal ectasia. They concluded that CXL limits the progression of KC, reduces the need for transplantation, and carries significant and long-term cost and safety benefits.[3] Two recent publications examined the quality of life in a cost-effectiveness analysis of CXL versus corneal transplantation. Leung et al and Godefrooj et al both utilizing large data sets confirmed significantly better cost effectiveness and quality of life indices for CXL as opposed to corneal transplant. Preservation of visual acuity is vital as well and previously it has been established that reduced best corrected visual acuity in the better eye is the strongest predictor of low vision-related quality of life.[4] We all know as clinicians, that this current generation of patients with access to CXL will go on to live potentially happier and more fulfilling lives with better career prospects than those generations before.

The following article will address what we know and do not know about some of the major areas in CXL and what the future may hold. At this point I must give profound thanks and acknowledgment to Wollensak et al without whom the field of CXL would not even exist. Nor the hope we can now give our patients with KC.

YOUNGER PATIENTS NEED CXL MORE THAN OLDER ONES

In the early days of CXL, CXL in younger or paediatric patients was contentious. Significant concerns over safety and effectiveness existed. Fortunately, reassurance came early thanks to the seminal work of Caporossi-Baiocchi-Mazzotta at Siena University published in 2012 showing good stability and safety in patients of 18 years and younger up to 36 months after CXL.[5] Other studies have reported efficacy in paediatric populations.[6–14] In 2019, the Siena group published 10-year results showing overall 80% of eyes were stable but highlighted a 24% regression rate in patients aged 15 years or younger. It is important therefore to follow up our paediatric patients long term and not assume stability after initial success.[10] The fellow or non–cross-linked eye must also be watched. In patients with asymmetric disease and milder or even no KC in the fellow eye, KC may emerge many years later. The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) found that 35% of unaffected eyes developed KC eventually with no apparent predictors of when this would occur.[15] As mentioned previously, reduced best corrected visual acuity in the better eye is a strong predictor of low vision-related quality of life.[4]

Acceptance of the importance of early CXL in our paediatric patients is crucial. A Delphi panel of international experts came to the consensus opinion that apart from atopy management and avoidance of eye rubbing in patients with coexistent allergy and KC, CXL was the recommended treatment for patients with

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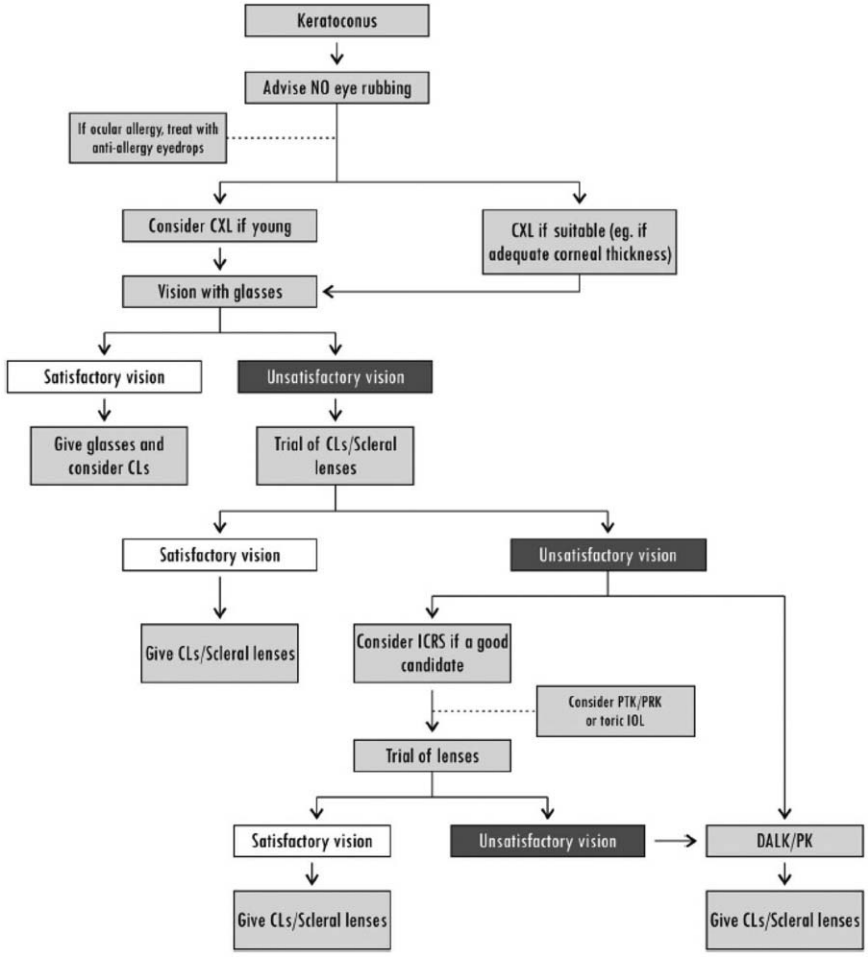

FIGURE 1. Suggested algorithm for treatment of keratoconus based on a Delphi expert consensus method. CL indicates contact lens; CXL, cross-linking; DALK, deep anterior lamellar keratoplasty; ICRS, intrastromal corneal ring surgery; IOL, intraocular lens; P, penetrating keratoplasty; PRK, photorefractive keratectomy; PTK, phototherapeutic keratectomy. Adapted from.[16]

progressive KC of all ages and particularly if patients were young (Fig. 1).[16]

Age appears to be a predictor of progression. The younger the patient is, the more she/he will progress and the more rapidly KC will progress. KC also tends to be more severe at presentation in a paediatric population. This may be because children may not express visual issues in the same way as adults and have a larger amplitude of accommodation to cope with defocus. In my experience, refractive cylinder is typically less than topographic cylinder and therefore a poor measure of KC degree and progression. A high degree of suspicion for the diagnosis is warranted in patients with a family history, new astigmatism development, atopy, and a history of eye rubbing.

Newer studies looking as prevalence of KC indicate a much higher rate than the traditionally quoted figure of 1:2000. There is limited evidence regarding the prevalence of KC in children. A study in Lebanon reported a prevalence of 1:200 and a more recent one in Saudi Arabia found a prevalence of 1 in 25.[17,18] As mentioned previously, the prevalence in the general population is believed to be between 1:375 and 1:2000.[19] No established guidelines exist as to recommendations for preschool and early school age screening for children, especially with first-degree relatives who have KC. Such guidelines would be welcomed by this author and has been called for by other authors.[19,20] A study in Beirut, Lebanon found a KC prevalence of 17.5% in children with a first-degree relative who has KC. However, it should be noted that 16.9% of the parents were consanguineous.[21] Better screening techniques could also account for the apparent higher prevalence. I routinely recommend topographic screening at age 5 for children of my patients with KC.

Tuft et al's, 1994 landmark study established that keratometry, cylinder refraction, visual acuity, ethnicity, and age significantly affected the time to corneal grafting. Ferdi et al's 2019 systematic review and meta-analysis of 11,529 eyes again established that younger patients and those with Kmax steeper than 55 D at presentation have a significantly greater risk of progression of KC. The authors recommended that "closer follow-up and a lower threshold for cross-linking should be adopted in patients younger than 17 years and steeper than 55 D Kmax."[22] The CLEK study found that pediatric patients tend to have more central cones which are more visually disabling than peripheral cones and present with more advanced KC compared with adults.[15,23] The majority (up to 88%) of pediatric patients progress rapidly with steepening >2 D within 12 months of presentation.[24–26] Therefore, younger patients have 2 intertwined risk factors for more rapid progression and poorer outcomes: age and steeper keratometry at presentation. I usually recommend repeat topography every 3 months if the CXL is being deferred in patients below the age of 15 years.

Penetrating keratoplasty has a poorer prognosis in the pediatric population due to an increased risk of rejection related to their robust inflammatory response to the graft.[9] For all these

reasons, pediatric patients with suspected KC and actual KC need careful monitoring or early cross-linking to prevent further loss of vision and disease progression.

CXL: CAN WE IMPROVE SAFETY AND DISCOMFORT?

Infectious keratitis, scarring/haze formation, and the need for corneal transplant after CXL are the most feared complications. A systematic review published in 2016 found only 10 published cases of infectious keratitis between 2000 and 2003.[3] One other study reported the incidence of infectious keratitis after CXL is extremely low, quoting a figure of 0.0017% even in nations where microbial keratitis incidence is higher.[27] Nevertheless, despite the low incidence, the risk of infectious keratitis remains one of the most commonly cited reasons for the move away from standard CXL (S-CXL) and epithelium off techniques.

Haze and scarring are another commonly cited reasons for the pursuit of protocols other than S-CXL. To a degree, haze is an expected outcome from all forms of CXL and the more pertinent question is whether it is clinically significant. With S-CXL, haze is usually greatest at 1 month and then reduced between month 3 and 12 as measured by corneal densitometry.[28] The US multicenter study on S-CXL found that corneal haze or a demarcation line was noted in 57% but only 1% of eyes had persistent haze.[29] Raiskup et al reported a much higher incidence of clinically significant haze of 8.6%[30] and found a risk factor was more advanced KC with thinner and steeper corneas.

Postoperative pain and healing are also another factor cited to promote nonstandard CXL protocols. The published literature is actually conflicting in this area. One study found that in a comparison of epi-on and epi-off CXL, that both techniques were able to stop progression; however, in contrast to expectations, the pain was felt more in epi-on CXL than epi-off CXL.[31] Another study found that both oral ketorolac and oral gabapentin can be used with similar results for pain and symptomatic control after epi-on or epi-off CXL procedures, inferring the pain is similar between the 2 types of CXL.[32] One recent article, in a revisit to times past when LASEK (laser assisted sub-epithelial keratectomy) or creation of an epithelial flap for photorefractive keratectomy (PRK) was popular, found that postoperative pain was less if the epithelium was removed as an intact flap and then replaced after CXL.[33]

Other ways to improve post-CXL comfort are choice of bandage contact lens and postoperative drop regimes. Bandage contact lens fit and therefore comfort can be a tricky issue for keratoconic eyes given limited available base curves and options for an irregular and steep cornea. Other alternatives are being evaluated including purified bovine collagen (Oasis Collagen Soft Shield) which provides a temporary protective barrier and is reabsorbed after 72 hours. This gives the added advantage of no removal being required which would be especially useful in paediatric patients.[34] The use of serum autologous tears to aid epithelial healing and comfort as well has also been reported. Sixty patients undergoing accelerated CXL were randomized to either the use of autologous serum tear drops or artificial tears. The group that received serum autologous tears had significantly faster epithelial healing times and reduced pain scores. However, logistic access to serum tears may present one hurdle for such a postoperative protocol.[35]

CXL PROTOCOLS: TOO MANY CHOICES?

The original often called standard or Dresden protocol CXL (S-CXL) has been robustly studied in both in lab and in large clinical studies in both the adult and paediatric studies. The parameters are well established.[5,25,36–39] However, concerns over complications, length of treatment, and potential over treatment have led to the emergence and wide spread use of newer CXL protocols including various versions of accelerated CXL, (A-CXL) and of transepithelial (T-CXL) one of which is iontophoresis CXL (I-ON CXL).

A-CXL is based on the reciprocity of the Bunsen Roscoe Law. This law states that the degree of a photochemical reaction is directly proportional to the total energy dose, irrespective of the time over which this dose is delivered. In A-CXL, the parameter of irradiance is increased from the standard 3.0 mW/cm^2 with a reciprocal decrease in exposure time so that the total amount of cumulative irradiation dose stays constant 5.4 J/cm^2. There are a multitude of different irradiance and duration protocols in clinical use. However, the Bunsen Roscoe Law strictly applies to the field of darkroom photography and not more complex photochemical applications like CXL. An everyday crude example of this is increasing the temperature of your oven to bake your cake in a shorter period of time. The controversy is around whether you get the cake is baked in the same way as the standard process.

T-CXL is based on various methods to enhance riboflavin penetrance into the cornea. This can be by chemical alteration of the riboflavin solution or by alteration of the corneal permeability itself. I-ON CXL employs the application of an electrical current to improve riboflavin permeation into the cornea. Issues which have been raised with I-ON CXL have included patient discomfort, creation of epithelial defects, and poor stromal loading with riboflavin.[40]

Rubinfeld et al argue persuasively that Bunsen-Roscoe Law does not strictly apply to A-CXL and that high irradiance levels may be less effective at achieving cross-linking due to rapid depletion of oxygen. This is reflected in a shallower demarcation line with increasing irradiance. The demarcation line has long been accepted as an indication of CXL effect and the border between cross-linked and non–cross-linked cornea.[36] This argument is supported by an elegant study by Bao et al looking at stress-strain measurements in vitro with different CXL protocols (Fig. 2). This demonstrates a reduction in cross-linking effect in the laboratory with increasing irradiance levels.[41] One other metric is interfibrillar spacing which decreases with CXL and appears to decrease less with A-CXL.[42] One option to allow oxygen stromal rediffusion is to use pulsed UVA light rather than continuous in A-CXL.[43]

Better understanding of the basic science may help us more critically examine the variable results seen in the recent literature on the effectiveness of S-CXL versus A-CXL versus T-CXL including I-ON -CXL. However, the clinical studies as opposed to the in vitro seem to indicate that CXL still is largely effective when the numerous protocols other than S-CXL currently employed. This seems to be the case with both adult and paediatric populations.[44–46] The argument for A-CXL in paediatric patients raised by a number of authors is the advantage of shorter duration of treatment and reduced haze compared to S-CXL.[47–51] A counter argument is that S-CXL should be used in paediatric patients as this group of patients tends to have more severe disease and the aim should be to achieve maximal cross-linking and a

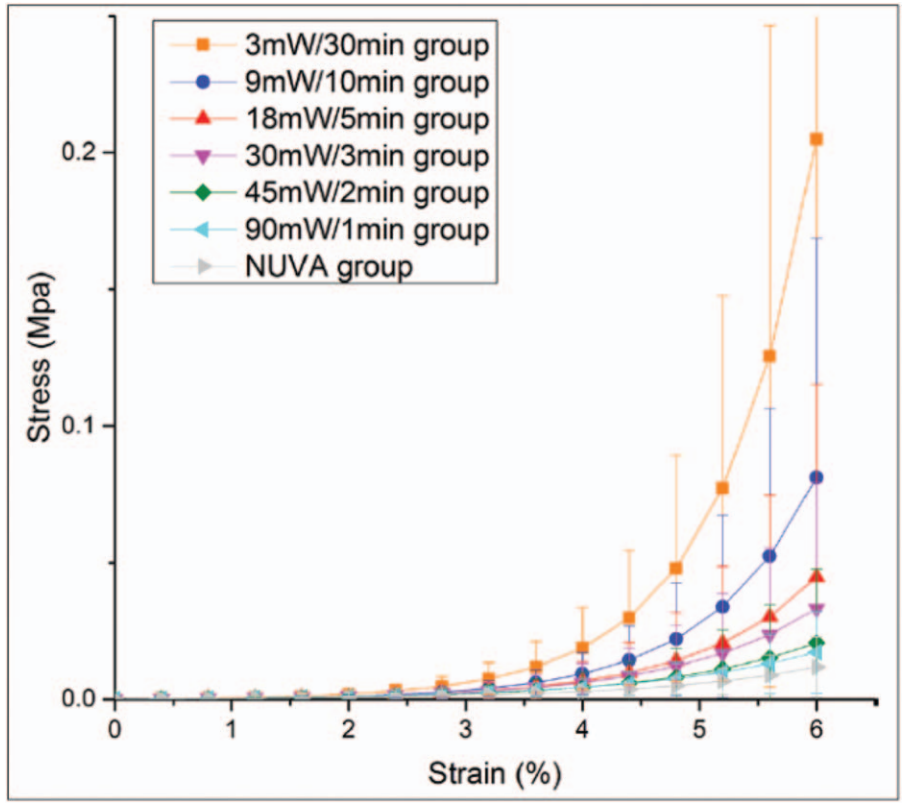

FIGURE 2. Graph demonstrating that increasing irradiance time correlates with increasing CXL effect. Adapted from.[41]

better chance of stopping progression than A-CXL and T-CXL and maximal flattening of the cornea.[52–55] These authors cite a higher failure rate in paediatric patients with A-CXL and T-CXL including I-ON CXL.

Many different kinds of riboflavin are available for use and the choice can be as confusing as to the method of UVA irradiance to choose. Riboflavin is poorly permeable across the lipid corneal epithelium as it is hydrophilic and has a negative charge. As mentioned previously, iontophoresis is one method used to improve corneal permeability. For example, Rapuano et al compared a dextran-containing and hydroxypropyl methylcellulose-containing riboflavin solution with S-CXL and found better visual results in the dextran group. However, dextran containing solutions may result in thinning of the cornea during the soak phase (which may also account for a more significant CXL effect as UVA may penetrate a dehydrated thinner cornea.).[56] However, most riboflavin solutions nowadays tend to be hydroxypropyl methylcellulose-containing. Work is going on also looking at riboflavin solutions containing molecules which enhance permeation such as VE-TPGS) a surfactant and epithelial disruption devices such as proparacaine loaded sponges which are brushed across the epithelium.[57,58] The most novel approach has been the use of oral riboflavin in small series of 7 patients with set daily exposure to sunlight over a 6-month period. Naturally, there are concerns over what other parts of the body might become cross-linked and stiffer.[59]

FUTURE CXL PROTOCOLS

There has been recent interest in topography-guided cross-linking also called customized cross-linking or photorefractive intrastromal cross-linking (piXL). The basis of piXL is asymmetric application of UVA based on topography to titrate the crosslinking effect across different parts of the cornea to induce a greater visual, refractive, and toppograhic improvement than regular CXL (Fig. 3) This was first described by Kanellopoulos et al in a case report in 2014.[60] In 2017, a group at Umea University in Sweden published a prospective study of 50 eyes with one group randomized to A-CXL and one group to one to piXL.[61] Overall piXL showed some potential but not significant visual changes compared to the A-CXL group and better reduction in Kmax readings. The authors concluded that the piXL method had potential but further studies and refinement of the algorithm, treatment zones, and irradiance levels may be required.

The quest for a "perfect" cross-linking protocol for all patients regardless of age and degree of KC may not be necessary. Based on the science, not all cross-linking is the same. There are perhaps enough protocols already in existence to adequately treat different patient groups. For example, a 28-year-old patient with mild and only slowly deteriorating KC most likely does not need S-CXL. Stratification of patients into different subsets based on individual factors may be achievable with big data analysis and artificial intelligence algorithms. I would like to share with you one of my favourite sayings. Howard Moskowitz, the famous market researcher and psychophysicist, stated that when it came to individual food tastes: "There is no perfect spaghetti sauce. There are only perfect spaghetti *sauces."* Much in the same way, it is unlikely with cross-linking that one size can fit all.

CXL COMBINED WITH LASER TO TREAT KC

The combination of CXL and laser refractive surgery in patients with KC is an emerging and exciting therapeutic modality. However, concerns remain on its long-term efficacy and

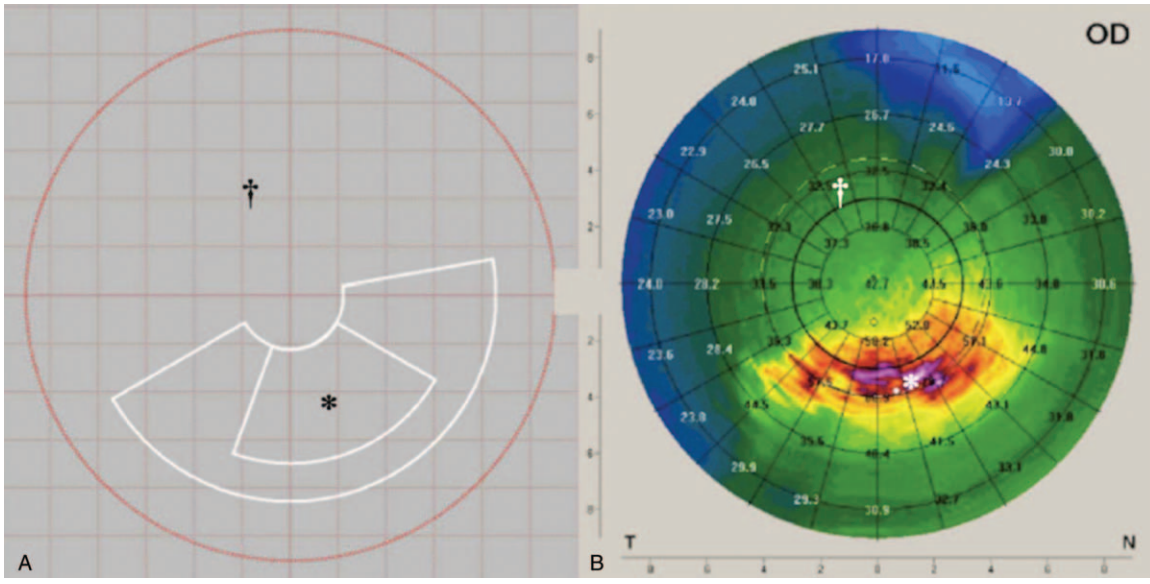

FIGURE 3. Topography-based pattern of CXL utilized in piXL. Adapted from.[61]

safety. One recent cautionary publication cited an incidence of clinically significant haze leading to loss of best corrected visual acuity of 7 of 26 eyes (27%).[62] Another source of concern is topographic-based PRK profiles maximally ablate the steepest part of the cone to flatten it which usually means that the ablation takes place over the thinnest part of the cornea, thereby thinning it further (Fig. 4).

Part of the lack of consensus is due to the variation in protocols across different international groups. Kanellopoulos was one of the first to describe and publish results of combined CXL and PRK and thus has the longest follow-up. The Athens Protocol was a single surgeon-driven protocol using the Alcon/Wavelight topographic ablation profile in patients >18 years of age with a total depth of up to 100 μm of treatment allowed (up to 50 μm for refractive treatment followed by 50 μm PTK for epithelium). Mitomycin 0.02% for 20 seconds was applied. This was followed same day by A-CXL (Vibex Rapid soak for 5 minutes, UVA 6 mW/cm^2 for 15 minutes). Recently, 10-year results of 144 eyes were published which showed that 94.4% showed no keratoconic progression and no eyes with loss of >1 line of best corrected visual acuity.[63]

Smaller cohorts with less follow-up time have also been reported. The Tel-Aviv Protocol group of 99 eyes also employed same day PRK followed by CXL but did not include data on whether there were ablation limits on the amount of PRK. The A-CXL was also at a different irradiance than the Athens Protocol (9 mW/cm^2 for 10 minutes). One eye (0.9%) lost 3 lines of CDVA and 2 patients (2 eyes, 1.9%) lost 2 CDVA lines, all due to

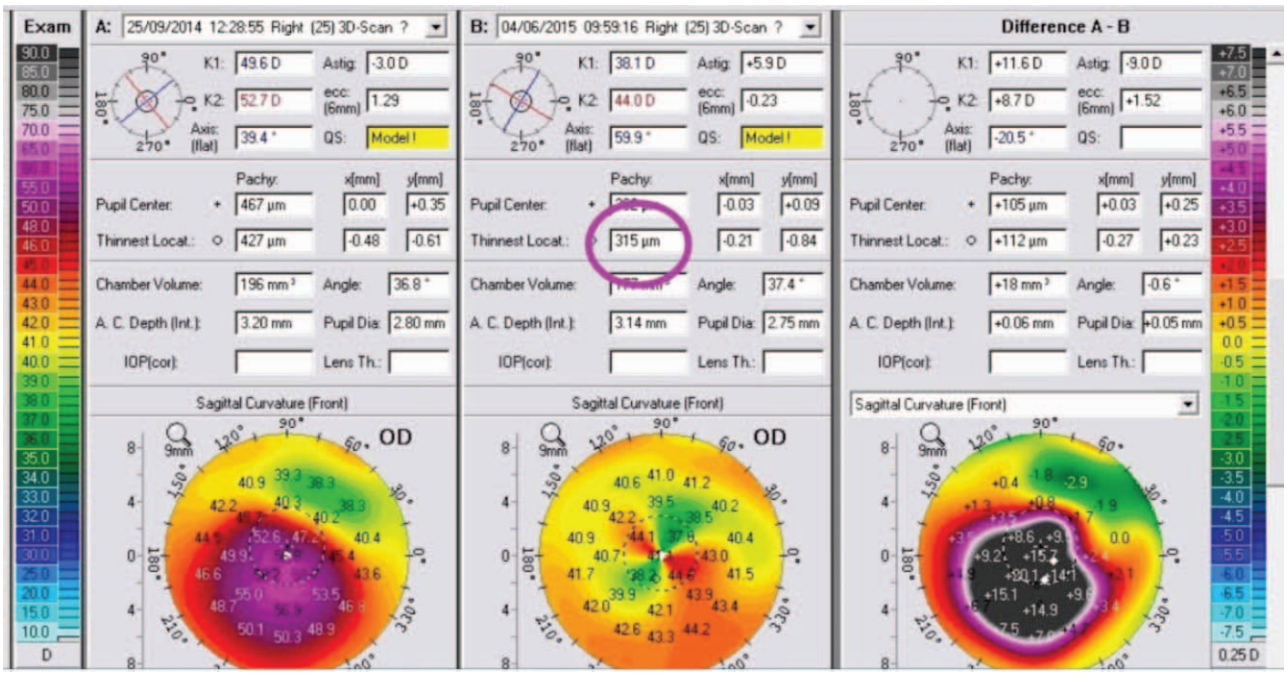

FIGURE 4. Example of topographic photorefractive keratectomy (PRK) following CXL using the Alcon Wavelight platform. Kindly supplied by Dr. Arthur Cheng, Hong Kong. CXL indicates corneal crosslinking with riboflavin.

significant corneal haze which could possibly reflect the lack of ablation limits.[64] The United States has also reported its early experience in study of 62 eyes. However, CXL was performed first with a 15 mW/cm^2 for 5 minutes protocol and then lack of progression documented before proceeding to PRK. While the mean results of improvement in uncorrected and best corrected visual acuity seem promising, the data may be flawed by the lack of consistency in the timing between CXL and PRK, no limits of ablation amount except to leave a minimum of 300 μm residual stromal thickness (RST). Also, the authors do not indicate whether any eyes lost lines of CDVA.[65]

Therefore, questions remain about the safety of CXL combined with PRK and more studies are certainly warranted, though the data from the Athens protocol seems to be the most robust.

SHOULD WE BE DOING CXL ROUTINELY AS PROPHYLAXIS IN LASER SURGERY PATIENTS?

High irradiance short duration CXL to reduce the risk of ectasia after LASIK is a controversial use of CXL (LASIK Xtra or CXL Xtra). Kanellopoulos and Pamel[66] described his technique of 30 MW/cm^2, for a total of 80 seconds on the exposed stromal bed after completion of LASIK in 2012. Lim at el, published an extensive review in 2019 of CXL + LASIK, SMILE and PRK, and concluded that "simultaneous accelerated CXL and refractive surgery is effective for the treatment of myopia. However, it is as yet unclear if the additional CXL step reduces the incidence of iatrogenic keratectasia." Furthermore, there are case reports of toxic keratopathy, diffuse lamellar keratitis and ectasia after the combined procedure.[67]

Another argument against CXL Xtra is that goes against the very principle that the purpose of refractive screening and role of the refractive surgeon is to exclude cases which are unsuitable and recommend against laser correction altogether. Ectasia incidence with modern screening methods is also very low. Incidence figures are actually hard to obtain because the figure is so low and the emergence time is so varied. Bohac et al's large retrospective review of 30,000 patients between 2007 and 2015 found an incidence of ectasia of 0.033%.[68] Ectasia has been reported up to 10 years after the original procedure.[69] Recently, I had a 60-year-old present to my practice with ectasia 17 years after the original LASIK. In this author's humble opinion, without a prospective two-armed study with >10-year follow up, it would be very difficult to prove that CXL Xtra effectively reduced the incidence of ectasia. Therefore, routine CXL Xtra may expose patients to unnecessary treatment and risks.

CONCLUSIONS

CXL is an accepted universal standard of care for our KC patients with progressive disease. It has been a game changer in how we manage KC. Future developments will improve its safety and efficacy and scope of utilization, but we must be careful not to leap too far ahead with clinical applications before publication of basic science research and good clinical results with standardized protocols.

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