Corneal collagen cross-linking in keratoconus: primum non nocere

Eye (2018) 32, 4–6; doi:10.1038/eye.2017.256; published online 1 December 2017

Prior to the mainstream introduction of corneal collagen cross-linking (CXL) in the late 2000s, there was no effective treatment to prevent progression of keratoconus, other than corneal grafting procedures, which may in some cases just serve to delay progression.¹ Over the last 15 years, however, there has been a significant shift in paradigm, with CXL emerging as an effective modality to prevent progression of ectatic disease. Whilst there is a significant body of evidence to support the scientific and clinical outcomes of CXL, we feel it is prudent to be mindful of the risks we expose our patients to, and it is important to be aware that whilst well-designed protocols do exist for CXL, it is still largely carried out in an unregulated manner.²

The presentation, rate, and end stage of keratoconus can vary greatly between affected individuals, though severity and age at presentation are recognised to be important. The risk factors for development of keratoconus are well described with ethnicity, family history, genetic susceptibility, eye rubbing, and syndromic associations all recognised to contribute to the development of keratoconus. The involvement of eye rubbing is supported by scientific literature, with an underlying hypothesis of trauma induced injury, subsequent involvement of inflammatory mediators in the wound-healing response, and an increased rate of keratocyte apoptosis.^{3,4}

Although progression of keratoconus is generally accepted to be reflected by an increasing steepness of corneal curvature, with attendant reduction in uncorrected visual acuity, no definite criteria for progression of keratoconus currently exist. Whilst in most studies an increase of greater than 1.0 dioptre (D) of keratometry is considered to represent significant progression of keratoconus, we must

consider a number of other factors. Topographic artefacts due to contact lens molding must always be avoided where possible, which can be achieved by at least 2 to 3 weeks rest from rigid gas permeable lens wear. Data quality of tomographic and topographic scans should be rigorously checked and the effect of tear film pooling, dryness and blinking should be addressed. Repeatability of topographic indices in keratoconus is recognised to be reduced in comparison to a healthy cornea, and so we should set our criterion of increased keratometry with this in mind.^{5,6} Certainly, in advanced keratoconus (maximum Keratometry >55 D) keratometric measurements are known to be even less reliable, and in these groups a >2.5 D increase in keratometry is likely to represent a real progressive change.⁷ Last of all, no consensus exists on decreasing corneal thickness as a criterion for progression detection.

Once progression of keratoconus is established, CXL may be offered to a patient. It is not unusual for both children and young adults to undergo immediate CXL at the first diagnosis of keratoconus. The effect of age on progression of keratoconus is uncertain, however, and no firm parameters exist to guide us on when to offer CXL, though an upcoming randomised controlled trial recruiting 10–16-year olds will hopefully shed light on this area. Commitment of patients to regular follow up, and the presence of a corneal graft in the fellow eye may also guide us on when to offer CXL. In addition, the evaluation and treatment of allergic eye disease and habitual eye rubbing should also play a role in the decision-making process. Inability to control itching and stop eye rubbing, especially knuckling, may guide us towards earlier treatment, while it is also very important to control ocular atopy before CXL to reduce complications such as scarring, infection and keratitis.⁸

While a significant amount of evidence exists for the use of CXL in the treatment of keratoconus, it is still acknowledged that there is

a lack of large well designed randomised controlled trials in this area. A Cochrane review in 2015 by Sykakis *et al* concluded that patients treated with CXL were less likely to encounter the well described complications of keratoconus. We must, however, consider that most follow-up periods in existing randomised controlled trials remain less than 6 to 18 months, which is likely to be too short a time to give an indication as to the long-term safety and efficacy of CXL. Certainly, there are only a handful of published prospective case series with follow-up greater than 5 years and none yet beyond 10 years.^{9–11}

Complications following CXL, both in the short and medium term, are well described. Corneal collagen cross-linking must be avoided in those with active ocular surface disease, poor wound healing, thin corneae, significant corneal scarring and previous herpes simplex infection to reduce the incidence of such problems. Sight-threatening complications include corneal scarring, endothelial damage and ulcerative keratitis, both infective, with bacterial, viral and acanthamoebic infections all described, and non-infective, with some rare reports of patients requiring penetrating keratoplasty after CXL.¹² There is some *in vitro* evidence to suggest that UVA damage to limbal stem cells may occur during CXL, with the long-term implications of such changes, in terms of mutagenesis and stem cell failure, still unknown due to limited published patient follow-up.^{13,14}

A further important and critical long term consideration of undertaking corneal collagen cross-linking is the possibility of treatment failure, with a 7.6% failure rate described in one study by Koller *et al*.¹⁵ We must also consider that shape stabilisation may occur naturally at a certain time point in keratoconus, especially after the age of 35 years. In addition, as the clear majority of published studies of CXL have short follow-up of <2 years, it is not unlikely that we are not seeing a true representation of CXL failure rate which may not become apparent until a few years after the procedure.

While it is clear that CXL plays an important role in the armamentarium of an anterior segment surgeon and has completely altered our management approach to our keratoconic patients, there is still 15 years after its inception a deficiency of standardised and evidence based guidance on who, when and how to cross-link. The definition of progression and therefore the time point at which to crosslink remains ever uncertain. Large scale, long-term, randomised trials investigating progression and timing of CXL are still lacking. As such we would advocate caution in offering treatment to adult patients with keratoconus at presentation. The treatment of allergic eye disease and measures to stop eye rubbing, and clear documentation of progression are

important pre-requisites before such patients undergo CXL.

Conflict of interest

The authors declare no conflict of interest.

References

- Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol* 2003; **135**(5): 620–627.
- Sykakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S *et al*. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev* 2015; **24**(3): CD010621.
- Sugar J, Macsai MS. What Causes Keratoconus? *Cornea* 2012; **31**(6): 716–719.
- McMonnies CW. Abnormal rubbing and keratectasia. *Eye Contact Lens* 2007; **33**(6 Pt 1): 265–271.
- Flynn TH, Sharma DP, Bunce C, Wilkins MR. Differential precision of corneal pentacam HR measurements in early and advanced keratoconus. *Br J Ophthalmol* 2016; **100**: 1183–1187.
- Hashemi K, Guber I, Bergin C, Majo F. Reduced precision of the Pentacam HR in eyes with mild to moderate keratoconus. *Ophthalmology* 2014; **122**: 211–212.
- Cassagne M, Pierne K, Galiacy SD, Asfaux-Marfaing MP, Fournié P, Maleceze F. Customized topography-guided corneal collagen cross-linking for keratoconus. *J Refract Surg* 2017; **33**: 290–297.
- Yeniad B, Alparslan N, Akarçay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea* 2009 May; **28**(4): 477–479.
- Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology* 2014; **121**(4): 812–821.
- O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *Br J Ophthalmol* 2011; **95**: 1519–1524.
- Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg* 2011; **37**: 149–160.
- 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**, pp 922–926.
- Moore JE, Schirotli D, Tara Moore CB. Potential Effects of corneal cross-linking upon the limbus. *Am J Ophthalmic* 2012; **154**(6): 922–926.
- Dhawan S, Rao K, Natrajan S. Complications of corneal collagen cross-linking. *J Ophthalmol* 2011; **2011**: 869015.
- Koller T., Mrochen M., Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg* 2009; **35**: 1358–1362.

H Oliphant^{1,2}, M Zarei-Ghanavati^{1,3}, A Shalaby Bardan^{1,4}, A Vasquez-Perez¹, D O'Brart⁵ and C Liu^{1,2,6}

¹Sussex Eye Hospital, Brighton & Sussex University
Hospitals NHS Trust, Brighton, UK

²Brighton and Sussex Medical School, BSMS Teaching
Building, University of Sussex, Falmer, Brighton, UK

³Eye Research Center, Farabi Eye Hospital, Tehran
University of Medical Sciences, Tehran, Iran

⁴Faculty of Medicine, University of Alexandria,
Alexandria, Egypt

⁵Department of Ophthalmology, Guy's and
St. Thomas' NHS Foundation Trust, London, UK

⁶Tongdean Eye Clinic, Hove, UK

Correspondence: C Liu, Sussex Eye Hospital, Brighton
and Sussex University Hospitals NHS Trust, Eastern
Road, Brighton, BN2 5BF, UK,
Tel: +44 (0)1273 696955;
E-mail: cscliu@aol.com