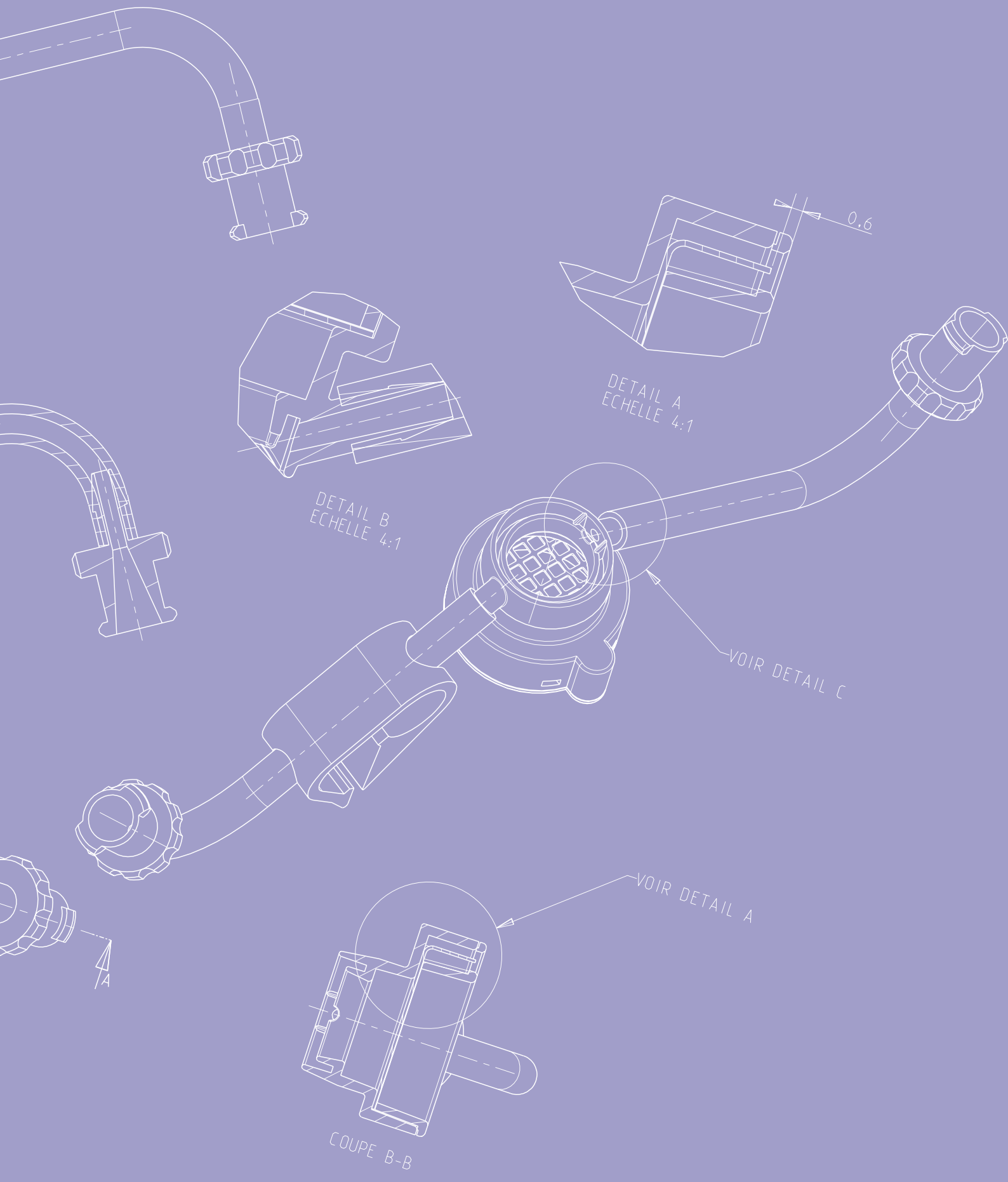
I-CXL

CORNEAL IONTOPHORESIS

EXPERIMENTAL EVIDENCE

CLINICAL EVIDENCE

SOOFT italia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VOIR DETAIL A
A
COUPE B-B

CORNEAL IONTOPHORESIS

PRINCIPALS

Iontophoresis consists of the transfer of molecules, with an ionic charge, inside the tissues to treat, thanks to a low intensity electric field. Among these molecules various drugs are included. The rapidity of passage of the ionic molecules can be increased by varying the intensity of the current applied or the characteristics of the preparation.

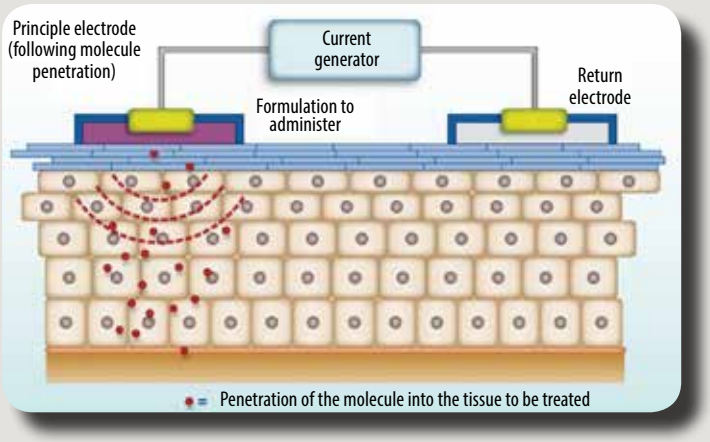


Fig.1 Diagram of the iontophoresis process.

Using the physical principle of ionic migration from one pole to another (Fig. 1), specific polarized pharmaceutical agents are prepared containing either positive or negative ions, or both (bipolar). These polarized drugs are applied to the electrodes according to their polarity: for example, if the drug has a positive polarity it will be applied to the positive electrode, if it has negative polarity to the negative electrode, if bipolar indifferently to one or the other, while the other pole is placed on the boundary of the area to be treated. Thus, applying the electrode with the drug on the area to be treated and the other at a maximum distance of about 10/20 cm, the current will transport the drug into the tissues, as the ions of the drug migrate towards the opposite polo until the drug is completely absorbed.

In corneal iontophoresis, the treatment is carried out by means of the application on the patient of two electrodes connected to a continuous current generator (Fig. 2).
The principal electrode (- pole) is in a polycarbonate ring, specific for medicinal use, which is applied by suction onto the cornea to be treated; the other electrode (+ pole) is a patch to be placed on the forehead of the patient. The current flow (low intensity) between the two electrodes allows a specific formulation of riboflavin (RICROLIN®+), specifically developed for iontophoretic administration, to rapidly penetrate into the corneal stroma, through the intact epithelium (that is without de-epithelization), guaranteeing optimal imbibition.
The charge flow is possible thanks to the continuous current from the battery power supply. The intensity that is produced for the iontophoresis is of 1 mA/min (5 minutes of treatment, 5 mA total). The duration of the treatment is automatically monitored by a suitable software package of the generator program. When 5 minutes of treatment is reached, the iontophoresis automatically stops. In ophthalmology iontophoresis is a well-known and documented technique, and has been studied for several years with many scientific publications. One can cite the research of Frucht-Pery et al. on trans-corneal and trans-conjunctival administration of dexamethasone or the studies conducted in the USA by the Eye-Gate company. Iontophoresis, at the current intensity of 1 mA, is completely harmless for the human cornea and the other sensitive structures of the eye.

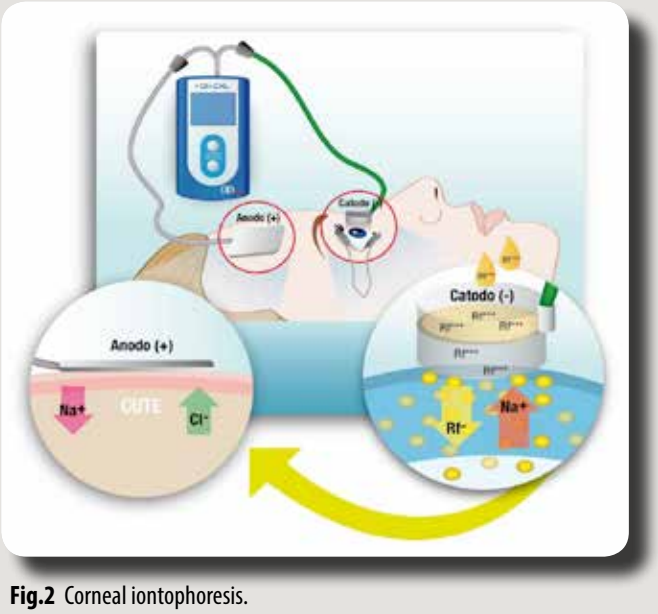
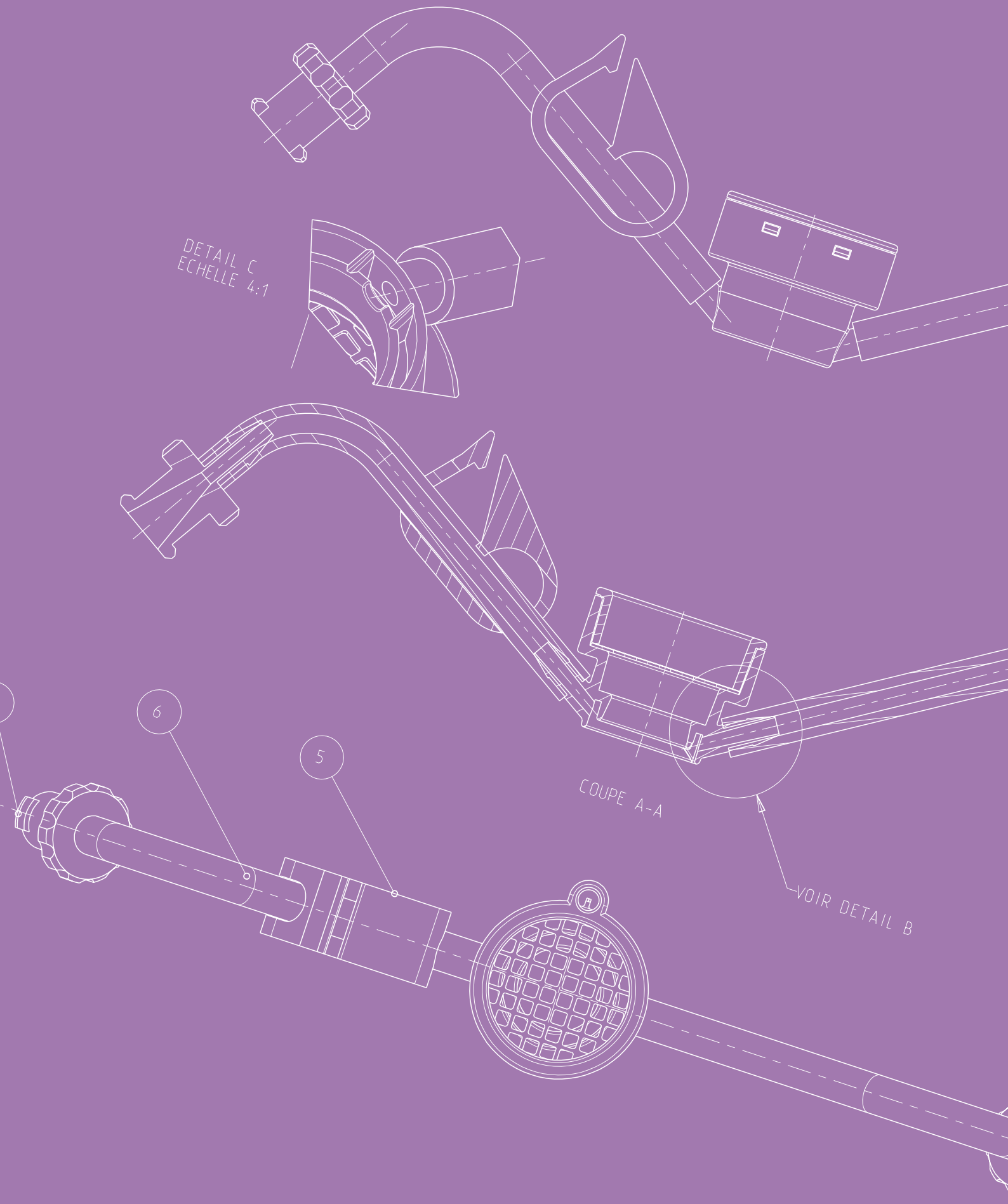


Fig.2 Corneal iontophoresis.


DETAIL C
ECHELLE 4:1
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COUPE A-A
VOIR DETAIL B

EXPERIMENTAL EVIDENCE

Experimental studies with the application of riboflavin by means of iontophoresis have shown the penetration of this molecule into animal corneas (in vivo) and in human corneas (ex vivo). The penetration was evaluated both directly (measured by means of the determination of the concentration of riboflavin in the corneal stroma and aqueous humor), and indirectly (by means of the biomechanical evaluation of the increase of stromal rigidity after CXL).
In the biomechanical studies all the corneas were treated, following imbibition with iontophoresis, with ultraviolet rays (UV-A) at the dose of 3 mW/cm^2 or 10 mW/cm^2 to evaluate the effect of different intensities of irradiation on the structural resistance of the corneal stroma.

CONCENTRATION AND DIFFUSION OF RIBOFLAVIN AND EFFECT ON STROMAL FIBERS

The studies carried out at the University of Toulouse (**Malecaze et al., IOVS 2014**) evaluated, on an animal model, the concentration of riboflavin (HPLC), the diffusion/distribution of riboflavin (two-photon microscopy) and the stromal modifications (dimensions and course of collagen fibers by means of two-photon microscopy, Second Harmonic Generation) after standard EPI-OFF CXL versus transepithelial cross-linking with iontophoresis and UV-A irradiation at 10 mW/cm2. The studies demonstrated that, notwithstanding the concentration of riboflavin administered by means of iontophoresis was half that of the standard treatment, its diffusion was optimal for all the cornea (Fig. 3) such that the effect of CXL on the stromal fibers is identical to that of the standard EPI-OFF technique (Fig. 4).
The quantity of riboflavin administered by means of iontophoresis was thus adequate to obtain an efficacious cross-linking of the anterior two-thirds of the stroma, similar to that obtained with the standard EPI-OFF technique.

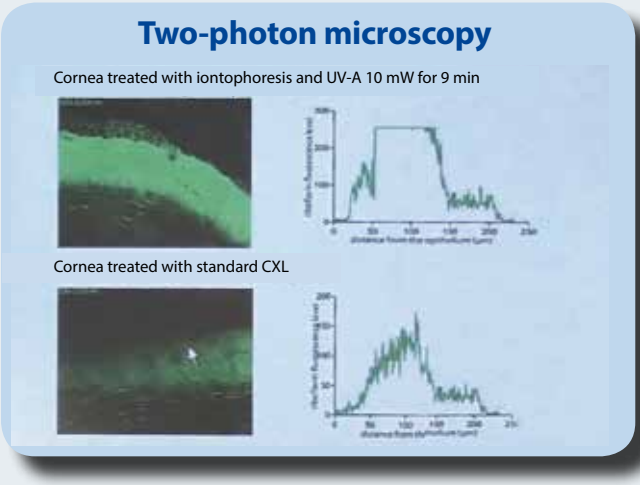

Fig. 3 Riboflavin diffusion.

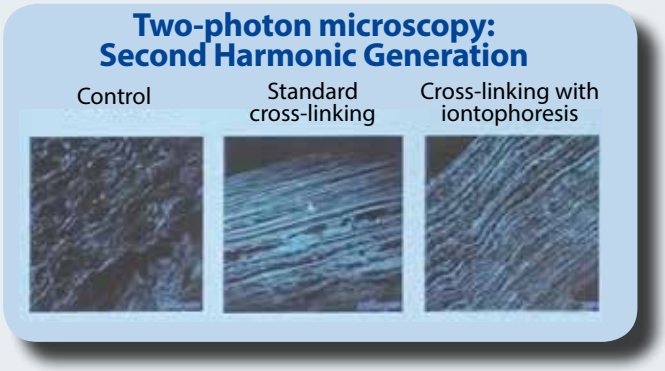

Fig. 4 Two-photon microscopy shows the corneal fibers perfectlycompact after CXL-iontophoresis, as in standard cross-linking (EPI-OFF).

CORNEAL IONTOPHORESIS

CONCENTRATION OF RIBOFLAVIN IN HUMAN CORNEAS

Mastropasqua et al., AJO 2014, carried out a kinetic study on ex vivo human corneas to determine the difference in concentration of the riboflavin in the anterior, intermediate and posterior stroma, 3 different procedures of imbibition (30' EPI-OFF with RICROLIN®; 30' EPI-ON with RICROLIN® TE; 5' Iontophoresis with RICROLIN®+). The corneas, after imbibition, were divided into 3 slices by means of a femtolaser cut (I: 0-150 microns; II: 151-300 microns; III: residual stromal bed, (Fig. 5) and then analyzed by HPLC. The results obtained (Fig. 6) confirm those obtained by Malecaze on an animal model.

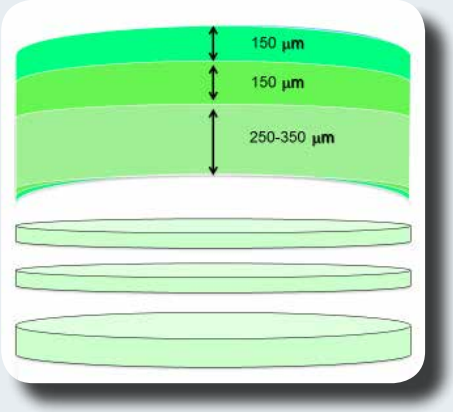

Fig. 5 Separation of the corneal stroma with femtolaser in 3 slices for HPLC analysis.

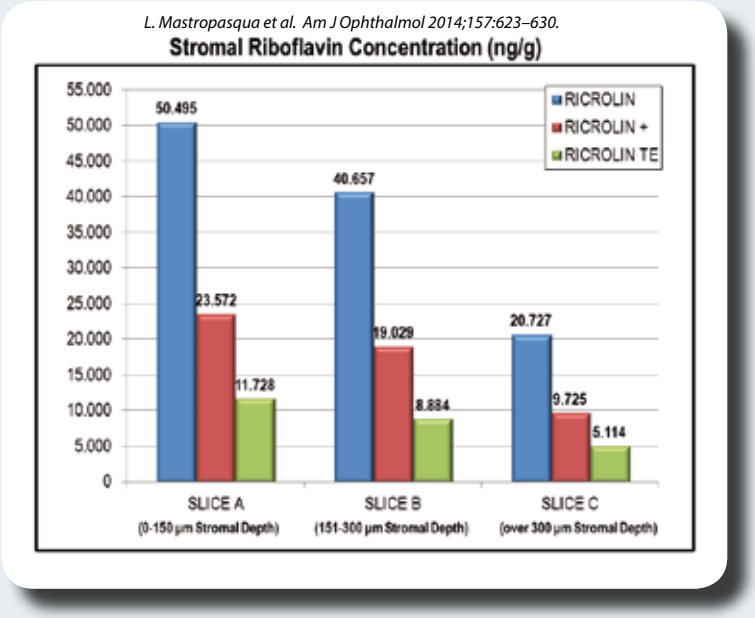

Fig. 6 Concentration of the riboflavin in the anterior (SLICE A), intermediate (SLICE B) andposterior (SLICE C) stroma after imbibition with the standard EPI-OFF (blue diagram), EPI-ON with IONTOPHORESIS (red) and EPI-ON (green) techniques. The results obtained confirm those of the study by Malecaze (page 5) that demonstrate how the quantity of riboflavin administered with iontophoresis is adequate to guarantee efficacious cross-linking.

STRUCTURAL RESISTANCE OF THE CORNEA

A study carried out in collaboration with the University of Dresda (**Spoerl et al.**) and the Clinical Institute Humanitas of Rozzano (**Vinciguerra et al.**) evaluated the efficacy of iontophoresis measuring the increase of the biomechanical resistance on human corneas (ex vivo) after UV-A irradiation without removing the epithelium and compared to other techniques of passive imbibition, both EPI-OFF and EPI-ON. The method used was the stress-strain test. The results showed how iontophoresis combined with UV-A irradiation at 10 mW was efficacious in increasing structural resistance of the treated corneas with respect to other techniques of impregnation and power of irradiation (Fig 7).

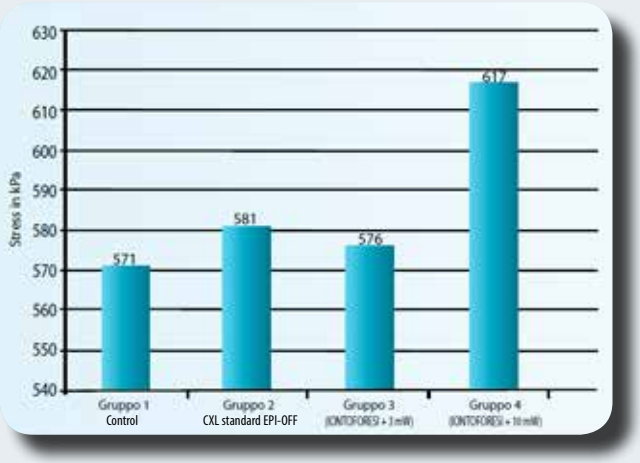

Fig. 7 Group 4 (iontophoresis + UV-A 10 mW, 9' irradiation) showed, with respect to Group 2 (standard CXL), an increase in structural resistance of the corneas of more than 6%. The treatment with iontophoresis + UV-A 10 mW was also more efficacious with respect to the combination iontophoresis + UV-A 3 mW (30' irradiation, Group 3).

CORNEAL IONTOPHORESIS

IS THE QUANTITY OF RIBOFLAVIN ADMINISTERED WITH IONTOPHORESIS ADEQUATE? IS THE EPITHELIUM A BARRIER?

The results of the study by **Malecaze** on an animal model were confirmed by an interesting experimental study carried out at the Bietti Foundation in Roma (**Lombardo et al.**). The study had the aim of analyzing the diffusion (scattering) of riboflavin before and after treatment with transepithelial CXL with iontophoresis compared with the standard CXL treatment. Iontophoresis was efficacious in distributing riboflavin in the corneal stroma through the integral epithelium. After transepithelial illumination of the corneawith a UV-A lamp of 10 mW/cm^2 it was also demonstrated how the quantity of stromal riboflavin was more than adequate for an efficacious corneal cross-linking (Fig. 8).

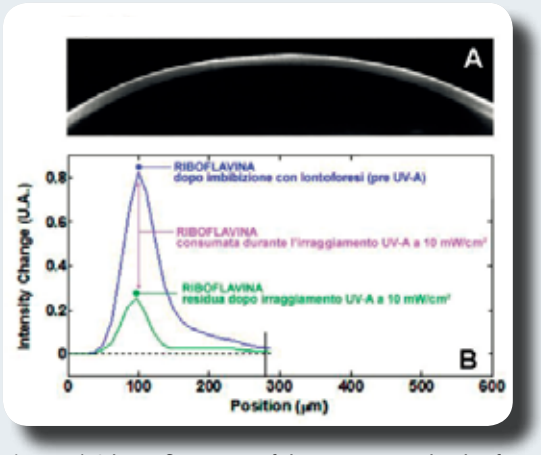

Fig. 8 A) Scheimpflug image of the cornea immediately after iontophoresis. B) Corneal densitometry (integrated values up to 280 microns of thickness and normalized with respect to the values of basal corneal scattering) immediately after iontophoresis with imbibition of RICROLIN®+ (blue curve) and after UV-A irradiation at 10 mW/cm^2 (green curve). After UV-A irradiation there was a residual signal of corneal scattering with respect to the base line demonstrating that the quantity of riboflavin diffused in the stroma by means of iontophoresis is more than adequate for an efficacious treatment with I-CXL.

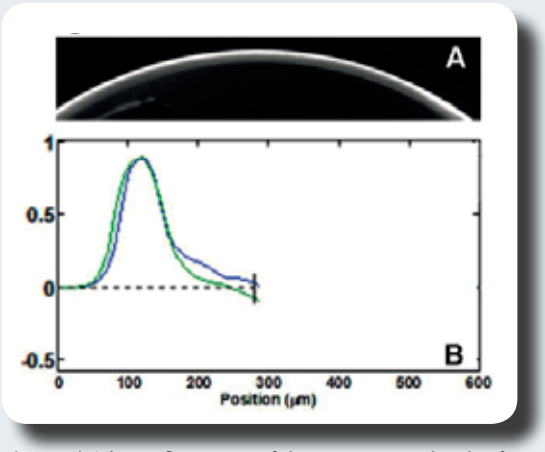

Fig. 9 A) Scheimpflug image of the cornea immediately after administration of RICROLIN®. B) Corneal densitometry (integrated values up to 280 microns of thickness) immediately after imbibitionwith standard RICROLIN® (blue curve) and after UV-A irradiation at 3 mW/cm^2 (green curve). After CXL, the corneal scattering signal is still saturated, with the exception of the intermediate stroma more than 150 microns.

The standard CXL procedure has been shown to impregnate the stroma with an elevated quantity of riboflavin, however, a part of which is not used during irradiation (Fig. 9). The study also demonstrated how the epithelium, during the CXL iontophoresis treatment, absorbs only 16-18% of the UV-A irradiation.

DOES THE TECHNIQUE GUARANTEE AN EFFICACIES APOPTOSIS OF THE KERATOCYTES? IS IT SAFE FOR THE ENDOTHELIUM?

The studies carried out at the Ophthalmological Clinic of the University of Florence (**Mencucci et al**.) showed, on human corneas ex vivo, how CXL treatment by means of corneal iontophoresis + UV- A irradiation at 10 mW/cm^2 causes an efficacious apoptosis of the keratocytes in the corneal stroma for at least 250 microns, greater than that obtained with iontophoresis + UV- irradiation A at 3 mW/cm^2 (Fig. 10). No corneas showed signs of fibrosis. There was no epithelial damage and no alteration of the nerve fibers. The conclusions of the study were that corneal iontophoresis applied to cross-linking can be considered an efficacious technique for improving the penetration of riboflavin into the corneal stroma and that the energy intensity of 10 mW/cm^2 is safe for irradiated tissue.

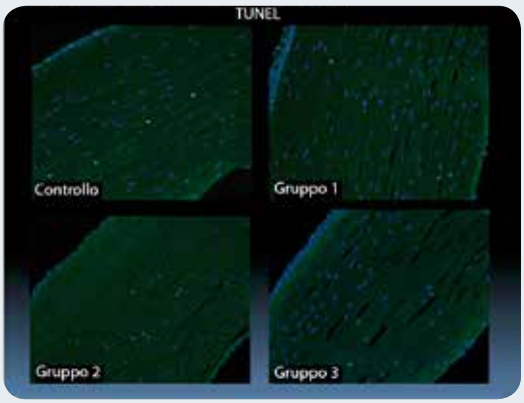

Fig.10 The Group treated with iontophoresis and irradiation a 10 mW/cm^2 (Group 2) shows clear signs of apoptosis of the keratocytes, greater than those from the treatment with iontophoresis + UV-A at 3 mW (Group 1). The iontophoresis without UV-A irradiation (Group 3) does not cause stromal effects.

CORNEAL IONTOPHORESIS

CLINICAL EVIDENCE

The mid-term results (12-18 months) available in scientific literature (**Bikbova et al., Acta Oftalmologica; Vinciguerra et al., JRS; Mastropasqua et al., EUCORNEA and ESCRS Congress 2014**) show how iontophoresis is an efficacious technique in stabilizing progressive keratoconus (reduction of Kmax, no variation in corneal thickness in the follow-up period) with a moderate inflammatory activation and no cases of haze in the treated patients.


SURGICAL TECHNIQUE

Transepithelial Iontophoresis Corneal Collagen Cross-linking for Progressive Keratoconus: Initial Clinical Outcomes

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ABSTRACT

PURPOSE: To report initial clinical results of transepithelial corneal collagen cross-linking with iontophoresis (I-CXL).

METHODS: Twenty eyes of 20 patients diagnosed as having progressive keratoconus who underwent I-CXL were included in this prospective, non-randomized clinical study. Corrected distance visual acuity (CDVA), spherical equivalent and cylinder refraction, various corneal topography and tomography pattern, aberrometry, anterior segment optical coherence tomography, and endothelial cell count were assessed at baseline and at 1, 3, 6, and 12 months postoperatively.

RESULTS: CDVA improved significantly at 3, 6, and 12 months postoperatively (logMAR difference of -0.07 ± 0.01, -0.09 ± 0.03, and -0.12 ± 0.06, respectively; $P < .05$). Abnormality remained stable during follow-up and a trend toward improvement was noted. All topographic parameters (including maximum keratometry) were stable during the follow-up, but exhibited a positive non-significant trend toward improvement. Minimum corneal thickness values were stable for up to 12 months postoperatively. None of the patients showed a progression of keratoconus. Endothelial cell counts did not change significantly ($P > .05$).

CONCLUSIONS: Preliminary results up to 1 year postoperatively indicate the efficacy of I-CXL in stabilizing the progression of this degenerative disease combined with significant improvement of CDVA. I-CXL, which spares the corneal epithelium, has the potential to become a valid alternative for halting the progression of keratoconus while reducing postoperative patient pain, risk of infection, and treatment time in select patients; however, the relative efficacy of this technique compared to standard epithelium-off techniques remains to be determined.

[J Refract Surg. 20XX;XX(X):XX-XX.]

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Corneal collagen cross-linking (CXL) is able to change the biomechanical properties of corneas and is currently the only treatment that can potentially slow or block the progression of ectatic disease.[1,2] Long-term follow-up studies on CXL mostly refer to the standard technique, which entails epithelial debridement to allow riboflavin penetration in the corneal stroma.[1,2] Epithelial removal causes pain[3] and a higher risk of corneal infection,[4] as well as visual loss for the first few months after treatment.[1,3] To avoid these drawbacks, transepithelial corneal collagen cross-linking (TE-CXL) was developed. The transepithelial protocol currently used employs a specially formulated riboflavin solution (Ricrolin TE; SOOFT, Montegiorgio, Italy) in which two enhancers (ie, benzalkonium and sodium ethylenediaminetetraacetic acid) are added to help riboflavin penetration in the corneal stroma.[5] However, results of TE-CXL are limited and have not achieved the same efficacy as standard CXL, frequently due to inadequate riboflavin penetration.[7-10]

The use of enhancers may not be the only way to increase riboflavin penetration through the epithelium. In other specialties (ie, dermatology), iontophoresis has been adopted for a long time. It is a non-invasive technique in which a small electric current is applied to enhance an ionized drug's penetration.

Preclinical results have shown that CXL with iontophoresis (I-CXL) is able to increase the concentration of riboflavin in the corneal stroma when compared to TE-CXL[11,12] with

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Dr. Paolo Vinciguerra is a consultant for Nidek, Inc. and Ocular Optikgeräte GmbH. The remaining authors have no financial or proprietary interest in the materials presented herein.

Dr. Randleman did not participate in the editorial review of this manuscript.

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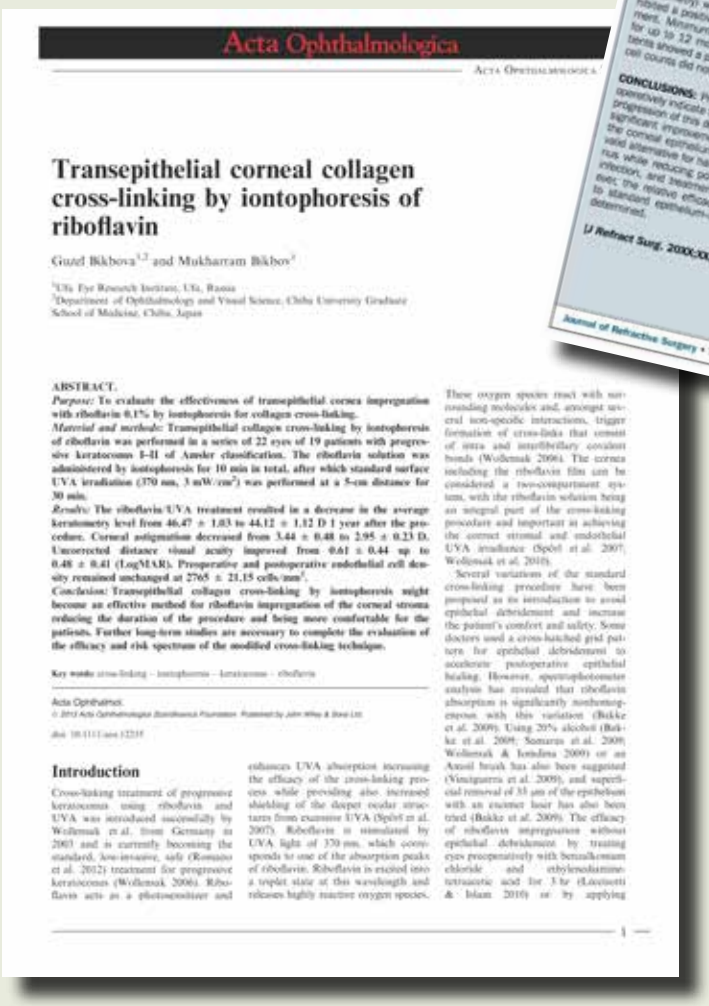
Acta Ophthalmologica

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Transepithelial corneal collagen cross-linking by iontophoresis of riboflavin

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ABSTRACT.

Purpose: **To evaluate the effectiveness of transepithelial cornea impregnation with riboflavin 0.1% by iontophoresis for collagen cross-linking.**

Material and methods: **Transepithelial collagen cross-linking by iontophoresis of riboflavin was performed in a series of 22 eyes of 19 patients with progressive keratoconus I–II of Amsler classification. The riboflavin solution was administered by iontophoresis for 10 min in total, after which standard surface UVA irradiation (370 nm, 3 mW/cm²) was performed at a 5-cm distance for 30 min.**

Results: **The riboflavin/UVA treatment resulted in a decrease in the average keratometry level from 46.47 ± 1.03 to 44.12 ± 1.12 D 1 year after the procedure. Corneal astigmatism decreased from 3.44 ± 0.48 to 2.95 ± 0.23 D. Uncorrected distance visual acuity improved from 0.61 ± 0.44 up to 0.48 ± 0.41 (LogMAR). Preoperative and postoperative endothelial cell density remained unchanged at 2765 ± 21.15 cells/mm².**

Conclusion: **Transepithelial collagen cross-linking by iontophoresis might become an effective method for riboflavin impregnation of the corneal stroma reducing the duration of the procedure and being more comfortable for the patients. Further long-term studies are necessary to complete the evaluation of the efficacy and risk spectrum of the modified cross-linking technique.**

Key words: cross-linking – iontophoresis – keratoconus – riboflavin

Acta Ophthalmol.

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Introduction

Cross-linking treatment of progressive keratoconus using riboflavin and UVA was introduced successfully by Wollensak et al. from Germany in 2003 and is currently becoming the standard, low-invasive, safe (Romano et al. 2012) treatment for progressive keratoconus (Wollensak 2006). Riboflavin acts as a photosensitizer and enhances UVA absorption increasing the efficacy of the cross-linking process while providing also increased shielding of the deeper ocular structures from excessive UVA (Spörl et al. 2007). Riboflavin is stimulated by UVA light of 370 nm, which corresponds to one of the absorption peaks of riboflavin. Riboflavin is excited into a triplet state at this wavelength and releases highly reactive oxygen species. These oxygen species react with surrounding molecules and, amongst several non-specific interactions, trigger formation of cross-links that consist of intra- and interfibrillary covalent bonds (Wollensak 2006). The cornea including the riboflavin film can be considered a two-compartment system, with the riboflavin solution being an integral part of the cross-linking procedure and important in achieving the correct stromal and endothelial UVA irradiance (Spörl et al. 2007, Wollensak et al. 2010).

Several variations of the standard cross-linking procedure have been proposed so to introduction to avoid epithelial debridement and increase the patient's comfort and safety. Some doctors used a cross-hatched grid pattern for epithelial debridement to accelerate postoperative epithelial healing. However, spectrophotometer analysis has revealed that riboflavin absorption is significantly nonhomogeneous with this variation (Bikbova et al. 2009). Using 20% alcohol (Bikbova et al. 2008; Samaras et al. 2009; Wollensak & Iomdina 2009) or an Amoil brush has also been suggested (Vinciguerra et al. 2009), and superficial removal of 35 μm of the epithelium with an excimer laser has also been tried (Bikbova et al. 2009). The efficacy of riboflavin impregnation without epithelial debridement by treating eyes preoperatively with benzalkonium chloride and ethylenediaminetetraacetic acid for 3 hr (Lhaciotti & Islam 2010) or by applying

Transepithelial corneal cross-linking with imbibition by means of iontophoresis: preliminary clinical results

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Aim of the study
Report the preliminary clinical results of transepithelial corneal cross-linking with Iontophoresis (I-CXL).

Methods
We included in the clinical study (prospective non randomized) 20 eyes of 20 patients with diagnosis of progressive keratoconus who had undergone I-CXL.
We evaluated pre-operatorially and after 1, 3, 6, and 12 months from treatment: corrected distance visual acuity (CDVA), spherical equivalent and cylindrical refraction, topographic and tomographic (Scheimpflug) parameters, aberrometry, OCT of the anterior segment, and endothelial cell count.

Results
The CDVA improved in a statistically significant way at 3, 6, and 12 months after treatment (difference of -0.07 $\pm$ 0.01 logMAR, -0.09 $\pm$ 0.03 logMAR, and -0.12 $\pm$ 0.06 logMAR, respectively; $p < 0.05$). Even if the aberrometric values and all the topographic parameters (including Kmax) remained stable in the follow-up period, there was a tendency towards improvement (without being statistically significant). The corneal thickness did not vary over the 12 months of observation. The endothelial cell count did not vary in a statistically significant way ($p > 0.05$).
None of the patients showed progression of keratoconus.

Conclusions
The preliminary results at one year from treatment show the efficacy of I-CXL in stabilizing the progression of keratoconus, with a significant improvement of the CDVA.
I-CXL, a technique that spares the corneal epithelium, could potentially be a valid therapeutic option to arrest the progression of keratoconus, with the benefit of reducing pain, risk of infection and the duration of treatment.
The efficacy of the treatment in the long-term still needs to be confirmed compared to the standard EPI-OFF technique.

Transepithelial corneal cross-linking with imbibition by means of iontophoresis: preliminary clinical results

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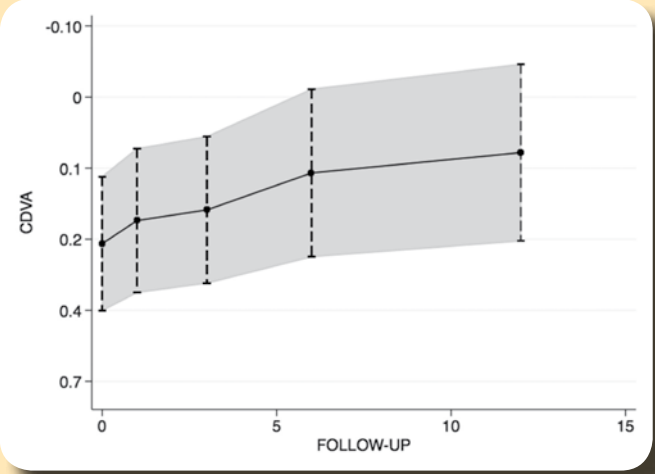

Fig.1 Variation of corrected distance visual acuity (CDVA) in the follow-up period (12 months). The CDVA shows a significant increase at 3, 6 and 12 months and a not significant increase at 1 month.

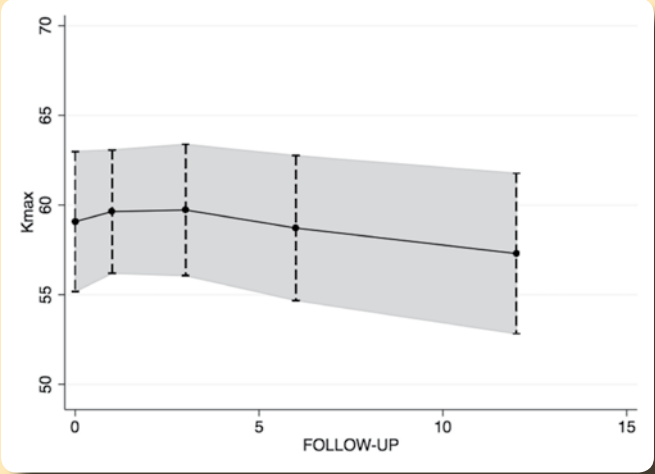

Fig. 2 Variation of max keratometry (Kmax) in the follow-up period (12 months). Kmax shows a statistically significant increase, 1 month after treatment, followed by a progressive decrease in the following follow-up period, even if not reaching statistical significance.

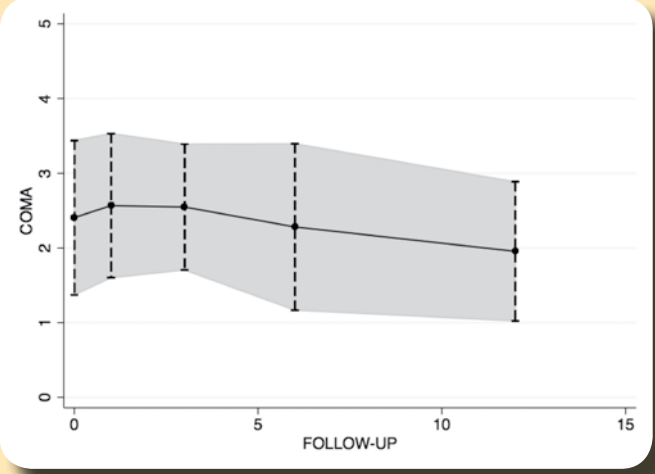

Fig. 3 Variation of the chromatic aberration in the follow-up period (12 months). The COMA shows a tendency towards improvement, without reaching statistical significance.

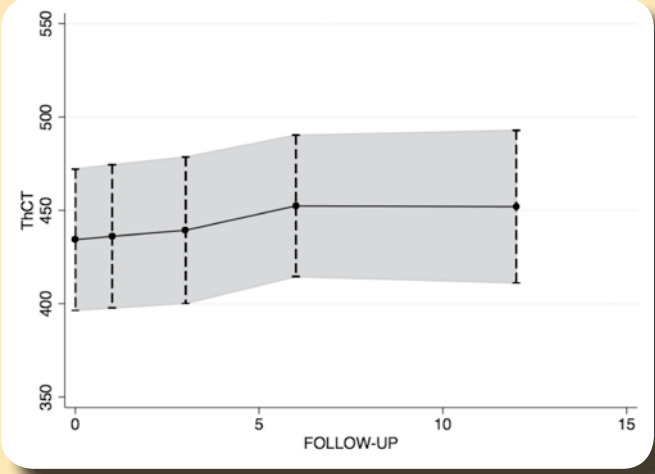

Fig. 4 Variation of the corneal pachymetry (thinnest point) in the follow-up period (12 months). The pre-operatory values (434.3 ± 37.8 µm) remained stable for all the follow-up period.

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Corneal cross-linking with iontophoresis: clinical and morphological results at 18 months

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Presented at the
V EUCORNEA Congress
London 12-13 September 2014

EuCornea European Society of Cornea & Ocular Surface Disease Specialists

Aim of the study

Investigate, on patients affected by progressive keratoconus, the clinical and morphological modifications after I-CXL that includes an imbibition by means of corneal iontophoresis (5 minutes) and successive exposure to a UV-A source at 10 mW/cm^2 for 9 minutes.

Methods

Prospective study carried out on 35 corneas of 35 patients, affected by progressive keratoconus having undergone I-CXL. We evaluated natural uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA), the topographic parameters (Kmax, Penta-cam), corneal pachymetry (thinnest point), the corneal modifications (Laser Scanning IVCM), the biomechanical variations of the cornea (Corvis). Follow-up: 1 day, 7 days, 1, 3, 6 , 12 and 18 months after treatment.

Results

UCVA and BCVA respectively went from 1.77 LogMAR (pre-operatory data) to 1.69 LogMAR (18 months) and from 0.2 LogMAR to 0.13 LogMAR ($p>0.05$). The Kmax decreased in a statistically significant way from 58.81 (pre-operatory) to 50.2 (18 months).
The pachymetric values (thinnest point) remained the same (from 449 um to 452 uni).
The in vivo confocal microscope (IVCM) showed no alteration in the of the nerve fibers, neither modifications in their density or endothelial damage. In the treated patients a moderate stromal edema and a slight inflammatory activation were seen. The deformation amplitude index (Corvis) showed, in the follow-up period, a progressive increase of structural resistance in the corneas treated with I-CXL with respect to the pre-operatory period.
The intraocular pressure, the endothelial cell count, the transparency of the crystalline and the ocular fundus showed no variation after 6 months from treatment with respect to the pre-operatory period.

Conclusions

The I-CXL treatment demonstrated to be a safe and efficacious technique in arresting the progression of keratoconus, documented not only by clinical experience, but also by basic research, without any relevant adverse effects.

Corneal cross-linking with iontophoresis: clinical and morphological results at 18 months

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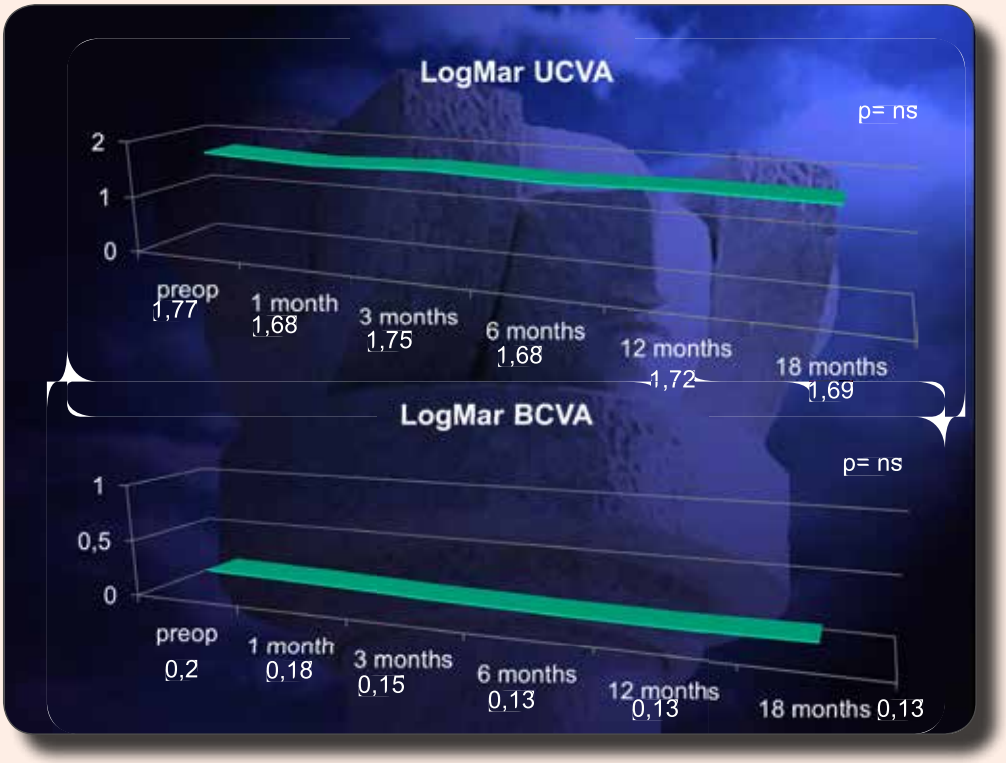

Fig. 1 Variations of uncorrected visual acuity (UCAV) and best-corrected visual acuity (BCVA) in the follow-up period.

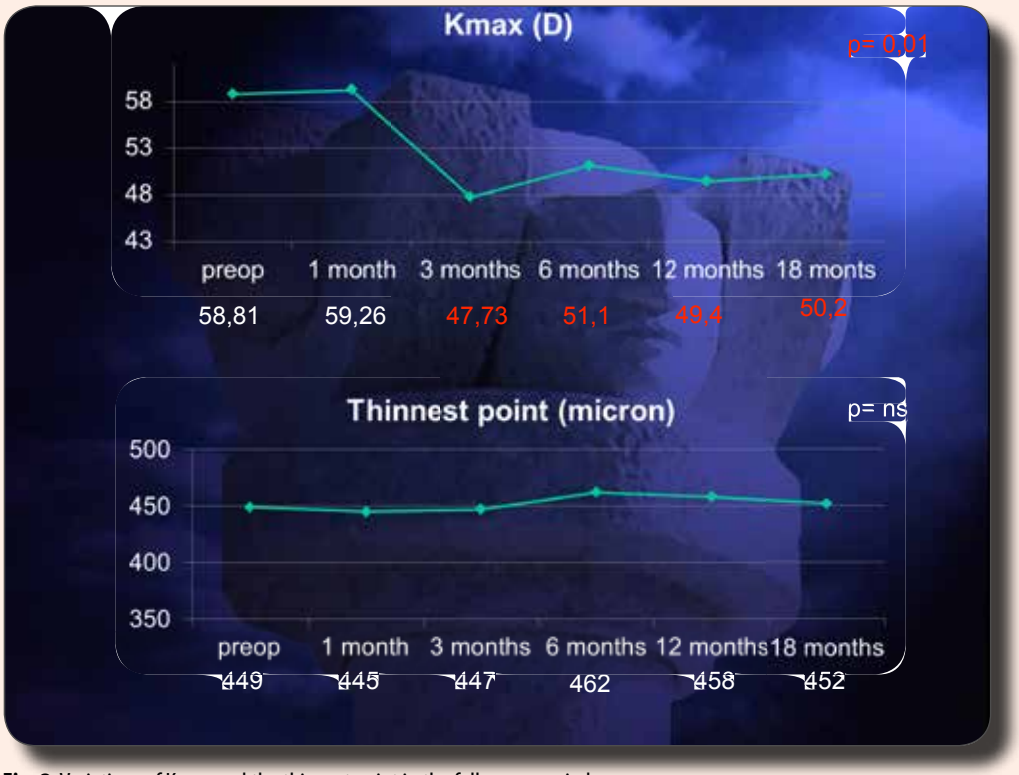

Fig. 2 Variations of Kmax and the thinnest point in the follow-up period.

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Cross-linking by means of iontophoresis: 6 months of follow-up with SD-OCT. Pilot study

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Presented at the
XXXII ESCRS Congress
London 13-17 September 2014

Aim of the study

To evaluate the efficacy of the new technique of transepithelial corneal cross-linking by means of iontophoresis (I-CXL) to increase the penetration of riboflavin through the intact epithelium in the treatment of progressive keratoconus.

Methods

Prospective study carried out on 19 eyes of 18 patients affected by progressive keratoconus (stage I-III according to the classification of Krumeich). The I-CXL treatment was carried out after topical anesthesia and the corneas were soaked with a formulation based on riboflavin 0.1% without dextran neither sodium chloride (RICROLIN®+, SOOFT Italia S.p.A) using a system for corneal iontophoresis (I-ON CXL®) for allow a rapid and uniform passage into stroma through the intact epithelium. The time of imbibition was 5 minutes, while that of UV-A irradiation (10 mW/cm^2) was 9 minutes. For all the follow-up period (1, 3 and 6 months) we evaluated: visual acuity, topographic parameters, the pachymetry (CASIA SD OCT) and endothelial cell count.

Results

Best-spectacle corrected acuity visual (BSCVA) improved from 0.198 ± 0.703 LogMAR up to 0.165 ± 0.667 LogMAR.
The analysis of the topographic data of the eyes treated showed a stabilization of the average keratometry (Kave) 6 months after the treatment (baseline: 46.52 ± 3.37 D; 6 months: 46.56 ± 3.49 D) and of the average posterior keratometry (baseline: -6.73 ± 0.73 D; 6 months: -6.73 ± 0.72 D). Astigmatism decreased from 2.94 ± 1.39 D to 2.71 ± 1.16 D.
The pachymetric values (thinnest point) were unvaried (from 465 ± 39.73 to 463 ± 40.95 um). The intraocular pressure, the endothelial cell count, the transparency of the crystalline and the ocular fundus showed no variations after 6 months from treatment with respect to the pre-operatory period.

Conclusions

The treatment with I-CXL has shown that it is able to improve the BSCVA and stabilize the K readings for all the follow-up period. Iontophoresis is a safe procedure and seems able to arrest the progression of keratoconus thanks to an optimal intrastromal diffusion of riboflavin through the intact epithelium. The advantage of the iontophoretic technique is the capacity to combine the efficacy of the standard EPI-OFF technique with absence of adverse effectstypical of the EPI-ON technique.

Cross-linking by means of iontophoresis: 6 months of follow-up with SD-OCT. Pilot study

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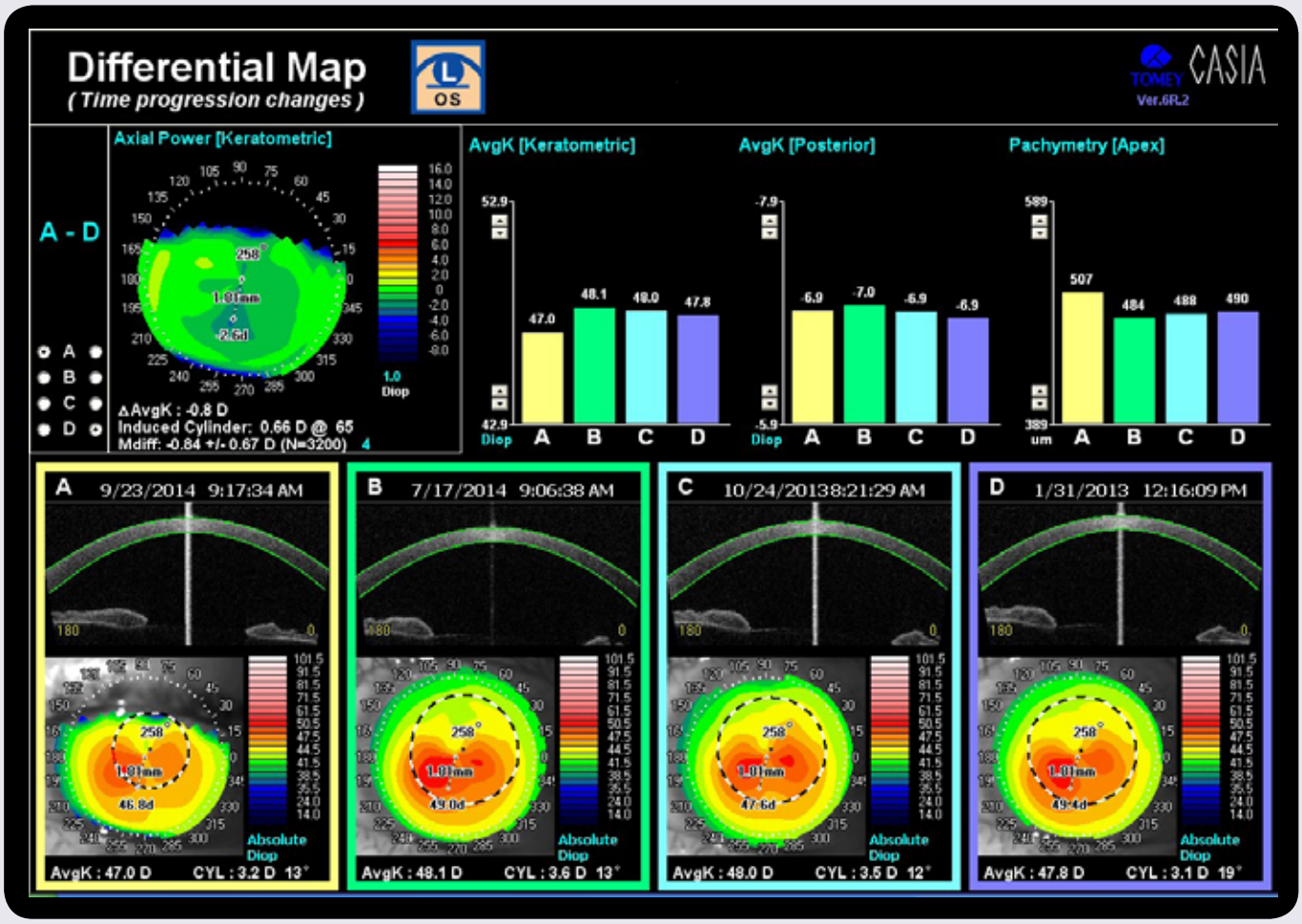

Fig.1 Variations of the average anterior and posterior keratometry and of the pachymetry in a patient who had undergone I-CXL in June 2013.
The map refers to the pre-treatment acquisition (D), after 4 months (C), 13 months (B) and 15 months (A) from treatment.
The diagrams top right show a reduction of the average anterior keratometry (0.8 D) and a stabilization of pachymetric data.
The differential map top left shows a notable reduction of Kmax of 2.6 D.
The parameters were evaluated with CASIA SD OCT.

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Demarcation Line Evaluation of Iontophoresis-Assisted Transepithelial Corneal Collagen Cross-linking for Keratoconus

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Journal of Refractive Surgery, 2015

Aim of the study
To evaluate the visualization and depth of the demarcation line with anterior segment optical coherence tomography (AS-OCT) after iontophoresisassisted transepithelial corneal collagen cross-linking (CXL).

Methods
This prospective, consecutive, single center, non-randomized clinical study involved 15 eyes of 12 patients with keratoconus who underwent an AS-OCT scan (Spectralis; Heidelberg Engineering, Inc., Carlsbad, CA) to search for a demarcation line and its depth at 1 month after iontophoresis-assisted transepithelial CXL. AS-OCT scan measurements were performed by two independent examiners.

Results
No intraoperative or postoperative complications were observed. Kappa coefficient estimation foroperator agreement in demarcation line visualization (whether it was visualized) was 70.6%. The corneal stromal demarcation line was identified in 9 eyes (60%) by both examiners. Mean depth of the corneal stromal demarcation line was 246.67 ± 50.72 µm (range: 183 to 339 µm) for the first examiner and 241.89 ± 62.52 µm (range: 163 to 358 µm) for the second examiner. There were no statistically significant differences for the measurements of the paired comparisons between the two examiners ($P = .61$). The Pearson correlation coefficient between the measurements was 0.910.

Conclusions
Iontophoresis-assisted transepithelial CXL creates a demarcation line that can be visualized with AS-OCT, which seems less easily distinguishable and shallower than in conventional CXL. However, its depth and visualization seems to be more similar to conventional CXL than transepithelial CXL.

Demarcation Line Evaluation of Iontophoresis-Assisted Transepithelial Corneal Collagen Cross-linking for Keratoconus

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Fig.1 High-resolution corneal anterior segment optical coherence tomography scan visualizing the corneal stromal demarcation line at a depth of 218 µm at 1 month after iontophoresis-assisted transepithelial corneal collagen cross-linking.

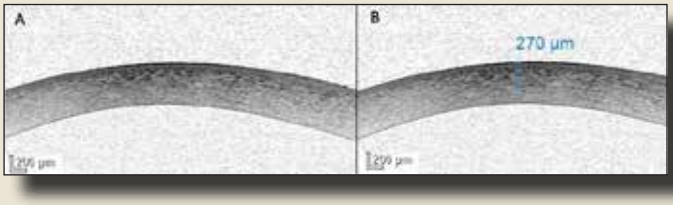

Fig. 2 High-resolution corneal anterior segment optical coherence tomography scan with a disagreement on visualizing the corneal stromal demarcation line 1 month after iontophoresis-assisted transepithelial corneal collagen crosslinking. The corneal stromal demarcation line is not visualized by the the (A) first examiner, whereas the (B) second examiner noticed a line at a depth of 270 µm.

TABLE 1
Score of Visualization and Depth of the Demarcation Line After Iontophoresis-Assisted Transepithelial Corneal Collagen Cross-linking With Anterior Segment Optical Coherence Tomography for the Two Examiners

	Examiner 1		Examiner 2	
Eye	Demarcation Line Visualization (Yes or No)	Demarcation Line Depth, µm (%)	Demarcation Line Visualization (Yes or No)	Demarcation Line Depth, µm (%)
1	Yes	232 (47.9)	Yes	220 (45.5)
2	Yes	183 (44.6)	Yes	163 (39.8)
3	Yes	185 (41.6)	Yes	184 (41.3)
4	No	–	Yes	250 (51.5)
5	No	–	No	–
6	Yes	262 (56.1)	Yes	270 (57.8)
7	Yes	265 (56.7)	Yes	203 (43.5)
8	Yes	297 (59.9)	Yes	301 (60.7)
9	Yes	239 (43.3)	Yes	270 (55.7)
10	No	–	No	–
11	No	–	No	–
12	Yes	339 (64.2)	Yes	358 (67.8)
13	No	–	Yes	270 (57.7)
14	No	–	No	–
15	Yes	218 (47.1)	Yes	208 (44.9)

Transepithelial corneal cross-linking with iontophoresis in pediatric patients. Preliminary results

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Presented at the
CORNEAL CROSS-LINKING
Up to Date
Rome, 20 September 2014

Aim of the study

Evaluate the efficacy of transepithelial corneal cross-linking with iontophoresis (I-CXL) in the stabilization of progressive keratoconus in pediatric patients.

Methods

Thirteen eyes from 8 pediatric age patients (average age: 13±2.9 years; range: 10-18 years) were treated with transepithelial corneal cross-linking by means of iontophoresis of riboflavin. The procedure began with 5 minutes of imbibition with RICROLIN®+ by means of IONTOforCXL® applicator, specific for corneal iontophoresis, and then UV-A irradiation at 10 mW/cm^2 for 9 minutes.
The patients, pre-operatively and after 3, 6 and 12 months from treatment, underwent the following examinations: DCVA (Distance Corrected Visual Acuity); corneal topography: Kmax, Kmin, Kavg; corneal aberrometry: COMA, spherical aberration and high order aberrations (HOAs) for a pupil diameter of 5.0 mm; pachymetry (thinnest point); endothelial cell count.

Results

Visual acuity DCVA improved in the 12 months of follow-up, passing from a value of 0.7±0.1 (pre-operatory) to 0.7±0.1 (3 months, p=0.04), to 0.8±0.2 (6 months, p=0.06), to 0.8±0.2 (12 months, p=0.07).
One year after treatment, the topographic and aberrometric parameters showed no significant variations (p>0.05). The thinnest point (average pre-operatory value: 485 um; average value after 12 months of follow-up: 483 um) and the density of the endothelial cell count (average pre-operatory value: 2962±214 cells/mm2; average value after 12 months of follow-up: 2940±241 cells/mm2) were stable in the follow-up period (p=0.01 and 0.09, respectively).
OCT analysis showed a not homogeneous hyper-reflective band but deep in the first 180 µm of the cornea. There were no post-operative complications.

Conclusions

Our preliminary results on pediatric patients appear to be promising, even if they have to be confirmed by studies on a greater cohort and with a longer follow-up.

Transepithelial corneal cross-linking with iontophoresis in pediatric patients. Preliminary results

L. Buzzonetti, G. Petrocelli
Ospedale Pediatrico IRCCS Bambino Gesù, Roma

	Preoperative	3 months postoperative	6 months postoperative	12months postoperative
DCVA[a]	0.7±0.1	0.7±0.1 (P=.04)	0.8±0.2 (P=.06)	0.8±0.2 (P=.07)
Spherical equivalent (D)[b]	-2.1±2.9	-1.6±2.6 (P=.6)	-1.2±1.3 (P=.3)	-1.0±1.1 (P=.1)
Refractive astigmatism (D)[b]	-1.7±2.2	-0.8±1.6 (P=.06)	-1.1±1.4 (P=.3)	-0.9±1.2 (P=.1)

[a] Distance Corrected Visual Acuity: DCVA
[b] Diopters: D

Table 1 Values of Distance Corrected Visual Acuity (DCVA), spherical equivalence and refractive astigmatism measured at baseline and after 3, 6 and 12 months from treatment with I-CXL.

	Preoperative	3 months postoperative	6 months postoperative	12months postoperative
Kmax (D)[a]	47.75±2.8	48.01±3.0 (P=.01)	48.27±2.9 (P=.04)	48.14±2.9 (P=.2)
Kmin (D)[a]	44.49±2.1	44.79±2.3 (P=.03)	44.91±2.3 (P=.04)	44.56±2.3 (P=.7)
Kavg (D)[a]	46.0±2.4	46.36±2.6 (P=.02)	46.54±2.4 (P=.02)	46.34±2.4 (P=.08)
Coma Aberration (μ)[b]	2.1±1.1	2.2±1.0 (P=.15)	2.3±1.1 (P=.01)	2.1±1.2 (P=.7)
Spherical Aberration (μ)[b]	0.3±0.2	0.3±0.2 (P=.3)	0.4±0.2 (P=.18)	0.3±0.2 (P=.6)
High Order Aberrations (μ)[b]	2.4±1.1	2.5±1.1 (P=.17)	2.6±1.1 (P=.01)	2.6±1.1 (P=.06)

[a] Diopters: D
[b] Micron: μ

Table 2 Topographic and aberrometric data measured at baseline and after 3, 6 and 12 months from I-CXL treatment.

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Transepithelial corneal cross-linking by means of iontophoresis in the treatment of progressive keratoconus in pediatric patients: one-year follow-up

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Ospedale Di Venere, Bari

Presented at the
XXXII ESCRS Congress
London 13-17 September 2014

Aim of the study

To verify the efficacy of transepithelial corneal cross-linking by means of the iontophoresis of riboflavin (I-CXL) in patients under 18 years old affected by progressive keratoconus.

Materials and methods

The treatment with I-CXL was carried out on 11 eyes of 7 patients affected by progressive keratoconus (stage II-III according to the classification of Amsler-Krumeich). Average age was 15±2.6 years. All the patients had pachymetric values above 400 microns (thinnest point). Corneal impregnation was carried out by means of a solution of hypotonic riboflavin, specific for corneal iontophoresis (RICROLIN®+), administered for 5 minutes by means of a special device (IONTOforCXL®). The cornea was then irradiated with ultraviolet light at 10 mW/cm^2 for 9 minutes. The following were measured at baseline and at 1, 3, 6 and 12 months: uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA), spherical equivalent, central corneal thickness and the Kmax.

Results

The average value of the UCVA and the BSCVA at one year had improved in a statistically significant way by 56.6% and 48.5%, respectively. None of the patients lost lines in BSCVA. Spherical equivalent showed, at 12 months from treatment, a decrease of 1 D (average value, $p>0.05$). I Kmax is diminuito of 0.7 D after 1 anno of follow-up. The central corneal thickness was the same. There were no reports of pain or adverse events. The endothelial cell count did not vary in a statistically significant way (3164.6±25.7 cells/mm^2).

Conclusions

The treatment with I-CXL appears to be safe and efficacious in the treatment of progressive keratoconus in pediatric patients. Further long-term studies are needed to establish a more complete profile of safety and efficacy of the technique for this new and promising technique of cross-linking.

Transepithelial corneal cross-linking by means of iontophoresis in the treatment of progressive keratoconus in pediatric patients: one-year follow-up

F. Montrone, L. Lapenna
Ospedale Di Venere, Bari

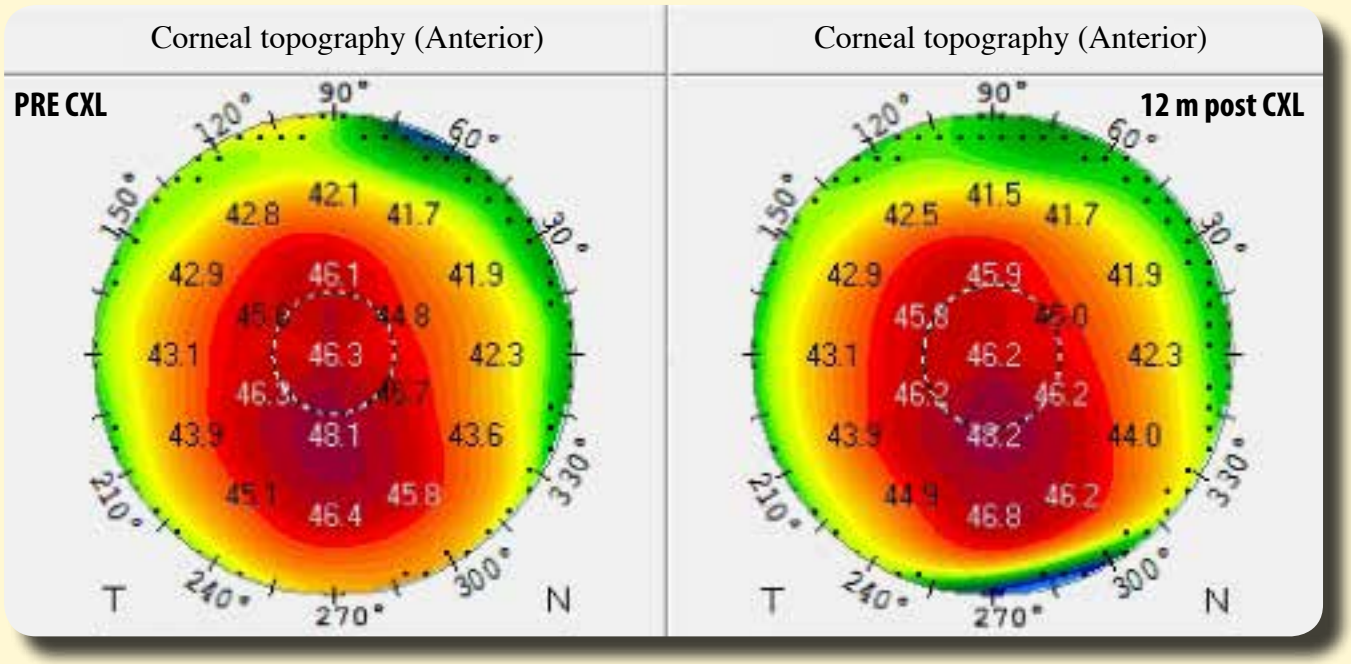

Fig. 1 Male patient (12 years old) affected by Down Syndrome with progressive keratoconus. Topographic evaluation pre-operatory and at 12 months after CXL with iontophoresis. The topographies show a clear stabilization of the ectasia.

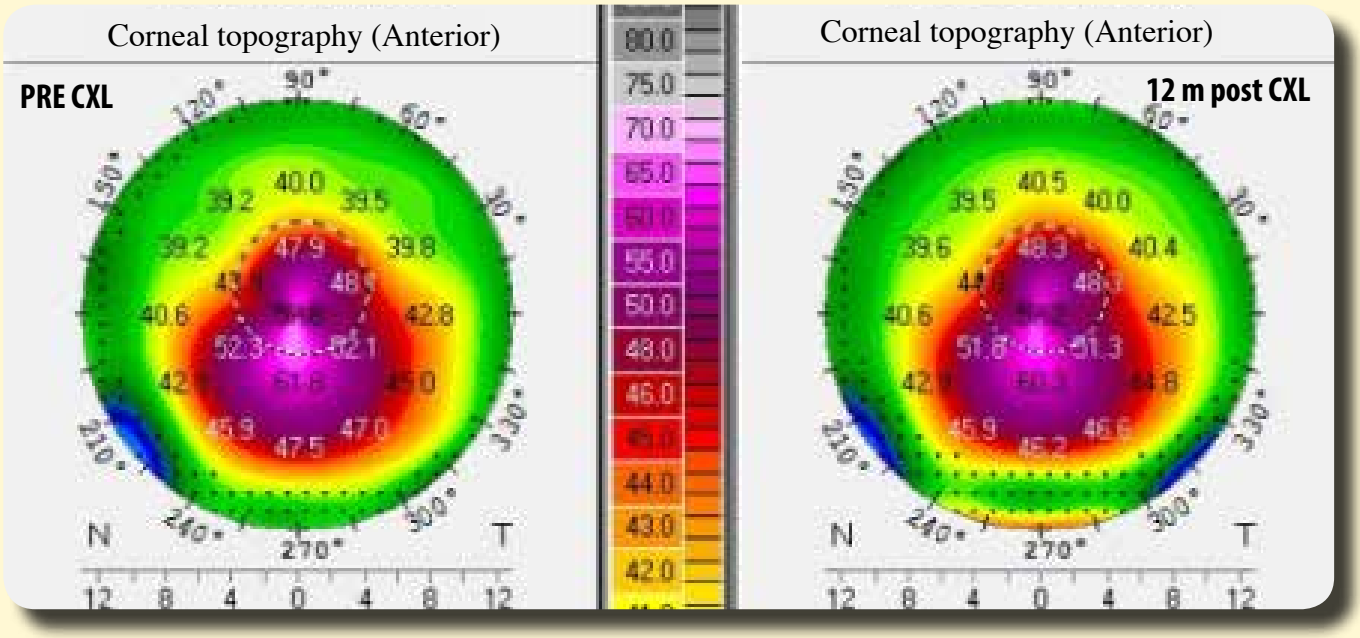

Fig. 2 Male patient (15 years old) with progressive keratoconus.
Topographic evaluation pre-operatory and at 12 months after CXL with iontophoresis. The topographies show a reduction of Kmax from 61.8 D to 60.2 Dreduction of Kmax from 61.8 D to 60.2 D.

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CORNEAL IONTOPHORESIS

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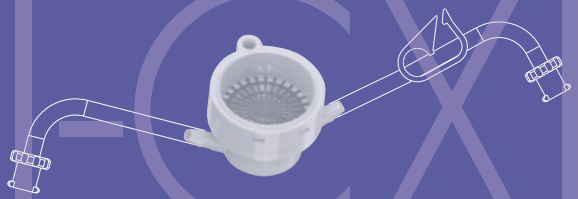

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