

# Update on Simultaneous Topo-guided Photorefractive Keratectomy Immediately Followed by Corneal Collagen Cross-linking for Treatment of Progressive Keratoconus

Vardhaman Kankariya, George Kymionis, George Kontadakis, Sonia Yoo

## ABSTRACT

Corneal collagen cross-linking (CXL) is a safe and effective technique for the management of corneal ectatic disorders. It has been proven that CXL is effectual in stopping the progression of keratoconus quasi 'freezing' the cornea and in many cases avoiding corneal transplantation. Nevertheless, patients' basic problem, which is the deterioration of their vision due to irregular astigmatism, remains. CXL combined with topography-guided photorefractive keratectomy (PRK) has been developed in order to achieve an important goal. To offer patients stability of their disorder and at the same time to assist them in achieving a functional vision by improving topographic outcomes. This article discusses update on this new combination therapy in the form of topo-guided PRK immediately followed by CXL as one-step procedure for treatment of progressive keratoconus.

**Keywords:** Ectasia, Collagen cross-linking, Topo-guided photorefractive.

**How to cite this article:** Kankariya V, Kymionis G, Kontadakis G, Yoo S. Update on Simultaneous Topo-guided Photorefractive Keratectomy Immediately Followed by Corneal Collagen Cross-linking for Treatment of Progressive Keratoconus. *Int J Kerat Ect Cor Dis* 2012;1(3):185-189.

**Source of support:** Nil

**Conflict of interest:** None declared

## INTRODUCTION

Successful treatment of corneal ectatic disorders such as keratoconus, pellucid marginal degeneration and iatrogenic corneal ectasia consists of confronting two distinct parameters; the corneal biomechanical instability and the optical inefficiency of the irregular cornea. The optical inefficiency due to irregular stigmatism has been treated for years conservatively with the use of developing contact lens technology (rigid gas permeable contact lenses – RGP) in mild to moderate keratoconus and then surgically with penetrating keratoplasty (PK) in advanced cases. Other successful surgical techniques are currently in use such as intracorneal ring segments (ICRS) implantation, and deep anterior lamellar keratoplasty (DALK) while others have been proposed and tested in the past such as conductive keratoplasty (CK) and epikeratophakia.<sup>1-3</sup>

Corneal collagen cross-linking (CXL) opened new chapter in treatment of keratoconus, in which combination of ultraviolet A (UVA) light with riboflavin as a

photosensitizing agent produced interfibrillary cross-linking between corneal stromal collagen fibers, thus increasing corneal rigidity, decreasing corneal deformability and stabilizing keratoconus. With CXL, issue of biomechanical instability has been successfully confronted, according to the current evidence CXL has been successful halting the progression of ectatic disorders.<sup>7,8</sup> Despite that, the topography and the visual performance of patients treated with only CXL show no or only minimal improvement due to remnant irregular astigmatism. Although RGP and specialized lenses form gold standard treatment for addressing irregular astigmatism, many patients become intolerant to them or do not want to use them. Excimer laser surgery in the form of topo-guided photorefractive keratectomy (T-PRK) has been also proposed for the regularization of anterior corneal shape, decreasing irregular astigmatism in order to improve visual outcomes.<sup>4-6</sup> The combination CXL and excimer laser enabled T-PRK is the new integrated emerging treatment for mild to moderate keratoconus. The goal of this combination is to treat keratoconic patients and offer them both stability and functional vision. Reaching functional vision consists of improvement of uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) and improvement of corneal topography.

## EVOLUTION OF THE TECHNIQUE

### Tips from the Past-T-PRK for stable/forme Fruste Keratoconus

The application of excimer laser enabled T-PRK has been introduced formerly for the correction of ametropia and irregular astigmatism in eyes with stable or forme fruste keratoconus. The technique demonstrated promising results with the main drawback being that it is a tissue removal technique.<sup>4-6</sup> There are several studies stating the application of surface ablation to correct astigmatism in patients with stable keratoconus. Alpíns et al<sup>4</sup> report a series of 32 eyes treated with photo-astigmatic refractive keratectomy (PARK) and followed up for up to 10 years with no evidence of keratoconic progression. Koller et al<sup>5</sup> treated 11 eyes with customized T-PRK and reported improvement in

refractive astigmatism, topography and quality of vision in all the patients. Twenty-five stable keratoconus eyes treated with topography-guided PRK reported by Cennamo et al<sup>6</sup> also demonstrated improved topography and visual outcomes.

### Topography-guided PRK after CXL as a Two-step Procedure

Kanellopoulos et al<sup>9</sup> proposed a two-step procedure in eyes with progressive keratoconus in which first CXL was performed to stabilize keratoconus and then after 1 year interval of stability, topography-guided limited PRK was performed to improve functional vision. The authors reported a single case of a patient that was treated with CXL and remained stable for 1 year after the procedure. Due to his inability to use contact lenses a limited topography-guided surface ablation was implemented with optimum results. Eighteen months after T-PRK keratoconus remained stable. Authors conclude that limited T-PRK after CXL is an effective two-step combination treatment for progressive keratoconus.

### Simultaneous T-PRK Immediately followed by CXL as Single-step Procedure: Initial Reports

Despite the encouraging results of the two-step combination therapy (CXL followed by T-PRK), there are three limitations with this approach. First, the stiffened cross-linked corneal tissue is removed in a second step by the PRK (potentially decreasing the possible benefits of CXL and possibility of progression of keratoconus). Second, the efficacy of this approach is limited since the corneal ablation rate could be different in cross-linked corneas than in the virgin cornea (this could lead to unpredictable refractive results). Third, there is an increased possibility of post-PRK haze formation (after CXL the anterior stroma is repopulated by new keratocytes after 6 months according to *in vivo* confocal microscopy).<sup>10</sup>

Due to these aspects, topography-guided PRK immediately followed by CXL in a single surgical procedure was considered to be a better option for treating progressive keratoconus. Kymionis et al<sup>11</sup> reported a case of pellucid marginal degeneration, in which both eyes of the patient were treated with combination of single-step T-PRK immediately followed by standard CXL. A limited topography-guided PRK was performed with Pulzar Z1 (CustomVis, Perth, WA) solid state laser linked with iTrace technology followed by standard CXL according to the Dresden protocol. Twelve months postoperatively, the uncorrected visual acuity was assessed at 20/40 in both eyes

compared with counting fingers preoperatively. The corrected visual acuity also improved from 20/50 and 20/63 to 20/25 and 20/32 in the right eye and left eye, respectively. Corneal topography revealed a significant improvement in both eyes. The main advantage of this technique is that ablation does not interfere with the already cross-linked part of the cornea.

The application 'simultaneous topo-guided partial PRK immediately followed by CXL' was described in progressive keratoconus in the same year by Kymionis et al.<sup>12</sup> Fourteen keratoconic eyes were treated with combination therapy and results demonstrated a marked improvement in topography and further stability during the follow-up period. Preoperative mean (LogMAR) uncorrected visual acuity was  $0.99 \pm 0.81$  and best spectacle-corrected visual acuity was  $0.21 \pm 0.19$ , which significantly improved postoperatively to  $0.16 \pm 0.15$  and  $0.11 \pm 0.15$ , respectively. The mean steepest keratometry was reduced from  $48.20 \pm 3.40$  D preoperatively to  $45.13 \pm 1.80$  D at last follow-up. T-PRK treatment was planned based on the patients' corneal thickness. While planning T-PRK treatment, maximum ablation was restricted up to 50  $\mu\text{m}$ , while the ablation depth was mapped out by modifying the target correction (expected central corneal thickness after PRK and prior CXL should be more than 400  $\mu\text{m}$ ). Maximum up to 40% of sphere and 50% cylinder correction was planned and the amount of customization was also adjusted to save tissue.<sup>12</sup>

At the same time, a comparison of sequential *vs* same day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus was reported by Kanellopoulos.<sup>13</sup> In this study, results of a series of patients treated with the same day single-step procedure, were compared retrospectively with a series of patients treated with the CXL followed by PRK after a time interval of at least 6 months as a two-step procedure. Comparisons were made between of groups in terms of visual acuity; manifest refraction spherical equivalent, keratometry, topography, central corneal thickness, endothelial cell count, corneal haze and ectatic progression. Mean follow-up was 36 months. According to the results, the group of patients treated with the same day procedure performed better in all parameters. The surface ablation in these cases was also limited to 50  $\mu\text{m}$ . The authors concludes that the same day procedure is superior to the sequential due to the superior results also due to three parameters: The patients' comfort (single-day procedure for each eye instead of two-step), lesser stromal scarring of the simultaneous procedure, and the fact that the sequential procedure removes cross-linked stroma as compared with sequential treatment.

### **FURTHER EVIDENCE: SIMULTANEOUS T-PRK IMMEDIATELY FOLLOWED BY CXL AS SINGLE-STEP PROCEDURE**

The combined procedure has been further reported by Stojanovitz et al<sup>14</sup> in a series of patients with keratoconus and pellucid marginal degeneration. The authors treated 12 eyes and followed them for 12 months, results demonstrated improvement in functional vision (mean uncorrected and corrected visual acuity). Authors further reported minimal changes in posterior surface of the patients, thus confirming stability after the procedure.

Krueger et al reported two cases of progressive keratoconus treated with simultaneous T-PRK and CXL with long-term follow-up up to 3 years.<sup>15</sup> In one case after the treatment, the progressive reduction of refractive myopia and keratometric power was demonstrated, similarly to that often observed in conventional CXL. The surgical technique in these cases consisted of limited topography-guided PRK using the WaveLight Allegretto Wave Eye-Q laser (Alcon Laboratories Inc, Ft Worth, Texas), adjuvant mitomycin-C (MMC) application and then CXL according to the standard Dresden protocol. The authors named the technique as 'the Athens protocol'.

The long-term results of simultaneous topography-guided PRK followed by CXL in a series of keratoconus patients were reported by Kymionis et al in 2011.<sup>16</sup> In this study, transepithelial phototherapeutic keratectomy (PTK) was performed for the removal of the epithelium prior to PRK in order to facilitate further smoothing the corneal surface due to the masking properties of the epithelium in corneas with keratoconus. After T-PRK, MMC was not applied and CXL was subsequently performed according to the Dresden protocol. Study demonstrated optimum visual outcome with improvement in functional vision with LogMAR uncorrected distance visual acuity and corrected distance visual acuity significantly improved by 0.46 and 0.084 LogMAR units ( $p < 0.001$ ), at the last follow-up and the long-term stability of the visual outcome was confirmed at 20 month follow-up. In further report, Kymionis et al demonstrated mild linear haze in the posterior stroma as a complication of the simultaneous procedure.<sup>17</sup> According to this report, posterior haze developed after simultaneous PRK followed by CXL in the deep stroma in about half of the studied patients. In confocal microscopic evaluation, authors detected an area with high reflectance at the level of the posterior stroma characterized by spindle-shaped and linear structures. The high-reflective, spindle-shaped structures were linked with migration and activation of keratocytes. Furthermore, the linear hyper-reflective structures could be associated with increased collagen

deposition, collagen disorganization and excessive production of extracellular material from the activated keratocytes. Posterior haze gradually moved anteriorly and became less dense in most of the patients as was also evident on slit lamp examination.

The impact of CXL and CXL combined with topography-guided PRK in patients' self-reported quality of life has been reported by Labiri et al in recent study of patients with early stage keratoconus.<sup>18</sup> The authors used the National Eye Institute Visual Function-25 item questionnaire, (NEI VFQ-25) which is a well validated tool for the quantitative evaluation of health-related quality of life. According to the authors both techniques offered the patients an improvement in self-reported quality of life. Additionally, the scores of the keratoconus patients were significantly lower than those of the matched healthy control group. The authors conclude that both techniques should be implemented as soon as possible for the treatment of keratoconus. Allesio et al<sup>19</sup> compared visual, refractive, topographic and corneal higher-order aberration outcome at the 2-year follow-up after customized T-PRK followed by cross-linking (CXL) as a single procedure vs CXL alone in eyes with progressive keratoconus. They demonstrated that functional vision improved statistically significantly in combined treatment as against CXL alone. Tuwairqi et al<sup>20</sup> reported 1 year visual and topographic outcomes and safety and efficacy of CXL combined with T-PRK to achieve near emmetropia in eyes with low-grade keratoconus. After 1 year, statistically significant improvement was noted in all study parameters ( $p < 0.01$ ). The safety and efficacy indices were 1.6 and 0.4, respectively. No cases progressed as evidenced by keratometry readings.

### **USE OF SIMULTANEOUS T-PRK AND CXL FOR OTHER CORNEAL ECTATIC CONDITIONS**

The use of this technique for the treatment of iatrogenic corneal ectasia has also been reported with good success.<sup>21,22</sup> Furthermore, the simultaneous procedure of PRK with CXL has been combined with other surgical techniques such as (ICRS) and phakic intraocular lens (IOLs) to improve the visual acuity of the patients. A case of a patient who was initially treated with ICRS implantation and 12 months later he underwent simultaneous topography-guided PRK followed by CXL was reported by Kymionis et al.<sup>23</sup> The patient had significant improvement and stability in 9 months follow-up. Iovieno et al<sup>24</sup> reported Intacs implantation and 6 months later simultaneous conventional limited PRK and CXL in five eyes that showed significant improvement and stability. Kanellopoulos reported a case of post-LASIK ectasia treated with combined topo-guided

PRK and CXL in an attempt to treat corneal irregularity and astigmatism, and following that a phakic IOL was implanted to treat high residual myopia.<sup>25</sup>

## TIPS AND DEBATES

Most of the authors that report the simultaneous procedure of T-PRK and CXL agree in the basic steps of surgery. It is important to remember that T-PRK is offered as a therapeutic treatment not as a refractive surgery in these patients. Initially the topography-guided PRK takes place in a limited fashion, in order to regularize anterior refractive surface while removing the least possible amount of tissue. Most of the authors arbitrary agree to the removal of maximum up to a 40 to 50  $\mu\text{m}$  stromal tissue till there is a minimum of 400  $\mu\text{m}$  residual stroma after the ablation, in order to perform CXL with safety in term of corneal endothelial health. Topography-guided ablation rather than wavefront guided is proposed from all the authors for the smoothening of the anterior corneal surface, which is the main cause of ocular aberrations in keratoconus. Following T-PRK the CXL takes place according to the standard protocol. The removal of the epithelium with PTK rather than with alcohol or mechanically was proposed, because of the known masking ability of the epithelium in keratoconus. By taking advantage of the ability of the epithelium to smoothen the surface by being thinner in the apex of the cone, we can further improve the stromal surface and visual outcomes with PTK.<sup>26</sup> In addition, the topo-guided PRK is more accurately implemented in the stromal surface since the information of topography that are taken from the epithelium surface, correspond more accurately to the stromal surface.

A significant debate in the literature is the use of MMC after the PRK procedure and prior to CXL. Combination treatments with use of MMC<sup>13-15</sup> and without the use of MMC<sup>11,12,16</sup> have been reported. The use of MMC is considered not necessary,<sup>16</sup> due to the dissertation effect of CXL on corneal keratocyte population in the anterior stroma which are responsible for post-PRK haze. This depopulation of keratocytes has been observed with *in vivo* corneal confocal microscopy.<sup>10</sup> Subsequently, additional effect of MMC on keratocytes is unnecessary and has unknown possible implications in the stromal repopulation of keratocytes. On the other hand, other authors report the use of MMC in the procedure,<sup>13-15</sup> but there is a lack of randomized controlled study in this regards to know whether MMC is required or not.

## CONCLUSION

According to current evidence simultaneous PRK followed by CXL seems to be a promising treatment capable of

offering patients a functional vision and halting progression of the disorder. Performing this technique with careful observance of safety aspects may offer patients with keratoconus the opportunity to gain a functional vision, avoid complications, achieve stability and also reduce the need for corneal transplantation.

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## ABOUT THE AUTHORS

### Vardhaman Kankariya (Corresponding Author)

Postdoctoral Fellow, Department of Cornea and Refractive Surgery  
Institute of Vision and Optics, University of Crete, Crete, Greece  
e-mail: vrdhmn@yahoo.com

### George Kymionis

Lecturer, Department of Ophthalmology, University Hospital of Heraklion, University of Crete, Crete, Greece

### George Kontadakis

Resident, Department of Cornea and Refractive Surgery, Institute of Vision and Optics, University of Crete, Crete, Greece

### Sonia Yoo

Professor, Department of Cornea and Refractive Surgery, Bascom Palmer Eye Institute, Miami, USA