Corneal Collagen Crosslinking

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Instructions for Use

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Related Policies
None

Applicable States

This Medical Policy only applies to the states of Arizona, Maryland, North Carolina, Oklahoma, Tennessee, Virginia, and Washington.

Coverage Rationale

Epithelium-Off Corneal Collagen Crosslinking using riboflavin and ultraviolet A light is proven and/or medically necessary for treating progressive Keratoconus and progressive Corneal Ectasia.

Epithelium-Off Corneal Collagen Crosslinking is unproven and/or not medically necessary for treating all other indications, due to insufficient clinical evidence of safety and/or efficacy.

Accelerated Corneal Collagen Crosslinking is unproven and/or not medically necessary for treating all indications due to insufficient clinical evidence of safety and/or efficacy.

Epithelium-On Corneal Collagen Crosslinking is unproven and/or not medically necessary for treating all indications due to insufficient clinical evidence of safety and/or efficacy.

Corneal Collagen Crosslinking-Plus is unproven and/or not medically necessary for treating all indications due to insufficient clinical evidence of safety and/or efficacy.

Definitions

Accelerated Corneal Collagen Crosslinking (CXL): Accelerated Corneal Collagen Crosslinking is a variation of Epithelium-Off Corneal Collagen Crosslinking or Epithelium-on Corneal Collagen Crosslinking in which the irradiance of ultraviolet A (UVA) light is increased and the procedure duration is decreased (American Academy of Ophthalmology, 2016).

Corneal Collagen Crosslinking Plus (CXL-plus): Corneal Collagen Crosslinking Plus is the performance of Epithelium-off Corneal Collagen Crosslinking or Epithelium-On Corneal Collagen Crosslinking in combination with other refractive eye procedures such as intrastromal corneal ring segments, or topography-guided photorefractive keratectomy (PRK).

Corneal Ectasia: Corneal Ectasia is also referred to as keratectasia.

Epithelium-Off Corneal Collagen Crosslinking (CXL): Epithelium-Off Corneal Collagen Crosslinking is the conventional method of performing the CXL procedure. After de-epithelializing the central (7-9mm) cornea, riboflavin activated by UVA light is used to generate reactive oxygen species that interact with collagen in the corneal stroma. Also referred to as the Dresden Protocol.

Epithelium-On Corneal Collagen Crosslinking (CXL): Epithelium-On Corneal Collagen Crosslinking a modification of Epithelium-off Corneal Collagen Crosslinking in which the corneal epithelium is left intact prior to instilling the eye with riboflavin followed by exposure to UVA light. Also referred to as transepithelial corneal collagen crosslinking.

Keratoconus: Keratoconus is a common corneal disorder in which the central or paracentral cornea undergoes progressive thinning and steepening causing irregular astigmatism (American Academy of Ophthalmology, 2017).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

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

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HCPCS Code	Description
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 ml

Description of Services

The main objective of corneal collagen crosslinking (CXL) is to achieve strengthening of corneal tissue as a means to stop further progression of keratoconus or corneal ectasia. In order to induce cross-links within and between collagen fibers of corneal stroma, long-wave ultraviolet A (UVA) radiation (370 nm) is used combined with a chromophore (riboflavin, vitamin B2). Riboflavin acts as photosensitizer that when exposed to UVA is activated, producing oxygen free radicals that initiate the creation of those new covalent bonds bridging the amino groups of collagen fibrils and possibly other corneal macromolecules such as proteoglycans and nucleic acids. This photopolymerization process results in the increased rigidity of corneal tissue (Galvis et al., 2017).

This procedure aims to decrease progressive visual loss due to the evolution of the pathology and delay or avoid invasive surgical procedures such as corneal transplantation (Mastropasqua, 2015).

In Epithelium-off CXL (also referred to as the Dresden protocol), the cornea is anesthetized after which the epithelium is removed from 7 to 9 mm in diameter and the corneal stroma is saturated with riboflavin for 30 minutes. After the first 30 minutes, the irradiation of the cornea for another 30 minutes begins with UVA light of 3 mW/cm^2 for a total of UVA fluence of 5.4 J/cm^2. During this time additional riboflavin is instilled to the corneal stroma every 5 minutes (Vastardis et al., 2017).

The crosslinking process is mediated by photo oxidation between UVA and riboflavin. UVA activation of riboflavin creates reactive oxygen species that interact with collagen in the corneal stroma. New chemical bonds are formed that increase mechanical strength. The crosslinking may slow or stop ectasia's progression. The standard or conventional procedure, also called the Dresden protocol, is minimally invasive and involves topical anesthesia, debriding the epithelium using aseptic techniques (epithelium-off), followed by instilling of the riboflavin solution at 1 drop every 2 minutes for 30 minutes. Then the eye is irradiated for 30 minutes while continuing the instillation with the riboflavin solution (ECRI, 2018).

Keratoconus is the most common corneal ectatic disease in which the cornea deforms to a more conical shape causing visual impairment (Shalchi et al., 2015).

Corneal ectasia is a noninflammatory condition, the hallmark of which is progressive corneal steepening and thinning. Types of corneal ectasia include keratoconus, pellucid marginal degeneration, keratoglobus, postkeratorefractive ectasia, and wound ectasia after penetrating keratoplasty (PK). Corneal ectasias are associated with decreased uncorrected visual acuity (UCVA), an increase in ocular aberrations, and often a loss of best-corrected distance visual acuity (BCVA). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention (Feder et al., 2013).

Corneal ectasia is a progressive thinning, bulging, or distortion of the cornea that has been associated with refractive surgery, especially laser-assisted in situ keratomileusis (LASIK). Ectasia is a form of keratoconus, a progressive disorder in which the cornea thins and begins to bulge into a cone-like shape. It can significantly affect vision since the altered shape deflects light away from the retina.

Laser in situ keratomileusis (LASIK) is a refractive surgery procedure that reshapes the surface of the cornea with an excimer laser to focus visual images directly onto the retina and improve visual acuity. Post-LASIK corneal ectasis is a serious side effect of refractive surgery that involves progressive thinning and steepening of the central and inferior portions of the cornea (Hayes, 2017).

The concept of accelerated CXL is based on the Bunden–Roscoe reciprocity law, where an overall cumulative dose of riboflavin and UVA light is achieved with treatment parameters set at higher intensity and simultaneous reduction in exposure time (Tsatsos et al., 2014).

After de-epithelializing the central (> 7mm) cornea, riboflavin activated by ultraviolet A light (UVA) is used to generate reactive oxygen species that interact with collagen in the corneal stroma. Riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) is then applied as a photosensitizer, with an initial 5 minute pre-treatment application followed by additional applications every 5 minutes for the duration of the treatment. The UVA treatment is applied at a 1cm distance for a total of 30 minutes, using 370 nm UVA with an irradiance of 3 mW/cm.

The cross-links formed are intended to increase mechanical strength and slow down or stop the progression of ectasia and keratoconus (ECRI, 2018). This is also referred to as the Dresden Protocol.

CXL-plus refers to several combined refractive procedures such as topography-guided photorefractive keratectomy (PRK), intrastromal corneal ring segments (ICRS), and phakic intraocular lens (PIOL) implantation which have been proposed to enhance the CXL result (Andreanos et al., 2017).

Clinical Evidence

Epithelial-Off Corneal Collagen Crosslinking

Keratoconus

In a case series (n=62 eyes), Mazzotta et al. (2018) assessed the 10-year follow-up efficacy and safety of conventional epithelium-off CXL in a population of pediatric patients aged 18 years and younger with progressive keratoconus. According to the authors, the study demonstrated the ability of CXL to slow down keratoconus progression in pediatric patients, improving functional performance. Long-term stability may be correlated with CXL-induced delay in corneal collagen turnover and with spontaneous age-related keratoconus stabilization. A 24% regression rate could be contemplated in the patients who were aged 15 years and younger at the time of inclusion in the treatment protocol. This study is limited by lack of comparison group.

In a prospective, multicenter randomized controlled trial (RCT), Hersh et al. (2017a) evaluated the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of progressive keratoconus (n=205). The treatment group underwent standard CXL and the sham control group received riboflavin alone without removal of the epithelium. The primary efficacy criterion was the change over 1 year of topography-derived maximum keratometry value, comparing treatment with control group. Secondary outcomes evaluated were corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), manifest refraction spherical equivalent, endothelial cell count, and adverse events. In the CXL treatment group, the maximum keratometry value decreased by 1.6 diopters (D) from baseline to 1 year, whereas keratoconus continued to progress in the control group. In the treatment group, the maximum keratometry value decreased by 2.0 D or more in 28 eyes (31.4%) and increased by 2.0 D or more in 5 eyes (5.6%). The CDVA improved by an average of 5.7 logarithm of the minimum angle of resolution (logMAR) units. Twenty-three eyes (27.7%) gained and 5 eyes lost (6.0%) 10 logMAR or more. The UDVA improved 4.4 logMAR. Corneal haze was the most frequently reported CXL-related adverse finding. There were no significant changes observed by the authors in endothelial cell count 1 year after treatment. Corneal collagen crosslinking was effective in improving the maximum keratometry value, CDVA, and UCVA in eyes with progressive keratoconus 1 year after treatment, with an excellent safety profile.

In a systematic review and meta-analysis of CXL in pediatric patients with keratoconus, McAnena et al. (2017) evaluated primary outcomes of uncorrected visual acuity (UCVA) and maximum keratometry (Kmax), and secondary outcomes of best-corrected visual acuity (BCVA), mean refractive spherical equivalent (MRSE), central corneal thickness (CCT) and endothelial cell density (ECD). Standardized mean differences (SMD) and 95% confidence intervals were calculated, comparing baseline values with those at 6, 12 and 24 months. A total of 13 papers, published between May 2011 and December 2014 examining 490 eyes of 401 patients with a mean age of 15.25 (±1.5) years, were included in the qualitative analysis in this review and included both epithelium-on and epithelium-off procedures. . Nine papers were included in the meta-analysis, showing significant improvement in UCVA and BCVA and stable Kmax at 12 months, and stable UCVA, improved BCVA and improved Kmax at 24 months in the standard protocol group UCVA, BCVA and KMax were stable at 12 months in the trans-epithelial group. In conclusion it was found that standard CXL may be effective in halting progression of keratoconus in pediatric patients at 1 year. However, larger, more long-term studies are required to ascertain its effectiveness. However, larger, more long-term studies are required to ascertain its effectiveness. All studies were limited by an observational design, which could introduce a bias in the findings.

Padmanabhan et al. (2017) reported in a case series the long-term outcomes of CXL for progressive keratoconus in pediatric patients. Epithelium-off CXL was performed in 377 eyes of 336 pediatric patients aged 8 to 18 years with progressive keratoconus. Spectacle-corrected distance visual acuity (CDVA), retinoscopy, topography, and tomography were documented preoperatively and postoperatively at 3 months, 6 months, 1 year, and annually thereafter. Follow-up beyond 2 years and up to 6.7 years occurred in 194 eyes. At last follow-up, there was significant improvement in mean CDVA from 0.33 ± 0.22 to 0.27 ± 0.19 logMAR (P ≤ 0.0001), reduction in mean topographic astigmatism from 7.22 ± 3.55 to 6.13 ± 3.28 D (P = 0.0001), mean flattening of 1.20 ± 3.55 diopters in maximum keratometry (Kmax) (P = 0.0002), and mean corneal thinning of 31.1 ± 36.0 μm (P < 0.0001) after CXL. Based on the long-term outcomes, the authors conclude that CXL remains effective in stabilizing keratoconus for longer than 2 years in a majority of pediatric eyes. Flattening of Kmax was greater in moderately advanced keratoconus and central cones. Long-term follow-up beyond 4 years revealed that a few eyes showed features suggestive of reversal of the effect of CXL. The study was limited by lack of comparison group.

Raiskup et al. (2015) reported 10-year outcomes from a retrospective interventional case series of 34 eyes treated with CXL for progressive keratoconus. The mean follow-up, 131.9 ± 20.1 months. The mean apical keratometry (K) value was 61.5 diopters (D) preoperatively and 55.3 D 10 years postoperatively; the decrease was statistically significant (P<.001). The mean values for maximum K (53.2 D and 49.56 D, respectively) and minimum K (47.5 D and 45.5 D, respectively) were also significantly lower (P<.001). The preoperative and postoperative CDVA were statistically significantly different (P=.002). The mean CDVA improved by 0.14 logMAR over preoperatively; the change was statistically significant (P=.002). The endothelial cell count was unchanged. The authors concluded that corneal CXL was effective in treating progressive keratoconus, achieving long-term stabilization of the condition. The findings are limited by lack of comparison group.

Li et al. (2015) conducted a meta-analysis of randomized controlled trials to evaluate the efficacy of CXL for the treatment of keratoconus. The primary outcome measures included changes of topographic parameters, visual acuity, and refraction. Efficacy estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the interested outcomes. A total of six RCTs fulfilling the eligibility criteria were included, with a total of 179 eyes in the CXL

group, and 182 eyes included in the control group. Duration of follow-up ranged from three months to 36 months. In the authors' opinion, their findings indicate that CXL is safe and effective for the treatment of keratoconus, which results in significant reductions in corneal topographic measurements, manifest cylinder error, and improvement in visual outcomes. Further studies with long-term duration and larger sample size will be necessary to conclude in stabilization and absence of iatrogenicity for CXL. This systematic review was limited by lack of clarity on the type of intervention (epithelium on or off) or study participants inclusion criteria.

Wittig-Salva et al. (2014) reported 3 year outcomes after CXL (after the corneal epithelium was removed to a diameter of 8.5mm) in the refractive, topographic, and clinical outcomes from a prospective RCT in 94 eyes with progressive keratoconus. The primary outcome measure was the maximum simulated keratometry value (Kmax). In control eyes (n=48), Kmax increased by a mean of 1.20±0.28 diopters (D), 1.70±0.36 D, and 1.75±0.38 D at 12, 24, and 36 months, respectively (all P <0.001). In treated eyes (n=46) , Kmax flattened by -0.72±0.15 D, -0.96±0.16 D, and -1.03±0.19 D at 12, 24, and 36 months, respectively (all P <0.001). The treated eyes also showed improvements in secondary outcomes which included uncorrected visual acuity (UCVA; measured in logarithm of the minimum angle of resolution [logMAR] units), and best spectacle-corrected visual acuity (BSCVA; measured in logMAR units), as compared to control eyes. At 36 months, there was a sustained improvement in Kmax, UCVA, and BSCVA after CXL, whereas eyes in the control group demonstrated further progression.

Hashemi et al. (2014) reported 5-year results on conventional CXL(epithelium removed) performed on a case series of 32 patients (40 eyes) with progressive keratoconus. After the first year, BCVA, MRSE, and CCT showed no change and stabilized, whereas elevation readings continued to decrease up to 5 years after CXL. Based on the results, the authors concluded that treatment of keratoconus with CXL can stop disease progression, without raising any concern for safety, and can eliminate the need for keratoplasty. This study is limited by lack of comparison group.

In their 2013 guideline on photochemical CXL, the National Institute of Health and Clinical Excellence (NICE) recommendations state that current evidence is adequate in quality and quantity and supports the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia.

Corneal Ectasia Following Refractive Surgery

Kobashi et al. (2018) conducted a meta-analysis involving seven randomized clinical trials with 505 eyes for individuals with progressive corneal ectasia. The review compared clinical outcomes between transepithelial corneal crosslinking and Epithelium-off Corneal Collagen Crosslinking. After a one year observation period, the Epithelium-off Corneal Collagen Crosslinking group demonstrated significantly better outcomes on halting progressive corneal ectasia. Findings on other outcomes were less consistent, with epithelium-on intervention appearing to be superior for best spectacle-corrected visual acuity at one year.

In the pivotal prospective, multicenter, randomized clinical trial (RCT), Hersh et al. (2017b) evaluated the safety and efficacy of CXL for the treatment of corneal ectasia after laser refractive surgery. The patient population was 179 subjects with corneal ectasia after previous refractive surgery. The treatment group underwent standard CXL, and the sham control group received riboflavin alone without removal of the epithelium. In the crosslinking treatment group, the maximum K value decreased by 0.7 diopters (D) from baseline to 1 year, whereas there was continued progression in the control group (1.3 D difference between treatment and control, P < 0.0001). In the treatment group, the maximum K value decreased by 2.0 D or more in 14 eyes (18%) and increased by 2.0 D or more in 3 eyes (4%). The CDVA improved by an average of 5.0 logarithm of the minimum angle of resolution (logMAR) letters. Twenty-three eyes (32%) gained and 3 eyes (4%) lost 10 or more logMAR letters. The UDVA improved 4.5 logMAR letters. Corneal haze was the most frequently reported crosslinking-related adverse finding. The authors concluded that CXL was effective in improving the maximum K value, CDVA, and UDVA in eyes with corneal ectasia 1 year after treatment, with an excellent safety profile. Additional RCTs with longer-term outcomes are needed to evaluate the efficacy of CXL for this indication.

Tong et al. (2017) conducted a small case series of 11 patients (14 eyes) to evaluate the long-term efficacy of epithelium-off CXL for post-LASIK ectasia. Follow-up ranged from 12-78 months. At the last follow-up, best corrected visual acuity improved significantly by 0.2 ± 0.06 logMAR (P = 0.01), and 12 of 14 eyes showed no keratometric deterioration. Of the corneal topography indices, index of height asymmetry showed a trend toward a significant improvement (P = 0.05). There was no progression of corneal HOAs. Central corneal thickness was not significantly altered (P = 0.6). No major postoperative complications were observed. The authors concluded that in this setting, CXL has proven effective at stabilizing the

progression of post-LASIK ectasia, inducing corneal regularity, and improving visual acuity. The findings are limited by lack of comparison group.

Wan et al. (2017) conducted a systematic review and meta-analysis to review the safety and stability of CXL for the treatment of keratectasia after Excimer Laser Refractive Surgery. Seven case series involving 118 patients treated with CXL for progressive ectasia after laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) (140 eyes; the follow-up time range from 12 to 62 months) were included in the meta-analysis of pre/post measures.

The primary outcome parameters included the changes of corrected distant visual acuity (CDVA), uncorrected visual acuity (UCVA), the maximum keratometry value (Kmax) and minimum keratometry value (Kmin), the surface regularity index (SRI), the surface asymmetry index (SAI), the keratoconus prediction index (KPI), corneal thickness, and endothelial cell count. Efficacy estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the interested outcomes. The authors concluded that CXL is a promising treatment to stabilize the keratectasia after Excimer Laser Refractive Surgery. Further long-term follow-up studies are necessary to assess the persistence of the effect of the CXL. Study limitations include lack of comparison group, variation in patient population, follow-up periods, clinical measurement, and quality.

Poli et al. (2015) reported 6-year follow-up from a prospective, consecutive, interventional case series of 36 eyes involving 25 individuals with progressive primary or iatrogenic corneal ectasia who underwent Epithelium-off Corneal Collagen Crosslinking with an 89% stabilization of their primary and iatrogenic corneal ectasia. The mean follow-up was 66 ± 6months (range, 60–78 months). The authors concluded that at “6 years, CXL maintains long-term results in halting the progression of corneal ectasia, with significant improvement in CDVA and long-term stability of keratometry”. Individuals with bilateral disease received equivalent results in both eyes. The findings are however limited by lack of comparison group

Accelerated Corneal Collagen Crosslinking

Artola et al. (2017) conducted a prospective case series to evaluate accelerated transepithelial CXL in a total of 19 keratoconus eyes of 12 patients between 26 and 69 years of age. One month after surgery, a non-statistically significant change was noted in sphere (P=0.18) and in spherical equivalent (P=0.17), whereas a significant improvement was observed in corrected distance visual acuity (P=0.04). A significant change was observed in topographic astigmatism (P=0.03) and posterior corneal a sphericity (P=0.04). In the authors’ opinion, accelerated transepithelial CXL may be a useful technique for the management of progressive keratoconus. CXL maintained the topographic and aberrometric profile of the cornea without significant changes for a period of 12 months after the procedure. The authors recommend future studies to show the corneal biomechanical changes that occur in-vivo with the use of this technique. The study is limited by a lack of comparison group.

Henriguez et al. (2017) evaluated and compared in a cohort study the effectiveness and safety of accelerated transepithelial (A-epi-on) CXL with standard CXL (epi-off) for children with progressive keratoconus. The first group (36 eyes) underwent accelerated epi-on CXL with 30 minutes of riboflavin application (0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, 0.007% benzalkonium chloride), followed by 5 minutes of irradiation at 18 mW/cm2. The second group (25 eyes) underwent standard epi-off CXL with 30 minutes of riboflavin application (riboflavin 0.1% solution, 20% dextran 500), followed by 30 minutes of irradiation at 3 mW/cm2. The groups showed similar changes in pachymetry and posterior elevation values. Keratoconus progression—defined as an increase of 1 D or more in maximum keratometry at 12 months postop—was observed in 5.6% and 12% of eyes in the A-epi-on and epi-off groups, respectively. Limitations of this study include that it was not randomized and a follow-up period of 12 months may not have been long enough to truly capture progression in this young population.

Woo et al. (2017) compared the visual, refractive, topographic and biomechanical outcomes of conventional CXL 3mW/cm2 for 30 minutes) or accelerated cross linking (KXL; 30mW/cm2 for 4 minutes) in a prospective, cohort study of 76 patients with progressive keratoconus. At the 1-year follow-up, both groups showed no significant increase in K1, K2 and Kmean from baseline. There was also no difference between the CXL and KXL group for postoperative corneal topography as well as central and minimal pachymetry up to 12 months. There was a significant increase in both corneal hysteresis (0.62mm Hg, P=0.04) and corneal resistance factor (0.91mm Hg, P=0.003) in the KXL group at 12 months but not in the CXL group. There was no significant endothelial cell loss throughout follow up in both the groups. Although the authors’ concluded that accelerated CXL provided a biochemical advantage,

Wang et al. (2017) conducted a cohort study of progression rate in keratoconus before and after CXL compared to 145 eyes were followed without CXL (no-CXL group) for a median duration of 31 months whereas 45 eyes were followed up for 41 months before (pre-CXL) and after (post-CXL) accelerated, epithelium-off CXL. Progression was defined based on significant slope found in linear mixed effect models against time. Swept-source optical coherence tomography was used for measurement of anterior steep keratometry, anterior flat keratometry (Ant Kf), anterior average keratometry (Ant Avg K); posterior steep keratometry, posterior flat keratometry (Post Kf), posterior average keratometry (Post Avg K) and corneal thickness. The patients in the pre-CXL group were significantly younger (26.3±5.48 years) compared with the patients in no-CXL group (32.7±10.24 years) (P=0.004). Significant differences were observed during baseline examination for all parameters (P≤0.035) between pre-CXL and no-CXL groups except Ant Cyl and Post Cyl. During the observation period, statistically significant differences were noted between pre-CXL and no-CXL groups in the progression rate of Ant Kf, Ant Avg K, Post Kf and Post Avg K (P≤0.045). After CXL, the progression rate in the post-CXL group was comparable to that in no-CXL group. All corneal parameters remained stable in the no-CXL group throughout the follow-up period. In their study, the authors observed a decrease in progression rate of corneal parameters after CXL. In cases with stable corneal parameters over time, careful monitoring can be considered instead of collagen crosslinking. The findings are limited by lack of randomization and differences between cohort at baseline.

In a retrospective, non-randomized and unmasked cohort study, Korteum et al. (2017) evaluated accelerated versus the standard protocol (epithelium-off CXL). One hundred forty-eight eyes were treated with the accelerated protocol and 138 patients with the standard protocol. Exclusion criteria were previous surgery, other corneal conditions or age above 50 years. Follow-up time was 36 months with clinical examination and keratometry at every visit. Outcome measures were the observed rate of corneal changes, differences between treatment groups and correlation with keratometry measurements. In patients with accelerated CXL, significantly more clear corneas were seen at three (p = 0.015) and six (p = 0.002) months after surgery than following the standard protocol. In patients with accelerated CXL, fewer morphological corneal changes were observed than after conventional CXL. However, rarely, corneal changes persisted for a long time. The findings are limited by lack of randomization, which could have introduced biases.

In a comparative, retrospective, consecutive cohort study of 78 eyes in 58 pediatric patients with keratoconus, Baenninger et al. (2017) evaluated visual and topographic outcomes 1 year after conventional (C-CXL) vs accelerated corneal cross-linking (A-CXL). In this single-center analysis, 39 eyes underwent C-CXL and 39 eyes A-CXL. No eyes were lost to follow-up after 12 months. No significant difference between changes in 12 months after as compared to the time before CXL for UCVA (0.01 log MAR; 95% confidence interval -0.14 to 0.15, P = .944), BCVA (0.05 log MAR; 95% confidence interval -0.05 to 0.15, P = .310), and Kmax (-0.77 diopters; 95% confidence interval -2.20 to 0.65, P = .282) between the C-CXL and A-CXL group were observed. Treatment failure rate was observed in 9 of 39 eyes (23.1%) in C-CXL and in 6 of 39 eyes (15.4%) in A-CXL (P = .389). Adverse events were seen only in 1 eye in the C-CXL group. In this retrospective comparison, the authors concluded that the accelerated approach was equally as effective as the conventional protocol to treat pediatric keratoconus. Randomized controlled trials with larger patient populations and longer follow-ups are needed to validate these findings.

In a prospective case series, Badawi (2016) evaluated the effects of accelerated CXL on corneal endothelium in keratoconus (n=40 eyes) and post-laser-assisted in situ keratomileusis (LASIK) ectasia (n=10 eyes). Over the course of 12 months (at 3-month intervals), qualitative and quantitative analyses of the corneal endothelial cells were conducted. There was a significant reduction in endothelial cell count particularly at 3 and 6 months post-CXL. In addition, the coefficient of variance was also statistically significantly higher at 3 and 6 months postoperatively than the pre-CXL value. There was a slight change in the percentage of hexagonal cells. In this patient population, the author concluded that the use of accelerated CXL (10 mW/cm2 for 9 minutes) has a transient negative impact on endothelial cell density and/or endothelial morphology. Well-designed RCTs with larger patient populations and longer follow-up periods are needed to compare accelerated CXL to conventional CXL in terms of safety and efficacy. The study is limited by lack of comparison group.

Epithelium-On Corneal Collagen Crosslinking

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.

In a RCT, Rush and Rush (2017) compared the outcomes of CXL for the treatment of progressive corneal ectasia using a standard epithelium-off technique versus a transepithelial technique with enhanced riboflavin solution. One hundred forty-four eyes with progressive corneal ectasia were prospectively randomized into a transepithelial CXL study arm or an epithelium-off CXL control arm. Follow-up examinations were set at 3, 6, 12 and 24 months. The primary outcome measure was change in the

maximum simulated keratometry value (Ksteep) after 24 months of follow-up. The secondary outcome measure was change in the best spectacle-corrected visual acuity (BSCVA) after 24 months follow-up. One hundred and thirty-one eyes completed the 24-month follow-up interval. Change in Ksteep was -1.52±0.66 dioptres (D) for the control group versus -0.54±0.58 D for the study group at 24 months of follow-up (p=0.0320). Change in BSCVA was -0.18±0.09 logMAR for the control group versus -0.14±0.08 logMAR for the study group at 24 months of follow-up (p=0.4978). Two eyes in the control group had minor postoperative complications that did not affect the final visual acuity, and one eye in the control group underwent keratoplasty during the study interval. At 24 months of follow-up, subjects in the epithelium-off CXL group demonstrated a greater improvement in Ksteep compared with subjects in the transepithelial CXL group, but no statistically significant difference in BSCVA was found between groups.

In a systematic review and meta-analysis, Li and Wang (2017) evaluated the efficacy and safety of transepithelial CXL versus standard CXL on keratoconus. Three trials involving 244 eyes were evaluated, with 111 eyes in the standard CXL group and 133 eyes in the transepithelial CXL group. The pooled results showed that there were significant differences between the two groups in maximum keratometry (mean difference = 1.05D, 95% CI 0.19 to 1.92, P = 0.02)),and that the standard CXL is more effective in decreasing the maximum keratometry at least 12 months after operation; the transepithelial CXL group gained more improvement in CDVA (mean difference = -0.07, 95% CI -0.12 to -0.02, P = 0.007);there were no significant differences in uncorrected distant visual acuity (UDVA) between the two groups (mean difference = -0.03, 95% CI -0.20 to 0.15, P = 0.75). A similar change was found in corneal thickness (mean difference = 4.35, 95% CI -0.43 to 9.13, P = 0.07)). The authors concluded that standard CXL is more effective in decreasing the maximum keratometry than the transepithelial CXL; the transepithelial CXL provided favorable visual outcomes; they both exhibit similar safety.

Bikbova and Bikbov (2016, reviewed in the systematic review by Li and Wang cited above) conducted an RCT of 149 eyes of 119 patients with keratoconus I-II of Amsler classification. Patients were divided into two groups: (1) 73 eyes with standard crosslinking (CXL) and (2) 76 eyes with transepithelial iontophoresis-assisted CXL. Depending on the group, epithelium removal or administration of riboflavin solution by iontophoresis for 10 min was performed, after which standard surface UVA irradiation (370 nm, 3 mW/cm2) was performed at a 5-cm distance for 30 min. The authors concluded that transepithelial iontophoresis-assisted collagen crosslinking showed to be less effective than standard CXL after 24 months of follow-up, possibly due to a more superficial formation of corneal collagen crosslinks; however the stopping of disease progression was achieved 24 months after procedure.

Lombardo et al. (2017, reviewed in the systematic review by Li and Wang cited above)) conducted a prospective RCT to compare clinical outcomes of transepithelial CXL using iontophoresis (T-ionto CL) and standard CXL for the treatment of progressive keratoconus 12 months after the operation. Thirty-four eyes of 25 participants with progressive keratoconus were randomized into T-ionto CL (22 eyes) or standard CL (12 eyes). The primary outcome measure was stabilization of keratoconus after 12 months through analysis of maximum simulated keratometry readings (K_{max}, diopters). Other outcome measures were corrected distance visual acuity (CDVA, logarithm of the minimum angle of resolution [logMAR]), manifest spherical equivalent refraction (D), central corneal thickness (CCT, micrometers) and endothelial cell density (ECD). Follow-up examinations were arranged at 3 and 7 days and 1, 3, 6, and 12 months. Twelve months after T-ionto CL and standard CL, K_{max} on average flattened by −0.52±1.30 D (P = 0.06) and −0.82±1.20 D (P = 0.04), respectively. The mean change in CDVA was −0.10±0.12 logMAR (P = 0.003) and −0.03±0.06 logMAR (P = 0.10) after T-ionto CL and standard CL, respectively. The manifest spherical equivalent refraction changed on average by +0.71±1.44 D (P = 0.03) and +0.21±0.76 D (P = 0.38), respectively. The CCT and ECD measures did not change significantly in any group at 12 months. Significant differences in the outcome measures between treatments were found in the first week postoperatively. No complications occurred in the T-ionto CL group; 1 eye (8%) had sterile corneal infiltrates, which did not affect the final visual acuity, in the standard CL group. Future comparative studies are needed to incorporate larger data sets and longer follow-up times. The study was limited by the small sample size, which may not have been sufficient to detect clinically significant differences between groups.

In an RCT, Soeters et al. (2015, reviewed in the systematic review by Li and Wang cited above) compared the clinical effects and safety of transepithelial CXL (n=35) to epithelium-off (epi-off) CXL (n=26) in progressive keratoconus (non-inferiority). The main outcome measure was clinical stabilization of keratoconus after 1 year, defined as a maximal keratometry (Kmax) increase <1 diopter (D). This study showed that although transepithelial CXL was a safe procedure without epithelial healing problems, 23% of cases showed a continued keratoconus progression after 1 year. Based on the results, the authors do not recommend replacing epi-off CXL by transepithelial CXL for treatment of progressive keratoconus.

Al Fayez et al. (2015) conducted a randomized controlled trial to compare the safety and efficacy of transepithelial CXL with epithelium-off CXL for progressive keratoconus. Seventy patients were randomized to undergo CXL with intact epithelium (n = 34) or after deepithelialization (n = 36). The main outcome measure was a change in the maximum K reading (Kmax). With 3-year follow-up, Kmax decreased in the epithelium-off group with a mean of 2.4 D and no patient showed evidence of progression. In the transepithelial group, Kmax increased by a mean of 1.1 D, and 20 patients (55%) showed progression of keratoconus. The authors concluded that in this study epithelium-off was significantly more effective than transepithelial corneal cross-linking in halting the progression of keratoconus ($P < 0.0001$).

Corneal Collagen Crosslinking for Other Indications

Photo-activated chromophore for infectious keratitis (PACK)-CXL has been proposed as a treatment for infectious keratitis suggesting the procedure provides an antimicrobial effect (Knyazer et al., 2018; Tabibian et al., 2015). The quality of the evidence for safety and efficacy is however insufficient.

Corneal Collagen Crosslinking-Plus (CXL-plus)

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.

Al-Amri (2018) reported 5-year results from a prospective, interventional, non-randomized, and non-controlled case series in which 60 eyes with mild, non-progressive keratoconus were treated with combined non-topography guided (TG) photorefractive keratectomy (PRK) and CXL. Refraction, uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), flat and steep keratometry readings, and adverse events were evaluated preoperatively and postoperatively. All study parameters showed a statistically significant improvement at 5y over baseline values. The author concluded that combined non-TG-PRK+CXL demonstrates positive 5-year outcomes in patients with mild, stable keratoconus. Based on these findings, the author recommends conducting future large scale, comparative, randomized trials with extended duration of follow-up to establish the long-term stability of this procedure in keratoconus. The findings are limited by the lack of a comparison group.

In a cohort study, Kontadakis et al. (2016) compared the results of CXL alone with combined simultaneous topography-guided photorefractive keratectomy plus CXL (tPRK-CXL) for progressive keratoconus for a 3-year interval (n=60 eyes). Thirty eyes underwent combined tPRK with a solid-state laser (maximum ablation depth, 50 μm) followed by CXL, and 30 eyes underwent CXL alone. Groups were matched in terms of age and keratoconus stage. Corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), keratometry, and corneal confocal microscopy were measured. In the authors' opinion, simultaneous tPRK followed by CXL in this series of keratoconus patients offered significantly improved vision to treated patients in comparison with CXL alone, and similar results regarding postoperative stability. Well-designed RCTs are needed to fully evaluate CXL-plus in the treatment of keratoconus. The study is limited by the lack of randomization and assignment to treatment based on participants' pre-intervention characteristics, which could have introduced biases.

Professional Societies

American Academy of Ophthalmology (AAO)

The AAO's 2017 Preferred Practice Pattern on external diseases of the cornea includes corneal collagen crosslinking as a potential surgical treatment for cornea ectasia, noting that the procedure can improve corneal rigidity by increasing bonds between fibers.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Corneal collagen cross-linking is a procedure and not subject to FDA regulations.

In April 2016, FDA granted approval for Avedro Inc.'s Photrexa® Viscous and PhoTrexa® (riboflavin solutions) for use in corneal collagen cross-linking in combination with the KXL™ System for the treatment of progressive keratoconus. The FDA expanded the indication for Photrexa In July 2016 to include corneal ectasia following refractive surgery. For additional information, refer to: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203324. (Accessed September 18, 2020)

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for corneal collagen cross-linking. Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed September 11, 2020)

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Policy History/Revision Information

Date	Summary of Changes
01/01/2021	• New Medical Policy

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.