Medical Policy Manual

**Topic:** Corneal Collagen Cross-Linking

**Section:** Medicine

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Corneal collagen cross-linking (CXL) is a procedure performed in the outpatient setting using topical anesthesia with the photosensitizer riboflavin (vitamin B2) and ultraviolet-A (UVA) irradiation done to increase corneal rigidity and stability for a number of corneal conditions.

**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, while the riboflavin continues to be applied. The interaction of riboflavin and UV-A causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules, resulting 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 laser in situ keratomileusis (LASIK), although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments 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 (i.e., 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, corneal CXL has the potential to slow the progression of disease.

Ectasia (also known as keratectasia, iatrogenic keratoconus or secondary keratoconus) is a serious long-term complication of LASIK surgery. Reported treatments for the management of post-LASIK ectasia include hard contact lenses, intraocular pressure-lowering drugs, and intracorneal ring segments. Frequently, a penetrating keratoplasty is required.

There are two different methods of cross-linking the collagen in the cornea. According to the National Institute for Health and Care Excellence (NICE) regarding the different variations of the collagen corneal cross-linking (CXL) procedure:[1]

1. **Epithelium-off CXL** (also known as “epi-off”): the epithelium is first removed or weakened, typically by abrasion, to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure. The corneal surface is exposed to UVA radiation: precise timings and treatment protocols vary. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on 1 eye at a time and may also be repeated if needed.

2. **Epithelium-on** (also known as “epi-on” or transepithelial) CXL: the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

Currently the only FDA-approved CXL treatment is the KXL® system (Avedro), which is only indicated using the epithelium-off method. There are no FDA approved CXL treatments using the epithelium-on method of CXL.

Other procedures performed to address various corneal conditions, including keratoconus, include:

1. **Photorefractive keratectomy (PRK)** is a refractive surgical procedure involving the reshaping of the surface of the cornea with an excimer laser for correction of refractive errors (e.g., myopia, hyperopia, astigmatism, and presbyopia) in persons with otherwise non-diseased corneas.
2. Intrastromal Corneal Ring Segments (INTACS) are flexible rings that come in different sizes that are inserted beneath the surface of the cornea to elevate the edge of the cornea. This procedure flattens the front of the eye, decreasing nearsightedness.

3. Phakic Implantable Contact Lenses (IOLs) are thin lenses implanted permanently into the eye to help reduce the need for glasses or contact lenses. Phakic refers to the fact that the lens is implanted into the eye without removing the eye's natural lens. During phakic lens implantation surgery, a small incision is made in the front of the eye and the lens is inserted through the incision and placed just in front of or just behind the iris.

### Regulatory Status

In April 2016 the US Food and Drug Administration (FDA) has approved a riboflavin ophthalmic solution (Photrex and Photrex Viscous, Avedro) in combination with the company's particular UVA irradiation device, marketed as the KXL® system (Avedro), for the treatment of progressive keratoconus. The KXL® system is used to perform corneal collagen cross-linking using Photrex (riboflavin 5'-phosphate ophthalmic solution) 0.146% for topical ophthalmic use or Photrex Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% for topical ophthalmic use with UV-A (NDA 203324). The FDA clinical trials that served as a basis for the FDA approval of the KXL System indicated that all 640 patients were treated with the "epithelium-off" CXL method. Also, as indicated in the "Dosage and Administration" section of the NDA document: the first step in the protocol is to debride the epithelium, which is the epithelium-off method.

In July 2016 the NDA was amended and the approval was extended for the use of the KXL System for the treatment of corneal ectasia following refractive surgery.

The KXL® system has not been approved for the use of infectious keratitis, corneal ulcers, or any other indication.

In addition, there have been FDA trials for the VEGA system (TopCon Medical Systems) that have been terminated based on administrative reasons before the data was analyzed. The status of the VEGA system is currently unknown.

### MEDICAL POLICY CRITERIA

I. Epithelium-off collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary for the treatment of keratoconus and keratectasia (corneal ectasia).

II. Epithelium-on (transepithelial) collagen cross-linking is considered investigational for keratoconus, keratectasia, and all other indications.

III. Any type of collagen cross-linking is considered investigational in all other situations, including but not limited to treatment of infectious keratitis and in combination with other procedures (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) (CXL-plus).
POLICY GUIDELINES

Epithelium-off (also referred to as “epi-off”) CXL is a procedure in which the epithelium is removed or weakened by various methods to allow penetration of riboflavin into the corneal tissue prior to crosslinking with UV-A light. Currently the only FDA-approved CXL treatment is the KXL® system (Avedro), which was approved using the epithelium-off procedure.

Epithelium-on (also known as transepithelial or “epi-on”) CXL is a procedure in which the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

SCIENTIFIC EVIDENCE

Literature Review

Evidence on whether corneal collagen cross-linking (CXL) improves health outcomes for patients with progressive keratoconus includes systematic reviews and six randomized controlled trials (RCTs), three of which were regulated by the U.S. Food and Drug Administration (FDA) under a new drug application (NDA), one of which is unpublished. In addition, there are a number of prospective controlled studies as well as uncontrolled trials that report on longer term outcomes of the procedure.[2,3] 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

In 2016 a systematic review assessed the efficacy and safety of CXL in pediatric patients with keratoconus, including 17 unique articles: 10 articles on epithelium-off cross-linking, 2 on accelerated cross-linking, 2 on transepithelial cross-linking, 1 on both epithelium-off and transepithelial cross-linking, and 2 on transepithelial cross-linking with iontophoresis.[4] The reviewers concluded that epithelium-off cross-linking is both apparently safe and effective when used to prevent keratoconus progression in pediatric patients. However, disease progression occurred in 22% of the treated eyes.

In 2016 a systematic review assessed the efficacy of CXL for the treatment of keratoconus (KCN). A modest, but not significant improvement in visual acuity of 1 to 2 Snellen lines was found three months or more after undergoing CXL.[5] Changes were more pronounced in uncorrected visual acuity. Some secondary outcomes were found to be improved (0.6-1 diopters) 12 to 24 months after CXL, but others were not. The reviewers concluded that although CXL appears to be effective for halting the deterioration of KCN it was only slightly effective at improving visual function.

In 2016 a systematic review assessed the efficacy of CXL in the management of infectious keratitis.[3] Twenty-five studies were included (2 randomized controlled trials, 13 case series, and 10 case reports) with a total of 210 eyes of 209 patients, of which 175 eyes underwent CXL. Proportion of eyes healed with CXL was 87.2% (95% confidence interval (CI), 81.9%, 91.8%). The reviewers concluded that although CXL seems promising in the management of infectious keratitis, more randomized controlled trials are required to assess its efficacy.
A Cochrane review on the use of corneal CXL for the treatment of keratoconus was published in 2015.[6] The literature search for this systematic review was conducted in August 2014 and does not include the three unpublished phase 3 trials that were submitted to FDA (described below). The review included three small RCTs conducted in Australia, the United Kingdom, and the United States that enrolled a total of 225 eyes and analyzed 219 eyes.[7-9] The total number of people enrolled was not clear in two of the studies. Only adults were enrolled into these studies. Out of the eyes analyzed, 119 were treated with CXL (all using the epithelium-off technique) and 100 served as controls. Only one study had sham treatments for controls. All three studies were at high risk for performance bias (lack of masking), detection bias (only one trial attempted to mask outcome assessment), and attrition bias (incomplete follow-up). It was not possible to pool data due to differences in measuring and reporting outcomes. The overall quality of the evidence was judged to be very low primarily due to downgrading the evidence due to risk of bias in the included studies, imprecision, indirectness and publication bias.

Randomized Controlled Trials

In 2014 Wittig-Silva et al. reported three-year results from the first RCT of corneal epithelium-off CXL in 2008.[9,10] Recruitment for the trial was completed in 2009 with 50 eyes randomized to CXL treatment 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 D in the steepest simulated keratometry reading (K-max); an increase in astigmatism determined by manifest subjective refraction of at least 1 D; an increase of 0.50 D in manifest refraction spherical equivalent; 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-treated 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 D, compared with 19 eyes in the control group. Uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA) improved in the CXL-treated eyes at 1, 2, and 3 years. In control eyes, UCVA was significantly reduced at 36 months (p=0.034) and there was a trend of a decrease in BSCVA (p=0.10). The difference between groups in UCVA was significant (p<0.001), but there was no between group difference in BSCVA. At three-year follow-up the authors concluded that “despite the growing body of literature and continuing efforts to optimize the treatment protocol, there remains a lack of randomized controlled studies with longer-term follow-up to support the widespread clinical use of CXL for keratoconus”.

In 2013 a small randomized trial was published which assessed CXL treatment for pseudophakic bullous keratopathy; however CXL followed by keratoplasty was performed in all 24 patients within the study, limiting any conclusion regarding the safety and efficacy of CXL treatment compared to other methods.[11]

In 2012, Renesto et al reported 2-year results of a randomized trial that compared CXL versus 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus.[12] 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.

Data submitted to FDA under the NDA for riboflavin ophthalmic solution/KXL System came from three RCTs with a total anticipated sample size of 640 patients. Results from the first of the trials were published in 2011 and 2012 (100 eyes in 76 patients) are described below. Each of the phase 3 trials was a parallel group, open-label trial in patients with keratoconus or corneal ectasia due to laser in situ keratomileusis (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 (UVA) light source turned on. The primary outcome was a difference of 1 D or more in the mean change in K-max (progression of steepening) between the CXL group and control group at 12 months. Control patients could cross over to CXL at 3 months; by 12 months, 99% had done so. Missing data were analyzed by last observation carried forward (LOCF), which 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 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. Pooled analysis showed that 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 BCVA was 5.6 letters following corneal CXL compared with 2 letters for sham treatment (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. Although these RCTs had sham-controlled groups for comparison, these sham patients were allowed to crossover into the treated group as early as three months into the study.

In 2011, Hersh and colleagues published one-year results of FDA-approved unblinded sham-controlled clinical of CXL for keratoconus or ectasia in 71 eyes of 58 patients (active treatment), 41 eyes received sham treatment and an additional 30 eyes were included as a “fellow-eye” control group. The control group consisted of a heterogeneous group of eyes from patients who had unilateral CXL treatment (eyes with some evidence of disease, but which may or may not have met study inclusion criteria and eyes without evidence of disease). Patients in the sham control group received riboflavin 0.1% ophthalmic solution without UVA treatment and at three months were given CXL treatment, thus ending the comparative portion of the trial. Visual acuity, refraction, astigmatism and maximum and average keratometry (k) values were primary outcomes. There were no statistically significant differences between treatment and control groups (results for sham and “fellow eye” groups were aggregated) at three months. However, interpretation of these results is limited by the lack of clear target population (results from patients with either keratoconus or ectasia were aggregated into the same treatment group, thus limiting the population to which these results can be generalized). Also, isolation of the impact of CXL on corneal disease requires that any control treatment group be identical to the treatment group in as many aspects as possible with the exception of the treatment itself. Such a heterogeneous control group as included here (the “fellow eye” group) may not allow for the isolation of this treatment effect from normal disease course or other components of care. These factors, along with the lack of comparative study beyond 3 months suggest that these results are inconclusive regarding the impact of CXL on corneal disease and that longer randomized controlled trials are needed to clearly evaluate the impact of this treatment.
Nonrandomized Studies

Longer term follow-up is being reported from Europe, where corneal CXL 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 to be fitted for new contact lenses more than once in two years. The largest and longest series to date are described next.

In 2015, Raiskup published 10-year follow-up of CXL treatment in 34 eyes (24 patients) with progressive keratoconus.\textsuperscript{[15]} 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 after 5 years and one after 10 years, without adverse sequelae. One of the 34 eyes treated developed a permanent corneal. The original study, published in 2008 by the same group, reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 months of follow-up.\textsuperscript{[16]} This was of a total of 488 eyes (272 patients) with progressive keratoconus and a corneal thickness of at least 400 um 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 58% of 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 2014, Said and colleagues published a small (n=40) study which compared corneal collagen cross-linking (CXL) with photoactivated riboflavin to antimicrobial therapy as a treatment of infectious keratitis with corneal melting.\textsuperscript{[17]} Authors reported comparable duration until healing; however the complication rate was 21% (3 patients) in the control group. No incidence of corneal perforation or recurrence of the infection in the CXL group was reported. This study was limited by lack of randomization, small sample size and relatively short-term follow-up.

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.\textsuperscript{[18]} Visual acuity increased by an average of 0.15 Snellen lines, whereas a clinically relevant change is generally considered to be 2 Snellen lines.

The French National Reference Center for Keratoconus published their findings in 2011.\textsuperscript{[19]} 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 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 two or more Snellen lines of visual acuity. This retrospective study is limited by the low proportion of patients available at 12-month follow-up.

A 2010 publication from the Siena Eye Cross Study reported a 52-month mean follow-up (range, 48-60 months) on their first 44 keratoconic eyes treated with CXL.\textsuperscript{[20]} Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after CXL. Topographic analysis showed the following mean K reading reductions: -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.

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. Treatment-related adverse events are generally transient, mild, and expected, based on the epithelial débridement and corneal remodeling. Persistent adverse events have been rarely observed. Adverse events reported to date include corneal endothelial damage, stromal haze, corneal melt, keratitis, gaping of corneal incisions, and corneal scarring.[21-23]

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 one trial have reported that these benefits are maintained at two to three years. In addition, retrospective studies have reported positive outcomes up 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. The available evidence reports that the procedure is generally safe.

Clinical Practice Guidelines

In 2013, the National Institute for Health and Care Excellence (NICE) issued an Interventional Procedure Guideline (IPG 466) that replaced the 2009 IPG 320 and were based on a systematic review of the evidence.[1] 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….”

Summary
There is enough research to show that epithelium-off collagen cross-linking using riboflavin and ultraviolet A improves health outcomes for patients with keratoconus and keratectasia (corneal ectasia). In addition, there are good quality evidence-based clinical practice guidelines that recommend the use of epithelium-off collagen cross-linking using riboflavin and ultraviolet A for the treatment of keratoconus and keratectasia. Therefore, epithelium-off collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary for the treatment of keratoconus and keratectasia.

There is not enough research to show that epithelium-on collagen cross-linking improves health outcomes for patients with keratoconus, keratectasia (corneal ectasia), or any other condition. In addition, evidence-based clinical practice guidelines recommend against the use of epithelium-on collagen cross-linking for the treatment of keratoconus and keratectasia. Therefore, epithelium-on collagen cross-linking is considered investigational for the treatment of any condition, including but not limited to keratoconus and keratectasia.

There is not enough research to show that collagen cross-linking of any type improves health outcomes in patients with infectious keratitis. In addition, there is not enough research to show that collagen cross-linking, when done in combination with other procedures (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) (known as CXL-plus), improves health outcomes in patients with any condition. Therefore, any type of collagen cross-linking, is considered investigational in all other situations, including but not limited to treatment of infectious keratitis and in combination with other procedures (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) (CXL-plus).

REFERENCES


CROSS REFERENCES

None

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