BlueCross BlueShield Federal Employee Program.

9.03.28 Corneal Collagen Cross-Linking

Last Review: September 2016
Next Review: September 2017

Effective Date: October 15, 2016

Related Policies

9.03.05 Corneal Topography/Computer-Assisted Corneal Topography/Photokeratoscopy

Corneal Collagen Cross-Linking

Summary

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 and has been evaluated for the treatment of bullous keratopathy and infectious keratitis.

The evidence for corneal CXL 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 these benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short term. Greater uncertainty exists regarding the long-term outcomes of corneal CXL for the treatment of keratoconus. Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with corneal CXL during the same time period. There is a need for prospective studies with larger numbers of patients who are followed over many years to determine whether corneal CXL improves longer-term outcomes. Several trials are ongoing, and their results are expected soon. Longer-term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. One device has received U.S. Food and Drug Administration (FDA) approval. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

FDA REGULATORY STATUS

In April 2016, Avedro,Inc. received approval from the U.S. Food and Drug Administration (FDA) for the combined drug and device system for Photrexa Viscous, Photrexa and the KXL System. Photrexa Viscous and Photrexa are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus.

Avedro's riboflavin ophthahnic solutions are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran and act as a photosensitizer. Avedro's KXL® system is a UVA inadiation system that uses a light emitting diode (LED) to deliver a dose of UVA light to

a targeted treatment area for illuminating the cornea during corneal collagen cross-linking. The KXL System delivers a spectral output of 365 ± 10 nm with an illumination intensity of 3.0 mW/cm2 and a treatment time of 30 minutes.

POLICY STATEMENT

**This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims*

Corneal collagen cross-linking using the FDA approved drugs and device for the treatment of progressive keratoconus is considered **medically necessary.**

RATIONALE

Natural History of Keratoconus
The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a multi-center 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 (1,855 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 1,032 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 corneal 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. 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 corneal CXL for the treatment of 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 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 III 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 debridement or have the ultraviolet A (UVA) 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 debridement 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. (11) After 3 months, all patients received intrastromal corneal ring segments (ICRS, see policy No. 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 uncorrected visual acuity (UCVA), BCVA or in 3 topographic parameters (flattest-K, steepest K, and average keratometry) throughout the 24 months of 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. (12) 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. (13) Mean patient age at the time of treatment was 28 years (range, 14-42). 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. (14) 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. (15) 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. (16) 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. (17-19)

Summary of Evidence

The evidence for corneal CXL 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 these benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short term. Greater uncertainty exists regarding the long-term outcomes of corneal CXL for the treatment of keratoconus. Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with corneal CXL during the same time period. There is a need for prospective studies with larger numbers of patients who are followed over many years to determine whether corneal CXL improves longer-term outcomes. Several trials are ongoing, and their results are expected soon. Longer-term outcomes from large cohorts will also be

useful to evaluate potential long-term complications of this new treatment approach. One device has received U.S. Food and Drug Administration (FDA) approval. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Ongoing and Unpublished Trials

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01972854[a]	A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus	206	Mar 2016
NCT01344187[a]	A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus	226	Dec 2016
NCT01604135	Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial	200	May 2017
NCT01672814	A Randomized, Controlled Study of the Vedera™ KXS Microwave System With Corneal Collagen Cross-Linking Compared With Corneal Collagen Cross-Linking Alone for Eyes With Keratoconus	130	Aug 2017
NCT00560651	German Corneal Cross-Linking Registry	7500	Nov 2017
Unpublished			
NCT01459679	A Multi-Center, Randomized, Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus or Corneal Ectasia After Refractive Surgery	4000	Jan 2016 (terminated)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

In 2013 the National Institute for Health and Care Excellence issued an Interventional Procedure Guideline (IPG 466) (20) that replaced the 2009 IPG 320. 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 corneal cross-linking and ongoing trials is provided by the National Keratoconus Foundation. (21)

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

No national coverage determination.

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POLICY HISTORY

Date	Action	Description
September 2012	New Policy	
June 2013	Update Policy	Policy updated with literature review. References 5, 6, 11 added. Policy statement unchanged.
June 2014	Update Policy	Policy updated with literature review, adding reference 4. The policy statement is unchanged.
June 2015	Update Policy	Policy updated with literature review through February 25, 2015; references 3-4 and 11 added; policy statement unchanged.
September 2016	Update Policy	Policy updated with literature review, references 4-5 added. Regulatory status updated with FDA approval information. Policy statement changed to medically necessary.