Summary Statement from the HTA centre of the Region Västra Götaland in Sweden

Corneal Crosslinking in Keratoconus

Question at issue:
Is corneal crosslinking (CXL) effective in stabilizing the cornea in keratoconus and in preventing the need for corneal transplants?

PICO

P = Patients (Caucasian) with keratoconus who have not been surgically treated
I = Corneal cross linking (CXL)
C = Contact lenses, no treatment, other treatment
O = Number of corneal transplants, curvature of the cornea (K max, K average, corneal radius), visual acuity, complications, side effects.

Summary of the health technology assessment:

Method and patient category:
Keratoconus is a noninflammatory, asymmetrical, progressive corneal ectasia caused by biomechanical instability of the corneal stroma. The result is induced myopia and irregular astigmatism leading to reduced vision. Treatment modalities are primarily glasses and or contact lenses. However, it has been estimated that one out of five patients will progress to such an extent that a corneal transplant is necessary to regain useful vision. Corneal crosslinking (CXL) is an intervention that strengthens the corneal tissue and, thereby, can block progression of keratoconus in the progressive phase.

Level of evidence:
The systematic literature search identified two randomised, controlled trials (RCTs) and five non-randomised, controlled observational studies reporting the effects of CXL on keratoconus. The follow-up ranged from three to 24 months. Both RCTs were of low-to-moderate quality. One of the controlled observational studies was of moderate and the other four were of low scientific quality.

Corneal transplantation
No study has reported the incidence of corneal transplantations in patients with progressive keratoconus. There are no available long-term follow-up studies of patient series that can answer whether CXL will reduce the need of corneal transplants or not.

Curvature of the cornea
Two RCTs and four observational studies reported the effect of CXL on the distortion and bow of the cornea. A fifth observational study has reported the effect of CXL without prior removal of the corneal epithelium. The studies have used various measurements of the curvature of the cornea. All reported a slight improvement over time in treated eyes in paired analyses, i.e. in statistical comparisons of the status of the eye preoperatively with the status postoperatively after follow-up. In contrast, in the untreated control study groups (i.e. fellow eyes) the keratoconus progressed significantly in two out of four studies (paired analysis within group). Only two studies compared CXL-treated eyes with control eyes.

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In this latter comparison there was no difference between groups in the observational study in which CXL was performed without prior removal of the epithelium, whereas the other study (of low quality) reported a significant effect by CXL.
The level of evidence in support of blocked progression of keratoconus by CXL versus no treatment is very low (GRADE ⊕).

Uncorrected distance visual acuity (UDVA)

Only one RCT compared the difference between CXL-treated eyes and control eyes. There was no statistical difference between these two groups after three months of follow-up. Three observational studies reported a slight improvement in paired analyses, i.e. within the treated before and after CXL.
The level of evidence to support an improvement of UDVA by CXL compared to no treatment is very low (GRADE ⊕).

Corrected distance visual acuity (CDVA)

Only one RCT compared the difference between CXL-treated eyes and control eyes. There was no statistical difference between these two groups after three months of follow-up. Four observational studies and one RCT reported a slight improvement in paired analyses, i.e. within the treated before and after CXL.
The level of evidence to support an improvement of CDVA by CXL compared to no treatment is very low (GRADE ⊕).

Side effects and complications:

Postoperative infections have been reported at a low incidence in patients where a soft contact lens has been used the first days after surgery. Transient haze may occur during the first postoperative month. Both of these complications are rare.

Ethical aspects:

There is a substantial patient benefit if CXL proves to be effective in preventing, or postponing, a corneal transplant in a young patient.
There is a risk of over treatment since at the present time adequate patient selection for CXL is not defined.

Economical aspects

The direct costs for the health care system for the treatment of keratoconus patients is lower with CXL treatment in comparison to the present costs of corneal transplantation.

Concluding remarks

Corneal crosslinking is simple, rather inexpensive, and associated with a very low frequency of complications that are not severe. The level of evidence of a potential beneficial effect of CXL to stabilise progressive keratoconus is very low (GRADE ⊕). There is no documentation on whether CXL may prevent the need for future corneal transplants.

On behalf of the Regional HTA Centre of the Western Region in Sweden
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