Reshaping procedures for the surgical management of corneal ectasia

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Corneal ectasia is a progressive, degenerative, and noninflammatory thinning disorder of the cornea. Recently developed corneal reshaping techniques have expanded the treatment armamentarium available to the corneal specialist by offering effective nontransplant options. This review summarizes the current evidence base for corneal collagen crosslinking, topography-guided photorefractive keratectomy, and intrastromal corneal ring segment implantation for the treatment of corneal ectasia by analyzing the data published between the years 2000 and 2014.

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Corneal ectasia is a progressive, noninflammatory thinning disorder of the cornea that compromises the stromal collagen matrix, resulting in protrusion and alteration of corneal shape. The types of ectasia include keratoconus, pellucid marginal degeneration (PMD), keratoglobus, posterior keratoconus, and post laser refractive–surgery ectasia.

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The incidence of keratoconus, the most common type of ectasia, is 1.3 to 25 per 100 000[1] with a reported prevalence of 50 to 230 cases per 100 000.[2] There is a strong association of ectasia with atopy,[3] and a growing body of evidence suggests genetic factors play an important role in its pathogenesis.[4] Although the total corneal collagen content of keratoconic eyes is normal, changes in epithelial basement membrane structure, stromal collagen fiber and extracellular matrix components, keratocyte morphology, and cell matrix interactions result in lamellar/fibrillar slippage, leading to a reduction in corneal stiffness by a factor of 0.7.[5,6] This in turn leads to protrusion of the corneal apex and an increase in corneal power.[7]

Pellucid marginal degeneration is a rare, idiopathic, progressive, nonhereditary, and noninflammatory ectatic disease classically affecting the inferior aspect of the cornea.[8] Histopathologic evaluation of PMD shows a thin or irregular Bowman layer,[9] while electron microscopy studies reveal fibrous long collagen with a periodicity of 100 to 110 nm scattered among regions of otherwise normal collagen fibers.[10]

Post laser refractive–surgery ectasia is an uncommon and complex entity that has been reported following both laser in situ keratomileusis (LASIK)[11] and photorefractive keratectomy (PRK),[12,13] with a reported prevalence of 1/2500[14] and 1/3000,[15] respectively. Iatrogenic ectasia has been associated with laser refractive

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correction in preexisting subclinical (forme fruste) keratoconus, excessive tissue ablation, enhancements, and attempted high myopic correction.[14]

Conservative management of keratectasia initially involves spectacle correction followed by contact lenses. Contact lenses represent the treatment of choice for most keratoconic patients.[16] However, surgical intervention is required in patients who become contact lens intolerant or are not capable of visual rehabilitation with contact lenses. For advanced disease with central corneal scarring, corneal transplantation, preferably with deep anterior lamellar keratoplasty (DALK) or alternatively penetrating keratoplasty, remains the only viable treatment option. Large prospective cohort studies report a keratoplasty rate of 11.8% after an 8-year period of follow-up[17] and 18.8% over a 20-year period.[18] However, the high financial burden of corneal transplantation,[19] limited patient satisfaction with postoperative vision, and contact lens intolerance,[20] coupled with an almost 50% failure rate at the 20-year timepoint after keratoplasty,[21] has led to the development of many new nontransplant surgical treatment options to both stabilize the ectatic process and improve vision.

There has been particular interest in the newer treatment modalities as they offer the potential to treat the disease at an earlier stage, prevent the morbidity associated with disease progression, and preclude the need for the more invasive keratoplasty procedure. For this reason, the Corneal Clinical Committee of the American Society of Cataract and Refractive Surgery thought it important to review corneal collagen crosslinking (CXL) and intrastromal corneal ring segments (ICRS) as treatment modalities in patients with keratectasia.

METHODS

This systematic review adopted a search strategy designed to identify all relevant published English articles using the Ovid Medline and PubMed databases. A literature search was performed to identify studies of photochemical corneal CXL with riboflavin (vitamin B2) and ultraviolet-A (UVA) and ICRS for the management of corneal ectasia published before January 1, 2014.

CORNEAL COLLAGEN CROSSLINKING

Crosslinking can be defined as the creation of bonds that connect 1 polymer chain to another. Corneal CXL is a technique to strengthen corneal tissue. It uses riboflavin as a photosensitizer and UVA to increase the formation of intrafibrillar and interfibrillar carbonyl-based covalent bonds through the process of photopolymerization.[22,23] Although the exact molecular response to CXL is not fully understood, experimental data suggest that it occurs via 2 mechanisms. After the riboflavin molecule is excited to its single or triplet state and in the early aerobic phase of CXL, photosensitized oxidation of stromal proteins occurs via interaction with reactive oxygen species (type II mechanism).[24] After the oxygen supply is depleted and in anaerobic conditions, reactive species of radical ions are produced and interact with numerous molecules in the corneal stroma (type I mechanism).[22] The liberation of these molecules in the corneal stroma coupled with the resulting wound-healing response to the procedure's mechanical and photochemical insult is thought to induce an increase in corneal rigidity in the anterior 200 μm of the stroma,[25–28] modulus of elasticity, collagen fiber thickness,[29] resistance to stretching,[28] and enzymatic degradation,[30] with an associated decrease in swelling and permeability.[31–33]

Although the major indication for CXL is to arrest the progression of keratoconus,[34] CXL has been used in the treatment and prophylaxis[35] of iatrogenic ectasia resulting from LASIK,[35–37] PRK,[36,38] and radial keratotomy.[39] It has also been used in combination with other treatments, such as ICRS implantation[40,41] and limited topography-guided photoablation.[42,43]

As the CXL process leads to compaction of the corneal stroma and reduces the potential space for fluid in edematous corneas,[44,45] it has been used effectively in short-term palliative treatment of patients with pseudophakic bullous keratopathy with a reported reduction in patient pain scores and central corneal thickness (CCT) but no significant improvement in visual acuity.[46]

Initial laboratory studies indicated potential antimicrobial properties, and subsequently small case series have reported successful treatment of bacterial (*Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli*), fungal (*Fusarium, Aspergillus*), protozoal (*Acanthamoeba*), and atypical (nontuberculous mycobacteria) keratitis using CXL.[47]

Dresden Protocol

The standard protocol, or what is now referred to as the Dresden protocol for CXL, as initially reported by Wollensak et al.,[34] requires epithelial removal, application of riboflavin 0.1% solution for 30 minutes before UV exposure, with a wavelength of 370 nm and homogenous irradiance of 3 mW/cm^2 for 30 minutes (5.4 J/cm^2). Collateral endothelial, lenticular, or retinal damage is not expected using this protocol.[48]

Alternative Treatment Protocols

More recent CXL techniques have departed from the original Dresden protocol. These newer techniques use different formulations and delivery methods of riboflavin as well as altered UV exposures to shorten

duration times, reduce patient discomfort, and minimize postoperative complications.

High-Fluency Collagen Crosslinking The theoretical foundation of high-fluency CXL is the Bunsen-Roscoe law of photochemical reciprocity, which states that the same photochemical effect can be achieved with a reduced irradiation interval provided the total energy level is kept constant through a corresponding increase in irradiation intensity. Commercially available ultrafast devices are now able to provide an irradiance intensity of 43 mW/cm^2. Using this setting, a total treatment time of 2 minutes would achieve the standard Dresden protocol energy dose of 3.4 J or a radiant exposure of 5.4 J/cm^2.[49]

Ex vivo human cornea studies using scanning acoustic microscopes have failed to demonstrate a significant difference in corneal stiffness between corneas treated with low and high intensity.[50] Early in vivo safety studies using high-fluency crosslinking have shown the procedure to be safe with no adverse effects on epithelial healing times or corneal limbal morphology.[51] However, a recent human safety study suggests transient but significant differences in endothelial cell density, percentages of hexagonality, and coefficient of variation of the endothelial cell area in the first month after treatment with high-fluency CXL.[52]

Pulsed Collagen Crosslinking There are currently no peer-reviewed publications on the use of this CXL modality.

Transepithelial Collagen Crosslinking The diffusion process of riboflavin 0.1% in the stroma is a time-dependent 1-dimensional process that is limited by corneal epithelial tight junctions.[53,54] Epithelial debridement is thought to be a major contributor to the postoperative complications of CXL, such as infective keratitis and an abnormal wound-healing response. This issue has perpetuated interest in the potential application of an epithelium-on technique.[55,56] The 2 main challenges associated with this technique are the limited diffusion of the riboflavin molecule with a molecular weight 376 g/mol through the lipophilic cornea and the molecule's epithelial tight junctions,[57,58] as well as the high UV absorption coefficients of the corneal epithelium and Bowman layer.[59]

The diffusion of riboflavin across an intact corneal epithelium can be achieved through a number of techniques, such as modifying the corneal epithelial permeability, changing the physicochemical properties of the riboflavin molecule, and directly delivering the riboflavin molecule into the corneal stroma. Modification of epithelial permeability can be an alternative to epithelial removal. In this approach, chemical enhancers such as benzalkonium chloride (BAK), ethylenediaminetetraacetic acid (EDTA), trometamol, or gentamicin are added individually or concurrently with the riboflavin solution to loosen epithelial tight junctions and facilitate the diffusion of riboflavin into the stroma.[31,55] A preparation of riboflavin 0.1% containing EDTA and trometamol is currently available commercially (Ricorlin TE).

Although human studies report a low complication rate of 0% to 3.9% (transient haze) in patients treated with transepithelial CXL,[60,61] the effectiveness of the technique remains uncertain and its use is still the subject of debate and controversy. Experimental data have shown that performing BAK 0.0005%-enhanced transepithelial CXL results in an increase in biomechanical rigidity of only one fifth the level expected with standard CXL in rabbit corneas (21.3% versus 102.4%).[62] Other studies have shown the technique to affect the collagen pattern profile and not the collagen fiber diameter.[63] Furthermore, limited keratocyte apoptosis has been demonstrated in transepithelial CXL,[64] as well as a more superficial CXL demarcation line at 100 to 140 μm of depth when 1 enhancer is used[64,65] and 250 μm when 2 enhancers are used.[66] This is in contrast to standard CXL in which a demarcation line is visible at a depth of 280 to 330 μm.[67,68]

To improve the diffusion of the negatively charged water-soluble riboflavin molecule through an intact epithelial layer, iontophoretic delivery using a mild electrical current has been investigated. Studies show that while this technique allows greater and deeper riboflavin penetration in the corneal stroma than the conventional epithelium-on technique, this concentration is half that seen with the epithelium-off method.[69] Confocal studies of eyes treated using this technique again show a keratocyte apoptotic effect at a 60 to 70 μm more superficial level than standard CXL, suggesting suboptimal penetration of the riboflavin into the corneal stroma.[70]

In another attempt to avoid disturbing the corneal epithelial integrity and to hasten postoperative healing, clinical investigators have used a grid-like pattern of deepithelialization,[71] riboflavin soaking of corneal pockets created for ICRS,[72] and superficial intrastromal administration of riboflavin using a femtosecond laser–created central corneal pocket.[73,74]

Early clinical and experimental data show that the grid-like pattern of deepithelialization is ineffective in increasing the absorption of riboflavin,[71,75] while the femtosecond pocket procedure has shown some promise, with 1 small human study demonstrating stabilization of the ectatic process as well as improved corrected distance visual acuity (CDVA) and maximum keratometry (K) values over a follow-up of up to 26 months.[73]

Corneal Crosslinking in Thin Corneas

Several alternative strategies have been used to protect the intraocular structures from UVA irradiance in patients with progressive ectasia who do not meet the minimum corneal thickness criteria for CXL treatment (440 μm including the epithelium). These include transepithelial CXL, pachymetry-guided epithelial debridement,[76] use of hypoosmolar preparations of riboflavin to produce corneal swelling,[77] decreasing the UVA irradiance dose, reducing the duration of riboflavin soaking, increasing the riboflavin concentration, or a combination of the above.[31] Although these modifications may protect the endothelium in thin corneas, they are yet to be standardized and it remains unclear whether they will yield results similar to those of conventional CXL.

Typical Postoperative Findings

Anterior corneal stromal haze often occurs in the first month after treatment and typically resolves after 12 to 20 weeks.[56] The posterior aspect of this haze is demarcated by an indistinct hyperreflective demarcation line seen in the midstroma. While no consensus about its etiology has been reached, it is in all probability a clinical manifestation of the depth of CXL and occurs as a result of a change in the stromal refractive index, an increase in collagen fiber diameter, and fibrillar spacing.[29,78]

Cellular and Ultrastructural Findings After Corneal Collagen Crosslinking

Corneal CXL induces a wound-healing response with associated changes in the structure and cellularity of the cornea evident on confocal microscopy from the early postoperative period up to 36 months after treatment.[79] Confocal microscopy studies performed immediately after CXL reveal stromal edema, thinning of the epithelial layer, keratocyte apoptosis, and a reduction in nerve fiber density in the anterior stroma (250 to 300 μm).[31] A human histopathologic study 24 hours after CXL in a normal cornea confirmed complete loss of anterior stromal keratocytes to a depth of 250 to 280 μm, whereas keratocyte densities were found to be normal in the posterior aspect of the stroma.[80] Three to 6 months after treatment, confocal microscopy shows a reduction in edema, increased density of the stromal extracellular matrix, and gradual repopulation of the stroma with activated keratocytes from the peripheral cornea.[81,82]

At the 1-year timepoint, posterior stromal and endothelial cell morphology has been shown to be unchanged.[83] Thirty-six months postoperatively, a "bridge-and-needle" shaped hyperreflective density in the anterior extracellular corneal matrix can be visualized and this has been interpreted as newly replaced collagen.[67,84]

In Messmer et al.'s histopathologic study of keratoconic eyes,[6] long-term changes in the anterior/middle corneal stroma with central and peripheral keratocyte loss were observed up to 30 months after CXL. While this study contradicts reported in vivo confocal studies of human corneas and animal histological studies, it is a worrisome report and shows the possible long-term consequences of this ever more popular procedure.

Clinical Outcomes

Keratoconus *Conventional Crosslinking (Dresden Protocol)* *Case Control Studies* Many studies have evaluated the role of CXL as a treatment modality for keratoconus since Wollensak et al.[34] reported the first controlled clinical study in 2003. In that groundbreaking study, CXL was performed in 23 eyes of 22 patients with progressive keratoconus. At the last follow-up (range 3 months to 4 years), there was no observable progression of keratoconus in any of the patients. A reduction in maximum K was observed in 16 eyes (70%): a mean reduction of 2.01 diopters (D) accompanied by a 1.14 D reduction in refractive error. A progression in the K readings (mean 1.48 D) occurred in 22% of untreated contralateral eyes.

Since the Wollensak et al. report, more than 20 cohort studies of the effect of standard CXL using different outcome measures have been reported. The results of these investigations are summarized in Table 1.[34,40,68,85–105]

The majority of the studies are prospective longitudinal studies (84%), whereas a small proportion are retrospective (16%). Of the 24 prospective longitudinal studies, 11 report the outcomes of the treated eye (usually the worse eye) with those in the untreated fellow eye serving as a control.

The studies report the effect of CXL in a patient group with a mean age between 16 years and 35 years and a follow-up duration between 3 months and 60 months. Half the studies have a mean follow-up period of up to 1 year; only 3 studies followed their patient cohort for more than 3 years.

The studies show an efficacy rate of 62% to 100% in halting keratoconus progression as assessed by maximum/mean K changes. All the studies (where data are available) report a reduction in keratometric measurements, while half the studies show the reduction to be statistically significant. The degree of flattening ranges between 0.01 D and 1.0 D (43% of studies), 1.0 D and 2.0 D (33% of studies), and 2.0 and 3.0 D (24% of studies). The flattening effect of CXL appears to continue up to 6 years[104] with no significant late complications.[96]

Table 1. Cohort studies of CXL in progressive keratoconus.

Author* (Year)	Eyes (n)	Mean Age (Y)	Mean FU (Mo)	Stabilization (Improvement) in Kmax/ Kmean (%)	Mean Change		
					Kmax/Kmean (D)	SE (D)	UDVA
Ivarsen[85] (2013)	28	(—)	22	96 (50)	1.1†	1.7†	(—)
Legare[86] (2013)	39	26.8	15.8	(—)	(—)	(—)	0.39 logMAR†
Poli[87] (2013)	45	21.7	20.8	100 (—)	0.19	(—)	0.18 logMAR†
Hashemi[88] (2013)	40	22.4	60	(—)	0.24	0.41	0.02 logMAR
O'Brart[89] (2013)	30	26.3	53.3	100 (34)	0.84†	0.82†	0.01 Snellen equivalent
Guber[90] (2013)	33	26.36	12	(—)	0.16	2.17†	(—)
Viswanathan[91] (2013)	51	24.2	13.8	(—)	0.96†	0.2	(—)
Goldich[92] (2010)	14	28.2	24	(—) (92)	2.4	1.3	0.19 logMAR
Koller[93] (2011)	151	29.3	(—)	98 (37)	0.89†	(—)	(—)
Henriquez[94] (2011)	10	29.7	12	(—) (80)	2.66†	2.25†	0.72 logMAR†
Asri[95] (2011)	142	24.1	10	91 (21)	0.49†	(—)	0 logMAR
Caporossi[96] (2010)	44	(—)	48	89 (85)	2.26 (—)	2.15†	2.85 Snellen lines
Saffarian[97] (2010)	92	21.5	12	(—)	0.94†	0.57†	0.30 logMAR†
Coskunseven[40] (2009)	38	22	9	(—)	1.57†	1.03†	0.06 logMAR†
Grewal[98] (2009)	102	25.6	12	(—)	1.07	1.43	(—)
Vinciguerra[99] (2009)	28	(—)	24	(—)	1.35†	0.81†	0.24 logMAR†
Koller[100] (2009)	117	(—)	12	92 (37)	(—)	(—)	(—)
Doors[68] (2009)	28	35.1	6.3	62 (25)	0.08	(—)	(—)
Arbelaez[101] (2009)	20	24.4	12	(—)	1.36†	1.88†	4.15 Snellen lines†
El-Raggal[102] (2011)	15	26.4	(—)	100 (—)	1.63†	(—)	0.04 logMAR†
Agrawal[103] (2009)	37	16.9	12	92 (54)	(—)	(—)	(—)
Raiskup-Wolf[104] (2008)	66	30	24	86 (56)	1.91†	(—)	(—)
Caporossi[105] (2006)	10	31.4	3	100 (—)	2.1 (—)	2.2 (—)	3.6 Snellen lines†
Wollensak[34] (2003)	23	31.7	23.2	100 (70)	2.01	1.14†	(—)

(—) = data not available; + = deterioration in parameters; CCT = central corneal thickness; CDVA = corrected distance visual acuity; CXL = crossinking; FU = follow-up; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

*First author

†Statistically significant result

‡Hypoosmolar solution used if <400

Table 1. (Cont.)

Mean Change CDVA	CCT (μm)	Permanent Complications	Study Design	CXL Device
0.07 logMAR	>400‡	Loss of CDVA (7%)	Retrospective pre–post longitudinal cohort	UV-XIROC
(—)	>400‡	None	Retrospective pre–post longitudinal cohort	UV-XIROC
0.22 logMAR†	>400	None	Prospective pre–post longitudinal cohort and comparative controls	Vega CBMX-linker
0.12 logMAR†	>400	None	Prospective pre–post longitudinal cohort	UV-XIROC
0.1 Snellen equivalent †	>400	1-line loss CDVA (17%)	Prospective pre–post longitudinal cohort	Vega CBMX-linker & Roithner Lasertechnik
0.04 logMAR†	>400	Corneal scar (6%)	Prospective pre–post longitudinal cohort	UV-XIROC
0.05 logMAR†	>400	(—)	Prospective pre–post longitudinal cohort	UV-XIROC
0.07 logMAR	>400	None	Prospective pre–post longitudinal cohort	UV-X Peschke
0.55 logMAR	>350‡	(—)	Prospective pre–post longitudinal cohort	UV-X Peschke
0.09 logMAR	>450	None	Prospective pre–post longitudinal cohort and comparative controls	UV-XIROC
0.01 logMAR†	>400	>2-line loss CDVA (3.5%)	Retrospective pre–post longitudinal cohort	(—)
2.0 Snellen lines	>400	None	Prospective pre–post longitudinal cohort and comparative controls	Vega CBMX-linker
0.06 logMAR†	>400	None	Prospective pre–post longitudinal cohort	UV-XIROC
0.10 logMAR†	>400	None	Prospective pre–post longitudinal cohort and comparative controls	UV-X Peschke
0.02 logMAR	>400	(—)	Prospective pre–post longitudinal cohort and comparative controls	Roithner Lasertechnik
0.15 logMAR†	>400	(—)	Prospective pre–post longitudinal cohort and comparative controls	UV-X Peschke
(—)	>400	Stromal scar (2.8%)	Prospective pre–post longitudinal cohort and comparative controls	UV-X Peschke
0.02 logMAR	>400	None	Prospective pre–post longitudinal cohort	Vega CBMX-linker
1.65 Snellen lines†	>400	None	Prospective pre–post longitudinal cohort	UV-X Peschke
0.02 logMAR	>420	Superficial corneal scar (6.67%)	Prospective pre–post longitudinal cohort	UV-X Peschke
(—)	>400	None	Retrospective pre–post longitudinal cohort	Vega CBMX-linker
0.09 logMAR†	>400	(—)	Prospective pre–post longitudinal cohort	UV-X Peschke
1.6 Snellen lines†	>400	None	Prospective pre–post longitudinal cohort and comparative controls	Exerion-Sas
1.26 Snellen line†	>400	None	Prospective pre–post longitudinal cohort and comparative controls	Roithner Lasertechnik

Table 2. Randomized controlled trials of CXL in progressive keratoconus.

Author* (Year)	Eyes (n)	Mean Age (Y)	Mean FU (Mo)	Stabilization (Improvement) in Kmax/Kmean (%)	Mean Change Kmax/Kmean (D)
Wittig-Silva[112] (2008)	66	26.9	12	100 (>50)	1.45†
Hersh[113] (2011)	49	(—)	12	90 (51)	2.0†
O'Brart[111] (2011)	24	29.6	18	100 (23)	0.62†
Wittig-Silva[114] (2014)	46	25.6	36	98 (—)	1.03†

(—) = data not available; + = deterioration in parameters; CCT = central corneal thickness; CDVA = corrected distance visual acuity; CXL = crosslinking; FU = follow-up; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

*First author

†Statistically significant results

‡Hypoosmolar solution used if <400

The improvement in corneal shape is accompanied by an improvement in uncorrected distance visual acuity (UDVA) of between 0.01 logMAR and 0.72 logMAR and an improvement in CDVA of 0.01 to 0.55 logMAR in all the studies (where data are available). The improvement in visual acuity after treatment has been attributed to a decrease in astigmatism, a reduction in corneal curvature, and topographical homogenization resulting from increased corneal rigidity. Coma-like aberrations, which are the most prevalent higher-order aberrations (HOAs) in keratoconic eyes,[106,107] have also been shown to be significantly reduced following CXL.[96,101,103,105]

The efficacy of the standard CXL procedure is accompanied by no significant changes in endothelial cell counts (ECCs),[92,94,96,105] intraocular pressure (IOP),[96,105] lens density,[98] or foveal thickness.[92,94,98] Although most of the studies report long-term stability of corneal thickness,[40,91,92,100,105] a long-term prospective randomized control trial (RCT) has shown that CXL induces an initial thinning of the central cornea that is followed by a gradual recovery toward baseline levels,[108] with the change in corneal thickness hypothesized to be due to changes in the spacing between individual collagen fibrils rather than to change in their diameter.[109,110]

It is worth noting that while the aforementioned studies tend to have well-defined inclusion and exclusion criteria and trial designs, they are largely single-center, nonrandomized, and nonconsecutive. As such, they are prone to a number of error sources such as selection and reporting bias. The studies have also used different topography devices and different measures, such as corneal surface curvatures, asymmetry indices, and higher-order corneal aberrations, to assess progression in ectatic eyes. Therefore, they represent low-quality evidence of the efficacy of CXL in treating keratectasia.

Randomized Controlled Trials To date, 4 RCTs have reported the clinical outcomes of conventional CXL in the treatment of keratoconus.[111–114] These RCTs are summarized in Table 2. Although small in size, the studies are of moderate quality based on the Jadad scale. They report a 90% to 100% success rate in halting the progression of the disease, and in all of them, significant corneal flattening was observed, with a reduction in the maximum K value between 0.62 D and 2.0 D. Three of the 4 studies also show evidence of disease progression in the control group as indicated by progressive steepening of the cornea.[112–114]

The impact of the CXL procedure on CDVA is encouraging, with all studies showing a statistically significant improvement in CDVA (0.09 to 0.14 logMAR) after treatment.[111,113,114] Although there was a trend toward improved UDVA and reduced mean spherical equivalent (SE) after CXL in the 4 studies, the trend did not reach statistical significance in most of the trials. O'Brart et al.[111] also report an improvement in cone apex power and wavefront measurements (root mean square [RMS], coma, and pentafoil) after the CXL procedure. No permanent vision-threatening complications were reported in any trial.

It should be noted that these RCTs are small with relatively short follow-up periods (12 to 36 months). It is also noteworthy that none had a sham controlled group of more than 3 months, nor were they double-blinded, and it is conceivable that the reported changes in corneal topography and visual acuity were affected by this error source.

Transepithelial Collagen Crosslinking A number of small studies have evaluated the role of transepithelial CXL in keratoconic patients. Most of the studies have a prospective longitudinal cohort design with a follow-up period between 1 year and 2 years. The results in these studies are summarized in Table 3.[60,61,65,66,70,115–119]

The studies report the effect of transepithelial CXL in a patient group with a mean age between 14 years and

Table 2. (Cont.)

Mean Change					
SE (D)	UDVA	CDVA	CCT (μm)	Permanent Complications	CXL Device
(—)	(—)	0.12 logMAR†	>400	None	UV-X IROC
0.85	0.05 logMAR	0.14 logMAR†	>400‡	(—)	UV-X IROC
0.82	0.06 Snellen decimal equivalent	0.12 Snellen decimal equivalent†	>400	None	CMB Vega X-linker & Roithner Lasertechnik
0.61	0.15 logMAR†	0.09 logMAR†	>400	None	UV-X IROC

34 years and a follow-up period between 6 months and 24 months. Seven of the 9 studies (where data are available) report an overall reduction in maximum K: between 0.01 D and 1.0 D (3 studies), 1.0 D and 2.0 D (1 study), and 2.0 D and 3.0 D (3 studies). This improvement in corneal shape is accompanied by an improvement in UDVA of 0.13 to 0.27 logMAR in all but 1 study and an improvement in CDVA of 0.02 to 0.11 logMAR in all the studies (where data are available).

Although transepithelial CXL appears to be a safe procedure with no significant adverse effects and stable postoperative ECCs,[61,66,70,115,116,119] 3 of the studies report significant corneal steepening despite treatment[60,61,117] and in 1 study nearly one fifth of patients required a repeat CXL procedure using the Dresden protocol.[117] There are also inconsistent results in pachymetric measurements after transepithelial CXL, with 3 studies reporting continued corneal thinning in treated patients,[60,70,117] 3 studies reporting stable CCT measurements,[65,115,119] and 1 study reporting increasing thickness after treatment.[118] The effect of treatment on HOAs is also debatable, with 2 studies reporting improved RMS, coma, and spherical aberration measurements[65,66] and 1 study reporting an increase in spherical aberration and no significant change in coma measurements after 2 years of follow-up.[117] Furthermore, the efficacy of transepithelial CXL in a pediatric population is debatable as Caporossi et al.[117] reported a 50% retreatment rate in this subgroup due to demonstrable progression after 1 year. This is in contrast to the only head-to-head study available in which Magli et al.[120] report that transepithelial CXL has safety and efficacy indices similar to those of conventional CXL in pediatric patients.

The diversity of surgical protocols and reported results make overall assessment of transepithelial CXL as a procedure to halt the progression of keratoconus problematic. While it seems likely that transepithelial CXL has a less tangible therapeutic effect than standard CXL,[60,61,116,117] it could be beneficial to patients with thin corneas, uncooperative individuals, or those with questionable progression, as it is expected to have a lower complication rate than standard CXL. A well-designed RCT comparing a standardized transepithelial CXL procedure and conventional CXL is required to establish its noninferiority, confirm its superiority in complication profile, and ultimately clarify the considerable uncertainty that surrounds the use of transepithelial CXL today.

High-Fluency Collagen Crosslinking In a long-term randomized contralateral eye comparative study by Kanellopoulos,[121] CXL using 7 mW/cm^2 irradiation for 15 minutes had a similar efficacy to 30 minutes of standard 3 mW/cm^2 treatment. In both groups, postoperative clinical outcomes such as UDVA, CDVA, maximum K, and SE were similar after a follow-up of 46 months. If these results are replicated in other randomized studies, it would be a major advantage to patients who currently have to have a longer, more cumbersome conventional CXL procedure.

Pellucid Marginal Degeneration

Two isolated reports demonstrate the efficacy of CXL in improving the CDVA,[122] keratometric astigmatism,[122] and corneal biomechanical parameters such as corneal hysteresis (CH) and corneal resistance factor[123] in patients with PMD. Topography-guided PRK combined with CXL has also been reported to result in improved visual, refractive, and topographic indices 1 year after treatment.[124,125] Although further studies are required to establish the role of CXL in PMD, treatment appears to be safe with no disease-specific adverse outcomes reported to date.

Iatrogenic Ectasia

Collagen crosslinking has successfully treated iatrogenic ectasia after LASIK and PRK. In 2005, Kohlhaas

Table 3. Cohort studies of transepithelial CXL in progressive keratoconus.

Author* (Year)	Eyes (n)	Mean Age (Y)	Mean FU (Mo)	Stabilization (Improvement) in Kmax/Kmean (%)	Mean Change		
					Kmax/Kmean (D)	SE (D)	UDVA
Koppen[60] (2012)	18	29.0	18	(—)	+1.76†	(—)	(—)
Leccisotti[61] (2010)	51	26.9	12	(—)	+0.51	0.35†	(—)
Filippello[65] (2012)	20	27.0	18	(—)	1.17†	(—)	0.23 logMAR†
Rechichi[66] (2013)	28	28.8	12	(—)	0.89†	0.96†	0.25 logMAR†
Bikbova[70] (2014)	22	32.1	12	(—)	2.3†	(—)	0.13 logMAR
Salman[115] (2013)	22	15.7	12	100 (—)	2.30†	0.30	0.27 logMAR†
Spadea[119] (2012)	7	34.4	12	(—)	(—)	0.32	0.21 logMAR
Buzzonetti[116] (2012)	13	14.4	18	(—)	3.0†	0.40	(—)
Caporossi[117] (2013)	26	22.0	24	(—)	+1.55†	(—)	+0.05 Snellen lines
Derakhshan[118] (2011)	31	22.3	6	90 (77)	0.65†	0.55†	2.0 Snellen lines†

(—) = data not available; + = deterioration in parameters; CCT = central corneal thickness; BAC = benzalkonium chloride; CDVA = corrected distance visual acuity; Trans CXL = transepithelial crossinking; EDTA = ethylenediaminetetraacetic acid; FU = follow-up; Kmax = maximum keratometry; Kmean = mean keratometry; NA = data not available; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

*First author

†Statistically significant result

et al.[126] reported the first successful treatment of a patient with post-LASIK ectasia using CXL, with stability reported at 18 months. Later, Hafezi et al.[127] reported a series of 10 eyes with follow-up of up to 25 months in which there was a reduction in maximum K at 12 months in all cases and a gain of more than 2 lines of CDVA in 40% of cases. These results mirror those of Vinciguerra et al.,[128] who reported the results of CXL in 13 eyes of 9 consecutive patients with iatrogenic ectasia. The group reported a statistically significant reduction in mean SE as well as improved CDVA at the 6-month timepoint. A statistically insignificant improvement in HOAs (coma, spherical, and higher-order astigmatism) was also observed. Salgado et al.[129] also reported stability of the ectatic process at 1 year in 22 eyes of 15 patients with post-LASIK ectasia treated with CXL.

In a prospective RCT performed by Hersh et al.,[113] a less notable reduction in maximum K and associated improvement in CDVA was seen in iatrogenic ectasia cases than in keratoconic eyes. This phenomenon is poorly understood as confocal microscopy studies have shown comparable morphologic changes after CXL in cases of iatrogenic ectasia and keratoconus.[82] Theoretically, CXL in post-LASIK eyes is likely to be less effective as CXL typically treats the anterior 300 µm of the cornea, which includes the LASIK flap. The flap affords no biomechanical stability, leaving 200 µm or less of treatment in the residual stromal bed. A reduced riboflavin diffusion in corneas that have had LASIK, as well as an intrinsic difference in the pathophysiology of iatrogenic ectasia and keratoconus, may also account for the less pronounced CXL effect.[130]

The published reports, although few and relatively short in terms of follow-up, provide some evidence that CXL may arrest or even improve iatrogenic ectasia, with only 1 reported case of keratectasia progression after CXL.[131]

Combined Treatment

Collagen Crosslinking Combined with Topography-Guided Photorefractive Keratectomy *Keratoconus* There is some rationale for the use of PRK instead of LASIK in thinner corneas to reduce the risk for ectasia, especially as PRK results in less corneal biomechanical destabilization. Keratoconus with a preexisting structural

Table 3. (Cont.)

Mean Change CDVA	Permanent Complications	Study Design	CXL Device (Trans CXL Method)
0.05 logMAR	None	Prospective pre–post longitudinal cohort	CBM Vega X-linker (proparacaine, BAC 0.005%)
0.03 logMAR †	None	Prospective pre–post longitudinal cohort and comparative controls	CBM Vega X-Linker (Ribomicin, oxybuprocaine, aceclidine)
0.11 logMAR†	None	Prospective pre–post longitudinal cohort and comparative controls	Vega, Costruzione (Ricrolin, trometamol, EDTA, oxybuprocaine, silicone ring)
0.05 logMAR†	(—)	Prospective pre–post longitudinal cohort and comparative controls	CBM Vega X-Linker (Ricrolin, netilmicin, oxybuprocaine, epithelial disruption)
0.05 logMAR	None	Prospective pre–post longitudinal cohort	UFalink crosslinking & Galvanizator iontophoresis device (riboflavin 0.1% hypotonic solution)
0.02 logMAR	None	Prospective pre–post longitudinal cohort and comparative controls	Opto X Link (Ricrolin, proparacaine)
0.03 logMAR	None	Prospective pre–post longitudinal cohort	CBM Vega X-Linker (Ricrolin, benoxinate)
0.09 logMAR†	None	Prospective pre–post longitudinal cohort	CBM Vega X-Linker (trometamol, EDTA, oxybuprocaine)
0.05 Snellen lines	19.2% retreatment with standard CXL	Prospective pre–post longitudinal cohort	CBM Vega X Linker Vega (benoxinate)
1.7 Snellen lines†	(—)	Prospective pre–post longitudinal cohort (—)	(—) (0.1% riboflavin in 20% dextran)

weakness was traditionally considered to be a contraindication to any photoablative procedure. However, with the almost 3-fold increase in the corneal rigidity of patients treated with CXL,[22] it is hypothesized that the crosslinked cornea may be able to withstand limited tissue ablation without an adverse biomechanical response. Various clinical investigators have demonstrated stability in corneas that have had a combination of CXL and PRK, either sequentially or combined.

Kanellopoulos and Binder[53] describe a case in which a keratoconic patient who had CXL a year earlier was treated with PRK. The cornea remained stable for 1 year after mitomycin-C (MMC)-enhanced topography-guided PRK. At the 18-month follow-up, the patient retained a CDVA of 20/20 with no clinical or topographic evidence of progression. Speculating that increased rigidity would result in a different rate of ablation, the authors advocate undercorrecting the treatment to 70% to 80% of the manifest refraction. Furthermore, the topographic ablation profile with a compensatory superior steepening reduced the need for a large amount of tissue removal centrally, further improving the safety of the procedure.

Favorable results have since been reported in keratoconic patients having simultaneous topography-guided PRK and CXL with an improvement in SE, defocus equivalent, UDVA, CDVA, and maximum K and no evidence of progression after a follow-up period of up to 12 months.[125,132,133] It appears that visual results are superior following phototherapeutic keratectomy removal of the corneal epithelium compared with mechanical debridement,[132] while a transepithelial nontopographic aspheric astigmatic ablation profile is proposed to minimize tissue removal and obtain a corrective effect based on the differential epithelial profile around the cone.[133]

In a prospective nonrandomized trial comparing the effects of CXL alone and combined CXL and PRK, Alessio et al.[134] report improved UDVA, SE, and corneal HOAs with the combined procedure, with no evidence of progression at 24 months.

The timing of the ablation treatment and CXL as well as the interval between the 2 procedures has become a topic of interest. Kanellopoulos and Binder[53] compared sequential versus same-day PRK in keratoconic patients having CXL. The sequential group had topography-guided PRK after a minimum observation period of 6 months after the CXL procedure. The same-day group had a CXL procedure immediately after

Table 4. Intrastromal corneal ring design specifications.

Parameter	Intacs	Intacs SK	Ferrara Ring	Keraring	Myoring
Design	Segment	Segment	Segment	Segment	Full ring
Material	PMMA	PMMA	PMMA & camphorquinone acrylic segments	PMMA & camphorquinone acrylic segments	PMMA
Arc length (degrees)	150	150	90, 120, 140, 160, 210	90, 120, 140, 160, 210, 355	360
Cross-section	Hexagonal transverse shape & conical longitudinal section	Elliptical	Triangular	Triangular	(—)
Thickness (μm)	250-450 (50 increments)	400 and 450	150–350 (50 increments)	150–350 (50 increments)	200–400 (20 increments)
Thickness base (μm)	210–450	(—)	600	600	500
Outer radius (mm)	6.77	(—)	4.40	4.40	5.0
Inner radius (mm)	8.10	6.0	5.60	5.60	(—)
Apical diameter (mm)	(—)	(—)	5.0–6.0	5.0–6.0	5.0–8.0
Additional	(—)	Diffractive effect to minimize photic phenomena	Prismatic effect to minimize photic phenomena	Prismatic effect to minimize photic phenomena	(—)

(—) = data not available; + = deterioration in parameters; PMMA = poly(methyl methacrylate)

MMC-enhanced topography-guided PRK. In both groups, the ablation was adjusted to correct only 70% of the refractive error and the ablations were less than 50 μm. The simultaneous group demonstrated statistically superior results in CDVA, SE reduction, maximum K reduction, and corneal haze score at the final follow-up. No progression of ectasia was reported in either group after a mean follow-up of 36 months.

The simultaneous approach appears to be a superior procedure as the ablation occurs in "virgin" corneal tissue with well-established and clinically tested ablation nomograms. When a consecutive approach is used, unpredictable refractive outcomes may be achieved given that the ablation rate in crosslinked corneal tissue is currently uncertain. It is also counterintuitive to ablate already strengthened corneal stromal tissue, and it may lead to a loss of efficacy. A further theoretical advantage of the simultaneous approach is that the photopolymerization process will lead to lower densities of keratocytes in the anterior 300 μm of stroma compared with the sequential technique, which may reduce the risk for post-PRK haze. However, there have been reports of stromal haze after the simultaneous procedure, which may be a result of keratocyte activation following the photoablative procedure.[135]

Iatrogenic Ectasia In the only study available to date, Kanellopoulos and Binder[43] used MMC-enhanced topography-guided transepithelial PRK followed by CXL with hypotonic riboflavin to treat patients with post-LASIK ectasia. The authors used an effective optical zone of 5.5 mm while aiming to correct 70% of the refractive error to minimize tissue ablation. They report topographic stability in all but 2 eyes and an improvement in UDVA in 27 of 32 cases.

There is no doubt that the combined surface ablation and CXL procedure has provided an exciting noninvasive treatment option for keratoectasia as it has the ability to offer patients functional vision and halt the progression of the ectatic process. There is, however, a current a lack of RCT evidence to confirm its efficacy and U.S. Food and Drug Administration (FDA) trial data are keenly anticipated.

Complications

Corneal CXL has become a ubiquitous treatment in early keratoconus, with a growing perception of the procedure as being routine. However, it is worth remembering that there are several complications associated with this technique and no long-term safety outcomes are available to date.

Reported adverse effects of CXL can be broadly categorized as treatment failures in which stabilization is not achieved as well as infectious, inflammatory, and suboptimal healing complications leading to loss of CDVA. Failure of treatment is usually defined as continued progression of the disease with an increase in maximum K readings of 1.0 D over the preoperative value. Reports indicate that this occurs in 7.6% to 9.8%

of patients in the first year following treatment.[100,113,136] Topographic progression after 3 years of stability has also been reported, suggesting that corneal stromal remodeling may lead to loss of treatment effect in some individuals.[137]

Koller et al.[100] evaluated 117 keratoconic eyes having conventional CXL and report a 7.6% treatment failure rate and a 2.9% rate of loss of 2 or more Snellen lines of CDVA. In that study, a preoperative maximum K value of 58.0 D or more was a significant risk factor for failure, while patients older than 35 years with a preoperative CDVA of 20/25 or better were thought to carry a higher risk for complications.

Some of the most common complications seen after the CXL procedure include sterile infiltrates (7.6%) and central stromal scars (2.8%).[100] Stromal haze formation has also been described after CXL[84,100] and is thought to be due to transient corneal fibroblast generation.[138] This phenomenon is most apparent at 1 month postoperatively, plateaus for 3 months, and usually fades 12 months after treatment.[56] Permanent corneal haze is reported to occur in 8.6% of treated eyes.[139]

Rarer adverse incidents following treatment have been reported. These include bacterial, protozoal, herpetic, and fungal keratitis[140]; corneal burns[95]; diffuse lamellar keratitis at the interface of a LASIK flap[141]; iritis; significantly elevated IOP[142]; and corneal melting requiring deep lamellar keratoplasty.[143]

Also of concern are reports of serious complications such as persistent corneal edema,[144] endothelial damage,[145,146] and conjunctival intraepithelial neoplasia[147] in the keratocyte-voided bed of the recipient cornea in a patient who had DALK following CXL failure.

INTRASTROMAL CORNEAL RING SEGMENTS

Intrastromal corneal ring segments were developed and FDA-approved in 1999 for the treatment of low myopia, but they were quickly overshadowed by laser refractive procedures. Interest in ICRS resurfaced when Colin et al.[148] reported their usefulness in treating mild to moderate keratoconus in 2000. The concept behind ICRS insertion in keratectasia is not to eliminate the ectatic process, but to modify the corneal shape without removing tissue or manipulating the central cornea. The goal of this treatment is to improve spectacle-corrected vision or contact lens tolerance, thus delaying or eliminating the need for a corneal transplant.[149] Intrastromal corneal ring segments as a treatment option offer the added advantage that the rings are removable if not effective or poorly tolerated, with eyes returning to their preoperative refractive status within 3 months of explantation.[150–152] Intrastromal corneal ring segments appear to be highly biocompatible,[153] with confocal studies showing normal central corneal images in all layers with normal epithelial cells, subepithelial nerve plexus, keratocyte scattering, and endothelial morphology in most individuals.[154,155]

Intrastromal corneal ring segments act as passive spacing elements that shorten the arc length of the anterior corneal surface and cause displacement of the collagen fibers, resulting in flattening of the cornea in myopic eyes.[A] As a consequence of this effect, the central portion of the anterior corneal surface tends to flatten and the peripheral area adjacent to the ring is displaced forward.[156,157] The Barraquer thickness law[158] can roughly predict the induced change in corneal shape after additive device implantation, whereby the outcome achieved is directly proportional to the thickness of the ICRS and inversely proportional to its diameter.[159–163]

Although the mechanism of action of ICRS is well documented in myopic eyes, the structural alterations responsible for topographic homogenization of ectatic corneas after ICRS implantation are not fully understood.[164] The response of the ectatic cornea to prosthesis implantation appears to be more complex, and this variable response is hypothesized to be due to the nonorthogonal lamellar architecture of these corneas.[165,166] The refractive results achieved with ICRS implantation in ectatic eyes are independent of patient age[167] and are thought to be due to a reduction in HOAs,[168–170] central and peripheral corneal flattening, anterior chamber depth shortening, and corneal apex displacement to a more physiologic location via a reduction in paracentral ectasia.[164] Intrastromal corneal ring segments do not appear to alter corneal viscoelastic biomechanical properties.[171,172]

Design

Currently, 2 main types of ICRS devices are available commercially. Incomplete ring segments, including Intacs (Addition Technology, Inc.) and Ferrara ring (Mediphacos, Inc.), have been available for some time, while the complete intrastromal Myoring (Dioptex GmbH) became available more recently. The Keraring (Mediphacos Ltda.) has been specifically developed for keratoconus patients and shares the same design, thickness, and composition as the Ferrara rings but includes different arc lengths for better management of astigmatism. Intacs SK (severe keratoconus or steep K) was recently introduced with significant design modifications to better suit the higher refractive errors associated with more advanced cases of keratectasia. The modifications include a smaller inner diameter of 6.0 mm and an elliptical cross-sectional design. These segments are available in 2 thickness profiles of 400 μm (steep K value of 57.0 to 62.0 D

Table 5. Cohort studies of Intacs/Intacs SK implantation in keratoconic eyes.

Author*/Device (Year)	Eyes (n)	FU (Mo)	Surgery	Incision	Mean Change SE (D)	Mean Change Sphere (D)
Colin/Intacs[148] (2000)	10	10	Mechanical	Temporal	2.1	1.7
Kymionis[154]/Intacs (2007)	17	67	Mechanical	Nasotemporal and inferosuperiorly	2.52†	(—)
Niknam[169]/Intacs SK (2012)	37	6	Mechanical	Steep/horizontal axis implantation	(—)	(—)
Sansanayudh[173]/Intacs SK (2010)	10	6	Femtosecond	Steep axis	3.05	(—)
Kubaloglu[181]/Intacs (2010)	68	12	Mechanical/Femtosecond	Steep axis	1.87†	2.0†
Zare[184]/Intacs (2007)	30	6	Mechanical	Temporal	3.7†	3.0†
Kanellopoulos[185]/Intacs (2006)	20	12	Mechanical	Temporal and superior to horizontal meridian	3.4†	1.9†
Colin/Intacs[187] (2006)	57	12	Mechanical	Temporal	1.5†	(—)
Alió[190]/Intacs (2005)	26	12	Mechanical Group I: 1 segment Group II: 2 segments	Temporal	Group I: 3.2† Group II: 2.25†	(—)
Ertan[191]/Intacs (2008)	306	10	Femtosecond	Temporal	3.0†	2.9†
Boxer Wachler[210]/Intacs (2003)	74	20	Mechanical	Steep axis	2.4	(—)
Shetty[196]/Intacs (2008)	14	12	Mechanical	Steep axis	5.0†	4.06†
Alió[197]/Intacs (2006)	13	48	Mechanical	Perpendicular to positive meridian	1.4	0.4
Colin[198]/Intacs (2007)	100	24	Mechanical	Temporal	3.13†	2.47†
Levinger[199]/Intacs (2005)	58	12	Mechanical	Temporal	2.84†	2.16†
Hellstedt[200]/Intacs (2005)	50	6	Mechanical	Temporal	2.78	(—)
Haddad[201]/Intacs SK (2012)	66	12	Femtosecond	Steep axis	2.97†	3.47†
Rho[202]/Intacs SK (2013)	25	3	Femtosecond	(—)	1.25†	−1.63†
Kotb[203]/Intacs SK (2013)	37	6	Femtosecond	Steep axis/perpendicular to the peripheral flattening	1.8†	(—)
Khan[204]/Intacs SK (2012)	31	12	Mechanical	Steep axis	3.73†	(—)
Fahd[205]/Intacs SK (2012)	24	6	Femtosecond	(—)	6.55†	(—)
Shetty[206]/Intacs (2009)	12	6	Mechanical	Steep axis	2.98	2.23
Ertan[207]/Intacs (2006)	118	12	Femtosecond	Temporal	3.8†	2.9†
Siganos[208]/Intacs (2003)	33	11	Mechanical	Steep axis	1.3	(—)
Colin[209]/Intacs (2001)	10	12	Mechanical	Temporal	(—)	(—)

(—) = data not available; + = deterioration in parameters; CDVA = corrected distance visual acuity; FU = follow-up; K = keratometry; SE = spherical equivalent

*First author

†Statistically significant result

Table 5. (Cont.)

Mean Change		% Gaining CDVA, Mean Change	Study Design	Complications
Cylinder (D)	K (D)			
1.5	4.8	(—)	Prospective nonrandomized	10.0% explanted
(—)	1.57 †	59%, (—)	Retrospective	70.5% superficial vascularization & deposits
(—)	4.48†	(—), 0.79 logMAR †	Prospective nonrandomized	2.7% explantation
1.15	7.87	70%, 0.26 logMAR †	Retrospective	None
1.17†	3.54†	81.8%, 0.2 Snellen lines†	Retrospective	4.4% decentration 5.8% extrusion
0.75†	1.94†	73.3%, 0.12 logMAR †	Prospective nonrandomized	13.3% exposure 3.3% keratitis
2.5†	2.9†	(—)	Prospective nonrandomized	5.0% perforation 30.0% exposure
2.8†	3.7†	62.0%, (—)	Prospective nonrandomized	12.2% explanted
Group I: 2.4† Group II: 2.3†	Group I: 4.6† Group II: 5.2†	81.8% Group I, 0.22 logMAR† 86.6% Group II, 0.24 logMAR†	Prospective nonrandomized	None
0.2	2.7†	71.6%, 0.20 logMAR†	Prospective nonrandomized	0.9% extrusion
(—)	(—)	45.0%, 0.17 logMAR (—)	Retrospective	1.3% superficial implantation 1.3% extrusion
1.87†	3.98†	69.2%, 0.20 logMAR†	Prospective nonrandomized	(—)
2.0	3.3	(—)	Retrospective	15.3% vascularization 30.7% channel deposits
1.31†	3.3†	68.3% , NA	Prospective nonrandomized	4.0% explantation
1.37†	3.44†	12%, 0	Retrospective	10.3% surgical adjustment
(—)	4.2	76.7%, 0.21 logMAR†	Prospective nonrandomized	8.0% explantation 14% refractive adjustment
0.99†	1.97†	(—), 0.12 logMAR†	Retrospective	(—)
+0.76	2.21†	72%, 0.21 logMAR†	Retrospective	(—)
−0.44	4.1†	55%, 0.06 logMAR	Prospective nonrandomized	5.4% localized edema 5.4% overcorrection 5.4% segment overlap
0.51	6.7†	(—), 0.15 logMAR†	Retrospective	19.3% extrusion
1.65†	(—)	(—), 0.25 logMAR†	Prospective nonrandomized	None
1.50	3.69†	66.6%, 0.18 decimal†	Retrospective	0.8% vascularization 25.0% deposits
1.7†	3.9†	73.7%, 1.8 Snellen lines†	Retrospective	8.5% deposits
(—)	3.2†	75.7%, 0.17 logMAR (—)	Prospective nonrandomized	3.0% superficial implantation 3.0% superficial vessels
2.7	4.6	(—), 0.16	Prospective nonrandomized	None

Table 6. Cohort studies of Ferrara and Keraring implantation in keratoconic eyes.

Author*/Device (Year)	Eyes (n)	FU (Mo)	Surgery	Incision	Mean Change SE (D)	Mean Change Sphere (D)
Torquetti[163]/Ferrara (2009)	35	60	Mechanical	(—)	(—)	(—)
Siganos[164]/Ferrara (2002)	26	6	Mechanical	(—)	5.8	4.69
Kubaloglu[182]/Keraring (2011)	96	6–18	Mechanical/femtosecond	Steep axis	3.62†	(—)
Haddad[201]/Keraring (2012)	107	12	Femtosecond	Steep axis	2.65	3.74
Ferrara[225]/Ferrara (2012)	1073	23	Mechanical Group I (160 arc) Group II (210 arc)	Steep axis	Group I: 1.73† Group II: 4.38†	(—)
Alfonso[226]/Keraring (2013)	41	6	Femtosecond	(—)	(—)	(—)
Shabayek[238]/Keraring (2007)	21	6	Femtosecond	Steep axis	2.23†	0.96†
Tunc[227]/Keraring (2013)	30	12	Mechanical	Steep axis	5.16†	(—)
Alfonso[228]/Keraring (2012)	56	6	Femtosecond	Flat axis	(—)	(—)
Gharaibeh[229]/Ferrara (2012)	55	6	Mechanical	Steep axis	0.06	2.96†
Coimbra[230]/Keraring (2012)	35	3	Femtosecond	Steep axis	2.58†	(—)
Ameerh[231]/Ferrara (2012)	79	6	Mechanical	Steep axis	3.36†	2.67†
Hamdi[232]/Ferrara (2011)	100	6	Mechanical	(—)	1.08	(—)
Alfonso[233]/Keraring (2011)	219	6	Femtosecond	Flat axis	(—)	(—)
Kubaloglu[234]/Keraring (2010)	100	12	Femtosecond	Steep axis	2.83†	2.24†
Pesando[235]/Ferrara (2010)	130	37	Mechanical	Steep axis	5.51	(—)
Ferrara[236]/Ferrara (2009)	80	6.6	Mechanical	90-degree meridian	2.96†	(—)
Kwitko[237]/Ferrara (2004)	51	13	Mechanical	Steep axis	1.53	(—)

(—) = data not available; + = deterioration in parameters; CDVA = corrected distance visual acuity; FU = follow-up; K = keratometry; SE = spherical equivalent
*First author
†Statistically significant result

and cylinder <5.0 D) and 450 µm (steep K >62.0 D and cylinder >5.0 D).[149] The smaller diameter of Intacs SK and its associated elliptical shape may reduce halos and glare.[173,174] The design features of these segments are summarized in Table 4.

Implantation

Two surgical methods have been described for ICRS implantation: mechanical and femtosecond laser assisted. The mechanical procedure is done under sterile conditions. For the centration point, the surgeon has various options: the pupil center, the geometric corneal center, or the visual axis. The decision will depend on several factors such as the angle kappa and the surgeon's criteria. This reference point will determine the final position of the segment, the location of the incision, as well as the center of intrastromal dissection. After the axis of incision is defined (usually the steepest K reading), an intraoperative ultrasonic pachymetric measurement is recommended before the incisions are created. With a calibrated diamond knife, a 1.0 mm radial incision is made at 70%

Table 6. (Cont.)

Mean Change				
Cylinder (D)	K (D)	% Gaining CDVA, Mean Change	Study Design	Complications
(—)	5.98†	74.2%, 0.21 logMAR†	Retrospective	(—)
2.22	(—)	(—), 0.23 logMAR†	Prospective nonrandomized	7.6% superficial implants 3.8% asymmetric implants
(—)	5.01†	90.6%, 0.42 logMAR†	Retrospective	58.3% deposits 1.0% extrusion 1.0% segment migration 1.0% superficial implantation
1.93	1.44	(—), 0.08 logMAR	Retrospective	(—)
(—)	Group I: 3.46† Group II: 3.82†	80% group I, 4.0 Snellen lines† 68.8% group II, 2.0 Snellen lines†	Retrospective	3.82% overall complication rate
(—)	1.62†	48.7%, 0.06 logMAR†	Prospective nonrandomized	None
2.67†	1.21†	(—), 0.16 logMAR†	Prospective nonrandomized	38% superficial corneal opacification 4.7% infectious keratitis
(—)	4.95†	93.3%, 0.34 logMAR†	Prospective nonrandomized	None
(—)	(—)	60%, 0.1 logMAR†	Prospective nonrandomized	None
1.05†	5.75†	87.3%, 0.21 logMAR†	Retrospective	1.8% spontaneous extrusion 3.6% superficial rings 3.6% bacterial keratitis
3.92†	3.07†	82.0%, 0.15 logMAR†	Retrospective	None
1.32†	4.59†	(—), 0.14 logMAR†	Retrospective	(—)
2.26†	3.05†	64.0%, (—)†	Prospective nonrandomized	13% overall complication rate
(—)	(—)	57.0%, 0.11 logMAR†	Prospective nonrandomized	None
1.33†	2.76†	85.0%, 3.0 Snellen lines†	Retrospective	4.0% decentration 1.0% extrusion 1.0% shallow implantation 1.0% perforation
(—)	3.59	97.6%, 0.19 logMAR†	Retrospective	3.0% explantations 3.0% asymmetric implants 0.76% perforation
(—)	5.19†	74.2%, 4 Snellen lines†	Retrospective	None
1.66	5.59	86.4%, (—)	Retrospective	3.9% decentration 19.6% extrusion 1.9% bacterial keratitis 1.9% disciform keratitis

of the pachymetric value. A blunt dissector is used to create the stromal tunnels after the application of a vacuum trephine, with dissection done in a clockwise and counterclockwise fashion. After the vacuum application is completed, the intrastromal segments are implanted, the incision site is closed with a single 10-0 nylon suture, and a therapeutic contact lens is applied.[175–177]

The other ICRS implantation method is the creation of a tunnel with the assistance of the femtosecond laser. The patient is positioned under the laser, and the globe is fixated with a disposable suction device. The cornea is marked at the pupil center,[173,178] and a disposable glass applanation cone affixed to the laser is lowered onto the eye to flatten the corneal surface and create a reference plane for the laser focus and application. The recommended settings to program the laser are as follows: channel depth of 400 µm, inner channel diameter of 6.6 mm, outer channel diameter of 7.4 mm, and incision length of 1.4 mm. After the channel is created, the suction device is removed and the segments are inserted using a technique similar to

Table 7. Cohort studies of Myoring implantation in keratoconic eyes.

Author* (Year)	Eyes (n)	FU (Mo)	Surgical Procedure	Incision Location	Mean Change SE (D)	Mean Change Sphere (D)
Jabbarvand[244] (2014)	42	12	Femtosecond Group I, 250 µm depth Group II, 300 µm depth	Steep axis	(—)	2.82 Group I† 2.6 Group II†
Jabbarvand[245] (2013)	98	12	Femtosecond	Steep axis	(—)	5.57†
Jabbarvand[246] (2013)	95	12	Femtosecond	Steep axis	7.25†	5.74†
Alio[247] (2011)	12	6	Femtosecond	Temporal	7.31†	5.15†
Daxer[72] (2010)	15	12	Mechanical	(—)	5.75†	5.23†

(—) = data not available; + = deterioration in parameters; CDVA = corrected distance visual acuity; FU = follow-up; K = keratometry; SE = spherical equivalent
*First author
†Statistically significant results

that in the mechanical procedure. Incision closure after surgery is as described above.[178]

Although the femtosecond laser–assisted procedure is easier and faster[170] and would theoretically create a more uniform and accurate stromal dissection plane, it has not resulted in superior visual/refractive outcomes compared with the manual technique.[170,179–183] In 1 study, however, the femtosecond laser–assisted technique was superior in aberrometric correction.[180]

Nomograms

The planning for ICRS insertion is a crucial step in determining the outcome of surgery. Some earlier studies describe uniform placement of symmetrical or asymmetric ICRS for all patients,[154] but since then there have been several nomograms that aim to improve the predictability of surgical intervention. The various parameters used to improve predictability include preoperative SE,[149,184,185] the location and morphology of the cone,[163] the magnitude of associated asymmetric astigmatism,[163,186,187] and preoperative CDVA levels.[188,189] These parameters are used to determine the thickness of the appropriate ring segment for a given patient.

The decision for asymmetric placement of segments is made after evaluation of the topographic maps. The thicker segment is usually placed to correspond to the steeper half of the cone (predominantly inferiorly placed) to lift the cone and produce the maximum flattening effect. The thinner segment is placed in the opposite half of the cornea to counterbalance the thicker segment and flatten the rest of the corneal surface.[190–192]

Even though the majority of proposed nomograms are based on empirical data, the results obtained are often satisfactory. To date, there has been no direct comparison of the various nomograms demonstrating the superiority of 1 particular technique. An interesting further development in this field would be incorporation of the biomechanical and aberrometric characteristics of the virgin corneal tissue in nomograms to further improve topographic predictability after ring insertion.[192]

Single- Versus Double-Segment Implantation

While Sharma and Boxer Wachler[193] reported superior postoperative results and a more physiologic corneal surface after single-ring implantation, others have found no significant difference between single- and double-segment implantation.[194] Larger prospective studies of this topic are anticipated.

Incision Location

Most surgeons make a temporal incision at or just superior to the horizontal meridian; others choose the 12 o'clock or 1 o'clock position. Another option is to place the incision in the axis of coma, in the positive cylinder axis (if it is not 90 degrees from the topographic axis), or in the steepest topographic meridian.[149,170,190,194] No comparative studies have evaluated the role of incision location on clinical outcomes.

Tunnel Size

No significant differences in visual outcomes have been reported when the ICRS segment is implanted in 2 different tunnel sizes of 6.7 mm × 8.2 mm (wide) and 6.6 mm × 7.6 mm (narrow). However, the narrow tunnel results in higher levels of complications after 6 months of follow-up (42% versus 15%).[195]

Table 7. (Cont.)

Mean Change				
Cylinder (D)	K(D)	CDVA	Study Design	Complications
2.6 Group I[†] 2.53 Group II[†]	5.43 Group I[†] 4.96 Group II[†]	0.02 logMAR Group I 0.12 logMAR Group II	Prospective nonrandomized	None
3.07[†]	6.9[†]	0.33 logMAR[†]	Prospective nonrandomized	1.0% explantation
3.02[†]	9.78[†]	0.26 logMAR[†]	Prospective nonrandomized	4% explantation
4.3[†]	8.03[†]	0.11 logMAR	Retrospective	8.3% explantation; 16.6% corneal opacities
2.23[†]	5.76[†]	0.35 logMAR	Prospective nonrandomized	None

Clinical Outcomes in Keratoconus

Intacs To date, more than 20 studies have evaluated the role of Intacs implantation in the management of keratoconic patients (Table 5).[148,154,169,173,181,184,185,187,190,191,193,196–210] Most of these are prospective nonrandomized studies with some reporting their results retrospectively.

The results show an impressive reduction in SE between 1.3 D and 6.5 D; almost 70% of studies report a reduction between 2.0 D and 4.0 D. Intacs implantation appears to effectively achieve corneal flattening, with all studies (where data are available) reporting a reduction in maximum K readings between 1.5 D and 7.8 D, with more than two thirds reporting a 3.0 to 5.0 D reduction in K readings. This improvement in corneal shape is associated with an improvement in CDVA in 12% to 86% of treated patients. However, the visual outcomes are variable, with the improvement in visual function attributable to an improvement in corneal shape and a reduction in HOAs after segment implantation.[168–170]

A growing body of evidence suggests that better visual acuity outcomes are to be expected in patients with less advanced keratoconus,[186] with visual outcomes becoming more unpredictable in advanced cases.[184,191] This issue is not universally accepted as some authors report an improvement in corneal shape and visual function in advanced cases of ectasia[191,196] and even in patients with corneal scarring.[193]

Restoration of contact lens tolerance is one of the main objectives of ICRS implantation and has been achieved in 35% to 100% of treated patients.[154,197] In a cohort of 100 patients who had Intacs implantation, 84% of the 44 patients requiring contact lens correction after surgery were able to tolerate their lenses at the 24-month follow-up.[198]

Intacs insertion has been found to positively affect vision-specific patient satisfaction in up to 87% of treated patients,[199,200] a phenomenon that gradually increases after the procedure[191] and is maintained up to 5 years after treatment.[154]

The impact of Intacs insertion on the thinning central to the ectatic process has been evaluated in several studies looking at CCT measurements after ring segment placement. Most studies show a nonsignificant change in CCT up to 24 months after surgery.[169,183,184,187,191,198,201] These findings coupled with the fact that long-term studies with up to 9 years of follow-up demonstrate stability and safety (92.9% of patients being stable after ICRS implantation in 1 study[210]) have led to suggestions that Intacs implantation might be considered a therapeutic option to halt the progression of the ectatic process.[211] Supplementary evidence in this domain is required, and further studies are awaited.

Iatrogenic Ectasia Several studies have shown that Intacs can be an effective option in secondary corneal ectasia, especially in patients with severe disease and in those who have lost 2 or more lines of CDVA after the development of the ectatic process.[212] According to these studies, more than 70% of post-LASIK ectatic cases can expect an improvement in CDVA after ICRS implantation.[194] Small case series show an improvement in visual acuity and topographic parameters after Intacs[177,179,210,213–217] and Intacs SK implantation[174,218] with stability reported up to 5 years after surgery.[154] Moreover, ICRS implantation has been shown to defer the need for corneal transplantation and may even help halt disease progression.[213]

Pellucid Marginal Degeneration Intacs can also be effective in reducing corneal astigmatism and 2nd-order aberrations and HOAs[219] in contact lens–intolerant patients with early to moderate PMD.[220–223] Several techniques have been proposed for treating such cases by

placing the segments to bisect the steepest part of the cornea[224] or implanting 1 segment above and 1 below the horizontal meridian.[208] It is generally advisable to place a thinner segment in the inferior cornea to avoid inadvertent corneal perforation.[223]

Ferrara and Kerarings In 1 of the first studies of the use of Ferrara rings in keratoconic patients, Siganos et al.[164] reported a significant improvement in UDVA, CDVA, SE, and topography in all treated patients with 6 months of follow-up. Since then, 17 studies have reported the effects of these rings in keratoconic eyes (Table 6).[163,164,182,201,225–238]

Although most of the studies are retrospective, they do demonstrate a significant reduction in SE of between 0.06 D and 5.8 D, with nearly 80% (where data are available) showing a mean reduction of more than 2.0 D. This is accompanied by a reduction in keratometry between 2.0 D and 6.0 D in approximately 80% of studies where data are available (range 1.21 to 5.98 D). This improvement in corneal shape is accompanied by an improvement in CDVA in all the studies in which data are available, with 48% to 97% of treated patients experiencing an improvement in visual function.

Overall, the studies suggest a good refractive and visual outcome, even in cases that require adjustment or reinsertion after removal.[239] The largest series to date, which includes more than 1000 consecutive cases, also confirms a low complication rate of less than 4%.[225] This low rate of ring-related complications is attributable to the "pachymetry law" in which the thickest portion of a pair of segments in the stromal bed cannot exceed half the thickness of the cornea. This large series also demonstrates that the 210-degree ring segments are more effective than their 160-degree counterpart in reducing K readings and asphericity.[225]

There appears to be no difference in topographic changes[166] or final visual outcomes[182,225,226] between the mechanical and femtosecond methods of creating the intrastromal channels. Furthermore, a statistically significant reduction in HOAs in patients with high coma aberration values (RMS greater than 3 μm) has been reported.[238] Keraring implantation has been shown to lead to a significant reduction in maximum elevation on both the anterior and posterior corneal surfaces,[166] with no significant changes in mean CCT values postoperatively.[225,227] Although these studies support the claim of efficacy, reversibility, and adjustability of the Ferrara and Kerarings in keratoconus, no randomized studies are available to date.

Pellucid Marginal Degeneration To date, 2 small retrospective case series have evaluated the effect of Keraring implantation in patients with PMD. They show an improvement in CDVA, SE, and keratometric power[219,234] as well as a reduction in 2nd-order aberrations and HOAs.[219]

There are isolated case reports of successful visual outcomes after ICRS implantation coupled with Artisan,[240] Artiflex,[240] or monofocal posterior chamber intraocular lens implantation.[241]

Iatrogenic Ectasia Regarding ectasia after refractive laser surgery (mainly LASIK), Torquetti and Ferrara[178] report statistically significant improvements in visual and refractive outcomes 6 months after manual implantation of a single Ferrara ring segment. They also report a significant reduction in keratometric values and corneal asphericity.

The study by Piñero et al.[242] shows that more advanced cases of iatrogenic ectasia with pronounced conical protrusion are poor candidates for ICRS implantation. While the group reported a significant improvement in visual acuity and an associated reduction in coma-like aberrations after ring implantation, there was some regression of effect after 12 months, suggesting that the procedure did not stop the ectatic process. This finding is in contrast to findings in other studies that show a stable CCT after ring implantation.[243]

Myoring

Since the first implantation of the Myoring in 2008, 5 studies have evaluated its role in the management of keratoconic eyes. The results of these studies are summarized in Table 7.[72,244–247]

It is apparent that this device is effective in reducing refractive error (SE reduction 5.7 to 7.3 D), flattening the cornea (maximum K reduction 4.9 to 8.0 D), and improving CDVA (logMAR improvement ranging between 0.02 and 0.35). The improvement in CDVA appears to be more profound than the improvement with incomplete ring segments. This phenomenon is thought to be because the complete continuous ring design may induce a more powerful arc-shortening effect for modifying the corneal curvature than incomplete ring segment designs.[245] The age of the patient[245] and the depth of ring implantation[246] did not significantly alter the clinical outcomes.

The studies also report a trend toward a reduction in coma,[244,247] an increase in CCT,[245,247] and stability in CH measurements after ring implantation.[244,245,247]

Although most of the reported studies are prospective, they are small with 3 reports originating from a single center. Further studies are therefore necessary to confirm the efficacy and long-term stability of this new procedure.

Pellucid Marginal Degenernation and Iatrogenic Ectasia To date, no published studies have evaluated the role of the Myoring in the management of these 2 disorders.

Comparison of Intrastromal Corneal Ring Segment Options

While all ICRS studies have demonstrated good visual and refractive outcomes, the commercially available segments have fundamental differences in design and various studies have evaluated whether a particular design is more efficacious in treating patients with keratectasia.

Intacs Versus Keraring Two retrospective studies show that while both these ICRS models are safe and effective, the Keraring is superior in controlling astigmatism and improving visual outcomes.[183,248] This is probably because the smaller optical zone of the Keraring has a more profound effect on visual performance, while the Intacs segment has been shown to induce a significant degree of negative primary spherical aberration.[248] A slight nonsignificant regression of spherical correction has been reported with both ICRS designs.[248]

Intacs Versus Ferrara Kaya et al.[249] report that both ICRS designs result in comparable refractive, topographic, and optical quality outcomes, whereas eyes implanted with the Ferrara segment experience a greater pupil-dependent reduction in scotopic contrast sensitivity.

Intacs SK Versus Keraring In the only retrospective study available, Haddad et al.[201] report a similar and significant improvement in refractive error, keratometric curvature, visual function, anterior and posterior corneal elevation, and coma values with both ring designs at the 1-year timepoint.

Although a smaller ring diameter is more effective in controlling astigmatism, it may also lead to scattering of light rays that can adversely affect visual function. Therefore, it seems logical that an optimal design can achieve effective control of refractive error with minimal induction of adverse visual phenomena. However, no prospective data endorsing the superiority of 1 ring design are available to date. Prospective randomized studies with longer follow-up are needed.

Combined Treatments

The future of complete visual rehabilitation in ectasia may well lie in combined treatments dedicated to resolving both the structural and refractive issues seen in this patient population. The most promising option in this arena is the combined use of ICRS, CXL, and advanced surface ablation techniques.

Collagen Crosslinking and Intrastromal Corneal Ring Segments Several studies show improved UDVA, CDVA, refraction, and keratometry 7 to 12 months after combined treatment in keratoconic eyes.[168,250–252] In a retrospective study,[253] Vicente and Boxer Wachler conclude that the patients with worse preoperative CDVA and SE had a better postoperative gain in CDVA after simultaneous ICRS and transepithelial CXL. Although the synergistic effect of the 2 treatments has not been universally confirmed, Chan et al.[252] report that the combined treatment group showed a significantly greater reduction in cylinder and maximum K than the group having ICRS implantation alone. Çakir et al.[254] could not demonstrate superiority of combined ICRS and CXL treatment over ICRS treatment alone.

In a prospective randomized study, Coskunseven et al.[255] show that ICRS placement followed by CXL led to statistically superior keratometric, refractive, and visual outcomes than CXL followed by ring implantation. The authors also demonstrate the safety of this combined approach, with no significant change reported in pachymetry or ECCs. Furthermore, the refractive changes after simultaneous treatment appear to be reversible after ring explanation while the topographic outcomes are maintained.[256]

It is worthwhile to note that femtosecond laser power must be modified in eyes that have had CXL to compensate for the increase in corneal rigidity and reduction in corneal clarity.[102]

Collagen crosslinking can be performed before, during, or after ICRS implantation, but the ideal sequence and timing of combined treatment is still uncertain.

Triple Procedure (Collagen Crosslinking, Intrastromal Corneal Ring Segments, and Photorefractive Keratectomy) Two small case series[257,258] show the efficacy of simultaneous Intacs implantation with same-day PRK and CXL, as well as sequential Intacs implantation followed by CXL and PRK 6 months later. After 6 to 12 months of follow-up, significant improvements were noted in UDVA, CDVA, refraction, and topography in both groups, with no eyes losing CDVA. Triple therapy has also been shown to result in a reduction in total aberrations,[257] as well as stable pachymetry, ECCs, and corneal viscoelastic properties.[258]

Sequential Intrastromal Corneal Ring Segment Implantation A new technique of double ICRS implantation has been adopted by several research groups, with 2 reports indicating successful refractive outcomes after implantation of a Myoring[259] and Keraring[260] in eyes with previous Intacs implantation.

Intrastromal Corneal Ring Segment Complications

Intacs-related intraoperative complications are very rare and often occur as isolated events related to a suboptimal surgical technique. Adverse events include superficial implantation of the segment, decentration, implant asymmetry,[148,209] and perforation into the anterior chamber.[149,261]

Postoperative complications also appear to be infrequent[262] but include microbial keratitis (1.4% of cases),[263] corneal thinning in the area over the segment, extrusion, reduced corneal sensation, deep neovascularization at the incision site,[264,265] persistent epithelial defects, corneal haze around the segments, corneal melting, iritis, and uveitis.[194] Other rare complications such as acute corneal hydrops,[266] corneal edema,[267] central stromal opacification,[268] stromal necrosis,[269] aberrant corneal nerve regeneration,[270] and chronic pain secondary to direct contact between the segment and corneal nerves[271] have been reported. Furthermore, histopathologic changes have been documented after ICRS implantation, with 1 study finding a reversible induction in keratocyte apoptosis.[272]

Explantation of segments is required in approximately 6.2% of cases; it is frequently due to segment migration.[262] Adjustment of the ring segment may be required in up to 10% of cases.[273]

A common occurrence after ring implantation is the formation of fine white deposits within the intrastromal channels and around the segments, a phenomenon that is almost always visually insignificant.[274–276] However, visually significant symptoms have been reported to occur after ICRS implantation and include diplopia, halos, difficulty in night vision, vision fluctuation, ocular discomfort, and photophobia.[149]

CONCLUSION

Keratectasia is a debilitating condition with a disproportionately high impact on public health resources and vision-specific quality of life.[277,278] It seems likely that early management of keratectasia is useful in preventing disease progression, preserving visual function, as well as deferring, reducing, and even precluding the need for corneal transplantation.

One of the most promising treatment modalities in the field today is CXL, which has revolutionized the management of keratectasia in recent years by effectively stabilizing the underlying ectatic process and in some cases reversing the disease as quantified by key topographic, refractive, and visual outcomes. The literature suggests that the results obtained are more convincing for keratoconus and less remarkable in eyes with other forms of ectasia.[113] This has not curbed the excitement regarding this new technology, with some predicting that it has the potential to prevent up to 50% of the corneal transplantations performed in the United States.[279]

The efficacy of standard CXL as a means of halting the ectatic process is backed by nearly 15 years of laboratory and clinical studies. The procedure appears to be safe with a reported complication rate of 1% to 3%,[280] most of which is attributable to corneal epithelial debridement. This has led to immense interest in the development of other innovative methods of treatment such as transepithelial crosslinking. While the effects of transepithelial crosslinking are still not fully understood, they appear to be less pronounced than that of "epithelium-off" crosslinking. However the noninvasive nature of this technique makes it potentially useful in cases in which epithelial debridement is ideally avoided, such as in patients with other ocular surface pathology, uncooperative patients, and in patients with very thin corneas.

Although there is no lack of clinical studies in the field of CXL, to date only a small number of RCTs exist. It is apparent that robust evidence will only be forthcoming from well-designed multicenter, prospective, sham-controlled RCTs with standardized case descriptions, progression definitions, outcome measures, and sufficient follow-up to clarify the uncertainty that surrounds the long-term effects of photopolymerization. A search for trials on CXL on the U.S. National Institutes of Health Clinical Trials database shows the substantial interest in this domain, with multiple ongoing studies of the various forms of CXL and its synergistic use with other treatment modalities.

One such synergistic treatment option that can be used concurrently with CXL is ICRS implantation. Although the evidence base for ICRS implantation consists solely of uncontrolled longitudinal follow-up studies, the introduction of this corneal reshaping technique for the correction of refractive errors in ectatic corneas has been a valuable and welcome event as it is a simple outpatient-based procedure with a high technical success rate and a complication rate of approximately 4.6%.[262] The procedure is also reversible and adjustable and in the event of failure, does not preclude subsequent corneal transplantation. Furthermore, multiple short-term and medium-term studies have shown statistically significant improvements in corneal topography, refractive error, and visual acuity after ICRS implantation. While these ring devices are a useful alternative treatment, further basic research is required to fully understand their impact on a cellular level, which will help determine the optimal size, shape, and design

of segments and further refine existing surgical nomograms.

So what does the future hold? It is evident that further progress in the field of keratectasia management will occur only with a better understanding of the basic pathophysiology of the disease process and the exact biomechanical response following CXL and ICRS implantation. Corneal hysteresis, elastography, waveform analysis, noncontact tonometry, multiphoton fluorescence, photon microscopy, and inverse computational analysis studies may well lead to new discoveries in this rapidly evolving field.

We envisage that the future norm of visual rehabilitation in keratectasia will lie in the field of combined treatments aiming to correct both the biomechanical instability of the underlying disease process and the resultant refractive error. One such approach is the so-called triple procedure in which ICRS implantation is combined with sequential/simultaneous corneal CXL and corneal reshaping using excimer laser ablation. Although the triple procedure is promising, further detailed in vitro and in vivo studies are required to better define the potential impact of ICRS implantation on riboflavin distribution, UVA irradiance, and the potential for an altered healing response. Further collaboration is also needed to adjust current ablation nomograms for combined treatments to reduce the potential for postoperative refractive surprises and the need for retreatment.

We foresee that CXL will continue to play an increasingly prominent role in the management of the patient with ectasia, as it has the capacity to prevent disease progression and its associated visual morbidity. As we gain more experience with this new treatment modality, the question of prophylactic treatment of all individuals at the time of diagnosis will undoubtedly arise. The answer to this fundamental question will only be definitively answered through a better understanding of the procedure's long-term safety and efficacy, not least because our current, albeit limited, understanding of keratocyte and collagen turnover suggests that the stability gained after crosslinking is likely to be impermanent if the renewed collagen does not exhibit the same increased tensile and resistance properties.[34] If long-term studies do show a regression of the crosslinking effect, further research will have to clearly define and clarify the efficacy and safety profile of retreatment.

Another important gap in our current understanding which requires further investigation is whether the full stiffening effects of the Dresden protocol is essential in halting the ectatic process in all individuals or whether the stiffening effect seen after newer treatments such as transepithelial, high-fluency, or pulsed crosslinking is sufficient to effectively prevent disease progression. Indeed, in this rapidly evolving field we may soon see more widespread use of customized crosslinking profiles while topical riboflavin treatment with exposure to natural sunlight may lead to the birth of a medical management option in the field of keratectasia.

Finally, if the promise of the antibacterial, antienzymolytic, antiedematous,[281] and neuroprotective properties[282] of CXL, as well as its potential to be used as an adjuvant treatment option in refractive surgery[283] and progressive myopia,[284] stand the test of time, photopolymerization will undoubtedly lead to a significant paradigm shift in the management of many other ocular pathologies.

SUMMARY

Collagen crosslinking and ICRS implantation are techniques that can be used as standalone treatments or synergistically to strengthen and reshape the ectatic cornea to improve visual outcomes and possibly circumvent the need for more invasive surgical interventions such as corneal transplantation. Multiple studies report patient outcomes after these reshaping procedures, but the optimal order, timing, and long-term effects of the interventions remain elusive.

Although reported adverse events are generally rare and often reversible, we encourage strict adherence to standardized guidelines and protocols to ensure patient safety. As always, the potential risks and benefits of intervention must be clearly discussed with potential patients, with the ophthalmologist acting as an enabler in the process of informed consent.

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