Corneal Collagen Cross-linking (CXL) Combined With Refractive Procedures for the Treatment of Corneal Ectatic Disorders: CXL Plus

George D. Kymionis, MD, PhD; Michael A. Grentzelos, MD; Dimitra M. Portaliou, MD; Vardhaman R. Kankariya, MD; J. Bradley Randleman, MD

ABSTRACT

PURPOSE: To discuss current combined corneal collagen cross-linking (CXL) and refractive surgical techniques (herein termed “CXL plus”) for the treatment of corneal ectatic disorders to improve functional visual acuity in addition to corneal stability from CXL alone.

METHODS: Literature review.

RESULTS: Efficacious combined treatments with CXL include: photorefractive keratectomy, transepithelial phototherapeutic keratectomy, intrastromal corneal ring segments implantation, phakic intraocular lens implantation, and multiple combined procedures. Some uncertainty remains as to the optimal strategies for each patient. A decision tree is proposed to facilitate optimal patient management.

CONCLUSIONS: With multiple adjuvant techniques, CXL plus is likely to benefit many patients with corneal ectatic disorders. The appropriate combined procedure will depend on multiple factors, such as refraction, corneal thickness, and degree of irregular astigmatism.


Corneal collagen cross-linking (CXL) is a minimally invasive procedure used for the stabilization of corneal ectatic disorders such as keratoconus, pellucid marginal corneal degeneration, and postoperative corneal ectasia. The use of riboflavin (ie, vitamin B2) in conjunction with ultraviolet-A irradiation increases corneal resistance and inhibits progression of the ectatic disorder.

Visual rehabilitation for ectatic corneas requires addressing three concerns: halting the ectatic process, decreasing corneal curvature irregularity, and minimizing the residual refractive error. CXL treatment can restore corneal tectonic integrity to increase the biomechanical rigidity and inhibit the progression of the ectatic disorder. After the first study in 2003 by Wollensak et al., several other studies reported promising results regarding CXL treatment; several ocular parameters have been shown to improve after CXL due to the stiffening effect and corneal curvature regularization.

Nevertheless, in many cases, patients cannot achieve a visual acuity sufficient to provide them functional vision after CXL without the use of rigid gas permeable contact lenses due to significant residual irregularity and refractive error.

Several adjuvant therapies in combination with CXL treatment (CXL plus) have been proposed to develop a combined technique that can treat patients diagnosed as having keratectasia and offer them stability together with improved...
functional vision. The term “CXL plus,” introduced in 2011, refers to the several combined refractive procedures studied to enhance the CXL result. Evidence exists for the use of the following complementary procedures to CXL: photorefractive keratectomy (PRK), transepithelial phototherapeutic keratectomy (PTK), intrastromal corneal ring segments (ICRS) implantation, phakic intraocular lens (PIOL) implantation, and multiple techniques combined with CXL.

The current study evaluates and compares the literature on the varying combination treatment strategies and presents a decision tree to facilitate optimal patient management.

**PRK AND CXL**

Topography-guided PRK in combination with CXL was the first combined CXL treatment performed with the use of excimer laser ablation and many iterations of this design have followed (Table 1). Reported variations in technique have included timing of procedures (simultaneous or sequential), maximal recommended ablation depth, and the use of mitomycin C.

Initially, Kanellopoulos and Binder presented a patient diagnosed as having keratoconus who underwent topography-guided PRK 1 year after CXL and showed significant clinical improvement. Then, simultaneous topography-guided PRK followed by CXL was reported as an alternative option for optimizing the outcome of CXL in the treatment of keratoconus. Kymeisis et al. described a patient with pellucid marginal corneal degeneration who underwent simultaneous topography-guided PRK followed by CXL and showed significant visual and topographic improvement. In a prospective study by Kymeisis et al., patients with keratoconus treated with simultaneous topography-guided PRK followed by CXL showed significant improvement in all parameters evaluated: spherical, equivalent, defocus, uncorrected and corrected distance visual acuity, and keratometric values. In a comparative study, Kanellopoulos showed that same-day simultaneous topography-guided PRK followed by CXL is more effective than sequential CXL with delayed (6 months or more) PRK in the visual rehabilitation of keratoconus. Several studies followed and confirmed the safety and/or efficacy of the simultaneous topography-guided PRK followed by CXL in patients with keratoconus and corneal ectasia after LASIK; long-term stability of this combined procedure has also been demonstrated. Recently, Kymeisis et al. reported that simultaneous conventional PRK and CXL could be an effective and safe treatment for the management of pellucid marginal corneal degeneration.

The major considerations in planning this combined procedure are ablation depth and postoperative corneal thickness; varying recommendations have been proposed, based mainly on maximal ablation depth and residual corneal thickness. Kymeisis et al. recommended PRK treatment planning based on the patient’s corneal thickness. Treatment modifications (eg, attempted correction, ablation zone, and percentage of customization in case of topography-guided PRK) were based on preoperative corneal pachymetry, corrected distance visual acuity, and manifest refraction to arrive at a recommended maximum ablation depth of 50 μm. Kanellopoulos et al. recommended a maximum ablation depth of 50 μm in their cases, but a corneal thickness of no less than 350 μm after PRK. Stojanovic et al. recommended a maximum ablation depth of 60 μm and a minimal postoperative corneal thickness of 400 μm. Tuwarirqi and Sinjab limited the ablation depth to achieve ±1 diopter of emmetropia and keep approximately 400 μm of stroma before proceeding with CXL, taking into account that the thickness of corneal epithelium is normally 50 μm. Lin et al. reported that the refractive treatment was limited by a minimal residual stromal depth of 300 μm and maximum stromal ablation depth of 80 μm. Alessio et al. planned an ablation stromal depth between 18 and 49 μm (mean: 31.1 ± 0.9 μm) in their study. In any case, corneal thickness plays a significant role in the planning of the combined PRK-CXL procedure. Moreover, thin corneas limit the possibility of tissue removal by PRK and therefore this combined procedure may not be performed in advanced cases of keratoconus.

Regarding mitomycin C use after laser ablation during PRK, Kanellopoulos et al. used mitomycin C 0.02% for 20 seconds after laser ablation in their cases. Kymeisis et al. did not use mitomycin C and considered that cross-linking of the ablated stroma offers the advantage of depopulating keratocytes in the anterior stroma, which could reduce the possibility of haze formation. Tuwarirqi and Sinjab used mitomycin C 0.02% after excimer laser ablation for 30 seconds in all cases.

**TRANSEPITHelial PTK AND CXL**

According to the Dresden protocol, the epithelium must be removed prior to CXL treatment to permit the penetration of riboflavin solution into the corneal stroma and ensure adequate corneal saturation with riboflavin. Mechanical or alcohol-assisted epithelial debridement during CXL can be replaced with excimer laser transepithelial PTK removal to enhance the postoperative outcome (Table 2). The aim of transepithelial PTK is epithelial removal and anterior
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Eyes</th>
<th>Surgical Procedures</th>
<th>Outcomes</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsarou et al.</td>
<td>Case report</td>
<td>1</td>
<td>CXL followed by topography-guided PRK 12 months later</td>
<td>Significant clinical improvement and stability</td>
<td>No complications</td>
</tr>
<tr>
<td>Katsarou et al.</td>
<td>Pilot Study</td>
<td>2</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
<td>No complications</td>
</tr>
<tr>
<td>Katsarou et al.</td>
<td>Case report</td>
<td>3</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant improvement in UDVA, CDVA, and topographic improvement</td>
<td>No complications</td>
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<td>4</td>
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<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
<td>No complications</td>
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<tr>
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<td>Case report</td>
<td>5</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
<td>No complications</td>
</tr>
<tr>
<td>Katsarou et al.</td>
<td>Case report</td>
<td>6</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
<td>No complications</td>
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<tr>
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<td>Case report</td>
<td>7</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
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</tr>
<tr>
<td>Katsarou et al.</td>
<td>Case report</td>
<td>8</td>
<td>Simultaneous topography-guided PRK and CXL</td>
<td>Significant visual UDVA and CDVA and topographic improvement in CXL</td>
<td>No complications</td>
</tr>
</tbody>
</table>

**TABLE 1: Outcomes With Combined PRK and CXL**

<table>
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<th>Author</th>
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PRK = photorefractive keratectomy; CXL = corneal collagen cross-linking; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; SE = spherical equivalent; PKP = penetrating keratoplasty.
TABLE 2
Outcomes With Combined t-PTK and CXL

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Eyes</th>
<th>Surgical Procedures</th>
<th>Follow-up</th>
<th>Outcomes</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymionis et al.</td>
<td>Case report</td>
<td>1</td>
<td>t-PTK followed by CXL</td>
<td>6 months</td>
<td>Visual and topographic improvement</td>
<td>No complications</td>
</tr>
<tr>
<td>Kymionis et al.</td>
<td>Prospective, comparative</td>
<td>38</td>
<td>t-PTK (group 1) and mechanical epithelial debridement (group 2) during CXL</td>
<td>12 months</td>
<td>UDVA, CDVA, steep keratometry, and corneal astigmatism improved significantly in patients with t-PTK epithelial removal during CXL</td>
<td>No complications</td>
</tr>
<tr>
<td>Kapasi et al.</td>
<td>Retrospective, comparative</td>
<td>34</td>
<td>t-PTK during CXL (t-PTK group) and mechanical epithelial removal during CXL (mechanical group)</td>
<td>1 month</td>
<td>CXL with laser epithelial removal resulted in significantly better change in SE and astigmatism compared to CXL with mechanical epithelial removal</td>
<td>No complications</td>
</tr>
</tbody>
</table>

t-PTK = transepithelial phototherapeutic keratectomy; CXL = corneal collagen cross-linking; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; SE = spherical equivalent

corneal stromal smoothing to decrease the keratoconic irregular astigmatism.

Kymionis et al. described a patient with keratoconus who demonstrated significant visual and topographic improvement after transepithelial PTK epithelial removal during CXL treatment. In a comparative case series, Kymionis et al. showed that epithelial removal using transepithelial PTK during CXL (Cretan protocol) results in better visual and refractive outcomes in comparison with mechanical epithelial removal. In a similarly designed comparative but retrospective study, transepithelial PTK removal during CXL was superior to CXL with mechanical epithelial removal. Explanation of why transepithelial PTK-CXL results in better outcomes in comparison with mechanical epithelial removal during CXL has been given in both relevant studies. It is well known that the epithelium does not form a uniform layer of thickness over the stroma, but is thinner usually in the region of the cone in patients with keratoconus or postoperative ectasia. Therefore, transepithelial PTK may result in epithelial removal in some areas, whereas in others it may include epithelial, Bowman’s layer, and partial stromal removal regularizing the corneal surface. In patients with keratoconus, transepithelial PTK uses the patients’ own epithelium as a masking agent, allowing excimer laser ablation to remove corneal epithelium along with corneal stromal tissue on the apex of the cone to regularize the anterior corneal surface.

CXL AND ICRS IMPLANTATION

ICRS implantation has been proven beneficial in keratoconus and corneal ectasia after LASIK because it can result in topographic and visual rehabilitation without interfering with patients’ visual axes. Despite the promising results, ICRS likely does not halt the progression, especially in young patients. Therefore, CXL in addition to ICRS use offers a “plus” in the biomechanical stability of the ectatic cornea. Reported variations in technique have included the number of segments implanted, location of segments, timing of channel creation, use of multiple segments of different styles, and timing of ICRS and CXL. Although there is limited literature on large samples and long-term results regarding this combined treatment, we report the already published studies (Table 3).

In a study by Chan et al., inferior Intacs segments (Addition Technology, Lombard, IL) insertion alone and with the addition of CXL were compared to evaluate the synergic effect of the combined procedure in patients with keratoconus. Intacs with the CXL group resulted in better keratoconus improvement than Intacs insertion alone. Coskunseven et al. published a comparative study of two sequences in patients with keratoconus: CXL followed by ICRS versus ICRS followed by CXL. ICRS implantation followed by CXL resulted in greater improvement of keratoconus.

El-Raggal evaluated the creation of a femtosecond laser-mediated channel for the insertion of ICRS 6 months after CXL in patients with keratoconus. The author concluded that although femtosecond laser channel creation can be performed safely after CXL, it is advised to perform it before or simultaneously with CXL to avoid increase in energy use, difficult dissection, and postoperative corneal haze formation. In contrast, Henriquez et al. reported that Ferrara ICRS implantation (Ferrara Ophthalmics Ltda, Belo Horizonte, Brazil) after CXL is a safe and efficacious treatment option. Renesto et al. reported on the refractive and topographic outcomes 24 months after CXL, and insertion of ICRS in keratoconic eyes; ICRS insertion, with or without prior CXL, showed no difference between groups in terms of refractive, topographic, pachymetric, and corneal biomechanical results.
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Eyes</th>
<th>Surgical Procedures</th>
<th>Follow-up</th>
<th>Outcomes</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al.</td>
<td>Retrospective, comparative</td>
<td>12/13</td>
<td>Intacs alone/Intacs and CXL</td>
<td>102 ± 39 days/97 ± 38 days</td>
<td>Intacs with CXL showed significantly greater reduction in cylinder, steep, and average keratometry, and topographic lower-upper ratio</td>
<td>No complications</td>
</tr>
<tr>
<td>Cukrasznien et al.</td>
<td>Prospective, comparative, and randomized</td>
<td>48</td>
<td>CXL followed by ICXRS followed by CXL (mean: 7 ± 2 months)</td>
<td>13 ± 1 months</td>
<td>ICXRS followed by CXL showed an overall higher increase of UDVA and decrease of the manifest cylinder and mean keratometry values</td>
<td>8 eyes had slight subepithelial and stromal edema with stromal opacities, which disappeared within 3 months</td>
</tr>
<tr>
<td>B-Ragat</td>
<td>Comparative</td>
<td>5 (1.5 m/), 5 (1.6 m/), 5 (1.7 m/)</td>
<td>Femtosecond-mediated channel creation using 1.5, 1.6, and 1.7 m/ power setting for ICXRS insertion 6 months after CXL</td>
<td>6 months</td>
<td>Femtosecond laser channel creation can be performed after CXL; the laser power must be modified. Channel dissection and ICXRS implantation should be performed before or concurrent with CXL.</td>
<td>Corneal haze resolved in all eyes within 6 weeks</td>
</tr>
<tr>
<td>Henriquez et al.</td>
<td>Prospective</td>
<td>9</td>
<td>CXL followed by Ferrara ICXRS 6 months later</td>
<td>6 months</td>
<td>Significant visual improvement, reductions in SE, and keratometry readings</td>
<td>No complications</td>
</tr>
<tr>
<td>Renesto et al.</td>
<td>Randomized clinical trial 2 groups</td>
<td>19/20</td>
<td>Riboflavin only and ICXRS with 3-month delay/CXL and ICXRS 3 months later</td>
<td>24 months</td>
<td>No significant difference was identified between groups in UDVA, CDVA, SE, and spherical or cylindrical components</td>
<td>No complications</td>
</tr>
<tr>
<td>B-Awady et al.</td>
<td>Prospective</td>
<td>21</td>
<td>Keraring implantation followed by CXL at least 3 months later</td>
<td>5.67 ± 1.89 months</td>
<td>All outcome measurements (UDVA, CDVA, SE, cylinder, and keratometry readings) were improved after Keraring implantation and showed further improvement after CXL.</td>
<td>No complications</td>
</tr>
<tr>
<td>B-Ragat</td>
<td>Prospective, comparative</td>
<td>9/7</td>
<td>Keraring insertion followed by CXL with a 6-month interval to same day procedure</td>
<td>12 months</td>
<td>No significant differences in UDVA, CDVA, refractive error; keratometric values showed greater reduction in the same day group</td>
<td>No complications</td>
</tr>
<tr>
<td>Saedlens et al.</td>
<td>Case series</td>
<td>7</td>
<td>Same-day Ferrara ICXRS Implantation and CXL</td>
<td>12 months</td>
<td>SE decreased significantly and keratometry values showed improvement</td>
<td>Inferior ring had to be removed in 1 patient 5 months postoperatively because of implant migration</td>
</tr>
<tr>
<td>K-Li et al.</td>
<td>Case series</td>
<td>131</td>
<td>Same-day combined ICXRS-CXL procedure, no epithelial removal</td>
<td>7.07 ± 4.66 months (range: 1 to 25 months)</td>
<td>Retractive and keratometric measurements were improved in all cases</td>
<td>No complications</td>
</tr>
<tr>
<td>Ehran et al.</td>
<td>Case series</td>
<td>25</td>
<td>ICXRS followed by transepithelial CXL, 9.98 month interval</td>
<td>3 months</td>
<td>Transepithelial CXL after Intacs resulted in an additional improvement in UDVA, CDVA, sphere, cylinder, and keratometry</td>
<td>No complications</td>
</tr>
<tr>
<td>Kamburugjtu &amp; Eris</td>
<td>Case report</td>
<td>2</td>
<td>CXL (1 month right eye), 1 day left eye after Intacs SK Implantation</td>
<td>8 months</td>
<td>Improvement in visual acuity and decrease in manifest refraction and keratometric values</td>
<td>No complications</td>
</tr>
<tr>
<td>Ahion et al.</td>
<td>Retrospective, comparative, nonrandomized</td>
<td>16 (classic group), 11 (pocket group)</td>
<td>ICXRS followed by CXL (3 to 12 months later) either with epithelial debridement (classic group) or intrastromal pocket for riboflavin delivery (pocket group)</td>
<td>12 months</td>
<td>No statistically significant differences between the 2 groups in any of the parameters measured (UDVA, CDVA, sphere, cylinder, and keratometry values, corneal aberrations, and corneal pachymetry)</td>
<td>Significant corneal haze was observed in all cases in the early postoperative period, which resolved over time</td>
</tr>
<tr>
<td>Lam et al.</td>
<td>Case report</td>
<td>1</td>
<td>CXL and ICXRS</td>
<td>7 months</td>
<td>Improvement in refractive and keratometric values</td>
<td>No complications</td>
</tr>
</tbody>
</table>

CXL = corneal collagen cross-linking; ICXRS = intrastral corneal ring segments; CDVA = corrected distance visual acuity; SE = spherical equivalent; UDVA = uncorrected distance visual acuity.

The Intacs and Intacs SK are manufactured by Addition Technology, Lombard, IL. The Ferrara ICXRS is manufactured by Ferrara Ophthalmics Ltda, Belo Horizonte, Brazil. The Keraring is manufactured by Mediphasco, Belo Horizonte, Brazil.
CXL With Refractive Procedures for Corneal Ectatic Disorders/Kymionis et al

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Eyes</th>
<th>Type of PIOL</th>
<th>Interval Between PIOL and CXL</th>
<th>Follow-up</th>
<th>Outcomes</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymionis et al.</td>
<td>Case report</td>
<td>1</td>
<td>Toric PIOL</td>
<td>12 months</td>
<td>3 months</td>
<td>Improvement in UDVA and CDVA</td>
<td>No complications</td>
</tr>
<tr>
<td>Kurian et al.</td>
<td>Prospective</td>
<td>5</td>
<td>PIOL</td>
<td>$11.4 \pm 7.7$ months</td>
<td>6 months</td>
<td>Significant visual and refractive improvement</td>
<td>2 eyes also received ICRS</td>
</tr>
<tr>
<td>Faciallah et al.</td>
<td>Retrospective</td>
<td>16</td>
<td>Toric PIOL</td>
<td>6 months</td>
<td>6 months</td>
<td>Significant visual and refractive improvement</td>
<td>No complications</td>
</tr>
<tr>
<td>Izquierdo et al.</td>
<td>Prospective</td>
<td>11</td>
<td>Iris claw PIOL (Artiflex)</td>
<td>6 months</td>
<td>6 months</td>
<td>Significant visual and refractive improvement</td>
<td>No complications</td>
</tr>
<tr>
<td>Guelle et al.</td>
<td>Case series</td>
<td>17</td>
<td>Toric iris-claw PIOL (Artiflex or Artisan)</td>
<td>$3.9 \pm 0.7$ months (range: 3.1 to 5.5 months)</td>
<td>36.9 ± 15.0 months (range: 14 to 58 months)</td>
<td>Significant visual and refractive improvement</td>
<td>No complications</td>
</tr>
</tbody>
</table>

CXL = corneal collagen cross-linking; PIOL = phakic intraocular lens; PIOL = phakic implantable collamer lens; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; ICRS = intrastromal corneal ring segments

The Artiflex and Artisan are manufactured by Ophtec BV, Groningen, The Netherlands.

El Awady et al. reported CXL has an additive effect after KeraRing implantation (Mediphacos, Belo Horizonte, Brazil) and may be considered as an enhancement/stabilizing procedure. El-Raggal reported that even though combined femtosecond-assisted KeraRing insertion and CXL can be performed safely in one or two sessions, the same-session procedure appears to be more effective regarding the improvement in the corneal shape. Comparable results were observed by Saelens et al. after same-day Ferrara ICRS implantation and CXL.

A same-day combined ICRS-CXL procedure, without epithelial removal, was investigated by Kilic et al. Similarly, a separate study demonstrated that transepithelial CXL has an additive effect on Intacs implantation in keratoconic eyes. A case of bilateral transepithelial CXL after Intacs SK implantation in a patient with ectasia after LASIK was also described. Results showed improvement in visual acuity and manifest refraction in both studies.

Aliò et al. reported the results in two groups of patients with keratoconus who previously underwent KeraRing segments implantation using an Intralase femtosecond laser (Abbott Medical Optics, Santa Ana, CA) and 3 to 12 months later underwent CXL either by using the standard epithelial removal protocol or by creating an instrastromal pocket for riboflavin delivery. There were no statistically significant differences between the two groups in any of the parameters measured.

Recently, Lam et al. reported another case of corneal ectasia after LASIK, which showed stabilization of the ectatic disorder and vision improvement after femtosecond laser-assisted ICRS implantation followed by CXL.

**CXL AND PIOL IMPLANTATION**

Three types of PIOL are currently available for intraocular refractive correction: angle supported, iris fixed, and posterior chamber. PIOL implantation in addition to CXL is another alternative combined treatment of keratoconus performed to optimize the CXL outcome (Table 4).

The combination of CXL and toric PIOL (toric Visian ICL; STAAR Surgical, Monrovia, CA) implantation was first reported in 2011 as a two-step approach for treatment of progressive keratoconus and high myopic astigmatism in a 29-year-old woman. Three months postoperatively, uncorrected distance visual acuity improved from counting fingers to 20/40 and corrected distance visual acuity improved from 20/100 to 20/30. Kurian et al. and Faciallah et al. also consequently reported the results of CXL followed by toric Visian ICL implantation in eyes with progressive keratoconus, demonstrating optimum efficacy, safety, and stability of visual and refractive outcomes.

Implantation of the foldable iris-claw PIOL (Artiflex; Ophtec BV, Groningen, The Netherlands) following CXL is another possible option to improve visual rehabilitation in keratoconic eyes. Izquierdo et al. implanted the Artiflex 6 months after CXL, resulting in significant improvement in visual acuity, keratometry, and refractive error. Güell et al. reported long-term outcomes of combined CXL and toric iris-claw
### TABLE 5

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<thead>
<tr>
<th>Author</th>
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<th>Eyes</th>
<th>Combined Procedure</th>
<th>Order of Procedures</th>
<th>Follow-up</th>
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<tr>
<td>Kymionis et al.</td>
<td>Case report</td>
<td>1</td>
<td>ICRS, PRK, and CXL</td>
<td>CXL followed by CXL 12 months after ICRS implantation</td>
<td>9 months</td>
<td>Improvement in vision (UDVA and CDVA) and keratometric values</td>
<td>No complications</td>
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<tr>
<td>Kanellopoulos &amp; Skoultzes</td>
<td>Case report</td>
<td>1</td>
<td>PRK, CXL, and PIOL</td>
<td>Topography-guided PRK and CXL and subsequent (1 year later) PIOL implantation</td>
<td>36 months</td>
<td>Improvement in vision and keratometric values</td>
<td>No complications</td>
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<tr>
<td>Iovine et al.</td>
<td>Case report</td>
<td>5</td>
<td>ICRS, PRK, and CXL</td>
<td>ICRS implantation followed by same-day PRK and CXL</td>
<td>6 months</td>
<td>Improvement in UDVA, CDVA, SE, keratometry values and total aberrations</td>
<td>No complications</td>
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<tr>
<td>Kremer et al.</td>
<td>Case series</td>
<td>45</td>
<td>ICRS, PRK, and CXL</td>
<td>ICRS implantation followed by (6 months later) simultaneous wavefront-guided PRK and CXL</td>
<td>12 months</td>
<td>Significant improvement in UDVA, CDVA, and keratometric values; no patient lost any line of CDVA; ECD changes</td>
<td>Mild haze in 11.1% of treated eyes, epithelial hyperplasia in 4 of 45 eyes</td>
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<tr>
<td>Coskunseven et al.</td>
<td>Prospective case series</td>
<td>16</td>
<td>ICRS, CXL, and PRK</td>
<td>ICRS implantation followed by CXL (after 6 months) and transepithelial topography-guided PRK (6 months after CXL)</td>
<td>6 months</td>
<td>All of the parameters analyzed (UDVA, CDVA, SE, and keratometric values) showed significant improvement; no eye lost any line of CDVA</td>
<td>No complications</td>
</tr>
<tr>
<td>Coskunseven et al.</td>
<td>Case series</td>
<td>14</td>
<td>ICRS, CXL, and PIOL</td>
<td>ICRS implantation followed by CXL (&gt; 6 months) and transepithelial topography-guided PRK (&gt; 6 months)</td>
<td>12 months</td>
<td>Significant improvement in UDVA and CDVA in keratoconic eyes with high refractive error</td>
<td>No complications</td>
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<tr>
<td>Yeung et al.</td>
<td>Retrospective case series</td>
<td>16</td>
<td>t-PTK, ICRS, and CXL</td>
<td>Same-day t-PTK followed by single ICRS implantation and CXL</td>
<td>6.9 ± 4.6 months</td>
<td>Significant improvement in UDVA, CDVA, and mean and steep keratometric values</td>
<td>No complications</td>
</tr>
</tbody>
</table>

**Notes:**
- **CXL** = corneal collagen cross-linking
- **ICRS** = intrastromal corneal ring segments
- **PRK** = photorefractive keratectomy
- **UDVA** = uncorrected distance visual acuity
- **CDVA** = corrected distance visual acuity
- **PIOL** = phakic intraocular lens
- **SE** = spherical equivalent
- **ECD** = endothelial cell density
- **t-PTK** = transepithelial phototherapeutic keratectomy

*To optimize the results of CXL, more care and meticulous attention to preoperative evaluation, patient selection, and surgical technique is required.*

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**Multiple Techniques Combined**

1. **CXL with PRK and ICRS implantation**
2. **CXL with PRK and PIOL implantation**
3. **CXL with PRK and PIOL implantation**
4. **CXL with transpupillary PTK and ICRS implantation**

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**References:**
- Kymionis et al.
- Kanellopoulos & Skoultzes
- Iovine et al.
- Kremer et al.
- Coskunseven et al.
- Yeung et al.
implantation followed by CXL in a three-step procedure. In another study, Coskunseven et al. reported collagen copolymer toric PIOL implantation for residual myopic astigmatism after ICRS implantation and CXL in a three-stage procedure for keratoconus. Recently, in an attempt to further enhance the CXL result, Yeung et al. investigated and showed the efficacy of transepithelial PTK followed by a single inferior ICRS implantation and CXL as a same-day triple procedure.

CONTROVERSIES FOR COMBINED TECHNIQUES
Simultaneous Ver Sus Sequential Pr K and CXL

The first approach of sequential CXL followed by PRK by Kanellopoulos and Binder had some limitations. First, this approach has limited efficacy because the cross-linked corneas may have a different ablation rate from that of normal corneas; this could lead to unpredictable results. Moreover, there is an increased possibility of haze formation after PRK. Finally, probably the most significant limitation of this approach was the removal of the stiffened cross-linked corneal tissue by PRK that could decrease or even reverse the possible effects of CXL. These aspects led to the consideration that the best option for optimizing the outcome of CXL in the treatment of keratoconus was simultaneous PRK followed by CXL. In his comparative study, Kanellopoulos confirmed this consideration, showing that same-day simultaneous topography-guided PRK followed by CXL is more effective than sequential CXL with delayed (6 months or more) PRK in the visual rehabilitation of keratoconus. The main advantage of simultaneous PRK followed by CXL is that laser ablation does not interfere with the already cross-linked part of the cornea. Nevertheless, this remains an area for future study.

Optimal Epithelial Removal Technique During CXL

Two comparative studies have shown that epithelial removal using transepithelial PTK during CXL seems to be a better option in comparison with mechanical epithelial removal because it results in better visual and refractive outcomes. It seems that transepithelial PTK during CXL could be performed in many cases of CXL for better visual and refractive outcomes, especially in cases in which PRK before CXL cannot be performed due to low corneal thickness. However, a larger patient series with a longer follow-up is needed to confirm the outcomes of combined transepithelial PTK-CXL.

Order of Combined Procedures

ICRS Implantation and CXL. The main goal of CXL is to stabilize the ectatic cornea and arrest the progression of the ectatic disorder. ICRS implantation is used to flatten the central corneal curvature while maintaining the biomechanical status in the underlying corneal stroma. Therefore, pretreatment with ICRS implantation would re-shape and flatten the cornea and subsequent CXL would stabilize the newly shaped cornea. In accordance with this consideration, the comparative study by Coskunseven et al., which is the only comparative study to date, showed that ICRS implantation followed by CXL resulted in greater improvement of keratoconus in comparison with CXL followed by ICRS implantation. The findings of the study suggest that although each treatment step flattens the cornea, a stiffer cornea that has been treated by CXL decreases the flattening effect of ICRS implantation, thus restricting its effect and decreasing the maximum flattening potential. Therefore, to achieve the maximum overall effect, ICRS implantation should be better performed first to reshape the cornea and CXL treatment applied afterward to further flatten the cornea and stabilize corneal disorder.

PIOL Implantation and CXL. CXL plus PIOL implantation is performed as a two-step approach: CXL is performed first to stabilize keratoconus followed by toric PIOL implantation once stability of manifest refraction and topography is achieved (typically after 6 to 12 months of CXL).

LIMITATIONS FOR THIS REVIEW

An apparent problem of this literature review is the great disparity of data presented in the studies analyzed. The scope of this review is to list the available information regarding combined CXL treatments; the heterogeneity of the methods presented (eg, prospective, retrospective, randomized, nonrandomized studies, etc.) is not further analyzed, but is clearly stated in the tables. The conclusions drawn by certain studies (ie, prospective randomized trials) might be of greater importance than others (ie, case reports). Moreover, the number of patients included and the follow-up period can play an important role in the evaluation of the outcome measures of a published study.

Another limitation is that long-term data of CXL alone show a continuous visual, refractive, and topographic improvement even several years after treatment, whereas the combined CXL techniques’ follow-up period was relatively shorter. Therefore, the addition of adjuvant techniques in CXL treatment interacts unpredictably with the continuation of improvement from CXL alone.

CXL PLUS DECISION TREE

Figure 1 shows a proposed treatment algorithm (decision tree) that could be used for patient manage-
CXL With Refractive Procedures for Corneal Ectatic Disorders/Kymionis et al

**CONCLUSION**

CXL alone is effective in halting the progression of keratoconus, but the improvement in visual acuity that studies have confirmed is usually not sufficient for functional vision and better quality of life. Combined CXL treatments (CXL plus) seem to be the way for optimization of the CXL result in the treatment of corneal ectatic disorders. Whatever the adjuvant technique, it seems that CXL plus may be the way of the future for appropriate candidates, a combined procedure that might represent an actual treatment for most of the cases of corneal ectatic disorders.

**AUTHOR CONTRIBUTIONS**

Study concept and design (GDK, JBR); data collection (MAG, DMP, VPK); analysis and interpretation of data (JBR); drafting of the manuscript (GDK, MAG, DMP, VPK, JBR); critical revision of the manuscript (GDK, MAG, JBR); supervision (GDK)

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