

## Trans-epithelial cross-linking with riboflavin solution: one-year clinical results

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**Purpose:** to report the clinical results of 25 keratoconic eyes, affected by progressive keratoconus, treated by trans-epithelial cross-linking (TE-CXL) with a riboflavin solution for TE CXL.

### Study Design

- Clinical, perspective, non-randomized study;
- Prospective, nonrandomized clinical study;
- Treated eyes: 25 (13 right, 12 left);
- The patients (Mean age: 26.68 +/- 7.44 years) were affected by progressive keratoconus clinically documented in the last 6 months (9 eyes stage 1), (7 eyes stage 2), (9 eyes stage 3) according Krumeich;
- Treatment: Trans-epithelial corneal cross-linking (TE-CXL) with a riboflavin solution for TE CXL;
- All eyes were affected by keratoconus, progressive in the last 6 months;
- Clinical observations were performed: before and after surgery (1,3,6,12, months after treatment)

### Every observation included:

- age <16 or >45 years;
- uncorrected visual acuity (with logMAR chart) (UCVA);
- Best spectacle corrected visual acuity (with logMAR chart) (BSCVA);
- Spherical correction measure (SPH);
- Cylindrical correction (CYL);
- Sphero-equivalent correction (SE);
- Steepest meridian keratometry;
- Flattest meridian keratometry;
- Average keratometry;
- Clinical (slit-lamp) examination of anterior and posterior segment;
- Intra-ocular pressure measures with Goldmann applanation tonometer (IOP);
- Corneal central thickness (CCT);
- Confocal microscopy;
- Endothelial corneal cell count.

### Treatment features:

- The treatment was not carried out in an operating room;
- Surgical drape was not used;

- Silicone ring placed on the corneoscleral limbus;
- Preliminary soaking: 20 minutes of topical application of the riboflavin solution;
- Slit-lamp examination to observe the complete yellow dyeing of corneal tissue and the greenish Tyndall aspect in anterior chamber with blue filter, indicating adequate passage of the riboflavin solution;
- Ultra-violet A (UV-A) irradiation: 3 mW/cm<sup>2</sup> (5,4 J/cm<sup>2</sup>), 8 mm. diameter, at 5 cm distance from corneal apex;
- Six irradiation steps of 5 minutes for a total of 30 minutes;
- No further soaking with the riboflavin solution during UV irradiation.

## Results

### Visual Acuity results (Table 1):

- Mean baseline UCVA was  $0.8 \pm 0.5$ . At 1 month post TE CXL, mean UCVA was  $0.8 \pm 0.5$  ( $p>0.05$ ). At 3 months  $0.7 \pm 0.5$  ( $p>0.05$ ). At 6 months  $0.6 \pm 0.4$  ( $p>0.05$ ). At 1 year  $0.5 \pm 0.4$  ( $p<0.05$ );
- Mean baseline BSCVA was  $0.1 \pm 0.1$ . At 1 month post TE-CXL, mean BSCVA was  $0.09 \pm 0.1$ . At 3 months  $0.05 \pm 0.1$  ( $p>0.05$ ). At 6 months  $0.01 \pm 0.1$  ( $p<0.05$ ). At 1 year  $0.03 \pm 0.1$  ( $p<0.05$ );
- The improvements in UCVA and BSCVA were statistically significant compared to reoperative levels ( $p<0.05$ ).

### Refractive results:

- The mean preoperative spherical equivalent (SE) was  $-4.6 \pm 3.3$  D with a mean sphere of  $-3.0 \pm 2.7$  D and a mean cylinder of  $-3.2 \pm 1.5$  D. Six months after TE-CXL mean SE was  $-4.1 \pm 3.3$  D ( $p>0.05$ ), mean sphere  $-2.8 \pm 2.7$  D ( $p>0.05$ ), and mean cylinder  $-2.5 \pm 1.5$  D ( $p>0.05$ ). 1 year after TE-CXL mean SE was  $-4.0 \pm 3.3$  D ( $p>0.05$ ), mean sphere  $-2.7 \pm 2.7$

D ( $p>0.05$ ), and mean cylinder  $-2.3 \pm 1.5$  D ( $p<0.05$ ).

- The difference in mean cylinder was significant ( $p<0.05$ ) at 1 year.

### Topographic Results:

- Topographic astigmatism measured with the Tomey and Orbscan Topographer during follow-up is shown in tables. Mean baseline flattest meridian keratometry, steepest meridian keratometry and average keratometry were  $46.0 \pm 4.2$  D,  $49.6 \pm 5.1$  D, and  $47.8 \pm 4.6$  D, respectively;
- At 12 months, these readings were  $45.7 \pm 3.7$  D ( $p>0.05$ ),  $48.7 \pm 4.5$  D ( $p>0.05$ ) and  $47.2 \pm 4.0$  D ( $p>0.05$ ), respectively, a difference that was statistically not significant for all parameters ( $p>0.05$ );
- Although in time we can observe an improvement of topographic results, such improvements are not statistically significant ( $p>0.05$ ).

### Endothelial Results:

- The difference between baseline and 1 year was not significant ( $p>0.05$ ), indicating that CXL did not induce endothelial damage in the 1-year follow-up period;
- The difference between baseline, 1,3,6, months and 1 year was not significant ( $p>0.05$ );
- Endothelial results were not significant ( $p>0.05$ ) indicating that CXL did not induce endothelial damage.

### IOP Results:

- The mean preoperative intraocular pressure was  $15.56 \pm 1.98$  mmHg. 1-year post TE-CXL was  $15.64 \pm 1.60$  mmHg.
- No significant intraocular pressure changes were seen.

Table 1: Visual Acuity results

	UCVA LogMAR					BSCVA LogMAR				
	PreTE-CXL	1 month	3 months	6 months	12 months	PreTE-CXL	1 month	3 months	6 months	12 months
AVERAGE	0,871	0,887	0,724	0,623	0,569	0,103	0,099	0,050	0,011	-0,003
DEV. STD.	0,569	0,582	0,507	0,453	0,442	0,132	0,135	0,131	0,117	0,114
SIGNIFICANCE		0,922	0,338	0,094	0,041		0,912	0,164	0,012	0,004

	SPH					CYL				
	PreTE-CXL	1 month	3 months	6 months	12 months	PreTE-CXL	1 month	3 months	6 months	12 months
AVERAGE	-3,075	-3,015	-2,890	-2,820	-2,790	-3,250	-3,220	-2,970	-2,520	-2,300
DEV. STD.	2,737	2,773	2,761	2,755	2,736	1,584	1,676	1,691	1,564	1,503
SIGNIFICANCE		0,939	0,813	0,744	0,715		0,948	0,549	0,108	0,035

	K MIN					K MAX				
	PreTE-CXL	1 month	3 months	6 months	12 months	PreTE-CXL	1 month	3 months	6 months	12 months
AVERAGE	46,025	46,318	46,168	45,880	45,744	49,644	49,999	49,734	49,093	48,764
DEV. STD.	4,258	4,121	3,894	3,825	3,742	5,196	4,889	4,867	4,565	4,511
SIGNIFICANCE		0,806	0,901	0,900	0,805		0,804	0,950	0,692	0,526

Table 2: Refractive results.

	MEAN K					MEAN K DECREASE			
	Pre TE-CXL	1 month	3 months	6 months	12 months	1 month	3 months	6 months	12 months
AVERAGE	47,8342	48,1584	47,9512	47,4864	47,2540	-0,3242	-0,1170	0,3478	0,5802
DEV. STD.	4,6623	4,4242	4,3184	4,1259	4,0545	0,6140	0,7264	0,8992	0,9935
SIGNIFICANCE		0,8020	0,9270	0,7812	0,6409	0,0143	0,4285	0,0650	0,0075

	CORNEAL THICKNESS					IOP	
	Pre TE-CXL	1 month	3 months	6 months	12 months	Pre TE-CXL	12 months
AVERAGE	456,0000	426,8000	427,9200	438,9200	447,1600	15,5600	15,6400
DEV. STD.	56,5862	53,1288	54,9135	57,4369	58,1003	1,9807	1,6042
SIGNIFICANCE		0,0661	0,0813	0,2948	0,5883		0,8760

	SPHERO-EQUIVALENT CORRECTION			SPHERO-EQUIVALENT CORRECTION DEREASE	
	Pre TE-CXL	6 months	12 months	6 months	12 months
AVERAGE	-4,6998	-4,1948	-4,0900	-0,5000	-0,6048
DEV. STD.	3,3768	3,3805	3,3418	0,5683	0,5276
SIGNIFICANCE		0,5996	0,5241	0,0002	0,0000

Chart 1:Uncorrected visual acuity (UCVA) in the 25 treated eyes before and after TE cross linking:  
UCVA LogMAR significant compared to preoperative levels(P<0.05)

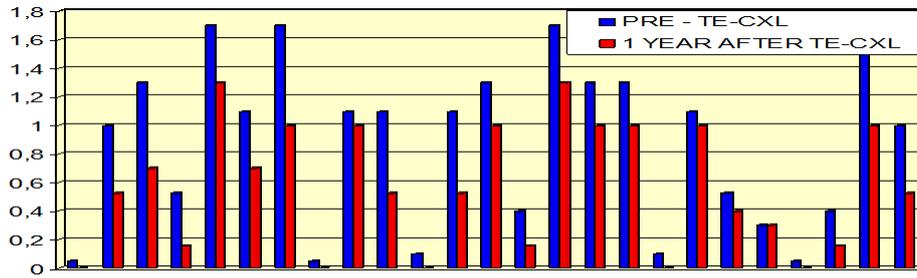


Chart 2: best spectacle-corrected visual acuity (BSCVA) in the 25 treated eyes before and after TE cross-linking: BSCVA LogMAR significant compared to preoperative levels(P<0.05)

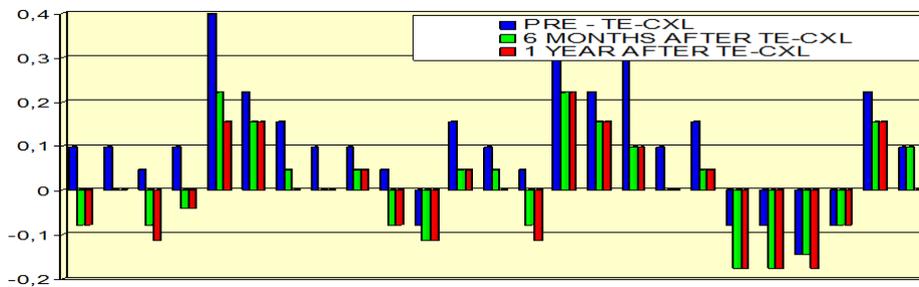


Chart 3: CYLINDER CORRECTION (Diopters) in the 25 treated eyes before and after TE cross-linking.  
Significant compared to preoperative levels(P<0.05).

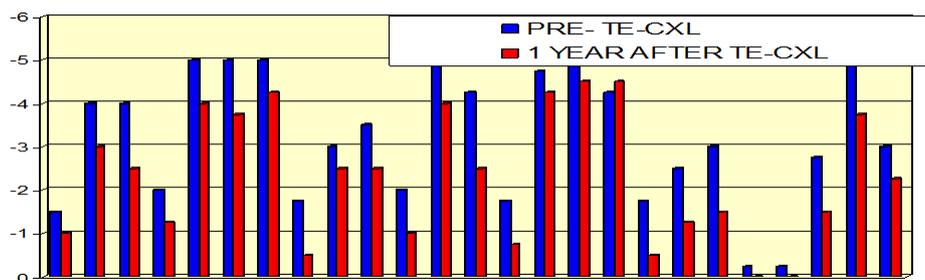
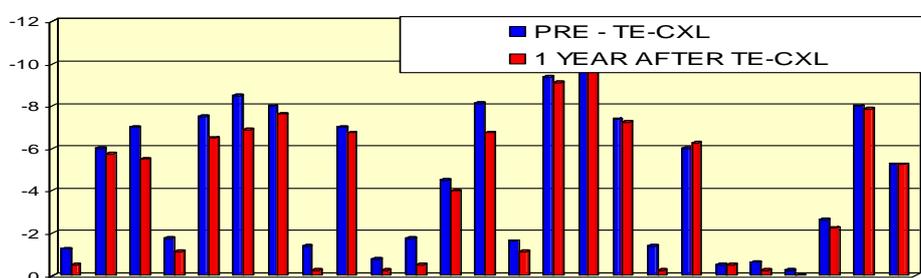


Chart 4: SPHERO-EQUIVALENT CORRECTION (Diopters) in the 25 treated eyes before and after TE cross-linking. Not significant compared to preoperative levels (P>0.05)



Further study results:

- By observing table 3 we can see in red those parameters with values that, on average, are significant compared to preoperative levels (P<0.05).
- Percentage variations (table 4): in those cases where the analysis has showed an improvement which is not significant, the

same analysis has been repeated using, as values, the percentage variations. Such analysis shows statistical significance in those cases as well (P<0.05).

Table 3: average parameters.

PARAMETER (AVERAGE)	PRE-OP	1 MONTH	3 MONTHS	6 MONTHS	1 YEAR
SPHERICAL CORRECTION (diopters)	- 4.69			- 4.19	- 4.09
SPHERO-EQUIVALENT DECREASE (diopters)				- 0,5	- 0.60
STEEPEST MERIDIAN KERATOMETRY (diopters)	49.64	49.99	49.73	49.09	48,76
FLATTEST MERIDIAN KERATOMETRY (diopters)	46.02	46.31	46.16	45.88	45.74
MEAN CORNEAL CURVATURE (diopters)	47.83	48.15	47.95	47.48	47.25
MEAN CORNEAL CURVATURE DECREASE (diopters)		- 0.32	- 0.11	0.34	0.58
CENTRAL CORNEAL THICKNESS (microns)	456	426.8	427.92	438.92	447.16
INTRA-OCULAR PRESSURE (mm.Hg)	15.56				15.64

Table 4: percentage variations.

PERCENTAGE VARIATIONS	1 MONTH	3 MONTHS	6 MONTHS	1 YEAR
SPHERICAL CORRECTION			- 0.232	- 0.296
STEEPEST MERIDIAN KERATOMETRY	0.008	0.003	- 0.009	- 0.016
FLATTEST MERIDIAN KERATOMETRY	0.007	0.004	- 0.002	- 0.004
AVERAGE KERATOMETRY	0.008	0.004	- 0.006	- 0.010
CENTRAL CORNEAL THICKNESS	- 0.064	- 0.062	- 0.037	- 0.019

Case Reports

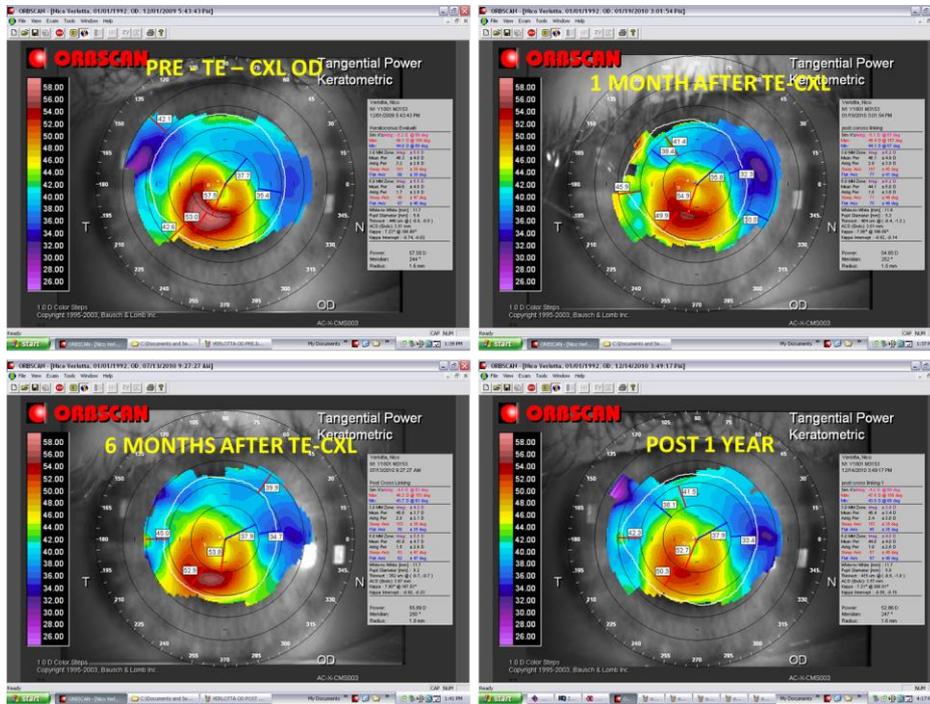


Figure 1: example of a pre-CXL case, compared with 1 month, 3 months and 1 year after treatment.

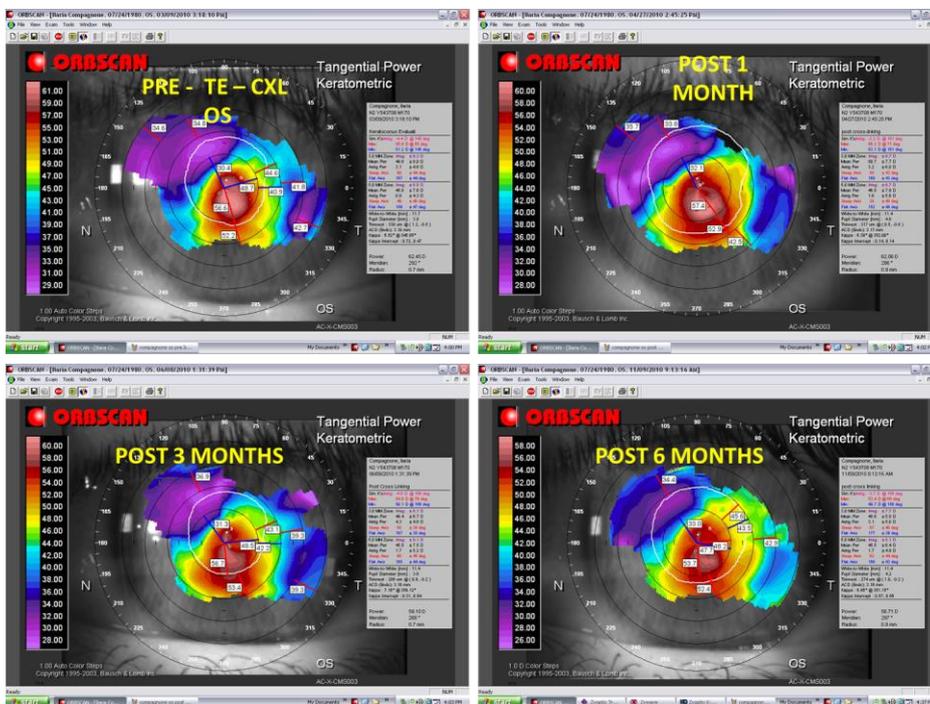


Figure 2: example of a pre-CXL case, compared with 1, 3 and 6 months after treatment.

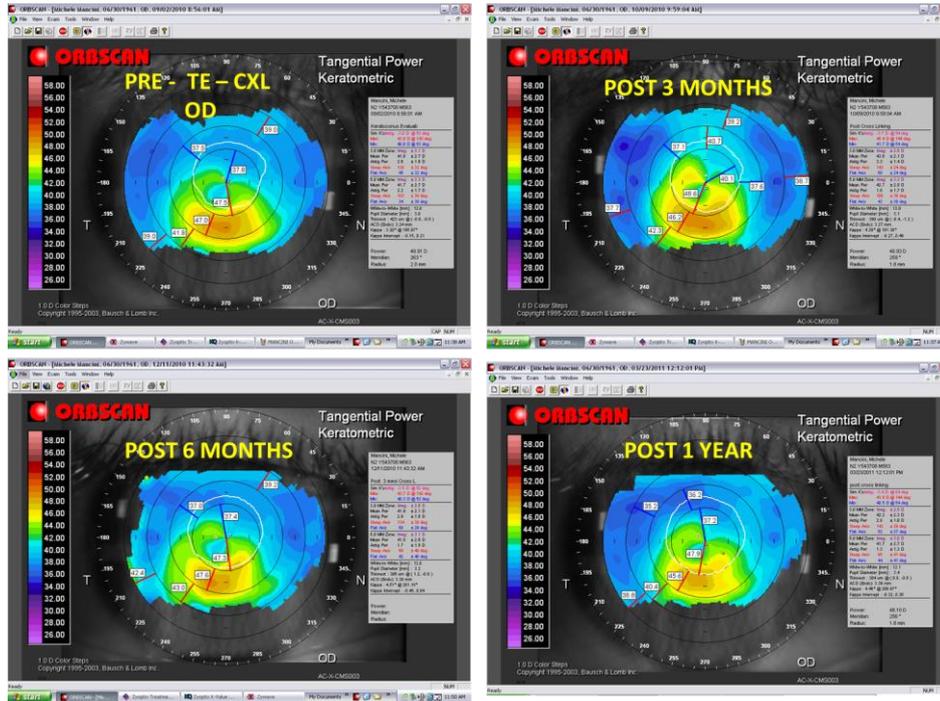


Figure 3: example of a pre-CXL case, compared with 3 months, 6 months and 1 year after treatment.

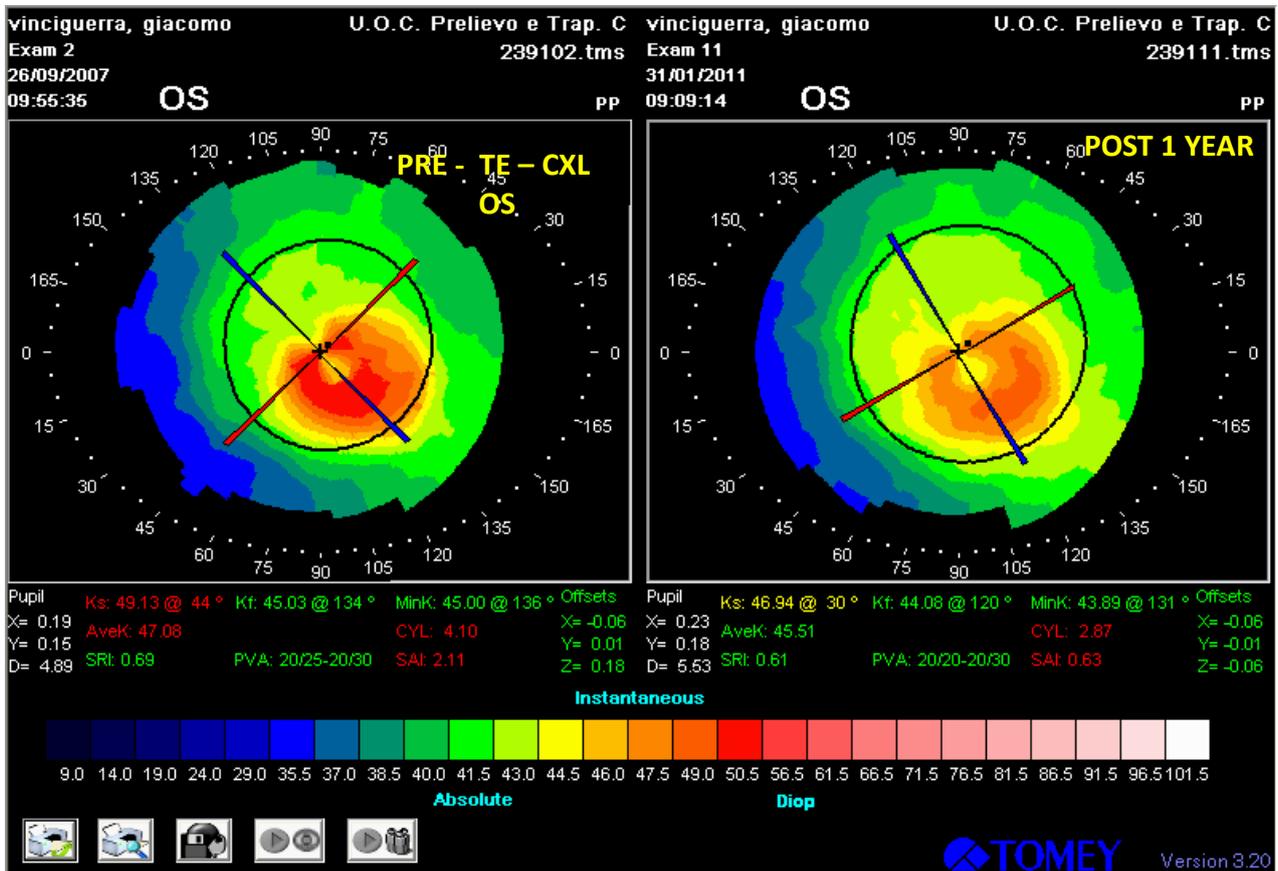


Figure 4: example of a pre-CXL case, compared with 1 year after treatment.



### **Conclusions**

The riboflavin solution for TE CXL is adapted to stop the progression of corneal ectasia, and to improve corneal curvatures and visual acuity. These results were confirmed after one year from

treatments. Further studies with larger groups of samples are needed, to confirm our results; Should our results be confirmed in further clinical studies, this solution will be a valid alternative to other solutions used in trans-epithelial cross-linking treatments.