Topography and Pachymetry Guided, Rapid Epi-on Corneal Cross-Linking for Keratoconus: 7-year Study Results

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Purpose: To evaluate custom fast cross-linking (cfCXL) treatment of keratoconus.

Methods: "Custom fast cross-linking" or "cfCXL" is a keratoconus treatment algorithm featuring no epithelial disruption, 15 minutes of corneal presoaking with a riboflavin–vitamin E TPGS solution, and a 370-nm ultraviolet A radiation beam centered on the most highly curved corneal region. Ultraviolet A radiation beam fluence, total energy, and exposure time are significantly less than those in the Dresden protocol. In this study, refraction, spectacle-corrected distance visual acuity, Kmax, and corneal hysteresis were monitored in 81 eyes of 81 patients for 7 years with 100% follow-up. Pretreatment Kmax and patient age averaged 53.01 ± 4.87 D and 25.9 ± 4.7 years, respectively.

Results: Average refractive cylinder magnitude was reduced by 26.1% at 1 month postoperatively and by 44.2% at 7 years postoperatively. Logarithm of the minimum angle of resolution average spectacle-corrected distance visual acuity (best spectacle-corrected distance visual acuity) improved from +0.26 ± 0.34 (20/36.4) to +0.15 ± 0.23 (20/28.25), +0.05 ± 0.20 (20/22.4), and +0.06 ± 0.20 (20/22.96) at 1 month, 1 year, and 7 years postoperatively, respectively. Best spectacle-corrected distance visual acuity improved in 54.3%, 74.1%, 84.0%, 87.7%, 84.0%, 84.0%, and 82.7% of patients at postoperative months 1, 3, 6, 12, 24, 48, and 84, respectively. Kmax did not increase in 96.3% of patients at 1 month, 97.5% at 1 year, and 98.8% at 7 years postoperatively, with average corneal apex flattening at 1 month and 7 years of −2.79 ± 1.70 D and −4.00 ± 2.40 D, respectively.

Conclusions: Custom fast cross-linking, epi-on, rapid, narrowed beam apex-centered treatment of keratoconus with riboflavin–vitamin E TPGS produced a significant, rapid, and lasting cone progression stoppage, astigmatism reduction, and visual acuity improvement.

Key Words: epi-on cross-linking, pachymetry-dependent cross-linking, custom fast cross-linking, cfCXL, narrower diameter

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Corneal cross-linking is an important therapy for keratoconus. It can significantly increase corneal biomechanical stiffness, thus limiting the progression of ectasia.[1–3] In the now standard "Dresden" cross-linking protocol, originally described by Spoerl et al,[4] the treated cornea is soaked with a 0.1% riboflavin solution for 30 minutes after epithelium removal. It is then exposed for 30 minutes to 370 nm ultraviolet A radiation (UV-A) with a power of 3 mW/cm^2 and a beam diameter of 9 mm for a total energy of 5.4 J/cm^2. During the UV-A irradiation, a continuous precorneal film of riboflavin must be maintained to avoid damage to the endothelial layer.[5–7] The Dresden protocol induces cross-linking to a 250/350-μm depth; thus, a minimum corneal thickness of 400 μm is recommended to avoid endothelial damage.[8] Alternatively, a hypotonic solution can be applied to swell the cornea up to the required 400 μm.[9]

More recently, a variety of newer cross-linking methods have been developed and were recently reviewed.[10,11] Among these methods is transepithelial cross-linking with riboflavin–vitamin E tocopherol polyethylene glycol succinate (TPGS). We have described the kinetics of riboflavin–vitamin E drug penetration, produced a mathematical model leading to a more rapid and lower UV-A fluence cross-linking protocol, and tested that system with 24-month clinical results.[12–18]

There has been progress by several groups of workers involving the biomechanics of corneal shape change in keratoconus using finite element analysis. Gefen et al[19] produced simulations demonstrating the effect of change in corneal elastic modulus, corneal thickness, and intraocular pressure on corneal deformation. They showed that maximal tissue stress occurred in the thinnest areas. Further studies[20–22] indicate that the cause of keratoconus is focal stress/strain rather than generalized tissue stress/strain.

In keratoconus and other ectasias, weakening of the cornea is not homogeneous. Weaker areas deform more easily in response to congenital, biochemical, and postsurgical factors. These areas stretch more and become thinner and progressively less resistant to stress from ordinary forces such as blinking and eyelid rubbing. Significant research[20,21,23–29]

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detailing the ultrastructure, biomechanics, and numerical modeling of the cornea underlie the rationale for our work. A fairly recent article on the subject was written by Whitford et al.[30]

We used finite element analysis of the cornea by applying elastic plate theory[31,32] to produce a three-dimensional model of keratoconus progression to design a cross-linking technique using a narrower UV-A beam than that is used in the Dresden protocol. We then combined the narrowed beam approach with our technique[12–14] of transepithelial, riboflavin–vitamin E solution, low fluence, briefer presoak, and irradiation technology to produce what we call "custom fast cross-linking" or "cfCXL." We used that technology to treat the present series of patients.

TABLE 1. Demographics and Pretreatment Enrolling Data in cfCXL

Eyes (men, women)	81 (43,38)
Age (yr)	25.88 (±4.70)
Best-corrected visual acuity 1 week before treatment (LogMAR)	0.26 (±0.34)
Refractive cylinder 6 months before treatment (D)	3.52 (±1.93)
Refractive cylinder 1 week before treatment (D)	4.18 (±1.80)
Kmax 6 months before treatment (D)	51.88 (±5.23)
Kmax 1 week before treatment (D)	53.01 (±4.87)
Minimum corneal thickness 6 months before treatment (μm)	473.88 (±38.47)
Minimum corneal thickness 1 week before treatment (μm)	448.67 (±35.99)

Kmax, maximum keratometry.

MATERIALS AND METHODS

Study Design and Patients

The clinical study reported here was conducted at the Corneal Transplant Center, Pellegrini Hospital (Naples, Italy) and at the I.R.O.S. (Institute of Refractive and Ophthalmic Surgery, Naples, Italy). It was entirely funded by the spin-off consortium "Fast Linking," approved and partially funded by the Italian Ministry of Education, Universities, and Research (DM 593/2000, Prog. 04/11, Prot. 3693, April 4, 2011), and was conducted according to the ethical standards of the Declaration of Helsinki (revised in 2000). Patients were informed about the nature of the study, then signed an informed consent form. No fees were charged to the patients during the study. An institutional review board/ethics committee approval was obtained (authorization no. 1269/2010).

We enrolled 81 patients with progressive keratoconus for treatment with cfCXL. Each potential study patient was seen for a first examination and then in a second visit held 6 months later. Progressive keratoconus was defined by the satisfaction of at least 2 of the following requirements for change between the first examination and the 1-week pretreatment examination: 1) an increase of 1 diopter or more in the steepest keratometry (Kmax), 2) a reduction of the thinnest corneal depth by at least 5%, and 3) at least 1 diopter of cylinder increase. The pertinent biological characteristics of the study patients are shown in Table 1.

The more highly affected eye with the higher value of Kmax was selected for the study treatment for each patient. Patients with keratoconus whose more affected eye did not demonstrate progression 6 months after the initial visit were not enrolled in the study. Other exclusion criteria for study patient selection were age less than 18 years, pregnancy, breastfeeding, unavailability for follow-up examinations, connective tissue disease, previous eye surgery, penetrating eye trauma, glaucoma, aphakia, endothelial cell count below 2200 cells/mm^2, pellucid marginal degeneration, corneal scars, and recurrent corneal erosion syndrome.

Every examination included slit-lamp examination, ocular pressure, fundus examination, corneal analysis, manifest refraction, and best spectacle-corrected distance visual acuity (BSCDVA) in logarithm of the minimum angle of resolution (LogMAR) units. All patients underwent a refractive examination using an optical path difference device.

Corneal analysis with 2 topographers was performed. An Orbscan IIz (Bausch & Lomb, Rochester, NY) was used to record Kmax, Kmin, and SimK, and a Pentacam conventional Scheimpflug system (Oculus, Lynwood, WA) was used to determine minimum pachymetry and to validate Orbscan Kmax values, and there was high agreement in values between the 2 devices. Endothelial cell density was determined using a Tomey EM-3000 (Tomey Corp, Nagoya, Japan), and corneal hysteresis was measured using an Ocular Response Analyzer (Reichert, Depew, NY). Corneal hysteresis measurements were taken pretreatment and at 2 years, 4 years, and 7 years posttreatment. The same Ocular Response Analyzer software was used throughout the study. Visual acuities were tested in a single clinic with an ESV-3000 ETDRS testing device (Good-Lite Co, Elgin, Illinois) using a variety of eye charts made for the unit so as to reduce the chance of patient memorization of letters.

Clinical data were collected before the treatment (6 months and 1 week pretreatment) to determine keratoconus progression and after cross-linking at 1, 3, 6, 12, 24, 48, and 84 months postoperatively to determine treatment effect. Corneal hysteresis data were collected only at 1 week before and at 24, 48, and 84 months after the treatment. The data collected 1 week before the treatment were considered as baseline data in this study.

Statistical Analysis

GraphPad Prism 7 software (GraphPad Inc, San Diego, CA) and Excel (Microsoft Corp, Redmond, WA) were used in the creation of graphs and statistical analysis.

Cross-Linking

All treatments were performed after instilling topical anesthetic and pilocarpine 2% in an operating room. Pretreatment therapy included antibiotic eye drops (moxifloxacin hydrochloride 0.5%). Moxifloxacin hydrochloride 0.5% and prednisolone 0.12% were applied at the end of the treatment. One drop of a solution containing 0.1% riboflavin, 0.5%

vitamin E d-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS), and 10% dextran was applied every 15 seconds for 15 minutes, without epithelium removal. The operative eye was then repeatedly rinsed with balanced salt solution to eliminate the precorneal riboflavin film. The cornea was then exposed to UV-A radiation using the CF-X Linker (IROMED Group srl, Rome, Italy). The beam was centered on the most highly curved area, according to the front tangential map (topo-link mode), to cover the apex of the keratoconus. To do this, we marked the conus apex and then centered it with the crosshair present in the eyepiece of the cross-linker. The topo-link mode is the way to automatically obtain the exact measurement of the UV-A beam diameter for individual treatments according to the front tangential map. The beam diameter varied from 4 to 7 mm. The modulated exposure profile (time, fluence) was automatically calculated from pretreatment data (corneal thinnest point and Kmax).[13,15,16] Modulated exposure had a mean fluence of 1.8 ± 0.9 mW/cm^2 for 10 ± 1.5 minutes (total energy: 1.08 ± 0.6 J/cm^2). At the end of the procedure, a drop of prednisolone acetate 0.12% was instilled into the operative eye.

RESULTS

No patient required prescription analgesics postoperatively. Slit-lamp examinations of patients at the end of the procedures revealed occasional mild epithelial edema which cleared the following day.

Average postoperative spectacle-corrected distance acuity LogMAR (Snellen) was +0.26 ± 0.34 (20/36.39) the week before treatment and was 0.15 ± 0.23 (20/28.25), 0.10 ± 0.22 (20/25.2), 0.07 ± 0.21 (20/23.5), 0.05 ± 0.20 (20/22.44), 0.06 ± 0.20 (20/22.96), 0.06 ± 0.20 (20/22.96), and 0.06 ± 0.20 (20/22.96), respectively, at 1, 3, 6, 12, 24, 48, and 84 months postoperatively. Change in spherical equivalent was −0.34 ± 2.28, −0.35 ± 2.27, −0.42 ± 2.16, −0.44 ± 2.15, −0.41 ± 2.12, −0.41 ± 2.14, and −0.42 ± 2.15, respectively at 1, 3, 6, 12, 24, 48, and 84 months. Cylinder (+) magnitude change was −1.09 ± 1.02, −1.37 ± 0.88, −1.56 ± 0.88, −1.64 ± 0.82, −1.79 ± 0.82, −1.83 ± 0.82, and −1.85 ± 0.94, respectively, at 1, 3, 6, 12, 24, 48, and 84 months. Average cylinder magnitude reduction (%) was 26.1%, 32.9%, 37.3%, 39.3%, 42.8%, 43.8%, and 44.2%, respectively, at 1, 3, 6, 12, 24, 48, and 84 months. Change in Kmax (D) was −2.79 ± 1.70, −3.17 ± 2.21, −3.36 ± 2.19, −3.60 ± 2.16, −3.64 ± 2.32, −3.86 ± 2.34, and −4.00 ± 2.40, respectively, at 1, 3, 6, 12, 24, 48, and 84 months.

Percent increase in hysteresis was 21.3 ± 10.0%, 21.4 ± 9.9%, and 22.1 ± 9.6%, respectively, at 24, 48 and 84 months.

The percentage of patients with improved BSCDVA was 54.3%, 74.1%, 84.0%, 87.7%, 84.0%, 84.0%, and 82.7%, respectively, at 1, 3, 6, 12, 24, 48, and 84 months. The percentage of patients with same or reduced Kmax was 96.3%, 93.8%, 97.5%, 98.8%, 97.5%, 98.8%, and 98.8%, respectively, at 1, 3, 6, 12, 24, 48, and 84 months. There were no infections and no cases of corneal scarring.

Average cylinder magnitude decreased at every postoperative visit with an average 26.1% reduction by postoperative month 1, rising to an average 44.2% reduction at 84 months postoperatively. Average Kmax values were reduced respectively by 2.79 ± 1.79 diopters 1 month after the treatment, 3.60 ± 2.16 diopters after the first year and 4.00 ± 2.40 diopters by the end of the seventh year. Best spectacle-corrected distance acuity improved by the first postoperative month, and the average LogMAR acuity continued to improve until stabilizing at 2 years postoperatively.

There was a statistically significant increase in corneal hysteresis from a preoperative average of 7.89 ± 0.49 mm Hg to 9.59 ± 0.49 mm Hg at 2 years postoperatively and stabilizing thereafter. The chart in Table 2 details the average results for LogMAR visual acuity, change in spherical equivalent, change in the absolute value of cylinder magnitude, change in Kmax, increase in corneal hysteresis, and the percentage of patients with improvements in visual acuity and with stabilization of Kmax.

The cfCXL protocol was effective in halting keratoconus progression by the index of Kmax at 7 years postoperatively in all but 1 patent. Over the 7 years of the cfCXL study, the average Kmax among the 81 study eyes decreased from 53.01 D 1 week before treatment to 49.02 D at 7 years postoperatively. Of the 3.99 D of change in average Kmax, 69.7% (2.79 D) occurred during the first month, 79.2% (3.17 D) during the first 3 months, 84.2% (3.36 D) by 6 months, and 90.2% (3.6 D) by the end of the first year. During the last 6 years of the study, the average Kmax decreased only 0.4 D and eyes still demonstrated a conical shape on average.

DISCUSSION

There was considerable improvement in vision (LogMAR BSCDVA) and reduction in Kmax, but the relationship between the 2 phenomena is rather weak (a 26% correlation between LogMAR (BSCDVA) and change in Kmax. Figure 1 is a scatter plot of the change in Kmax versus the change in LogMAR BSCDVA at 7 years after cross-linking with cfCXL.

Average spherical equivalent shifted slightly in the myopic direction with most of the shift evident by the first postoperative month with essentially no further change after postoperative month 6. Spherical equivalent change ranged from −2D to +3D in the series with the spherical equivalent changing on average in the myopic direction by −0.44D, and there was a slight reduction in the absolute value of the spherical equivalent both for myopes and hyperopes, so the cross-linking yielded a slight emmetropization effect. Figure 2 is a scatter plot of the change in spherical equivalent 1 year after cfCXL versus the preoperative spherical equivalent. Figure 3 is a scatter plot of the change in spherical equivalent versus the change in Kmax. There is only a 23% correlation between the 2. The anomaly of slight average myopization with high variation in the presence of corneal flattening of the cone can be explained by the fact that in many cases, the flattened cone was off the central optical axis. In keratoconus, it is typical to see high curvature over the cone and often lower than average corneal curvature away from the cone and at least part of that unaffected area may be within the optical axis. With cfCXL, the cone tends to flatten, whereas the lower

TABLE 2. Clinical Outcomes of cfCXL Protocol

Parameters	Pre-op	1 mo	3 mo	6 mo	12 mo	24 mo	48 mo	84 mo
No. eyes (%)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)	81 (100)
Refractive parameters								
BSCVA (LogMAR)	+0.26 ± 0.34	+0.15 ± 0.23	+0.10 ± 0.22	+0.07 ± 0.21	0.05 ± 0.20	+0.06 ± 0.20	+0.06 ± 0.20	+0.06 ± 0.20
BSCVA (Snellen conversion)	20/36.4	20/28.3	20/25.2	20/23.5	20/22.4	20/23	20/23	20/23
Spherical equivalent change from pre-op		−0.34 ± 2.28	−0.35 ± 2.27	−0.42 ± 2.16	−0.44 ± 2.15	−0.41 ± 2.12	−0.41 ± 2.14	−0.42 ± 2.15
Cylinder (+) magnitude change from pre-op		−1.09 ± 1.02	−1.37 ± 0.88	−1.56 ± 0.88	−1.64 ± 0.82	−1.79 ± 0.82	−1.83 ± 0.82	−1.85 ± 0.94
Average cylinder magnitude reduction (%)		26.1%	32.9%	37.3%	39.3%	42.8%	43.8%	44.2%
Gains and losses of vision among 81 patients after cfCXL for keratoconus								
Gained VA		44 (54.3%)	60 (74.1%)	68 (84.%)	71 (87.7%)	68 (84%)	68 (84%)	67 (82.7%)
Gained VA more than 1 LogMAR chart line		24 (29.6%)	30 (37%)	43 (53.1%)	43 (53.1%)	38 (46.9%)	38 (46.9%)	38 (46.9%)
Lost VA		14 (17.3%)	10 (12.3%)	7 (8.6%)	7 (8.6%)	7 (8.6%)	7 (8.6%)	8 (9.9%)
Lost VA more than 1 LogMAR chart line		2 (2.5%)	2 (2.5%)	2 (2.5%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)
Topography and hysteresis								
Kmax								
Change in Kmax (D)		−2.79 ± 1.70	−3.17 ± 2.21	−3.36 ± 2.19	−3.60 ± 2.16	−3.64 ± 2.32	−3.86 ± 2.34	−3.99 ± 2.40
% increase in hysteresis			21.3 ± 10.0%		21.4 ± 9.9%		22.1 ± 9.6%	
% of patient with the same or reduced Kmax		96.3%	93.8%	97.5%	98.8%	97.5%	98.8%	98.8%

curvature over the unaffected and untreated area can steepen toward normal.

In evaluating the effect of corneal cross-linking, 1 item to acknowledge is the preoperative Kmax of the eyes treated. Figure 4 is a scatter plot of the change in Kmax at 1 year versus the preoperative Kmax. There is a general trend to greater flattening of maximum corneal curvature among those eyes with greater pretreatment Kmax. There is a −26% correlation between the 2 quantities in this series.

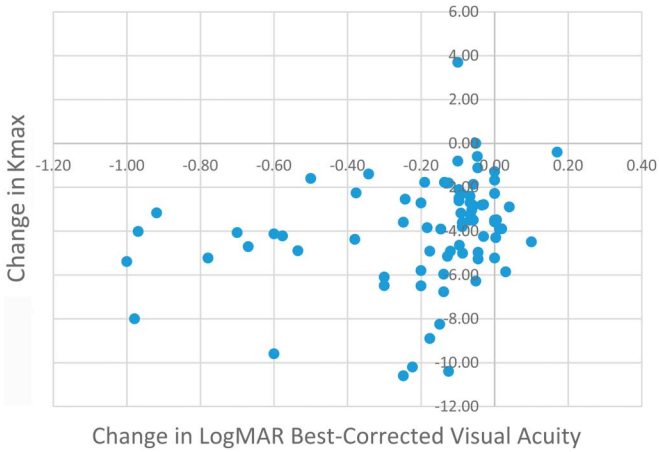

FIGURE 1. Scatter plot of the change in BSCDVA (LogMAR) versus the change in Kmax at 7 years postoperatively. The correlation coefficient is 26%.

The current 7-year study is consistent with the theory that applying corneal cross-linking to the weaker areas of the cornea can produce a significant and long-lasting effect in making the corneal curvature more uniform.

Standard cross-linking treatments such as in the Dresden protocol target the central 9 mm of the cornea to obtain a greater area of corneal stiffening for the stabilization of the

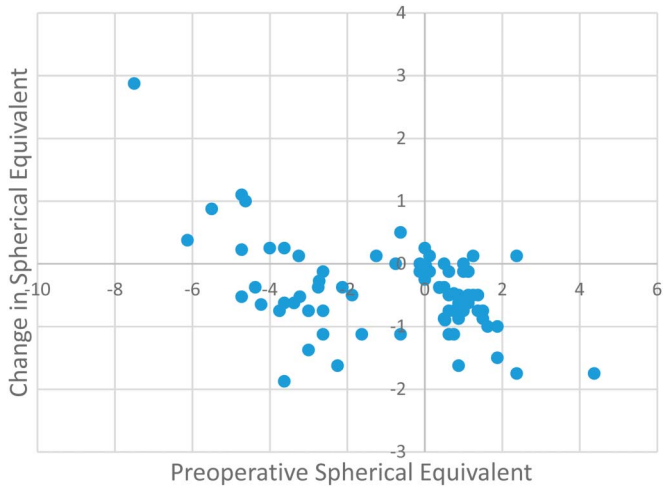

FIGURE 2. Change in spherical equivalent 1 year after cfCXL. The tendency was for slight myopization likely because of the fact that many of the cones were off the central optical axis, and there was a slight tendency toward overall reduction in the absolute value of the spherical equivalent.

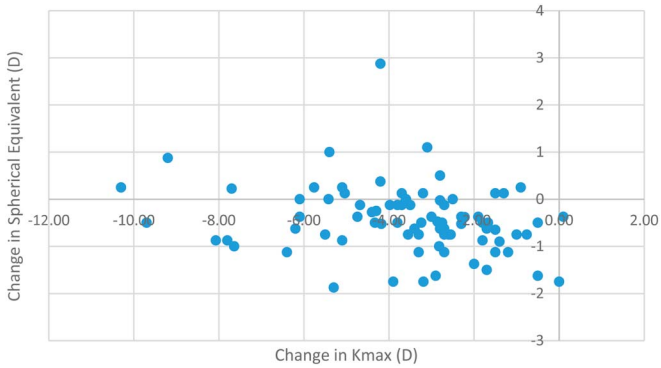

FIGURE 3. Scatter plot of the change in spherical equivalent versus the change in Kmax.

ectatic disease. The custom fast protocol treatment, conversely, targets only the steepest area.

In keratoconus, a limited corneal region becomes more steep and a different portion becomes relatively more flat. Large cross-linking treatment areas that include those flatter areas reduce the mechanical lever for shape change.

By limiting treatment to the diseased areas, a greater flattening in the cone region occurs. Cone flattening requires a compensatory steepening of the surrounding less steep areas, and that process is not hindered if the less steep areas remain untreated. The change in the corneal shape therefore depends on the size and spatial extent of the stiffening effect produced by corneal cross-linking. This relationship derives directly from the dynamics of shape change described in our mathematical model. Following this mathematical model, our clinical study used a beam diameter that never exceeded 7 mm during UV-A exposure. Informed by significant research and writing of others,[20,21,23–32] our mathematical model is presented in the Appendix of the current article (see Supplemental Digital Content 1, http://links.lww.com/ICO/A868).

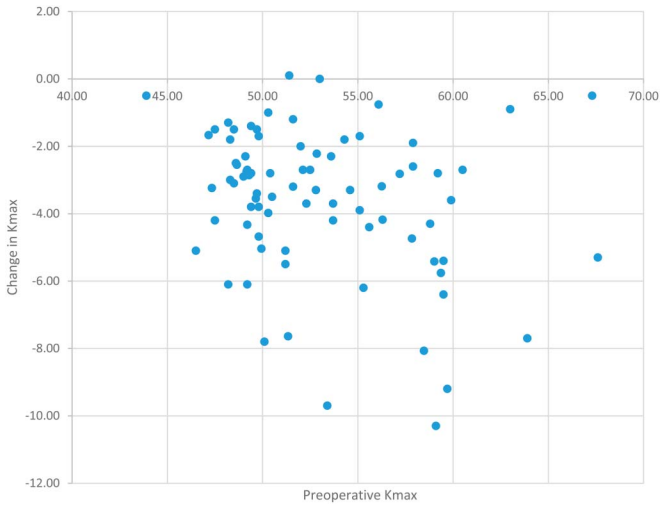

FIGURE 4. Scatter plot showing the change in Kmax 1 year after custom fast epi-on corneal cross-linking with riboflavin–vitamin E TPGS. Significant corneal flattening in these patients with keratoconus occurred in nearly every case. Kmax decrease is 26% correlated with preoperative Kmax.

Wide beam treatments such as the standard Dresden protocol and other wide beam treatments such as our own transepithelial cross-linking series, previously reported in this journal,[14] stiffen the entire cornea. With the wider beam, it is more difficult to bend the flatter peripheral portion of the cornea surrounding the more curved corneal cone because the peripheral cornea has also been hardened.

Hashemi et al[33] reported on Dresden protocol cross-linking in 40 eyes with a 5-year follow-up. In that study, Kmax continued to increase until the sixth postoperative month. At 48 months, Kmax had decreased only very slightly from 49.37 ± 3.48 to 49.28 ± 3.27, which is only 0.09 diopters of Kmax flattening. In that study, there was improvement in spectacle-corrected visual acuity by the third postoperative month and there was a net average improvement in spectacle-corrected visual acuity (LogMAR) from +0.31 ± 0.28 preoperatively to +0.19 ± 0.19, thus an improvement of 0.12 LogMAR units at 48 months postoperatively. These data can be compared with those shown in Table 2, where we found a change in average Kmax of −3.86 ± 2.34 units and an increase in LogMAR spectacle-corrected visual acuity of 0.2 LogMAR units at 48 months.

Revisiting our own previously reported results,[14] of 25 eyes using wide beam transepithelial cross-linking with the very same riboflavin–vitamin E TPGS as used in our current study, the average Kmax actually increased at 1 month postoperatively 0.36 D from 49.64 to 50.0 D.

In our current study, there is a rapid relative flattening of the cone by −2.79 D at 1 month postoperatively.

Comparing the current work with our own 24-month wide beam cross-linking study with the same riboflavin–vitamin E as presently used, at 1 year after corneal cross-linking with the wide beam, the average Kmax changed at 1 year postoperatively in the wide beam study by −0.88 ± 1.02 D, but 5 of the 25 eyes had measured increases in Kmax. In the present narrower beam study, only 1 patient of the 81 had an increase in Kmax at 1 year compared with preoperative levels and the average Kmax change at 1 year was −3.60 ± 2.16 D. Pretreatment progression of Kmax was greater (1.99 D) in our wide beam study than in our current narrow beam study (1.13 D). In our wide beam study, we reported an improvement in BSCDVA of 0.11 LogMAR units at 1 year postoperatively. In the current study of 81 patients, the improvement was 0.2 LogMAR units. Thus, it appears that we have attained a more rapid and greater improvement in corneal curvature and spectacle-corrected vision with the newer narrow-beam technique than with the wide-beam approach either epithelium-on or epithelium-off.

Some authors have already proposed this new approach. Topography has been proposed for the evaluation and identification of the steepest area (tangential, anterior, or posterior elevation maps).[34,35] Clinical experience with customized cross-linking for corneal ectasia is still in its infancy, but significant optical improvements have already been demonstrated compared with large diameter corneal cross-linking treatments.[36]

There are limitations in the current reported work. Tracking of the operated eye was manually performed during this study although for future studies we have developed superior methods. The theory that a smaller treatment area over the corneal apex results in improvement by allowing compensatory steepening of the peripheral cornea is not yet proven. One very serious question to settle would be the matter of keratoconus recurrence in postpenetrating keratoplasty corneas, and a retrospective study of pretransplant topography cases would be warranted to see whether cone recurrence resulted from grafts not encompassing the full extent of the affected area.

To move closer to a proof of the theory, a prospective randomized study comparing cfCXL with wide beam cross-linking as well as a similar study comparing the technique of the present study to that of the Dresden protocol is planned. When determining the success or failure of an individual cross-linking treatment, we were limited by the accuracy of the Kmax measurements. We used the Orbscan for Kmax values and the Pentacam for pachymetry readings because we were aware of the published accuracy report on the Kmax of the Orbscan, but accuracy measurements were not available to us for the Pentacam HR when our study was planned. In future studies, we expect to use the Pentacam HR for all measurements and we will take 5 Pentacam HR readings per patient to increase the accuracy of Kmax measurements and measurement of treatment success rate.[37]

CONCLUSION

The promising clinical results of this study, although in a limited number of cases, seem to confirm the predictions of our mathematical model of the biomechanical and structural variation of the cornea after cross-linking. These mathematical considerations were based on the theory of elastic shells, and they show that the cfCXL procedure with UV-A beam diameters up to 7 mm, located on the most curved corneal area, causes a rapid flattening, together with a more rapid flexing of the untreated portion.

The cross-linking protocol described here was able to achieve a significant flattening of the steepest corneal area, with improved biomechanical, topographic, and refractive parameters within 1 month of treatment. Patients showed rapid visual rehabilitation, and the results at 84 months also showed stabilization of the ectatic disease. Although our data are consistent with the theoretical expectations, additional studies including a greater number of patients will be necessary for further validation of our findings.

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