selecthealth

MEDICAL POLICY

CORNEAL CROSSLINKING FOR TREATMENT OF KERATOCONUS

Policy # 580

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Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for SelectHealth Commercial, SelectHealth Advantage (Medicare/CMS), and SelectHealth Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Keratoconus is the most common corneal dystrophy in the United States and reportedly affects approximately 1 in every 2000 Americans. This progressive bilateral eye dystrophy is more prevalent in teens and young adults and is characterized by central steepening and normal thinning of the cornea that impairs visual acuity. Initial treatment usually consists of hard contact lenses which flatten the corneal and help it maintain its shape. As the disease progresses or if the patient does not tolerate the contact lens therapy, a penetrating keratoplasty (i.e., corneal graft/transplant) is the next line of treatment. As an alternative, a variety of keratorefractive procedures have been attempted, broadly divided into subtractive and additive techniques. These therapies are intended to reduce some of the complications from a corneal transplant. Subtractive techniques include LASIK. In general, results of this technique have been poor. Implantation of intrastromal corneal ring segments represents another technique intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for a penetrating keratoplasty.

Corneal ectasia is a noninflammatory condition where progressive corneal steepening and thinning occur, whether it is natural (Genetic, mechanical, chromosomal and enzyme abnormalities) or surgically induced (LASIK and PRK). There are different types of corneal ectasia these include pellucid marginal degeneration, keratoglobus, keratoconus, postkeratorefractive ectasia, and wound ectasia after penetrating keratoplasty (PK). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention.

Another therapy recently developed is corneal collagen cross-linking. Corneal collagen cross-linking involves the application of riboflavin (vitamin B2) drops to the eye and exposure to ultraviolet (UV) light. In some cases, the most superficial layer of the cornea (corneal epithelium) is debrided prior to the administration of eye drops and UV light.

Corneal cross-linking (CXL) is an in-office eye procedure that strengthens the cornea if it has been weakened by keratoconus, other corneal disease, or (rarely) a complication of LASIK surgery. Alternative and brand names for the procedure include corneal crosslinking, corneal collagen crosslinking, C3-R, CCL, and KXL. The minimally invasive CXL procedure involves applying liquid riboflavin (vitamin B2) to the surface of the eye, followed by treatment with a controlled application of ultraviolet light, to eliminate corneal ectasia. The two basic types of corneal cross-linking are Epithelium-off CXL and epithelium-on CXL. In the first type of cross-linking procedure, the thin outer layer (epithelium) of the cornea is removed to allow the liquid riboflavin to more easily penetrate the corneal tissue. In the second procedure (also called transepithelial CXL), the protective corneal epithelium is left intact, requiring a longer riboflavin "loading" time.

In April 2016, the pharmaceutical and medical device company Avedro received FDA approval for the company's KXL System that provides corneal collagen cross-linking for the treatment of progressive keratoconus. The approval includes Avedro's Photrexa Viscous and Photrexa, which are riboflavin solutions used with the KXL System during the procedure.

Commercial Plan Policy

SelectHealth **covers epithelium-off corneal cross-linking once per lifetime if the following criteria are met:**

1. **Patient has a diagnosis of keratoconus or corneal ectasia.**
2. **The medicine used is Photrexa Viscous/Photrexa with the KXL device**
3. **The procedure is performed by a fellowship trained corneal provider**

SelectHealth **does NOT cover corneal crosslinking in conjunction with intrastromal ring segment placement as it is considered investigational.**

SelectHealth Advantage (Medicare/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the SelectHealth Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SelectHealth Community Care (Medicaid/CHIP)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the SelectHealth Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

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, which CXL leads to short-term improvements in corneal steepening, 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.

The evidence in the published peer-reviewed medical literature on the treatment of progressive keratoconus with corneal collagen cross-linking using riboflavin and ultraviolet is evolving. Additional results of well-designed controlled clinical trials are needed to firmly establish the role of this procedure in treating ectasia associated with keratoconus, and to determine the preferred technique (i.e., epithelium-off, epithelium-on).

There have been a large volume of studies published on corneal crosslinking as it has been available in Europe and other parts of the world since approximately 2002. The search of the literature identified 72 primary studies and 8 systematic reviews for inclusion in this review. A full list of the abstracts for these

reviews is available in Appendix A. Fourteen of the studies were pediatric studies. As corneal crosslinking is not FDA approved below age 14, these studies were not included in the overall review. The 63 adult studies included for review involved 3190 patients with outcomes assessed from 1 month to 10 years (Rechichi et al., 2013). Several studies had outcomes to 5+ years (Galvis et al., 2016, Parissi et al., 2016, Kim at al., 2016). Most studies had outcomes 12 months or less. There was significant heterogeneity to the studies with many comparing outcomes of “epi-on versus epi-off” and others exploring standard versus accelerated regimens. Most studies focused on impact on keratometry measurements and not necessarily impact on changes in refraction or reduction in corneal transplantation. Refractive changes are not as impressive as the keratometric measurements, and data from well-designed randomized studies are limited.

On the whole the 8 systematic reviews supported the efficacy of corneal crosslinking in slowing the progression of keratoconus. The reviews were for the most part from 2016 though one went as far back as 2013. This suggests the most up to date information was available in deriving their conclusions. The Hayes review from 2016 epitomizes the findings of the other systematic reviews which not the only did evidence seems to support corneal crosslinking as effective and safe but noted the quality of the literature is low (despite the volume – most studies are smaller case series and do not have randomization or controls or are retrospective reviews) and only support “use of conventional corneal cross-linking (C-CXL) for the treatment of progressive keratoconus in adolescent and adult patients).

Only Godefrooij et al. from 2016 looked at the economic implication of this therapy as it relates to corneal transplant. This study retrospectively assessed transplant occurrence over 3 years and noted a 25% reduction. Limiting the ability to generalize this finding in the US is the fact this is a Dutch study and corneal transplant access may differ in the Netherlands than in the US. Its retrospective design and lack of other validating studies also limit conclusion on its findings.

Two particular questions related to corneal crosslinking evaluated in the literature are epithelium off (epi-off) vs epithelium on (epi-on) therapy and standard vs. accelerated protocols. Notably, the FDA approval is currently for the standard regimen using the epithelium off method. With regard to the epi-off vs epi-on, 10 studies were identified specifically comparing epi-on vs epi-off. These studies suffer from multiple methodological issues including poor study design (many though comparative were retrospective and lack randomization), were of small size or used different techniques to perform the epi –on portion. These studies generally supported epi-on to have equal benefit to epi-off technique though the study by Gatzioufas et al. from 2016 did not show epi-on to have any benefit on progression of keratoconus. This outcome was also noted in the study by Kocak et al from 2014. Razmjoo et al, 2014 noted “total epithelium off technique resulted in better improvement of K-max and Q-value.”

With regard to standard vs accelerated protocols, this review identified 11 studies related to use of an accelerated protocols. One study combined an accelerated protocol with corneal ring implants making conclusions regarding effectiveness murky at best. Many of the other studies suffer from methodological issues similar to those seen with the epi-on vs epi off studies. Many were small case series and others lacked a comparative arm. Additionally, though many employed a 10 minute accelerated protocol several studies used a 5 minute protocol. Many of these studies also were of small size. Nonetheless, the studies tended to demonstrate a beneficial effect on keratometry though they lacked endpoints around visual acuity or corneal transplant impact.

Two studies also looked at corneal crosslinking performed in conjunction with intrastromal corneal rings/implants. One study by Ferenczy et al in 2015 only looked at 31 patients of which only 10 got CXL with as the study by Gordillo et al from 2016 looked at 82 patients. These studies focused on impact on keratometry and corneal shape with relatively short study intervals of 1-2 years. Current evidence is insufficient to draw conclusions as to whether the combination of intrastromal corneal rings and CXL were more effective and safe than either alone.

Lastly, several studies focused on the safety of the procedure. These studies tended to note a slight increase in corneal hazing which occurred more commonly with the epi-off treatment but resolved in approximately 3 months. Overall, this therapy has few short term and no apparent long term safety concerns.

While the goal of therapy is to either halt or reverse a progressive condition (keratoconus or ectasia) the various studies have not all clearly defined "progression". In fact, many studies have either failed to define this starting point of enrollment (eyes with "progressive" disease) or have defined it in a way that may not be acceptable to the ophthalmology community.

In conclusion, the observational evidence for the role of corneal crosslinking has been strong. This data is also supported by several well designed randomized controlled clinical trials. The most consistent finding of observational and randomized controlled studies has been that corneal crosslinking induces a slight decrease in keratometry values that tends to be maintained over at least a year. This is an important finding, as in progressive keratoconus keratometry typically rises over time and is a marker of disease progression.

Billing/Coding Information

CPT CODES

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

HCPCS CODES

No codes identified

ICD-10 CODES

H18.601	Keratoconus, unspecified, right eye
H18.602	Keratoconus, unspecified, left eye
H18.603	Keratoconus, unspecified, bilateral
H18.609	Keratoconus, unspecified, unspecified eye
H18.611	Keratoconus, stable, right eye
H18.612	Keratoconus, stable, left eye
H18.613	Keratoconus, stable, bilateral
H18.619	Keratoconus, stable, unspecified eye
H18.621	Keratoconus, unstable, right eye
H18.622	Keratoconus, unstable, left eye
H18.623	Keratoconus, unstable, bilateral
H18.629	Keratoconus, unstable, unspecified eye
H18.70	Unspecified corneal deformity
H18.711	Corneal ectasia, right eye
H18.712	Corneal ectasia, left eye
H18.713	Corneal ectasia, bilateral
H18.719	Corneal ectasia, unspecified eye
H18.791	Other corneal deformities, right eye
H18.792	Other corneal deformities, left eye
H18.793	Other corneal deformities, bilateral
H18.799	Other corneal deformities, unspecified eye
Q15.8	Other specified congenital malformations of eye
Q13.4	Other congenital corneal malformations

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