Corneal Collagen Cross-Linking

Policy Number: 9.03.28  Last Review: 05/2016
Origination: 5/2016  Next Review: 05/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Corneal Collagen Cross-Linking. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Corneal collagen cross-linking is considered investigational for all indications.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>▪ With keratoconus</td>
<td>▪ Corneal collagen cross-linking</td>
<td>▪ Observation</td>
<td>▪ Change in disease status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Penetrating keratoplasty</td>
<td>▪ Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Treatment-related morbidity</td>
</tr>
</tbody>
</table>

Corneal collagen cross-linking (CXL) is a photochemical procedure that is being evaluated as a method to stabilize the cornea in patients with progressive keratectasia such as keratoconus and pellucid marginal degeneration. CXL may also have anti-edematous and antimicrobial properties.

The evidence for corneal collagen cross-linking in individuals who have keratoconus includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. There is evidence from RCTs, including several pivotal trials, that CXL leads to short-term improvements in corneal steepening and visual acuity compared with untreated eyes, and results from 1 trial have reported that benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL is able to reduce, and in some cases, reverse the corneal steepening that leads to a reduction in visual acuity in the short term. There is greater uncertainty about the long-term outcomes of CXL for the treatment of keratoconus. Some retrospective studies report positive outcomes out to 10 years, although these reports are limited by the small sample size at long-term follow-up and limited information on the entire population of patients treated with CXL during the same time period. There is a need for prospective studies with larger
numbers of patients that are followed over many years to determine whether CXL improves longer-term outcomes. Several trials are ongoing, and results from these other trials are expected soon. Longer-term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. Although one device is currently under U.S. Food and Drug Administration (FDA) review, no CXL devices have received FDA approval at this time. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Corneal collagen cross-linking (CXL) is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UV-A) irradiation. A common CXL protocol removes about 8 mm of the central corneal epithelium under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1-3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with 370 nm ultraviolet A, a maximal wavelength for absorption by riboflavin, together with the continued application of riboflavin. The interaction of riboflavin and UV-A causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules that results in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-micron thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to a UV dose that is above the cytotoxic threshold.

CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus. CXL may also have anti-edematous and antimicrobial properties.

Keratoconus is a bilateral dystrophy that is characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. While frequently diagnosed at a young age, the progression of keratoconus is variable. Initial treatment often consists of hard contact lenses. A variety of keratorefractive procedures have also been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or LASIK, but in general, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (see evidence review 9.03.14) is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for penetrating keratoplasty. Penetrating keratoplasty (ie, corneal grafting) is the last line of treatment. About 20% of patients with keratoconus will require corneal transplantation. All of these treatments attempt to improve the refractive errors, but are not disease-modifying. In contrast, CXL has the potential to slow the progression of disease.

Pellucid marginal degeneration is a noninflammatory progressive degenerative disease, typically characterized by bilateral peripheral thinning (ectasia) of the
inferior cornea. Deterioration of visual function results from the irregular astigmatism induced by asymmetric distortion of the cornea, and visual acuity typically cannot be restored by using spherocylindrical lenses. Rigid gas permeable contact lenses may be used to treat pellucid marginal degeneration. Intrastromal ring segment implantation, crescentic lamellar keratoplasty, penetrating keratoplasty, and corneal wedge excision have also been proposed.

**Regulatory Status**
No ultraviolet A (UV-A) devices for treatment of keratoconus are currently approved by the U.S. Food and Drug Administration. A search of online site ClinicalTrials.gov showed ongoing phase 3 safety and efficacy trials of UV-A Illumination Systems by Topcon Medical (VEGA) and Avedro Inc. (KXL or UV-X). FDA has granted Avedro a priority review of their new drug application (NDA) for the riboflavin ophthalmic solution/KXL II™ system as an orphan drug (<200,000 individuals affected in the United States). If approved, Avedro would have 7 years of market exclusivity in the United States.

**Rationale**
This evidence review was created in 2012 and has been updated periodically using the MEDLINE database. The most recent literature update was performed through January 29, 2016.

**Natural History of Keratoconus**
The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a multicenter long-term observational study of the natural history of keratoconus. Two reports were published from the CLEK study in 2006 that showed slow changes over 7 years of follow-up.(1,2) Davis et al reported changes in high- and low-contrast visual acuity from 953 patients (1855 eyes).(1) Over a period of 7 years, there was a decrease of 2 high- and 4 low-contrast letters. High-contrast visual acuity decreases of 10 or more letters occurred in 19.0% of patients; low-contrast visual acuity decreases of 10 or more letters occurred in 30.8% of patients. McMahon et al reported longitudinal changes in corneal curvature over 8 years of follow-up in 1032 patients.(2) The slope for First Definite Apical Clearance Lens (FDACL) was 0.18 diopters (D) per year, and the slope for flatter keratometric reading (Flat K) was 0.20 D per year. These translated into mean increases of 1.44 D in FDACL and 1.6 D in Flat K during the 8-year follow-up period. Close to 25% of patients had projected increases of 3 D or more in FDACL, while 24% had projected increases of 3 D or more in Flat K.

**Corneal Collagen Cross-Linking**
Evidence on whether corneal collagen cross-linking (CXL) improves health outcomes for patients with progressive keratoconus includes systematic reviews and 5 randomized controlled trials (RCTs), 3 of which were regulated by the U.S. Food and Drug Administration (FDA) under a new drug application (NDA). In addition, there are a number of prospective controlled studies as well as uncontrolled trials that report on longer term outcomes of the procedure.(3,4) The main health outcome for CXL treatment is improvement, or stabilization, of visual
acuity. Other outcomes commonly reported in trials of CXL include physiologic measures, such as the steepness of the corneal curvature measured by maximum keratometry (K-max) and/or the manifest refraction spherical equivalent (MRSE). These are intermediate outcomes that may corroborate whether improvements in visual acuity correlate with physiologic changes.

**Systematic Reviews**

A Cochrane review on the use of CXL for treating keratoconus was published in 2015.(5) The literature search for this systematic review was conducted in August 2014 and does not include all of the phase 3 trials that were submitted to the FDA (described next).

**Randomized Controlled Trials**

Data submitted to FDA under the NDA for riboflavin ophthalmic solution/KXL® came from 3 RCTs with a total sample size of 640 patients.6 Results from one of the trials were published in 2011 and 2012.(7,8) Each of the phase 3 trials was a parallel group, open-label trial in patients with keratoconus or corneal ectasia due to LASIK or photorefractive keratectomy. Sham-control eyes were treated with a topical anesthetic and riboflavin solution (1 drop every 2 minutes for 30 minutes) but did not undergo epithelial débridement or have the ultraviolet A (UV-A) light source turned on. The primary outcome was a 1 D difference in the mean change in K-max (progression of steepening) between the CXL and control groups at 12 months. Control patients could cross over to CXL at 3 months, and missing data were analyzed by last observation carried forward (LOCF). Ninety-nine percent of control patients had crossed over by 12 months. LOCF analysis is a conservative method of analysis in this situation, because it reduces the expected worsening over time in untreated patients. In the pooled analysis of patients with keratoconus, steepening worsened by 1.0 D in the control group and improved by 1.6 D in the CXL group, for a total difference between groups of 2.6 D. CXL resulted in either stabilization or improvement in K-max in 72% of keratoconus patients. In the sham control group, there was no statistically significant change in K-max. The mean improvement in best-corrected visual acuity (BCVA) was 5.6 letters following CXL compared with 2.0 letters for controls (p=0.009). Although this difference is not typically considered clinically significant, it is limited by the use of 3-month data for many of the patients in the control group, which would minimize between-group differences over time. The proportion of patients who had a clinically significant 3-line or greater improvement in BCVA was 19.4% for the CXL-treated patients and 8.1% for controls. Treatment-related adverse events were generally transient, mild, and expected based on the epithelial débridement and corneal remodeling.

Wittig-Silva et al reported the first RCT of corneal CXL in 2008.(9) Three-year results were published in 2014.(10) Recruitment for the trial was completed in 2009 with 50 eyes randomized to CXL and 50 randomized to untreated control. To be eligible for enrollment, clear evidence of progression of ectasia over the preceding 6 to 12 months was required. Progression was confirmed if at least one of the following criteria were met: an increase of at least 1.00 D in the steepest simulated keratometry reading (K-max); an increase in astigmatism determined
by manifest subjective refraction of at least 1.00 D; an increase of 0.50 D in MRSE; or a 0.1 mm or more decrease in back optic zone radius of the best fitting contact lens. At the time of analysis for the 2008 report, 20 eyes had reached 1-year follow-up. The 3-year results included 46 CXL and 48 control eyes. LOCF was used for 26 eyes, including 17 eyes from the control group with progressive disease that underwent compassionate use CXL or corneal transplantation. In the CXL group, there was a flattening of K-max by -1.03 D, compared with an increase in K-max of 1.75 in the control group. One eye in the CXL group progressed by more than 2.0 D, compared with 19 eyes in the control group. Uncorrected visual acuity (UCVA) and BCVA improved in the CXL-treated eyes at 1, 2, and 3 years. In control eyes, UCVA was significantly reduced at 36 months and there was a trend of a decrease in BCVA (p=0.10). The difference between groups in UCVA was statistically significant. Follow-up is continuing through 5 years.

In 2012, Renesto et al reported results of a randomized trial that compared CXL versus 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus. After 3 months, all patients received intrastromal corneal ring segments (ICRS; see evidence review 9.03.14). Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12, and 24 months after ICRS insertion. There was no significant difference between the 2 groups for UCVA, BCVA, or in 3 topographic parameters (flattest-K, steepest K, and average keratometry) throughout the 24-month follow-up.

**Uncontrolled Studies**

Longer term follow-up is being reported from Europe, where the procedure has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in K-max by at least 1 D in 1 year), deteriorating visual acuity, or the need for new contact lens-fitting more than once in 2 years. The largest and longest series to date are described next.

In 2008, Raiskup-Wolfe et al reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 months of follow-up. This was of a total of 488 eyes (272 patients) with progressive keratoconus and a corneal thickness of at least 400 μm treated at their center in Germany. Follow-up examinations were performed at 1, 6, and 12 months, and then annually. Mean follow-up was 26 months with a range of 12 months (n=142) to 6 years (n=5). In the first year (n=142), steepening (K-max) improved or remained stable in 86% of eyes, and BCVA improved by at least 1 line in 53% of the eyes. Three years after treatment (n=33), K-max improved by a mean of 2.57 D in 67% of eyes while BCVA improved by at least 1 line in 58% of eyes. In 2015, the same group published 10-year follow-up of CXL treatment in 34 eyes (24 patients) with progressive keratoconus. Mean patient age at the time of treatment was 28 years (range, 14-42 years). Corneal steepening improved slightly between baseline and 10-year follow-up (p<0.001), while corrected distance visual acuity improved by 0.14 logMAR (p=0.002). Two eyes had repeat CXL, one at 5 years and one at 10 years, without adverse sequelae. One of the 34 eyes treated developed a permanent corneal scar. These studies are limited by the retrospective nature and the small number of cases with extended follow-up.
A 2010 publication from the Siena Eye Cross Study reported a 52-month mean follow-up (range, 48-60) on their first 44 keratoconic eyes treated with CXL. Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after CXL. Topographic analysis showed a mean K reading reduction of -1.96 D after 1 year, -2.12 D after 2 years, -2.24 D after 3 years, and -2.26 D after 4 years of follow-up. By comparison, in fellow eyes untreated for the first 24 months, the mean K value increased by 1.2 D at 1 year and 2.2 D at 2 years. In treated eyes, UCVA improved by a mean of 2.41 lines after 12 months, 2.75 lines after 24 months, 2.80 lines after 36 months, and 2.85 lines after 48 months. There was no significant decrease in endothelial cell density, central corneal thickness, or intraocular pressure over follow-up.

Temporary adverse effects included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent adverse effects were observed.

A 2012 publication from the Siena CXL Pediatrics trial reported 12- to 36-month follow-up after CXL in 152 patients aged 18 years or younger with keratoconus progression. Visual acuity increased by an average of 0.15 Snellen lines, whereas a clinically relevant change is generally considered to be 2 Snellen lines.

One of the oldest reports is from the French National Reference Center for Keratoconus in 2011. Of 142 eyes enrolled in the study, 6-month follow-up was available for 104 (73%), and 12-month follow-up was available for 64 (45%). At 12 months after treatment, the BCVA had stabilized in 48% of eyes, improved in 40%, and decreased in 12%. Keratoconus progression had stopped in 69%, and K-max had decreased by more than 2.0 D in 21% of eyes. There was a 7% complication rate in the total sample, with 5 eyes (3.5% of 142 or 7.8% of 64) losing more than 2 Snellen lines of visual acuity. This retrospective study is limited by the low proportion of patients available at 12-month follow-up.

**Adverse Events**

Reported adverse events are relatively uncommon, but precise rates of adverse events are not available because of the lack of large studies with long-term follow-up. Adverse events reported to date include corneal endothelial damage, stromal haze, corneal melt, keratitis, gaping of corneal incisions, and corneal scarring.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary of Evidence
The evidence for corneal collagen cross-linking in individuals who have keratoconus includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. There is evidence from RCTs, including several pivotal trials, that CXL leads to short-term improvements in corneal steepening and visual acuity compared with untreated eyes, and results from 1 trial have reported that benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL is able to reduce, and in some cases, reverse the corneal steepening that leads to a reduction in visual acuity in the short term. There is greater uncertainty about the long-term outcomes of CXL for the treatment of keratoconus. Some retrospective studies report positive outcomes out to 10 years, although these reports are limited by the small sample size at long-term follow-up and limited information on the entire population of patients treated with CXL during the same time period. There is a need for prospective studies with larger numbers of patients that are followed over many years to determine whether CXL improves longer-term outcomes. Several trials are ongoing, and results from these other trials are expected soon. Longer-term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. Although one device is currently under U.S. Food and Drug Administration (FDA) review, no CXL devices have received FDA approval at this
time. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 1 academic medical center (2 reviewers) while this policy was under review in 2012. The input from all reviewers was mixed, noting the limited literature and lack of Food and Drug Administration (FDA) approval for this procedure, although there are ongoing FDA-regulated clinical trials. The reviewers also commented on the lack of alternatives to slow the progression of disease and that data indicate that the procedure is safe and effective enough to offer to patients with adequate informed consent under an investigational protocol.

**Practice Guidelines and Position Statements**

In 2013 the National Institute for Health and Care Excellence issued an Interventional Procedure Guideline (IPG 466) that replaced the 2009 IPG 320.(20) The new IPG now stratifies their recommendations for corneal CXL as follows:

“Most of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off' CXL. 'Epithelium-on (transepithelial) CXL' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows:

1.1 Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit.
1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research.”

Information on CXL and ongoing trials is provided by the National Keratoconus Foundation.(21)
**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


**Billing Coding/Physician Documentation Information**

| 0402T | Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed) |

**ICD10 Codes**

| H18.601 | Keratoconus code range |
| H18.629 |
| H18.711 | Corneal ectasia code range |
| H18.719 |

Effective in 2016, there is a specific CPT category III code for this service: 0402T: Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)

Prior to 2016, there were no specific CPT codes for this treatment. It would have been reported using CPT code 66999 - unlisted procedure, anterior segment of eye.

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

5/1/16 New Policy; considered investigational.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.