



REVIEW

Combined Protocols for Corneal Collagen Cross-Linking with Photorefractive Surgery for Refractive Management of Keratoconus: Update on Techniques and Review of Literature

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ABSTRACT

With the development and gradual dissemination of corneal collagen cross-linking (CXL) in the twenty-first century as an early treatment for keratoconus, the management paradigm has shifted to include a greater focus on complete refractive correction for these patients. Though supplemental hard contact lens therapy remains a mainstay of visual rehabilitation in keratoconus, there has been increasing appeal in a completely surgical approach by combining CXL with adjuvant refractive procedures to both halt the ectatic process and enhance functional visual outcomes. Collectively termed “CXL plus” procedures, several combined protocols have been studied to various degrees in conjunction with CXL, involving photorefractive keratectomy (PRK), transepithelial phototherapeutic keratectomy (PTK), conductive keratoplasty (CK), intrastromal corneal ring segments (ICRS) implantation, phakic intraocular lens (PIOL) implantation, or multiple of these techniques together. The scope of this review aims to encompass a summary of current

CXL protocols and present the current status of studies involving adjunctive keratorefractive procedures combined with CXL. By discussing the results to date of these CXL plus protocols, we can assess what further areas of investigation are necessary within this field as the next step to optimizing treatment modalities and outcomes for our keratoconus patients, regardless of disease severity.

Keywords: Combined CXL protocol; Corneal collagen cross-linking (CXL); CXL plus; Keratoconus; Photorefractive surgery

INTRODUCTION

With the advent of corneal collagen cross-linking (CXL) in 1997 and its gradual acceptance in the beginning of the twenty-first century, the treatment paradigm for keratoconus and other corneal ectatic disorders has shifted dramatically [1]. In general, visual rehabilitation in keratoconus involves both managing the ectatic process and addressing the myopic and astigmatic refractive changes resulting from the abnormal corneal architecture. The latter was formerly accomplished by conservative management with hard contact lens correction until disease progression was too significant, requiring corneal transplantation to obtain a more normalized corneal surface. In the two decades

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since CXL was introduced, multiple prospective studies have firmly established its role as an integral aspect of the management of early keratoconus to tackle the previously unaddressed component of halting the ectatic process [2]. However, CXL alone in advanced but progressive disease does not lead to visual rehabilitation, so these patients still rely on contact lens correction or other forms of treatment, which will be discussed herein.

Keratoconus is a bilateral corneal disease characterized by progressive but self-limited thinning and associated steepening of the central or paracentral cornea [3]. Reported prevalence rates range from 50 to 265 per 100,000, depending on a variety of environmental and genetic factors, but it remains the primary indication for corneal transplantation throughout most of the world (specifically, in Europe, Australia, the Middle East, Africa, and South America) [4–7]. While the pathophysiology of the disease remains elusive, alterations in stromal matrix collagen production and apoptosis of anterior stromal keratocytes are hallmarks of the disorder and trigger pathologic changes in corneal shape and biomechanics [8–11]. Given the likely polygenetic nature of keratoconus and multifactorial contribution of associated conditions (e.g. atopy), it has been difficult to develop an etiology-based cure for prevention of disease progression [12].

CXL is a minimally invasive procedure utilizing riboflavin and ultraviolet-A (UVA) light to increase the biomechanical stability of the cornea and halt ectatic progression by inducing intrastromal cross-links [13]. While CXL has been shown to improve corneal curvature and maintain best-corrected visual acuity (BCVA) over long-term follow-up periods, most patients with moderate to advanced disease still need supplemental refractive correction to achieve functional vision [14–16]. For this reason, there has been increasing appeal in combining CXL with adjuvant refractive procedures to provide both disease stability and enhanced functional visual correction. Coined “CXL plus” in 2011, there are now several combined protocols involving photorefractive keratectomy (PRK), transepithelial phototherapeutic keratectomy (PTK), conductive keratoplasty (CK),

intrastromal corneal ring segment (ICRS) implantation, phakic intraocular lens (PIOL) implantation, or multiple of these techniques in conjunction with CXL. This review aims to summarize the current status of studies surrounding these combined CXL plus techniques and discuss the future potential of these protocols.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CORNEAL COLLAGEN CROSS-LINKING (CXL) PROTOCOLS

Conventional (Dresden) Protocol

The original CXL protocol developed by Wollensak et al. has been termed the conventional or Dresden protocol [13]. This involves debridement of the central 8–9 mm zone of corneal epithelium after application of topical anesthesia in a sterile setting, then instilling a solution of 0.1% riboflavin in 20% dextran every 2 min for 30 min. After this pre-treatment phase, UVA light (370 nm) is used to irradiate the cornea for 30 min at 3 mW/cm² irradiance (5.4 J/cm² total energy), during which the riboflavin solution is again administered every 2 min. With a minimum central corneal thickness of 400 μm prior to UV irradiation, no collateral damage to the endothelium or other intraocular structures is expected [17, 18].

Studies on conventional CXL show that the procedure is highly effective, with a mean reduction in maximum keratometry readings of 1.6 ± 4.2 D at 12 months postoperatively in a US multicenter clinical trial, with other randomized control studies corroborating this range of keratometry flattening [19–21]. While overall improvement in visual acuity has been modest and has generally not reached statistical significance, the failure rate (percentage of eyes with continued progression) has been relatively

low at approximately 6–8% at 12 months postoperatively [22–24]. Additionally, the effects of treatment have been shown to remain stable for as long as 10 years in the original Dresden cohort [16].

High-Fluence (Accelerated) Protocol

Given the prolonged treatment time described by the Dresden protocol, many groups have attempted to achieve comparable outcomes with shorter treatment duration by altering irradiation fluence or riboflavin preparations, referred to as “accelerated CXL”. In these protocols, high-energy application of UVA is utilized—up to 30 mW/cm², compared with the conventional 3 mW/cm²—but the total energy limit is kept constant at 5.4 J/cm² to avoid phototoxicity [25]. A comparison between accelerated and conventional protocols showed no significant difference in safety, efficacy, or visual gains between the two groups, but the studies were constrained by a small number of cases and short follow-up time [26, 27]. While many other studies have since reported acceptable refractive and keratometric outcomes for these accelerated treatments, there is some concern that the biomechanical stiffening effects may not be as significant or long-lasting as with the conventional protocol, but this remains to be corroborated with long-term outcomes of randomized controlled trials [28, 29].

Transepithelial CXL

Another modification to the Dresden protocol that has arisen over the past decade is the attempt to limit disturbance of the corneal epithelium to hasten postoperative healing and further protect the endothelium (especially in cases of thinner corneas), nicknamed “epi-on CXL” [30]. This has necessitated modifications to the riboflavin solution or specialized procedures to increase corneal epithelial permeability in order to achieve adequate penetration of both the riboflavin cross-linking agent and UVA light. For example, chemical enhancers such as trometamol, benzalkonium chloride (BAK),

ethylenediaminetetraacetic acid (EDTA), and gentamicin have been added concurrently with the riboflavin solution to loosen epithelial tight junctions; iontophoresis systems have attempted electrical disruption of the epithelium to promote intrastromal delivery of riboflavin; and superficial intrastromal administration of riboflavin via femtosecond laser-generated corneal pockets have also been reported [30–32]. However, these protocols remain controversial, as most have resulted in suboptimal results compared with conventional CXL, with a few recent small studies showing somewhat comparable but limited outcomes between the groups over a 2-year period [33]. These “epi-on” methods may continue to gain popularity as improved techniques are developed for enhancing intrastromal riboflavin diffusion to efficacy levels consistently comparable to conventional protocols.

COMBINED CXL PROCEDURES FOR REFRACTIVE CORRECTION (CXL PLUS) (TABLE 1)

Combined CXL and Photorefractive Keratectomy (PRK)

Topography-guided PRK was the first reported combined CXL treatment performed, initially in a keratoconus patient who underwent unilateral PRK 1 year after undergoing CXL, with excellent visual outcome (uncorrected visual acuity [UCVA] 20/20, BCVA 20/15) [34]. Based on the anecdotal success of a few such patients, it was postulated that simultaneous topography-guided PRK with CXL might be an alternative option for optimizing refractive outcomes of keratoconus with one treatment, and the Athens protocol was subsequently developed [35]. This procedure involves sequential excimer laser debridement of epithelium (50 μm) and partial topography-guided excimer laser stromal ablation (maximum 80 μm), followed by high-fluence CXL (10 mW/cm² for 10 min) [36, 37]. Significant fluctuations in refractive and topometric measures were noted within the first postoperative

Table 1 Summary of most recently published results for CXL plus protocols in the treatment of keratoconus

Authors	Protocol	No. of eyes	Study design (level of evidence ^b)	Follow-up (months)	VA outcomes	Keratometry outcomes	Complications
Combined CXL + PRK							
Kanellopoulos and Binder [36]	Athens	32	Prospective case series (level 4)	27 (range 6–59)	27/32 eyes with UCVA and BCVA improved better than 2.25 logMAR	Minimal reduced K in 30/32 eyes	6.25% haze, 6.25% progress
Kanellopoulos and Asimellis [39]	Athens	231	Prospective case series (level 4)	36	UCVA improved 0.38 ± 0.31, BCVA improved 0.20 ± 0.21 logMAR ^a	Flat K reduced −3.34 D ^a	None
Kanellopoulos [40]	Athens (simultaneous vs. sequential)	127 simultaneous 198 sequential	Retrospective, comparative (level 4)	36 ± 18 (range 24–68)	Sequential: UCVA improved 0.41, BCVA improved 0.25 logMAR Simultaneous: UCVA reduced 0.66, BCVA improved 0.28 logMAR	Sequential: mean K reduced 2.75 ± 1.3 D Simultaneous: mean K reduced 3.5 ± 1.3 D	19 eyes with haze (17 of sequential, 2 of simultaneous)
Tuwairqi and Sinjab [43]	Athens	22	Prospective case series (level 4)	12	Improved UCVA and BCVA ^a	K values reduced in all, significant in 55% ^a	None
Alessio et al. [44]	Athens	34 (17 CXL only, 17 PRK + CXL)	Prospective, non-randomized trial (level 3)	24	CXL only: UCVA improved 0.07, BCVA improved 0.04 logMAR PRK + CXL: UCVA improved 0.44, BCVA improved 0.03 logMAR ^a	CXL only: mean K reduced −1.15 D PRK + CXL: mean K reduced −2.07 D ^a	None (32.35% haze resolved)

Table 1 continued

Authors	Protocol	No. of eyes	Study design (level of evidence) ^b	Follow-up (months)	VA outcomes	Keratometry outcomes	Complications
Ohana et al. [45]	Athens	98	Retrospective case series (level 5)	25.3 ± 11.5 (range 12–36)	UCVA improved 1.23 logMAR, BCVA no improvement	Mean K reduced -4.03 D ^a	5% significant haze
Iqbal et al. [46]	Athens	125 (58 CXL only, 67 PRK + CXL)	Prospective, non-randomized trial (level 3)	24	CXL only: SE reduced 2.25 D, UCVA improved 0.54 logMAR ^a PRK + CXL: SE reduced 2.31 D, UCVA improved 0.68 logMAR ^a	CXL only: mean K reduced -2.12 D ^a PRK + CXL: mean K reduced -1.44 D ^a	CXL only: 12.1% haze resolved, 1.7% stromal scar PRK + CXL: 5.9% haze resolved, 1.3% stromal scar
Gore et al. [48]	Athens	47	Prospective, non-randomized trial (level 3)	24	BCVA improved 0.13 logMAR in PRK + CXL group ^a	Steep K reduced -5.4 D ^a , flat K reduced -1.1 D	1 eye microbial keratitis
Nattis et al. [54]	Sequential CXL then TG-PRK	62 (34 refractive PRK, 28 topographic PRK)	Retrospective, comparative series (level 5)	6 after PRK	Refractive: UCVA improved 20/100–20/60 ^a , BCVA improved 20/50–20/30 Topographic: UCVA and BCVA no improvement	Refractive: mean K reduced -0.36 D Topographic: no change in K	None
COMBINED CXL + PTK							
Kymionis et al. [56]	Cretan	38 (19 PTK + CXL, 19 CXL only)	Prospective, comparative randomized trial (level 2)	12	PTK + CXL: UCVA improved 0.36, BCVA improved 0.12 logMAR ^a CXL only: UCVA and BCVA no improvement	PTK + CXL: steep K reduced -2.07 D ^a CXL only: steep K reduced -0.34 D	None

Table 1 continued

Authors	Protocol	No. of eyes	Study design (level of evidence ^b)	Follow-up (months)	VA outcomes	Keratometry outcomes	Complications
Kymionis et al. [57]	Cretan	23	Prospective case series (level 4)	24–48	UCVA improved 0.38, BCVA improved 0.10 logMAR ^a	Steep K reduced –3.40 D, flat K reduced –1.60 D ^a	None
Kapasi et al. [58]	Cretan	34 (17 PTK + CXL, 17 CXL only)	Retrospective, comparative case series (level 5)	1	PTK + CXL: BCVA improved 0.33 lines CXL only: BCVA decreased –0.58 lines	Not reported	None
Kymionis et al. [52]	Cretan plus	31	Prospective case series (level 4)	19.53 ± 3.97 (range 12–25)	UCVA improved 0.46, BCVA improved 0.084 logMAR ^a	Steep K reduced –2.35 D, flat K reduced –1.18 D ^a	50% posterior haze
Grentzelos et al. [59]	Cretan plus	55	Prospective case series (level 4)	12	UCVA improved 0.59, BCVA improved 0.12 logMAR ^a	Steep K reduced –4.03 D, flat K reduced –2.16 D ^a	7.3% significant haze
COMBINED CXL + ICRS							
Chan et al. [66]	Intacs alone vs. same-day Intacs + CXL	25 (12 Intacs only, 13 Intacs/CXL)	Retrospective, comparative case series (level 5)	3 (Intacs alone: 102 ± 39 days, Intacs/CXL: 97 ± 38 days)	Intacs: UCVA improved 0.93 ± 0.89, BCVA improved 0.13 ± 0.20 Intacs/CXL: UCVA improved 0.76 ± 0.80, BCVA improved 0.11 ± 0.12 logMAR	Steep and mean K reduced more in Intacs/CXL group vs. Intacs only ^a	None
Kilic et al. [67]	Same-day Intacs + epi- on CXL	131	Prospective case series (level 4)	7.07 ± 4.66 (range 1–25)	UCVA improved 0.26 ± 0.16, BCVA improved 0.24 ± 0.16 logMAR ^a	Mean K reduced –4.47 D ^a	None

Table 1 continued

Authors	Protocol	No. of eyes	Study design (level of evidence ^b)	Follow-up (months)	VA outcomes	Keratometry outcomes	Complications
Ertan et al. [68]	Sequential Intacs then epi- on CXL (mean 3.98 months between)	25	Retrospective case series (level 5)	3	UCVA improved additional 1.2, BCVA improved additional 0.36 Snellen lines after CXL ^a	Mean K reduced -0.35 D, Steep K reduced -0.76 D after CXL ^a	None
El Awady et al. [69]	Sequential ICRS then CXL	21	Prospective case series (level 4)	5.67 ± 1.89	UCVA and BCVA improved after ICRS, no significant improvement after CXL	Mean K reduced additional -0.09 D after CXL	None
Renesto Ada et al. [70]	Sequential riboflavin only vs. CXL then Intacs (3 months between)	39 (19 Intacs only, 20 CXL/Intacs)	Prospective, randomized, comparative trial (level 2)	24	Intacs: UCVA improved 0.16, BCVA improved 0.13 logMAR CXL/Intacs: UCVA improved 0.33, BCVA improved 0.22 logMAR (no difference between groups)	No difference between groups for all K values	None
Saelens et al. [75]	Same-day Ferrara ICRS + CXL	7	Retrospective case series (level 5)	11.7 ± 3.6 (range 5–17)	UCVA improved 0.50, BCVA improved 0.26 decimal ^a	Mean K reduced -3.0 D, steep K reduced -3.6 D ^a	1 explanted for migration
Coskunseven et al. [77]	Sequential CXL then ICRS vs. ICRS then CXL (mean 7 ± 2 months between procedures)	48 (24 CXL/ICRS, 24 ICRS/CXL)	Prospective, randomized, comparative trial (level 2)	13 ± 1	CXL/ICRS: UCVA improved 0.18, BCVA improved 0.17 decimal ^a ICRS/CXL: UCVA improved 0.21, BCVA improved 0.33 decimal ^a	CXL/ICRS: Mean K reduced -4.16 D ^a ICRS/CXL: Mean K reduced -3.98 D ^a	8 eyes with stromal edema (resolved by 3 months)

Table 1 continued

Authors	Protocol	No. of eyes	Study design (level of evidence ^b)	Follow-up (months)	VA outcomes	Keratometry outcomes	Complications
Multiple combined procedures							
Iovieno et al. [80]	Sequential Intacs then same-day PRK + CXL (6 months between)	5	Prospective case series (level 4)	6	BCVA improved additional 0.2 after PRK + CXL ^a	Mean K reduced additional -1.1 D after PRK + CXL ^a	None
Kremer et al. [81]	Sequential Intacs then same-day PRK + CXL (> 6 months between)	45	Prospective case series (level 4)	12	UCVA improved 0.35, BCVA improved 0.19 decimal additional after PRK + CXL ^a	Apex K reduced additional -4.30 D after PRK + CXL ^a	11.1% mild haze, 8.9% epithelial hyperplasia
Coskunseven et al. [82]	Sequential ICRS then CXL then PRK (6 months between each)	16	Prospective case series (level 4)	6	UCVA improved 0.89, BCVA improved 0.62 logMAR ^a	Steep K reduced -8.66 D, flat K reduced -3.11 D ^a	None
Yeung et al. [83]	Simultaneous PTK + ICERS + conventional CXL	16	Prospective case series (level 4)	6.9 ± 4.6	UCVA improved 0.73, BCVA improved 0.16 logMAR ^a	Mean K reduced -2.70 D, steep K reduced -5.78 D ^a	None
Rocha et al. [84]	Simultaneous Intacs + PTK + conventional CXL	55	Retrospective case series (level 4)	6	UCVA improved 0.39, BCVA improved 0.08 logMAR ^a	Cylinder improved 2.12 D ^a	1 eye (2%) lost > 3 lines BCVA (haze)
Assaf and Kotb [85]	Sequential Athens protocol then PIOL (2–4 months between)	22	Prospective case series (level 4)	10.9 ± 1.6 (range 6–14)	UCVA improved 0.87, BCVA improved 0.34 logMAR ^a	Mean K reduced -1.75 D ^a	None

Studies were excluded from this table if they were case reports (≤ 2 eyes), non-keratoconic ectatic eyes were included in the treatment groups, or they were preliminary results (only most updated long-term follow-up outcomes included)

CXL corneal collagen cross-linking, TG-PRK topography-guided photorefractive keratectomy, PTK phototherapeutic keratectomy, ICERS intrastromal corneal ring segments, PIOL phakic intraocular lens, SE spherical equivalent, VA visual acuity, BCVA best-corrected visual acuity, UCVA uncorrected visual acuity, K keratometry, D diopter

^a Denotes a statistically significant value as established by the individual study's criteria

^b Denotes level of evidence as classified by the Oxford Centre for Evidence-based Medicine (2009)

6 months, but 12-month postoperative results showed significant improvement in multiple topographic indices, independent of keratoconus grade or imaging platform (Scheimpflug vs. Placido disc), with only minimal changes in visual acuity from preoperative measures (gain $+0.19 \pm 0.20$ decimal BCVA at best) [38]. Further analysis of 231 eyes revealed gradual stabilization but persistent flattening of pachymetric and topographic indices over a 3-year period, implying a downstream effect of CXL-induced stromal changes to promote longer-term corneal flattening and thickening, and cautioning against overcorrection with this combined protocol [39]. Of note, while UCVA and BCVA improved postoperatively on average throughout the 3-year follow-up period, there was considerable variability in standard deviations equivalent to the absolute gains measured (range UCVA -0.34 to $+1.10$, BCVA -0.32 to $+0.90$) [39]. Because these studies were primarily prospective observational trials without a control group, the true significance of the reported outcomes may be overstated.

Controversy remains around whether simultaneous procedures or sequential CXL followed by PRK is optimal. Kanellopoulos et al. initially showed same-day topography-guided PRK with CXL as more effective for visual rehabilitation (as incorporated into the Athens protocol), with subsequent studies corroborating increased efficacy of simultaneous CXL and PRK compared with CXL alone [40–45]. However, a recent prospective multicenter study comparing conventional CXL (Dresden protocol) to simultaneous combined PRK and CXL (Athens protocol) showed nearly equivalent results in visual outcomes and refractive improvement after 2 years, suggesting that there may not be a significant benefit with the Athens protocol over the longer-term refractive advantages of the conventional protocol [46]. Primary considerations for planning simultaneous combined CXL and PRK concern ablation depth and corneal thickness, so most protocols specify a maximum ablation depth between 50 and 80 μm [34, 41, 42].

Another major concern with simultaneous procedures is in treatment planning, as CXL alone has been shown to gradually induce

changes in anterior corneal curvature that do not stabilize until 6–12 months postoperatively [19]. It is therefore difficult to determine the precise ablation pattern or refraction that simultaneous topography-guided PRK should target, as the combination of procedures introduces significant unpredictability into current software models. A few groups have examined high-resolution wavefront-guided (HRWG) PRK or special treatment algorithms designed to target higher-order aberrations (HOAs) combined with accelerated CXL, with promising results from small preliminary studies demonstrating UCVA and BCVA gains without compromising CXL efficacy at 12–24 months postoperatively [47, 48]. Another technique has utilized topography-guided PRK in conjunction with customized, variable-pattern CXL (“enhanced Athens protocol”), with preliminary data also showing encouraging improvements in UCVA, and keratometry values remaining stable, at 3-year follow-up [49]. However, these studies only enrolled patients with mild to moderate disease without severe ectasia, as demonstrated by relatively preserved preoperative corneal thickness and keratometry readings.

Additionally, increased risk of stromal haze after simultaneous combined procedures remains a substantial barrier to generalized adoption of this treatment method [50, 51]. Consequently, the use of mitomycin C following PRK during combined CXL plus treatments remains a topic of debate: while most protocols used mitomycin C 0.02% for 20–30 s after ablation, all reported postoperative haze formation. Kymionis et al. specifically avoided it due to the theoretical advantage that cross-linking itself leads to additional depopulation of anterior stromal keratocytes and may therefore reduce the risk of haze [40, 52]. However, there was also mild (grade 1) posterior haze formation in 50% of their patients at 1 year, as is sometimes seen in patients undergoing CXL alone [52]. This unique pattern of haze formation suggests that the mechanism of haze induction is still poorly understood, and thus prevention remains challenging.

A recent meta-analysis revealed greater improvements in BCVA, spherical equivalent,

astigmatism, and disease stability without progression in the sequential protocol studies, though direct comparisons between the studies were limited by the variety of different protocols used [53]. Since the ablation rate in cross-linked stroma may differ from that in native tissue, the refractive outcomes may be more unpredictable [53]. Early results from a retrospective US series of CXL patients undergoing sequential topography-guided PRK showed a significant improvement in UCVA and BCVA compared with those who received only CXL [54]. While these studies all intimate significant additive visual gains with combined PRK and CXL, further investigation is necessary to delineate optimal treatment conditions for this combined procedure and to identify specific disease subgroups who are more likely to benefit.

Combined CXL and Phototherapeutic Keratectomy (PTK)

As an alternative to mechanical epithelial debridement, transepithelial PTK has been proposed to both remove epithelium and increase anterior stromal regularity by decreasing keratoconic astigmatism [55]. Named the Cretan protocol, this arose from a case report of a keratoconus patient who demonstrated visual and topographic improvement after PTK-based epithelial removal during conventional CXL [55]. The Cretan protocol includes transepithelial PTK ablation of 50 μm intended depth in a 6.5–7.0 mm zone, then mechanical debridement to enlarge the de-epithelialized area to an 8.0–9.0 mm zone, followed by conventional CXL [56]. Subsequent case-control studies showed comparable safety, with improvements in visual and refractive outcomes, in a small series of 23 eyes followed for at least 24 months, with seven eyes followed through 4 years postoperatively [57]. Based on these reports, it is hypothesized that partial removal of Bowman's layer over the keratoconic corneal apex adds refractive advantage over CXL alone [58]. Unfortunately, reports on such small numbers of treated eyes preclude meaningful conclusions

on the overall management of keratoconus patients.

The Cretan protocol has been further extended to include adjunctive PRK and for supplemental refractive correction. Referred to as the Cretan plus protocol, transepithelial PTK is combined with conventional PRK (maximum 50 μm ablation depth) and simultaneous conventional CXL [59]. This small, uncontrolled case series showed significant improvements in UCVA, BCVA, keratometry, and refractive values, with acceptable safety metrics, at 1 year. A similar protocol allowing 75 μm ablation depth by PRK also showed promising early results in a small cohort of Chinese patients [60]. This particular combination may therefore be worth further exploring to determine whether there is an added benefit to laser-assisted de-epithelialization rather than mechanical debridement along with combined PRK photoablation and CXL.

Combined CXL and Conductive Keratoplasty (CK)

Conductive keratoplasty (CK) is a noninvasive, tissue-preserving procedure that utilizes radiofrequency energy (350 Hz), which penetrates 90% of corneal stroma when applied directly to cause permanent collagen shrinkage [61]. It is traditionally approved for the treatment of low to moderate hyperopia and astigmatism if applied circumferentially around the corneal mid-periphery to cause central steepening, but a few attempts have been made to apply it to keratoconic corneas to achieve selective steepening in flat, non-ectatic areas. Kato et al. first evaluated “topography-guided conductive keratoplasty” (TGCK) for moderate to advanced keratoconus by delivering radioprobe applications based on preoperative topography and intraoperative keratometry in 21 eyes; while small, non-statistically significant improvements in UCVA and BCVA were noted at 1 year postoperatively in the 10 eyes completing follow-up, regression toward baseline keratometry values was noted, similar to those observed with classic CK treatments in hyperopic corneas [61]. Initial endeavors to combine

CK with simultaneous conventional CXL in order to theoretically stabilize CK effects further showed significant regression of CK effects by postoperative month 3 [62]. More recently, Rubinfeld et al. reported two cases of post-LASIK ectasia that failed conventional CXL and were subsequently treated with TGCK, aiming for immediate 4.0–6.0 D overcorrection, followed by sequential transepithelial CXL with a proprietary riboflavin solution after 24 h, which resulted in stable improvements in BCVA, astigmatism, and keratometric flattening at 1–3 years postoperatively [63, 64]. While these results may not be generalizable in the long term to the keratoconus population, and the safety profile remains unknown, these case reports of early successes with this new combined protocol are encouraging.

Combined CXL and Intraström Corneal Ring Segments (ICRS)

Originally developed as a treatment for myopia, intrastromal corneal ring segments (ICRS) are polymethyl methacrylate (PMMA) pieces implanted in the mid-peripheral deep stroma to reduce central corneal curvature. Intacs® (Addition technology, Inc.) and Ferrara Rings (Mediphacos, Inc.) are the most common commercially available brands. While ICRS have been shown to be effective in improving visual acuity in keratoconus by regularizing and decreasing pathologic corneal steepening and irregular astigmatism, their use alone does not prevent disease progression [65]. They have recently regained popularity as an adjunctive treatment with CXL for mild to moderate keratoconus, with studies showing small improvements in UCVA associated with significant reductions in K values, suggesting normalization of corneal shape, albeit with variable improvement over ICRS implantation alone [66–70]. Ultimate surgical success is highly dependent upon patient selection and various intraoperative factors, including proper ring placement, accurate depth of implantation, and optical zone diameter. Ring extrusion remains a potential postoperative complication, with rates up to 10% reported in ICRS implantation alone

in keratoconus patients, though only a few rare cases of postoperative migration have been reported thus far during the short (< 1 year) follow-up for the combined CXL and ICRS procedures [71–75]. The feasibility of ICRS combined with CXL is also currently limited by moderate predictability of refractive outcomes, and the overall costs of the procedure may be dramatically increased.

Moreover, and similar to other combined protocols, the optimal timing for ICRS implantation remains unclear: simultaneous ICRS with CXL, CXL followed by ICRS, or ICRS followed by CXL. A few studies have shown that CXL followed by ICRS has the least postoperative improvement, with increased difficulty of surgical dissection, femtosecond laser energy needs, and risk of corneal haze that may be related to channel generation in already cross-linked corneal tissue [70, 76, 77]. It is also hypothesized that there may be an additive effect of same-day combined ICRS and CXL, with CXL serving as a stabilizing procedure, enhancing the benefits of ICRS [66, 67, 72, 73, 78]. Interestingly, reports of purposefully delayed ICRS explantation (not for extrusion) after initial combined same-day CXL described some persistence in beneficial topographic changes without complete regression to pre-CXL/ICRS values, implying that CXL may prolong the structural effects of ICRS despite the reversibility of implants [79]. However, not enough large studies with extended follow-up have been conducted to fully determine the ideal technical protocol and long-term outcomes for combined ICRS with CXL.

Multiple Combined CXL Procedures

It appears that even combining CXL with other refractive procedures does not currently lead to optimal visual acuity, so some studies have addressed potential combinations of multiple procedures with CXL. Triple therapy with CXL, PRK, and ICRS and with PTK, CXL, and ICRS has been reported in a few small case series as both a simultaneous and staged procedure. Improvements in vision, topography, and refraction (including reduced total aberrations) were

noted after 6–12 months of follow-up regardless of whether the procedures were performed simultaneously or sequentially with ICRS implantation followed by combined CXL-PRK [80–84]. Another triple therapy with simultaneous CXL and PRK (Athens protocol) followed by delayed phakic intraocular lens (PIOL) implantation after 2–4 months has been described as well, with short-term (6-month) follow-up results in a small case series showing significant stabilization of uncorrected vision gains [85]. These triple procedures also warrant further large-scale studies to elucidate whether their overall safety profile is acceptable and whether there is enough supplementary benefit to justify the additional risk.

GRADE PRACTICE RECOMMENDATIONS

In general, no level 1 evidence yet exists for any of these combined CXL plus procedures, as no large randomized controlled trials have been conducted or published results. Most studies have also been relatively small case series, and findings have varied among different protocols and groups. Thus, none merit a grade A or B recommendation at this time.

For combined CXL with PRK (Athens protocol), there is consistent level 4 evidence that shows its safety and efficacy. However, there is some controversy within level 3 studies that suggest the longer-term results may not be significantly improved compared with CXL alone [44, 46]. For this reason, we offer a grade C recommendation for this procedure.

For combined CXL with ICRS, we also offer a grade C recommendation, due to consistent level 4 evidence showing acceptable safety and efficacy outcomes. There are a few level 2 studies that show questionable benefit of the combined procedure over ICRS alone, but all were small, relatively underpowered studies.

For all other combined CXL plus procedures (CXL with PTK, CK, or multiple combined procedures), we can only offer a grade D recommendation at this time, due to the paucity of higher-level evidence showing a significant benefit with the combined protocols.

FUTURE OF REFRACTIVE SURGICAL OPTIONS FOR KERATOCONUS

Despite decades of research, the complete pathophysiology of keratoconus remains enigmatic, although detection methods have advanced enough that more keratoconus patients may be diagnosed early in the disease process, when visual acuity is relatively preserved. CXL in these early stages will hopefully prevent these patients from having to undergo additional procedures to address their refractive consequences. However, the management of patients with moderate to advanced disease remains challenging; although the plethora of methods reviewed above provide greater flexibility to both patients and clinicians, representing a significant expansion of treatment options compared with previous decades, there is still work to be done until the elusive “cure” can be attained. Since CXL alone does not fully address the refractive visual component of keratoconus therapy, many of the described combined CXL plus protocols require further investigation with larger, controlled trials with longer follow-up periods to better optimize outcomes. As topography-driven refractive technologies continue to progress, there is great hope that these protocols may be able to be personalized for each individual patient and their particular disease status.

Furthermore, CXL alone may be able to be developed to achieve a larger standalone impact on refractive error. Efforts to generate customized cross-linking systems may produce algorithms by which CXL treatments can be topography-guided [86]. Even prior to using CXL to halt progression of established keratoconus, there has been some recent exploration of utilizing CXL as a prophylactic measure in conjunction with LASIK or PRK on healthy myopes, suggesting that simultaneous CXL may even reduce postoperative regression along with development of ectasia [87, 88]. With these endeavors to actively prevent corneal ectatic disorders from becoming clinically manifest, it is imaginable that CXL may eventually be able to supplant entirely or remain a fundamental

adjunct in our armamentarium of refractive surgical procedures.

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