Review Article

Corneal cross-linking (CXL) combined with refractive surgery for the comprehensive management of keratoconus: CXL plus

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The past two decades have witnessed an unprecedented evolution in the management of keratoconus that demands a holistic approach comprising of inhibiting the ectatic progression as well as visual rehabilitation. The advent of corneal cross-linking (CXL) in the late 1990s resulted in long-term stabilization of the ectatic cornea along with limited reduction in corneal steepening and regularization of corneal curvature. However, CXL as a standalone procedure does not suffice in rehabilitating the functional vision especially in patients who are unwilling or intolerant towards contact lenses. The concept of "CXL plus" was proposed which incorporates adjunctive use of refractive procedures with CXL in order to overcome the optical inefficiency due to corneal irregularity, decrease the irregular astigmatism, correct the residual refractive error and improve functional visual outcome in keratoconus. Several refractive procedures such as conductive keratoplasty (CK), photorefractive keratectomy (PRK), transepithelial phototherapeutic keratectomy (t-PTK), intrastromal corneal ring segments (ICRS) implantation, phakic intraocular lens (PIOL) implantation and multiple other techniques have been combined with CXL to optimize and enhance the CXL outcome. This review aimed to summarize the different protocols of CXL plus, provide guidelines for selection of the optimum CXL plus technique and aid in decision-making for the comprehensive management of cases with primary keratoconus in addition to discussing the future and scope for innovations in the existing treatment protocols.

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Keratoconus in the past was considered a hindrance to complete visual rehabilitation and surgeons around the world resorted to spectacles, contact lenses and corneal transplantation which were the only options available until recently.[1] Being a non-inflammatory corneal ectatic condition, it is characterized by progressive thinning of corneal stroma and central or paracentral corneal steepening leading to induced regular or irregular astigmatism and decrease in visual acuity.[2,3] The past two decades have witnessed an unprecedented evolution in the management of this disease with the help of advanced diagnostic techniques and newer treatment protocols.[3] The concept of corneal cross-linking (CXL) as a minimally invasive procedure to stabilize corneal ectatic disorders was introduced in the late 1990s.[4] Wollensak *et al*. in 2003 reported CXL as a potential treatment for halting the progression of keratectasia and alleviating the need for corneal transplantation in keratoconus.[5] CXL constitutes the use of riboflavin and ultraviolet-A (UVA) light to increase the biomechanical corneal stability and halt ectatic progression in keratoconus.[4-7] Numerous studies have reported long-term stabilization of the ectatic cornea, reduction in corneal steepening and regularization of corneal curvature with the use of CXL in keratoconus.[7-11]

Concept of CXL plus

Management of keratoconus demands a holistic approach that comprises of inhibiting the ectatic progression along with visual rehabilitation. Thus, several concerns which need to be sequentially addressed in keratoconus to ensure visual recovery include halting the keratectasia, reducing or rectifying irregular astigmatism and correcting the residual refractive error. CXL as a standalone procedure without subsequent use of contact lenses does not suffice in overcoming the optical inefficiency due to corneal irregularity and achieving a satisfactory visual outcome. Adjunctive use of refractive procedures with CXL was proposed so as to regularize and reshape the cornea and improve functional vision in keratoconic patients.[12,13] The term "CXL plus" coined by Kymionis in 2011 incorporates such adjuvant therapies to CXL which offer both stability and functional vision in keratoconus.[12,14] Various refractive procedures targeting the corneal curvature, corneal irregularity, irregular astigmatism and residual refractive error have been combined with CXL to optimize and enhance the CXL outcome in keratoconus. Combinations of CXL with conductive keratoplasty (CK), photorefractive keratectomy (PRK),

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transepithelial phototherapeutic keratectomy (t-PTK), intrastromal corneal ring segments (ICRS) implantation, phakic intraocular lens (PIOL) implantation and multiple other techniques have been studied and suggested. This review aimed to summarize the different protocols of CXL plus, provide guidelines for selection of the optimum CXL plus technique and discuss the future and scope for innovations in keratoconus management. This study attempts to elucidate the rationale and indication for each of the recommended CXL plus techniques and intends to aid in decision-making for the comprehensive management of cases with primary keratoconus while excluding eyes with post-surgical ectasia and other corneal ectatic diseases.

Conductive keratoplasty (CK) with CXL

Conductive keratoplasty (CK) has been described for the treatment of irregular corneas in keratoconus.[15] This non-invasive technique involves no corneal incision.[16,17] It works on the principle of corneal remodeling through heating of collagen fibrils at a specified temperature with radio frequency current (350 kHz) applied to selective spots in the peripheral corneal stroma at a depth of 500 μm in order to achieve the intended correction.[16,17] Kato *et al*. reported regression of visual acuity and corneal topography to the preoperative state following CK in advanced keratoconus.[18] Kymionis *et al*. reported the combined effect of CK and CXL procedures in two patients with advanced keratoconus.[19] Conductive keratoplasty was applied on topographically more flattened areas of the corneal periphery to steepen them and decrease the irregular astigmatism.[19] The number of the spots applied in each case depended upon the severity of irregularity and the topography.[19] The CXL procedure was performed 24 hours later in the first patient and immediately after CK in the second patient aiming to stabilize the corneal remodeling effect of CK.[19] Nevertheless, corneal remodeling was found to be temporary despite post-CK application of CXL and regression was noticed 3 months postoperatively.[19] This study concluded that although combining CXL with CK offered theoretical advantage, no added benefit of this combination was observed over CXL alone due to potential regression.[19]

Photorefractive keratectomy (PRK) with CXL

The very first attempt to seek the benefits of CXL plus by conjunction of excimer laser technology with CXL was accomplished by combining topography guided (topo-guided) photorefractive keratectomy (PRK) and CXL [Table 1]. Initially, a two-step sequential approach was presented by Kanellopoulos and Binder.[20] The authors reported a case of keratoconus who was treated with CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) and after one year of corneal stability underwent sequential topo-guided PRK resulting in significant clinical improvement.[20]

Despite the promising results of this case report, there were several limitations with this two-step approach. The ablation rate might be different in a cross-linked than in a non-operated, virgin cornea leading to unpredictable refractive results and possible limited effectiveness of PRK. The risk of post-PRK haze formation is higher as the anterior stroma is repopulated by new keratocytes six months after CXL. Lastly and probably the most significant limitation of this approach is that the second-step PRK removes part of the cross-linked corneal tissue thereby potentially decreasing the stiffening effect of CXL.

On account of these limitations, it was anticipated that simultaneous topo-guided PRK followed immediately by CXL so as to strengthen the cornea at a targeted and uniform depth may be a better approach to optimize the benefits of this combined treatment. This technique was performed for the first time by Kymionis *et al*. on a contact lens intolerant patient with pellucid marginal corneal degeneration (PMD).[21] Kymionis *et al*. subsequently applied the simultaneous topo-guided PRK-CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) approach on patients with progressive keratoconus and reported significant improvement in all evaluated parameters including spherical equivalent (SE), defocus, uncorrected and corrected distance visual acuity (UDVA and CDVA) and keratometric values.[22] The PRK treatment was modified (e.g., attempted correction, optical zone, percentage of topographic customization) based on the preoperative corneal thickness (CT), corneal high order aberrations (HOAs) and manifest refraction to limit the maximum ablation depth at 50 μm; expected thinnest pachymetry after PRK was aimed at more than 400 μm.[22]

The simultaneous technique seemed to overcome the drawbacks of the initial two-step CXL-PRK procedure due to its main advantage that laser ablation does not interfere with already cross-linked corneal tissue. This consideration was also confirmed with the comparative clinical study by Kanellopoulos which showed that same-day simultaneous topo-guided PRK-CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) is more effective than sequential CXL with delayed (six months or more) PRK.[23] Kanellopoulos recommended 70% treatment of cylinder and up to 70% treatment of sphere so as not to exceed an ablation depth of 50 μm and achieve an expected CT of no less than 350 μm after PRK.[23] The simultaneous approach was reported to be superior on account of three factors; patients' comfort, minimization of the potential stromal scarring and preservation of cross-linked corneal stromal tissue.[23] In another case series, Krueger and Kanellopoulos presented two cases of keratoconus who underwent simultaneous topo-guided transepithelial PRK followed by CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) and showed stability and progressive improvement over a long observation period of at least 30 months; the technique was named "Athens protocol" by the authors.[24]

Several other studies confirmed the safety and efficacy of the simultaneous topo-guided PRK-CXL technique in keratoconic patients. Stojanovic *et al*. performed topo-guided custom surface ablation followed by CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) using transepithelial approach so as to avoid potential custom ablation planning error due to epithelial remodeling observed after traditional manual epithelial debridement.[25] This study recommended the maximum ablation depth of 60 μm with minimum postoperative CT of 400 μm and reported stability over a period of 12 months.[25] Kymionis *et al*. presented the long-term results of simultaneous topo-guided PRK after epithelial removal with transepithelial phototherapeutic keratectomy (t-PTK) followed by CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) and showed significant topographic and clinical improvement that remained stable throughout the follow-up period.[26] Tuwairqi and Sinjab reported significant visual, refractive and topographic improvement after simultaneous topo-guided PRK-CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) in patients with low grade keratoconus.[27] The ablation depth was targeted to achieve ±1.00 diopter of emmetropia and to preserve 400 μm of stroma before proceeding with CXL, taking into account the normal thickness of corneal epithelium as 50 μm.[27]

Table 1: Summary of Outcomes with Combined PRK and CXL

Author	Study design	Surgical Procedure (Number of eyes)	Follow-up	Outcomes
Kanellopoulos and Binder[20]	Case report	CXL followed by topo-guided PRK 12 months later (1)	18 months	Significant clinical improvement and stability; no complications observed
Kymionis *et al.*[22]	Pilot study (Prospective)	Simultaneous topo-guided PRK followed by CXL (14)	10.69±5.95 months (range: 3 to 16 months)	Significant improvement in UDVA, CDVA, SE, defocus and keratometry readings; no complications observed
Kanellopoulos[23]	Retrospective, comparative study	Sequential CXL with delayed PRK and simultaneous topo-guided PRK followed by CXL (127 and 198, respectively)	36±18 months (range: 24 to 68 months)	Simultaneous group performed better in all parameters (UDVA, CDVA, keratometry, SE, corneal haze); significant haze noted in 19 eyes (17 of sequential and 2 of simultaneous group)
Krueger and Kanellopoulos[24]	Case series	Simultaneous topo-guided PRK and CXL (2)	36 and 30 months	Reduction of spherocylindrical refraction and improvement in functional vision; no complications observed
Stojanovic *et al.*[25]	Case series	Topography-guided transepithelial custom ablation followed by CXL (7)	12 months	Visual, refractive, and topographic improvement; no complications observed
Kymionis *et al.*[26]	Prospective case series	Simultaneous topo-guided PRK followed by CXL (31)	19.53±3.97 months, (range: 12 to 25 months)	Significant improvement in UDVA, CDVA, SE and keratometry; no progression of keratoconus; 16 of 31 eyes showed posterior linear stromal haze
Tuwairqi and Sinjab[27]	Prospective, non-randomized, non-controlled study	Simultaneous topography-guided PRK and CXL (22)	12 months	Significant improvement in all study parameters (UDVA, CDVA, sphere, SE, manifest and topographic astigmatism, keratometry); no complications observed
Alessio *et al.*[28]	Prospective, non-randomized clinical trial	Simultaneous transepithelial topo-guided PRK and CXL versus CXL only (17 in each group)	24 months	PRK-CXL provided better UDVA/CDVA and lower SE, spherical/cylindrical power and keratometric values than CXL; no complications observed
Kontadakis *et al.*[29]	Prospective, comparative case series	Simultaneous topo-guided PRK and CXL versus CXL only (60)	39±11 months	Significant improvement in UDVA, CDVA, keratometry, SE and defocus equivalent with significant corneal flattening in PRK-CXL group; no complications observed
Iqbal *et al.*[30]	Prospective, multicentre, comparative, clinical	Standard CXL (group A) versus non-topo-guided PRK and accelerated CXL (group B) (58/67)	24 months	Group B showed significant and early reduction in myopia and astigmatism, Group A showed similar effect on corneal flattening, sphere reduction and equivalent visual outcome at 24 months postoperatively; delayed epithelial healing in 9 eyes and corneal haze in 11 eyes resolved completely; one eye in group B developed stromal scarring
Kanellopoulos[31]	Prospective	Simultaneous topo-Guided Partial-Refraction PRK and CXL (144)	128±4 months (range: 120 to 146 months)	Significant and stable improvement in UDVA, CDVA and keratometry
Kanellopoulos and Asimellis[32]	Case series	Simultaneous topo-guided PRK and high-fluence CXL (231)	36 months	Visual (UDVA and CDVA) and topographic improvement; no complications observed
Kaiserman *et al.*[33]	Retrospective, case series	Epithelial PRK and accelerated CXL (20)	822.5±336.7 days (range: 266 to 1,749 days)	Significant improvement in UDVA, CDVA and keratometry; no complications observed
Shetty *et al.*[34]	Prospective, case series	Combined same-day topography-guided custom ablation treatment (T-CAT) followed by accelerated CXL (2)	6 months	Improvement in UDVA, CDVA and keratometry

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Author	Study design	Surgical Procedure (Number of eyes)	Follow-up	Outcomes
Shetty *et al*.[35]	Prospective, comparative case series	Simultaneous topo-guided PRK followed by enhanced-intensity CXL (29)	12 months	Improvement in visual and keratometric parameters
Fadlallah *et al*.[36]	Retrospective, non-randomized study	Non-topo-guided PRK and CXL (140)	24 months	Significant improvement in UDVA, SE and mean cylinder; 4 eyes developed mild haze
Al-Amri[37]	Prospective, interventional, non-randomized, non-controlled case series	Non-topo-guided PRK and CXL (60)	68.20±4.71 months (range: 60-106 months)	Significant improvement in UDVA, CDVA, SE and keratometry, no serious complications observed, 4 eyes developed mild haze
Shaheen *et al*.[38]	Prospective uncontrolled interventional case series	CXL followed by WFG PRK 12 months later (34)	12 months	Significant improvement in UDVA, CDVA, manifest sphere and cylinder as well as ocular HOAs
Gore *et al*.[39]	Prospective case series	Simultaneous transepithelial WFG PRK and accelerated CXL (47)	24 months	Significant improvement in CDVA, keratometric parameters and coma; one eye lost ≥2 lines of CDVA
Abou Samra *et al*.[40]	Prospective	Simultaneous WFG PRK and accelerated CXL versus sequential WFG PRK 6 months after CXL (62)	12 months	Significant improvement in visual, refractive, keratometric and aberrometric parameters with no significant difference between the 2 groups

PRK=Photorefractive keratectomy; CXL=Corneal cross-linking; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; SE=Spherical equivalent; topo-guided=Topography guided; HOAs=Higher order aberrations; WFG=Wavefront guided

Two studies compared the long-term clinical outcomes of simultaneous transepithelial topo-guided PRK followed by CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) with the outcomes obtained by CXL treatment alone and reported significant improvement in UDVA, CDVA and keratometric values in the PRK-CXL group.[28,29] Alessio *et al*. also analyzed the corneal HOAs and showed better reduction in root mean square (RMS) values after topo-guided PRK-CXL (with a planned ablation stromal depth between 18 and 49 μm) than after CXL alone.[28] Kontadakis *et al*. reported keratometric improvement in both PRK-CXL and CXL alone groups, but corneal flattening was more prominent in the PRK-CXL group.[29] Iqbal *et al*. compared the safety and efficacy of non-topo-guided PRK combined with accelerated epithelium-off CXL (30 mW/cm^2, 7.2 J/cm^2, 8 min) versus standard CXL alone.[30] This study reported significant reduction of both the myopic and astigmatic component in the early postoperative period which remained stable at 24 months following the combined procedure in contrast to the significant late improvement of only the myopic component at 1-2 years following standard CXL procedure.[30]

Recently, Kanellopoulos confirmed long-term safety and efficacy of topo-guided PRK-CXL (6 mW/cm^2, 5.4 J/cm^2, 15 min) in a ten-year follow-up study.[31] The significant improvement in visual acuity noticed at the first postoperative year was reported to be stable at the ten-year evaluation.[31] The accelerated CXL technique used concurrently with topo-guided PRK was also reported to provide long-term stability in keratoconus.[32,33]

Shetty *et al*. reported the results of combined same-day topography-guided custom ablation treatment (T-CAT) followed by accelerated CXL (30 mW/cm^2, 7.2 J/cm^2, 4 min) in keratoconic patients with different types of cones and asphericities.[34] The treatment protocol described by the authors was based on the correlation between corneal asphericity (Q) and cone location in keratoconus and was targeted to achieve the desired post-operative corneal asphericity with the stromal ablation restricted to a depth of 40 μm.[34] Subsequently, Shetty *et al*. also evaluated the impact of keratoconus cone location on the change in refraction, corneal aberrations and biomechanics after simultaneous topo-guided PRK and enhanced-intensity CXL (30 mW/cm^2, 7.2 J/cm^2, 4 min) by comparing two groups; group 1, cone located within the central 2-mm zone and group 2 outside the central 2-mm zone.[35] The authors concluded that cone location affected only visual acuity and biomechanics and reported better improvement in CDVA in group 1 than in group 2.[35]

Several studies have evaluated the efficacy of PRK (after mechanical epithelial removal) using a non-topo-guided approach combined with CXL and have reported significant visual improvement in patients with early stage keratoconus.[36,37] It is also worth noting that the combination of sequential or simultaneous wavefront-guided PRK and CXL has also been studied.[38-40]

Two studies evaluated the outcomes of PRK with CXL performed in keratoconic patients as a primary refractive treatment rather than the recommended therapeutic approach, using a high stromal ablation depth determined on the basis of targeted emmetropia and reported a high incidence of complications such as corneal haze and stromal scarring.[41-43]

It is palpably clear from the aforementioned studies that several recommendations in the planning of the PRK-CXL technique have been reported regarding the maximal ablation depth and the estimated postoperative CT. However, another issue that still remains a debate is the use of mitomycin C (MMC) after PRK and prior to CXL. In several studies, MMC has not been used (or its use is not mentioned) during PRK-CXL.[24,27,29,30,34-36] Kymionis *et al*. have described a

desolation effect of CXL on the keratocyte population in the anterior stroma with *in vivo* confocal microscopy.[44] This effect which reduces, at least theoretically, the possibility of haze formation is considered the main reason for avoiding the use of MMC. On the contrary, other studies have described this combined technique with the use of MMC.[22,25,26,28,32,33,37]

Rationale and Indication: Based on the published data, the topo-guided PRK-CXL treatment aims to stabilize the disease progression as well as normalize the corneal surface in keratoconic eyes by reducing the irregular astigmatism and potentially reducing the refractive error.[22-24] This customized approach; thus, attempts to reverse the impact of corneal irregularity on visual performance of the patient. The combined topo-guided PRK-CXL treatment can be performed in keratoconic patients who have sufficient CT that allows stromal ablation at a depth within the recommended maximum limit of 50 μm.[22-24] The ablation performed is used for therapeutic correction of corneal topographic irregularities and is not targeted for refractive correction; however, partial correction of refractive error can be attempted based on preoperative CT.

Transepithelial phototherapeutic keratectomy (t-PTK) with CXL (Cretan protocol)

According to the conventional CXL protocol, removal of corneal epithelium is an essential step which is traditionally performed by mechanical debridement.[5] However, corneal epithelium during CXL can also be removed by alternative techniques such as transepithelial phototherapeutic keratectomy (t-PTK) [Table 2]. In 2010, Kymionis *et al*. were the first to describe the combination of t-PTK and CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) in a keratoconic patient resulting in significant visual and topographic improvement.[45] The aim of t-PTK was not only to remove the corneal epithelium for the following cross-linking process, but also to regularize the anterior irregular cornea.[45] This combined technique of t-PTK-CXL has been called "Cretan protocol".[46] This protocol constitutes epithelial removal by t-PTK ablation at an intended depth of 50 μm in a 6.5-7.0 mm zone; the de-epithelialized area is then enlarged by mechanical debridement till the targeted diameter of 8.0-9.0 mm followed by CXL.[47,48]

After the first report, Kymionis *et al*. compared the two techniques for epithelial removal during CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) between two well-matched groups and showed that t-PTK-CXL resulted in better visual and refractive outcomes than conventional CXL.[47] The improvement in UDVA, CDVA, steep keratometry and corneal astigmatism was reported to be significant in the t-PTK-CXL group at twelve months postoperatively.[47] In a following study, the initial encouraging outcomes of this protocol were confirmed in the long-term and significant improvement was reported at all postoperative intervals.[48]

Several other studies followed and evaluated the combination of t-PTK and CXL. Kapasi *et al*. in a short-term comparative study showed early results corresponding to the previous studies.[49] Subsequently, another study by the same authors indicated better visual outcome 12 months after treatment with t-PTK-CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) technique.[50] MMC was used following t-PTK ablation in both of these studies.[49,50]

Gaster *et al*. on the contrary reported equivalent outcomes up to 24 months with both t-PTK and mechanical debridement during CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min).[51] Despite the comparable outcomes, the improvement in CDVA in t-PTK-CXL group was reported to be significant at the last follow-up.[51,52] Recently, Grentzelos *et al*. in a prospective comparative long-term study confirmed the outcomes of previously published reports and concluded that t-PTK-CXL (3 mW/cm^2, 5.4 J/cm^2, 30 min) is advantageous over mechanical epithelial removal during CXL.[53]

The effectiveness of the Cretan protocol encompassing the combination of t-PTK and accelerated CXL treatment instead of conventional CXL has also been evaluated. Chen *et al*. confirmed the efficacy of the t-PTK-CXL technique using high intensity CXL (18 or 15 mW/cm^2, 5.4 J/cm^2, 5 or 6 min).[54] Moreover, they evaluated the epithelial thickness profile and showed a more uniform regional epithelial thickness distribution after the combined treatment.[54] Shetty *et al*. reported three cases of keratoconus management using topography-based removal of corneal epithelium (TREK) combined with accelerated CXL (9 mW/cm^2, 5.4 J/cm^2, 10 min) and showed promising results.[55] Sarac *et al*. compared the outcomes of mechanical or t-PTK epithelial removal followed by accelerated CXL (9 mW/cm^2, 5.4 J/cm^2, 10 min) in pediatric keratoconus and reported significant visual and topographic improvement at 12 months in the t-PTK group only followed by comparable results between the two groups at 24 and 36 months postoperatively.[56] The overall decrease in HOA RMS and spherical aberration was reported to be significant in the t-PTK group only indicating better visual quality.[56]

Cretan protocol could also be extended and combined with conventional PRK in cases with adequate corneal thickness. Thus, in a procedure called Cretan protocol plus, t-PTK was performed as described previously in the Cretan protocol, whereas conventional PRK was limited to a maximum ablation depth of 50 μm in a maximum zone of 5.5 mm which was immediately followed by CXL.[57] No eye was estimated to have a corneal thickness less than 350 μm after combined t-PTK-PRK.[57] The authors concluded that Cretan protocol plus is a promising alternative surgical approach in keratoconic patients with adequate corneal thickness.[57]

Rationale and Indication: As it has been thoroughly described in the published studies, t-PTK during CXL actually acts as a treatment customized for irregular corneas in keratoconus. Reinstein *et al*. has shown an epithelial doughnut pattern in keratoconic corneas characterized by localized central thinning surrounded by an annulus of thickened epithelium.[58] Due to the epithelial doughnut pattern, t-PTK in Cretan protocol uses patient's own epithelium as a masking agent and facilitates removal of small quantity of anterior stromal tissue on the cone apex along with the epithelium.[47,48,58] Therefore, t-PTK during CXL additionally targets to smoothen the irregular anterior corneal stroma, decrease the corneal astigmatism and enhance the postoperative outcome.[47,48] It is also worthwhile to note that Cretan protocol can be performed in any case of CXL, even in those in which combined PRK-CXL procedure could not be an option due to low CT.

Intrastromal Corneal Ring Segments (ICRS) with CXL

Intrastromal corneal ring segments (ICRS) implantation either manual or femtosecond laser assisted, aims for flattening and regularization of central cornea and therefore acts as a potential treatment option for keratoconus.[59] In general, ICRS induce more flattening of the corneal curvature as their thickness increases

Table 2: Summary of Outcomes with Combined t-PTK and CXL

Author	Study design	Surgical Procedure (Number of eyes)	Follow-up	Outcomes
Kymionis *et al.*[45]	Case report	t-PTK followed by CXL (1)	6 months	Visual and topographic improvement; no complications observed
Kymionis *et al.*[47]	Prospective, comparative, interventional case series	t-PTK (group 1) and mechanical epithelial debridement (group 2) during CXL (38)	12 months	Significant improvement in UDVA, CDVA, steep keratometry and corneal astigmatism with t-PTK epithelial removal; no complications observed
Kymionis *et al.*[48]	Prospective case series	t-PTK followed by CXL (23)	33.83±10.82 months (range: 24-56 months)	Significant improvement in UDVA, CDVA, keratometric values and corneal astigmatism; no complications observed
Kapasi *et al.*[49]	Retrospective, comparative	t-PTK during CXL (PTK group) and mechanical epithelial removal during CXL (mechanical group) (34)	1 month	Significant improvement in SE and astigmatism in PTK group compared to mechanical group; no complications observed
Kapasi *et al.*[50]	Comparative	t-PTK during CXL (PTK group) and mechanical epithelial removal during CXL (mechanical group) (34)	12 months	Significant improvement in CDVA and gain of CDVA lines in PTK group; no complications observed
Gaster *et al.*[51]	Retrospective, comparative study	manual epithelial debridement and ablation via PTK followed by CXL (339)	24 months	Equivalent visual, refractive and keratometric outcomes between the two techniques
Grentzelos *et al.*[53]	Prospective, comparative, interventional case series	t-PTK (Cretan protocol group) and mechanical epithelial debridement (Dresden protocol group) during CXL (30)	4 years	Significant and faster improvement in visual, refractive and keratometric values in Cretan protocol group; no complications observed
Chen *et al.*[54]	Retrospective case series	t-PTK followed by high intensity CXL (46)	21.0±7.6 months (range: 10-43 months)	Significant improvement in CDVA and keratometric values and decrease in corneal HOAs; three eyes lost ≥2 lines of CDVA
Shetty *et al.*[55]	Case report	t-PTK with topography based ablation followed by accelerated CXL (3)	3 months	Significant improvement in CDVA in 2/3 eyes, topography-based t-PTK technique ablated less stroma and achieved comparable outcomes
Sarac *et al.*[56]	Retrospective, comparative case series	mechanical (group 1) and t-PTK (group 2) based epithelial removal followed by accelerated CXL in pediatric population (40)	36 months	UDVA, total RMS and keratometry improved significantly in both groups, however, improvement in CDVA, SE, HOA RMS and spherical aberration was significant in only group 2; corneal haze ratio was similar; no complications observed
Grentzelos *et al.*[57]	Prospective case series	t-PTK followed by simultaneous PRK and CXL (55)	12 months	Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed

t-PTK=Transepithelial phototherapeutic keratectomy; CXL=Corneal cross-linking; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; SE=Spherical equivalent; HOAs=Higher order aberrations, RMS=Root mean square

and placement gets more proximal to the visual axis.[60,61] Due to the asymmetric cornea commonly present in keratoconus, a combination of thick (placed at the steep areas, usually inferiorly) and thin (placed at the flat areas, usually superiorly) segments may be implanted in order to gain significant corneal surface regularization.[62] On the contrary, equal thickness segments are suggested for managing central cones.[63]

Even though, ICRS may improve corneal irregularity and provide patients with improved visual performance they do not consist of a 'true' treatment for keratoconus, as they do not interfere with the pathophysiology of the condition.[13] Hence, combining CXL with ICRS implantation may lead to keratoconic corneal stiffening and inhibition of ectatic progression in addition to improvement of the irregular cornea.[13,59-63]

Several studies have reported the use of ICRS adjuvant to CXL in keratoconic patients [Table 3]. The combination of ICRS implantation and CXL was shown to result in comparable or better refractive and topographic outcomes than ICRS insertion alone.[64-66] The safety and efficacy of CXL and single or paired ICRS used adjunctively was assessed by many studies and significant improvement was reported in UDVA, CDVA and manifest refraction along with significant reduction in cylinder and keratometry.[61,67-74] A recently published clinical trial reported improvement in anterior corneal HOAs after ICRS implantation and concurrent or sequential CXL.[75] However, no correlation was established between the improvement in HOAs and subjective or objective visual performance.[75]

Several other studies with conflicting data have also been published, with respect to the optimal sequence and timing of ICRS and CXL, with the main argument being which combination may achieve superior outcomes in terms of maximizing corneal flattening.[66-69,76-79] It seems that ICRS implantation followed by same-session or delayed CXL offers superior corneal flattening, whereas ICRS implantation following CXL (two-step procedure) limits the flattening

Table 3: Summary of Outcomes with Combined ICRS Implantation and CXL

Author	Study design	Surgical procedures (Number of eyes)	Follow-up	Outcomes
Chan *et al.*[64]	Retrospective, comparative	Intacs alone/Intacs and CXL (12/13)	102±39 days/97±38 days	Intacs with CXL showed significantly greater reduction in cylinder, topographic lower - upper ratio and steep and average keratometry, no complications observed
Renesto *et al.*[65]	Randomized clinical trial with 2 groups	Riboflavin only and ICRS 3 months later/CXL followed by ICRS 3 months later (19/20)	24 months	No significant difference was identified between groups in UDVA, CDVA, SE, and spherical or cylindrical components; no complications observed
Legare *et al.*[66]	Retrospective, comparative	ICRS and same day CXL/ICRS alone (66)	12 months	Significant improvement in UDVA, CDVA, sphere, cylinder, SE, keratometry and total HOAs in both the groups; no complications observed
Hersh *et al.*[61]	Prospective randomized clinical trial	ICRS with concurrent CXL/ ICRS followed by CXL 3 months later (104/94)	6 months	Substantial improvement in corneal topography with no significant difference between the sequential and concurrent groups, thicker segment size and single segment placement showed greater topographic improvement; No increase in the complication rate in comparison to each procedure alone; infectious keratitis in 2 eyes, inflammation around ICRS in 3 eyes (ICRS explanted in 2 eyes), glare symptoms in one eye (ICRS was explanted)
Henriquez *et al.*[67]	Prospective	CXL followed by Ferrara ICRS 6 months later (9)	6 months	Significant visual improvement, reductions in SE and keratometry readings; no complications observed
El-Raggal[68]	Prospective, Comparative	KeraRing insertion followed by CXL with a 6-month interval/2 step same day procedure (9/7)	12 months	No significant differences in UDVA, CDVA, refractive error; however keratometric values showed greater reduction in the same day group; no complications observed
Saelens *et al.*[69]	Case series	Same-day Ferrara ICRS implantation and CXL (7)	12 months	Significant improvement in SE and keratometry; inferior ring had to be removed in 1 patient because of implant migration
Ertan *et al.*[70]	Case series	ICRS followed by transepithelial CXL, 3.98 month interval (25)	3 months	Additional improvement in UDVA, CDVA, sphere, cylinder and keratometry; no complications observed
El Awady *et al.*[71]	Prospective	KeraRing implantation followed by CXL at least 3 months later (21)	5.67±1.89 months	All outcome measurements (UDVA, CDVA, SE, cylinder, and keratometry readings) were improved after KeraRing implantation and showed further improvement after CXL; no complications observed
Sharma *et al.*[72]	Prospective randomized	CXL alone/CXL combined with simultaneous ICRS implantation (20/18)	12 months	CXL with ICRS yielded additional improvement in UDVA with significant reduction in cylinder and SE; no complications observed
Yeung *et al.*[73]	Retrospective comparative case series	Single or paired ICRS implantation with CXL (85)	12 months	Outcomes were equivalent with single and paired implantation; no complications observed
Saleem *et al.*[74]	Retrospective, multicentre clinical	Paired KeraRing implantation with same session epithelium-on accelerated CXL (43)	36 months	All outcome measurements (UDVA, CDVA, cylinder and keratometry readings) significantly improved; significant reduction in corneal thickness at the thinnest location was noted; 6 eyes showed progression who underwent standard CXL; 1 eye had exposure of ICRS but was stable after a repeat procedure 3 months later
Greenstein *et al.*[75]	Prospective, randomized clinical trial	Same session Intacs and CXL/ sequential, Intacs followed by CXL 3 months later (158)	6 months	Total anterior corneal HOA including vertical and horizontal coma significantly improved, spherical anterior corneal HOAs increased postoperatively with no change in trefoil

Contd...

Table 3: Contd...

Author	Study design	Surgical procedures (Number of eyes)	Follow-up	Outcomes
Nicula *et al*.[76]	Retrospective, comparative	KeraRing implantation followed by CXL 6 months later (group 1)/CXL followed by KeraRing implantation 6 months later (group 2) (41/30)	12 months	Group 1 showed more significant improvement in SE, keratometry and cylinder compared to group 2; no complications observed
Coskunseven *et al*.[77]	Prospective, comparative, randomized	CXL followed by ICRS (group 1)/ ICRS followed by CXL (group 2); mean interval: 7±2 months (48)	13±1 months	Group 2 showed more improvement in CDVA, SE and mean keratometry than group 1; 8 eyes had slight corneal edema with stromal opacities, which disappeared within 3 months
El-Raggal[78]	Comparative case series	Femtosecond-mediated channel creation using 1.5, 1.6, and 1.7 mJ power setting for ICRS insertion 6 months after CXL (15)	6 months	Although channel for ICRS can be created after CXL by modifying the femtosecond laser power, channel dissection and ICRS implantation should be performed before or concurrent with CXL; corneal haze in all eyes resolved within 6 weeks
Kilic *et al*.[79]	Case series	Same-day combined ICRS and transepithelial CXL procedure, with 20% alcohol application and riboflavin injection into the corneal channel (131)	7.07±4.66 months (range: 1 to 25 months)	Refractive and keratometric measurements improved in all cases; no complications observed
Alió *et al*.[80]	Retrospective, comparative, nonrandomized	ICRS followed by CXL (3 to 12 months later) either with epithelial debridement (classic group) or intrastromal pocket for riboflavin delivery (pocket group) (16/11)	12 months	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); significant corneal haze in all cases which resolved over time

ICRS=Intrastromal corneal ring segments; CXL=Corneal cross-linking; CDVA=Corrected distance visual acuity; SE=Spherical equivalent; UDVA=Uncorrected distance visual acuity; HOAs=Higher order aberrations. The Intacs and Intacs SK are manufactured by Addition Technology, Lombard, IL. The Ferrara ICRS is manufactured by Ferrara Ophthalmics Ltda, Belo Horizonte, Brazil. The KeraRing is manufactured by Mediphacos, Belo Horizonte, Brazil

capabilities of the ring segments as the cornea has already been fixed into a suboptimal configuration after the induced CXL stiffening.[61,66-69,76-79] Variations in the CXL technique such as the use of transepithelial approach with application of riboflavin in the corneal channel or an intrastromal corneal pocket have also been evaluated.[70,79,80]

A significant advantage of ICRS is the procedure's reversibility. ICRS can be safely and easily explanted from keratoconic eyes with previous CXL.[81] Although there is reversal of refractive outcomes, some of the topographic benefits gained from implantation may persist after explantation.[81]

Rationale and Indication: Based on the above studies, ICRS implantation followed by CXL improves the corneal curvature, decreases the irregular astigmatism, retards disease progression and rehabilitates functional vision. This combined approach is indicated in keratoconic patients with low spectacle-assisted CDVA due to decentered cones and high corneal irregularity.

Phakic Intraocular Lens (PIOL) Implantation with CXL

Studies have reported the use of phakic intraocular lens (PIOL) following CXL as an alternative approach for the correction of moderate-to-high refractive error in patients with progressive keratoconus intolerant to contact lenses.[82,83] The types of PIOL that have been implanted in keratoconic patients include both iris-fixated and posterior chamber [Table 4].[84-90] This two-step approach was reported for the first time in 2011 by Kymionis *et al*. in a 29-year-old woman with progressive keratoconus and high myopic astigmatism who underwent toric implantable Collamer lens (ICL) implantation 12 months after CXL.[84] Significant improvement was noticed in UDVA and CDVA three months postoperatively and the short-term results of this combined approach were reported to be encouraging.[84]

Two studies reported the outcomes of iris-fixated PIOL implantation following CXL.[85,86] Izquierdo *et al*. studied the safety and efficacy of foldable anterior iris-claw PIOL implanted 6 months after CXL in eyes with progressive keratoconus.[85] Güell *et al*. also performed toric Artiflex/Artisan PIOL implantation following CXL and confirmed the long-term stability of this combined treatment.[86]

Other studies reported short to long-term outcomes of Visian ICL implantation following CXL.[87-90] Kurian *et al*. reported that although it is possible to safely correct the refractive error in keratoconus with posterior chamber PIOL, the aberrations associated with it are uncorrected by the PIOL.[88] Antonios *et al*. evaluated the long-term clinical outcome of Visian toric ICL insertion after CXL in progressive keratoconus.[89] Although significant visual improvement was maintained throughout the follow-up, a small hyperopic shift was observed at 2 years which did not affect the visual outcome.[89] Shafik *et al*. evaluated the predictability, efficacy and long-term stability of toric Visian ICL implanted 12 months after CXL and reported significant visual improvement.[90] None of the eyes needed explantation or repositioning of the ICL during the 3-year follow-up.[90] The decrease in endothelial cell count that was observed in the long-term studies was not significant.[86,90] However, yearly monitoring of endothelial cell count has been recommended.[82]

Table 4: Summary of Outcomes with Combined CXL and PIOL Implantation

Author	Study Design	Type of PIOL (Number of Eyes)	Interval between CXL and PIOL (Duration of follow-up)	Outcomes
Kymionis *et al.*[84]	Case Report	Posterior chamber: Toric Visian ICL (1)	12 months (3 months)	Improvement in UDVA and CDVA; no complications observed
Izquierdo *et al.*[85]	Prospective	Iris claw: Artiflex (11)	6 months (12 months)	Significant visual and refractive improvement with very low residual refractive error; no complications observed
Güell *et al.*[86]	Case series	Toric iris-fixated: Artiflex/Artisan (17)	3.9±0.7 months; range: 3.1 to 5.5 months (36.9 months±15.0; range: 14 to 58 months)	Significant visual and refractive improvement, 94% eyes achieved UDVA of 20/40 or better and none of the eyes lost lines of CDVA; no complications observed
Fadlallah *et al.*[87]	Retrospective	Posterior chamber: Toric Visian ICL (16)	6 months (6 months)	Significant visual and refractive improvement; no complications observed
Kurian *et al.*[88]	Prospective, Case series	Posterior chamber: Visian ICL (5)	11.4±7.7 months (6 months)	Significant visual and refractive improvement; 2 eyes required adjunct ICRS implantation with CXL
Antonios *et al.*[89]	Retrospective	Posterior chamber: Toric Visian ICL (30)	6 months (2 years)	Significant visual and refractive improvement; no complications observed
Shafik *et al.*[90]	Prospective, Interventional Case series	Posterior chamber: Toric Visian ICL (16)	12 months (3 years)	Significant visual and refractive improvement; no complications observed

CXL=Corneal cross-linking; PIOL=Phakic intraocular lens; ICL=Implantable collamer lens; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; ICRS=Intrastromal corneal ring segments. The Visian ICL is manufactured by STAAR Surgical, Monrovia, CA. The Artiflex and Artisan are manufactured by Ophtec BV, Groningen, The Netherlands

Rationale and Indication: After achieving stability of ectatic progression with CXL, PIOL implantation can be performed in selective keratoconic patients having good or acceptable spectacle-assisted CDVA in addition to high refractive error with or without anisometropia. All of the aforementioned studies have reported PIOL implantation after a minimum of 3 months following CXL.[76-82]

Combination of Multiple Techniques

The combination of CXL with a single refractive procedure may sometimes lead to partial gain of functional vision. Therefore, surgeons have proposed combinations of two or more of the above mentioned modalities with CXL so as to maximize the visual outcome. A multimodal approach serves to combine the desirable attributes of each of the included procedures while minimizing their individual limitations. The following combinations of multiple procedures have been reported [Table 5] –

1. CXL with PRK and ICRS implantation
2. CXL with PRK and PIOL implantation
3. CXL with ICRS and PIOL implantation
4. CXL with t-PTK and ICRS implantation
5. CXL with ICRS, PIOL and PRK (Quadruple approach).

The combination of ICRS and PRK incorporates the synergistic use of a tissue-sparing and a tissue-removing procedure with CXL. PRK and CXL may be performed either sequentially or simultaneously with ICRS implantation to address the mild residual refractive error encountered following ICRS insertion in keratoconic patients.[91-96] Despite the variations in the timing and the interval between each of the three procedures, this technique has been reported as safe and effective in providing functional visual acuity to patients with low to moderate keratoconus.[91-96]

Another study evaluated the combination of Athens protocol (PRK with CXL) followed by PIOL implantation to treat the high residual refractive error and reported improved and stabilized visual performance in keratoconic patients.[97]

Several studies have confirmed the safety, efficacy and long-term stability of PIOL implantation following sequential ICRS insertion and CXL in patients with moderate to severe keratoconus.[98-100] PIOL implantation was targeted to correct the moderate to severe ametropia persistent after the initial procedures and improve the visual outcome.[98-100]

The combination of ICRS implantation with CXL and t-PTK performed on the same day has been shown as safe, effective and predictable in patients with moderate keratoconus.[101,102]

A recent retrospective interventional study evaluated a four-stage combined treatment comprising of ICRS, CXL, PIOL and PRK performed sequentially in the same order and confirmed the safety and efficacy of this combined approach in suitable keratoconic patients.[103] All eyes in this series had low preoperative spectacle-assisted CDVA which improved significantly after ICRS implantation compared to improvement in UDVA.[103] The patients underwent CXL treatment followed by PIOL implantation with an interval of 6 months between each of the procedures to correct the high residual refractive error which led to a significant improvement in UDVA and SE.[103] The eyes were later subjected to topo-guided PRK treatment which resulted in added improvement in these parameters.[103] The end result after the four-stage procedure showed significant improvement in visual acuity, with all eyes achieving better postoperative UDVA than preoperative spectacle-assisted CDVA.[103]

LASIK Xtra, SMILE Xtra and PRK Xtra

Laser *in situ* keratomileusis (LASIK) Xtra is a modified procedure that combines LASIK with prophylactic accelerated CXL for the correction of refractive error in an attempt to decrease the risk of postoperative corneal ectasia. Similarly, the combination of small incision lenticule extraction (SMILE) and PRK with CXL

Table 5: Summary of Outcomes with Combinations of Multiple Techniques and CXL

Author	Study Design	Combined procedures (number of Eyes)	Order of the procedures (Duration of follow-up)	Outcomes
Kremer *et al.*[91]	Case series	ICRS, PRK, and CXL (45)	ICRS implantation followed by (6 months later) simultaneous wavefront-guided PRK and CXL (12 months)	Significant improvement in UDVA, CDVA, and keratometry values; no patient lost any line of CDVA; no ECD changes; Epithelial hyperplasia in 4 of 45 eyes
Coskunseven *et al.*[92]	Prospective	ICRS, CXL and PRK (16)	ICRS implantation followed by CXL followed by transepithelial topography-guided PRK with an interval of 6 months between each procedure (6 months)	UDVA, CDVA, SE, and keratometry values showed significant improvement; no eye lost any line of CDVA; no complications observed
Dirani *et al.*[93]	Retrospective	ICRS, CXL and PRK (17)	ICRS implantation followed by CXL with a 4-week interval followed by non-topography-guided PRK 6 months later (6 months)	UDVA, CDVA, SE, and keratometry values showed significant improvement; no complications observed
Al-Tuwairqi *et al.*[94]	Prospective	ICRS, CXL and PRK (41)	ICRS implantation followed by (6 months later) simultaneous topography-guided PRK and CXL (12 months)	Significant improvement in UDVA, SE and keratometry values, 85% of eyes maintained or gained multiple lines of CDVA; no complications observed
Lee *et al.*[95]	Retrospective	ICRS, PRK, and CXL (23)	ICRS implantation followed by combined corneal WFG-PRK (transepithelial) and high-fluence accelerated CXL 1 month later (6 months)	Significant improvement in UDVA, CDVA, SE, keratometry values and HOAs; no complications observed
Koh *et al.*[96]	Prospective	ICRS, PRK, and CXL (30)	ICRS implantation followed by (3 months later) simultaneous wavefront-guided PRK and CXL (12 months)	UDVA, CDVA, SE, and keratometry values improved with reduction in HOAs; no complications observed
Assaf *et al.*[97]	Prospective non-randomized	CXL, PRK, PIOL (22)	Topography-guided PRK followed by same day CXL (Athens protocol), followed by iris claw or angle-supported PIOL implantation 2-4 months later (6 months)	Significant improvement in CDVA, SE and keratometry values; no complications observed
Coskunseven *et al.*[98]	Case series	ICRS, CXL and PIOL (14)	ICRS implantation followed by CXL (>6 months) and then toric PIOL implantation (>6 months) (12 months)	Significant improvement in UDVA and CDVA in keratoconic eyes with high refractive error; no complications observed
Dirani *et al.*[99]	Retrospective	ICRS, CXL and PIOL (11)	ICRS implantation followed by CXL (4-week interval) and then toric PIOL implantation 6 months later (12 months)	Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed
Abdelmassih *et al.*[100]	Consecutive case series	ICRS, CXL and PIOL (16)	ICRS implantation followed by CXL (4-week interval) and then toric PIOL implantation 6 months later (24 months)	Significant improvement in UDVA, CDVA, SE and keratometry; no complications observed
Yeung *et al.*[101]	Retrospective case series	t-PTK, ICRS and CXL (16)	Same-day t-PTK followed by single ICRS implantation and CXL (6.9±4.6 months)	Significant improvement in UDVA, CDVA and mean and steep keratometry values; no complications observed
Rocha *et al.*[102]	Prospective case series	t-PTK, ICRS and CXL (55)	ICRS implantation, followed by CXL and PTK (6 months)	Significant improvement in UDVA, CDVA sphere and cylinder; no complications observed
Coskunseven *et al.*[103]	Retrospective interventional case series	ICRS, CXL, PIOL, PRK (11)	ICRS implantation, followed by CXL followed by PIOL followed by topography-guided PRK with interval of 6 months between each procedure (12 months)	Significant improvement in UDVA, CDVA, SE and astigmatism; no complications observed

CXL=Corneal 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; HOAs=Higher order aberrations, WFG=Wavefront-guided

termed as SMILE Xtra and PRK Xtra, respectively, has also been reported with the same rationale. These procedures are mainly used in patients with high refractive error or borderline corneal parameters seeking refractive correction and therefore, have not been extensively discussed as it is beyond the scope of this study.

Several studies reported comparable results in terms of safety, efficacy and predictability between LASIK Xtra and conventional LASIK [Table 6].[104-108] Despite the initial supportive evidence, long-term studies are required to determine whether LASIK Xtra is beneficial in preventing

Table 6: Summary of Outcomes with LASIK Xtra, SMILE Xtra and PRK Xtra

Author	Study Design	Surgical procedure (Number of Eyes)	Follow-up	Outcomes
Tomita *et al.*[104]	Contralateral eye, comparative case series	LASIK in one eye and LASIK Xtra in contralateral, non-dominant eye (24)	12 months	No significant differences in UDVA, CDVA, MRSE, ECD, CH and CRF were found between the 2 procedures
Wu *et al.*[105]	Prospective controlled clinical trial	LASIK Xtra versus LASIK (96)	6 months	No statistically significant differences in UDVA, CDVA, MRSE, keratometry, pachymetry and ECD; 2 eyes lost one or more lines in the LASIK-Xtra group
Low *et al.*[106]	Retrospective	LASIK Xtra versus LASIK (100)	5.7 months (range: 1.5-13.3 months)	No significant difference in UDVA and efficacy and safety indices between the 2 groups
Kohnen *et al.*[107]	Prospective, randomized, fellow-eye controlled clinical trial	LASIK Xtra versus LASIK (52)	12 months	No statistically significant differences in UDVA and MRSE between the 2 procedures
Seiler *et al.*[108]	Prospective, comparative study	LASIK Xtra versus LASIK (152)	12 months	One month postoperatively, 5 eyes in LASIK Xtra group lost 1 line of CDVA compared with 1 eye in LASIK only group; refractive improvement was similar
Ganesh *et al.*[110]	Prospective	SMILE Xtra (40)	12 months±28.12 days	No complications like haze, keratitis, ectasia or regression were observed; no eye lost lines of CDVA
Ng *et al.*[111]	Prospective, comparative interventional	SMILE Xtra/SMILE (21/32)	6 months	No eye lost ≥1 line of CDVA with good safety and efficacy indices in SMILE Xtra
Osman *et al.*[112]	Retrospective, comparative interventional	SMILE Xtra/SMILE (30/30)	24 months	Significantly higher UDVA, CDVA, MRSE and CRF in SMILE Xtra group
Graue-Hernandez *et al.*[113]	Prospective, interventional, case series	SMILE Xtra in forme-fruste keratoconus (15)	24 months	No intraoperative or postoperative complications observed
Sachdev *et al.*[114]	Interventional comparative case series	PRK Xtra/PRK (109/118)	12 months	No iatrogenic ectasia or hyperopic shift noted in the PRK Xtra group; no significant difference in CDVA or incidence of haze
Ohana *et al.*[115]	Retrospective cohort	PRK Xtra (98)	12 months	Refractive results less accurate than the published data for PRK-only procedure, No corneal ectasia noted, one eye lost 3 CDVA lines and 2 eyes lost 2 CDVA lines due to significant corneal haze

LASIK=Laser in situ keratomileusis; SMILE=Small incision lenticule extraction; PRK=Photorefractive keratectomy; UDVA=Uncorrected distance visual acuity; CDVA=Corrected distance visual acuity; MRSE=Manifest refraction spherical equivalent; ECD=Endothelial cell density; CH=Corneal hysteresis; CRF=Corneal resistance factor

postoperative keratectasia.[106,108] Tomita *et al*. showed insignificant changes in corneal biomechanics after LASIK Xtra as compared to LASIK.[104] Kohnen *et al*. reported topographic and refractive stability with no signs of keratectasia at 12 months postoperatively in both LASIK Xtra and conventional LASIK groups and showed no advantage of LASIK Xtra over LASIK.[107] Taneri *et al*. reported a case of unilateral corneal ectasia that developed 2 years after LASIK Xtra.[109]

Studies have evaluated the initial safety and efficacy of SMILE Xtra at 1-2 years postoperatively.[110-112] In a comparative study, a slight trend towards myopic shift after SMILE Xtra has been reported.[111] Although SMILE Xtra has been safely used in forme-fruste keratoconus, authors have mentioned the need for longer duration of follow-up and larger sample size to fully confirm these findings.[113]

Sachdev *et al*. showed the initial safety and efficacy of PRK Xtra in myopic eyes with thinner pachymetry and tomographic abnormalities at one year postoperatively.[114] Ohana *et al*. reported that although the improvement in visual outcome was significant after PRK Xtra in eyes with thin or irregular cornea, the refractive outcome was less accurate compared to the published results of PRK-only procedure.[115]

Rationale and indication: Although the use of adjuvant accelerated CXL after LASIK, SMILE and PRK in eyes with thin corneas, borderline topography and high refractive error has been presented in several aforementioned studies, there is no long-term evidence supporting their role in the prevention of keratectasia. As a result, due to paucity of long-term studies and lack of conclusive evidence regarding the efficacy of these protocols in preventing ectasia, currently, PIOL implantation may be preferred over corneal procedures in such susceptible eyes for refractive correction.

Guidelines for Selection of CXL Plus Technique

In patients with documented keratoconus progression, CXL is required in order to increase the corneal biomechanical

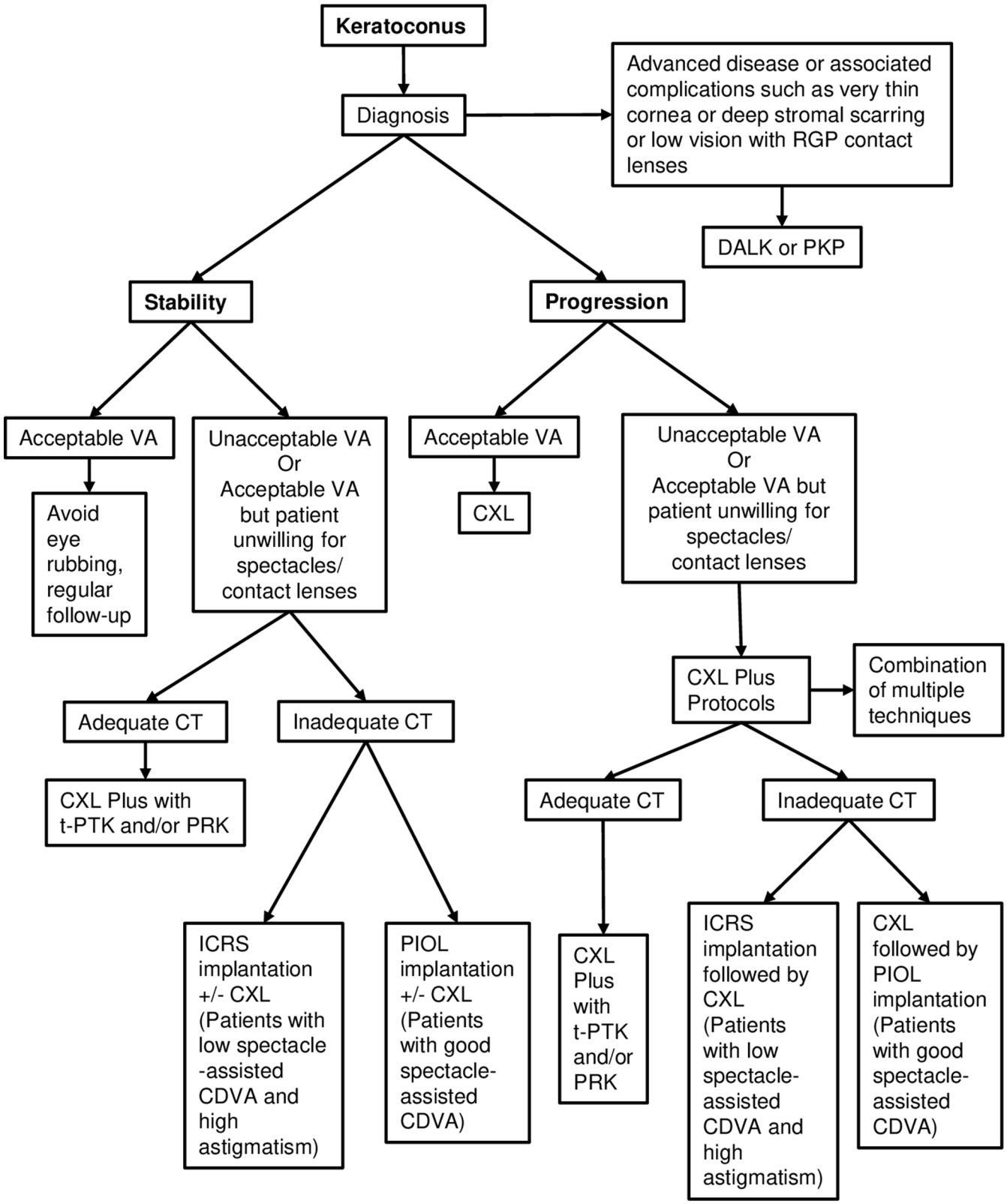

Figure 1: Proposed algorithm to aid in decision-making for the comprehensive management of keratoconus. After diagnosing the disease, the treatment is planned after taking into consideration the stage of keratoconus, disease stability or progression, functional vision, preoperative corneal irregularity and astigmatism, corneal thickness and patient's willingness or tolerance towards contact lenses. VA = Visual acuity; RGP-CL = Rigid gas-permeable contact lens; DALK = Deep anterior lamellar keratoplasty; PKP = Penetrating keratoplasty; CXL = Corneal cross-linking; t-PTK = Transepithelial phototherapeutic keratectomy; PRK = Photorefractive keratectomy; ICRS = Intrastromal corneal ring segments; PIOL = Phakic intraocular lens; CT = Corneal thickness

stability and thus halt the ectatic process. Although CXL alone might improve the vision and few corneal parameters to some extent, the majority of patients, with moderate to advanced keratoconus, will still require adjunctive refractive therapies for resolving the corneal irregularities and enhancing the visual outcome. For this reason, combined CXL treatments (CXL plus) are gaining more ground and popularity in order to provide a better quality of life to keratoconic patients.

To date, no algorithm exists for determining the most efficient and effective CXL plus protocol for each individual patient. The treatment needs to be planned and customized after taking into consideration many parameters such as patient's age, refractive status, personal needs, stage of keratoconus, disease progression rate, corneal irregularity and willingness or tolerance towards spectacle and contact lenses.[116] Combined CXL treatment protocols are indicated in patients with documented progression of the disease showing unsatisfactory visual function or aversion/intolerance towards contact lenses and spectacles [Fig. 1]. In eyes with cones located within the central 2-mm zone, the combination of CXL with topo-guided PRK and/or t-PTK appears to be the most appropriate treatment approach in an attempt to both stabilize keratoconus progression and regularize the anterior corneal surface. The prerequisites for combining CXL with laser ablation techniques are maximum stromal ablation depth up to 50 μm and predicted postoperative thinnest pachymetry of more than 400 μm.[22,25] In more advanced cases where the safety requirements regarding CT are not met and in eyes with cones located outside the central 2-mm zone, simultaneous ICRS implantation and CXL seems to provide satisfactory results in terms of disease stabilization, corneal reshaping and reduction of irregular astigmatism. Additionally, the two-step approach of CXL followed by PIOL implantation after an interval of 3-6 months offers a promising alternative for patients with high residual refractive errors (myopia and regular astigmatism) and ectatic progression. The aforementioned combined treatment techniques may also be used in stable keratoconic cases or keratoconus suspects with non-satisfactory visual function (contact lens/spectacle intolerance, irregular astigmatism, high refractive error etc.) in order to improve their refractive profile without causing biomechanical destabilization of the cornea. Lastly, in order to further enhance refractive outcomes of CXL plus, a triple or quadruple approach can also be performed by combining multiple refractive techniques with CXL. Nevertheless, further studies are required in order to draw definite conclusions regarding their safety, efficacy and long-term stability.

Conclusion

Although CXL remains the gold standard for halting the ectatic process, it does not offer the advantage of fully addressing the refractive component of keratoconus. For this reason, a plethora of combined treatment protocols, as presented above, have been introduced in clinical practice, but no definitive management strategy has been described yet. Several parameters need to be further explored in order to standardize treatment planning and improve predictability, especially that of combined CXL and laser ablation techniques. Till date, no algorithm has been developed that takes into account all the possible factors (patient's age, refractive status, personal needs, keratoconus stage etc.) affecting the final refractive outcome of combined CXL protocols. The future aim is to develop nomograms that can incorporate all the aforementioned parameters and help in achieving highly accurate and predictable refractive results. Further prospective long-term randomized controlled studies are required for the development of customized CXL plus techniques that can be individualized as per each patient's status and needs.

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Conflicts of interest

There are no conflicts of interest.

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