Specialists intrigued by new approaches to cross-linking thin corneas

Corneal cross-linking for keratoconus, first introduced by Theo Seiler, MD, PhD, in 1998, has become a well-established technique, with proven long-term safety and efficacy. The original Dresden protocol prescribed a corneal thickness of no less than 400 µm after epithelium removal to prevent possible irreversible damage to the endothelium by UV radiation. The possibility of cross-linking thinner corneas, which could potentially benefit from the treatment, became the next challenge, and several options have been proposed over the last 5 years. The ultimate answer has not yet been found, but ongoing research is producing promising results.

Basically, all techniques for thin corneas have been trying to manipulate one or more of the parameters involved, namely corneal thickness, the photosensitizing agent and the UV energy, **Farhad Hafezi, MD, PhD**, OSN Europe Edition Board Member, said.

Image: Hafezi F

Farhad Hafezi, MD, PhD, noted that all techniques for thin corneas have been trying to manipulate one or more of the parameters involved, namely corneal thickness, the photosensitizing agent and the UV energy.

"The first technique, which I developed with Theo Seiler in 2009, used an hypo-osmolar riboflavin solution to swell the cornea up to the minimum thickness of 400 µm. It is easy to perform, and

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results are good on corneas that are no less than 325 µm without the epithelium and prior to swelling. However, when we tried to apply it on thinner corneas, though the swelling went well, thickness over 400 µm was achieved, and no cellular damage occurred, no cross-linking occurred and the keratoconus progressed," he said.

The explanation might be that when the cornea returns to the original thickness after the treatment, the amount of cross-linked tissue is reduced in proportion.

"The thinner the cornea is, the more you have to swell it, and when it gets back to the original thickness, too little tissue has been actually cross-linked to produce the biomechanical changes that halt disease progression," Hafezi said.

According to OSN Europe Edition Board Member **A. John Kanellopoulos, MD,** the lower efficacy of this technique could be attributed to the fact that the aqueous attracted by the hypotonic solution into the stroma dilutes the 0.1% riboflavin, causing a much lower bioavailability of the active photosensitizer that essentially "drives" the cross-linking photochemical reaction. A less robust cross-linking effect is therefore achieved.


A. John Kanellopoulos

"A second serious concern for the cornea specialist when using hypotonic solutions in a de-epithelialized cornea is that hypotony within the cornea is extremely endothelial-toxic itself. It causes, along with swelling, significant cornea striae and endothelial cell injury and possible irreversible loss. I have early on stopped using this technique for these reasons," he said.

"The lack of cross-linking effect with use of hypotonic solutions to swell the cornea may be purely mechanical because the collagen strands may be too far apart or not properly aligned for maximum efficacy," **Francis W. Price Jr., MD,** OSN U.S. Edition Board Member, said. "This lack of effect is very similar to what we observed using

cross-linking to treat bullous keratopathy. Even when we took measures to reduce the corneal swelling before the treatment, the cross-linking effect was minimal and transient. Proper alignment or spacing of collagen fibers may be necessary for effective cross-linking."

Contact lens-assisted collagen cross-linking

A technique that attempts to artificially increase corneal thickness was recently published by OSN APAO Edition Board Member **Soosan Jacob, MS, FRCS, DNB.**

"[CACXL] has the advantage of avoiding the need for excessive swelling of the cornea while retaining the advantages of an epi-off technique."

— SOOSAN JACOB, MS, FRCS, DNB

Contact lens-assisted collagen cross-linking (CACXL) uses a thin soft contact lens with no UV barrier. Both the lens and the cornea, after removal of the epithelium, are soaked in riboflavin for 30 minutes. Pachymetry is then performed at the thinnest point with the lens in place, and if a total thickness of more than 400 μm is achieved, a standard cross-linking procedure is performed.

"For the small subgroup of patients who need a few additional microns, I remove the lens and wet the cornea with a couple of drops of distilled water. In 3 to 4 minutes, the cornea swells by the additional minimal amount required to top up the deficient thickness, and then I put the lens back and do the procedure. This has the advantage of avoiding the need for excessive swelling of the cornea while retain-

ing the advantages of an epi-off technique," Jacob explained.

This technique should only be used in corneas that are not too thin and can achieve a thickness of more than 400 µm with the addition of the lens, she recommended. She started performing this treatment about 1.5 years ago, and results in the approximately 30 patients treated so far are rewarding. Confocal studies performed in collaboration with **Cosimo Mazzotta, MD, PhD,** have also shown promising results.

Simple and effective, CACXL has gained popularity among cornea specialists.

"We were pleasantly surprised by how well these patients do," Price said. "We had no problem with endothelial toxicity. We get demarcation lines that are really deep, sometimes 100%. It has really expanded the number of people we can treat with this technique. We were concerned that it might block a lot of the treatment, but it has worked out well with our patients — just as Soosan Jacob said."


Francis W. Price Jr.

"I have used Soosan Jacob's technique, which I think is brilliant. It is very easy, and for someone who has the standard technology 3 mW/cm^2 and the standard riboflavin solution, I think there is no other technique that is better," Kanellopoulos said.

Experimental studies recently done by Hafezi, however, have shown that the contact lens barrier may cause about 20% loss of the cross-linking effect.

"We used ex vivo porcine corneas and living mouse corneas. We performed standard hypo-osmolaric CXL and CACXL and looked at UV availability in the depth of the tissue, oxygen availability and biomechanics after the three procedures. Taking the standard CXL as the gold standard, we found a 6% loss of cross-linking effect with the hypo-osmolaric CXL and a 20% loss with CACXL," Hafezi said.

Oxygen diffusion, which has been demonstrated to be crucial in the cross-linking process, seems to be hindered by the contact lens,

leading to a loss of almost one-quarter of the efficacy.

"All this is academic because 20% less cross-linking might still be enough to stop keratoconus. We simply need a longer follow-up in a greater number of patients to prove that the procedure is clinically effective. If keratoconus can be stabilized with a simple contact lens, that would be even easier than doing it with my hypo-osmolar solution. Also, we currently test this method using other contact lenses with higher oxygen permeability," he said.

Epithelial island cross-linking

After the letdown of the transepithelial approach of cross-linking, which neither the modified riboflavin formula nor the iontophoresis process were able to overcome, a new technique was developed by a group at Siena University.

"This technique, which we named epithelial island CXL, main-


Cosimo Mazzotta

tains only a small portion of the epithelium, 3.5 mm approximately, over the thinnest point of the cone to protect it from UV radiation. The epithelium is removed from the surrounding area. The cornea is then soaked with standard riboflavin for 10 minutes, and UVA irradiation is performed at 3 mW/cm^2 for 30 minutes," Mazzotta said.

Removing the epithelium where the cornea is thicker allows a better penetration in the paracentral area and periphery, ensuring a stronger biomechanical effect compared with the transepithelial technique. At the same time, the thin apical point is protected, he explained.

Compared with the contact lens technique, epithelial island cross-linking can be used in corneas that are thinner than 350 µm because UV penetration under the island is no more than 200 µm, as shown by confocal microscopy.

"We have treated about 100 patients with this method, and results are good over 2 years of follow-up. Visual outcomes are inferior compared to the standard technique, with an average gain of 1 D, but keratoconus progression was stopped in all our cases," Mazzotta said.

Energy modulation

Other options aim at concentrating the cross-linking effect more anteriorly in thin corneas by decreasing UV light exposure and/or increasing UV light fluence.

Kanellopoulos and his team in Athens have introduced over the last 10 years many of the current concepts of alternate cross-linking techniques, such as higher UV fluence and shorter time exposure, non-dextran riboflavin solution, epithelium-on cross-linking by injecting riboflavin solution through a femtosecond laser-created intracorneal pocket, combining high-fluence cross-linking and topography-guided excimer laser normalization of the irregular kera-

toconic cornea, combining high-fluence cross-linking and routine myopic and hyperopic LASIK, as well as "refractive" cross-linking by utilizing a variable-fluence topography-guided UV light beam. In the latter area, Kanellopoulos has worked with emerging technology from Avedro. None of these techniques, though, have been standardized, and most reports in the literature are individual center results that may still need proper comparative evaluation.

"There has been no standardized effect documented for each of the different techniques, so there is still debate and confusion on the parameters that should be used," Kanellopoulos said. "We have worked in our clinical and research institute in Athens in several comparative protocols ex vivo in an attempt to validate the efficacy

Cross-linking in thin corneas

Technique	Pros	Cons
Hypo-osmolaric solution	Longest published follow-up. Works in corneas thicker than 325 µm without the epithelium.	Does not work below 325 µm of thickness without epithelium and prior to swelling. Hypo-osmolarity might be toxic to the endothelium.
CACXL	Ease of use. Elegant way to bypass thin stroma.	Recent and unpublished data from Hafezi's research group suggests 20% less efficacy. However, even reduced efficacy might be enough to stabilize corneas. Room for improvement: contact lenses with higher oxygen permeability.
Epithelial island technique	Ease of use.	Theoretically, 20% of the UV energy is blocked by the epithelium over the thinnest area, which may mean less effect.
Energy modulation	Ease of use.	Needs to prove itself in long-term follow-up.

Source: Hafezi F

between several different CXL techniques. These studies have been already presented in major meetings this last year and are in the process of publication. Additionally, large FDA comparative studies are being currently performed under the auspices of Avedro in the U.S., which may be able to provide us with some of the answers we need."

This approach, however, looks promising, and several surgeons believe that energy modulation is the key to effectively treating thin corneas.

"The new machines allow us to work epithelium-off and stay more superficial. I use the Avedro system for pulsed-light accelerated CXL with 8 minutes (1 second on/1 second off) of UVA exposure at 30 mW/cm^2. The pulsed light modality increases the effect of the treatment as compared with continuous light because it increases oxygen availability on the corneal surface," **Miguel Rechichi, MD, PhD,** said.


Miguel Rechichi

"Three years ago, we thought we could use this high energy only in thick corneas, but experience taught us that it was the exact opposite. It is the same principle we apply to cooking steaks: low and slow if we want to cook them deep, and high and fast if we want to cook only the outer layers," he said.

By modulating exposure time and power, corneas of various thicknesses can be effectively and safely cross-linked, including thin corneas up to 325 μm, he said.

"In corneas that are between 350 μm and 400 μm, I simply use the hypo-osmolaric solution. In corneas that are thinner, I adapt the total energy of the light to the thickness of the cornea. With my postdoc Sabine Kling, we are in the process of establishing a nomogram to calculate fluence in relation to corneal thickness," Hafezi said.

Future approaches include topography-guided cross-linking with the possibility to differentiate between areas and apply more or less intensity according to the local thickness, he said.

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Kanellopoulos is currently using the Avedro KXL II system for topography-guided accelerated cross-linking.

"This new system has the ability to produce variable fluence and high-energy collagen cross-linking patterns of any type, limited only by the imagination of the surgeon, in multiple applications," he said. "We have proven its facility to effectively correct small refractive errors on virgin healthy corneas, such as myopia, hyperopia and astigmatism, and have been using the multitude of potential that this device offers in our clinical practice in LASIK plus CXL cases, as well as in cases that combine topography-guided excimer normalization and topography-guided CXL in an 'enhanced' Athens protocol procedure for young keratoconus patients with excellent results."

Tackling the root of the problem

According to Mazzotta, these techniques and technologies may indeed be the future, but studies are needed to prove safety of high energy delivery to thin corneas.

"The doubt remains that high power radiation may cause damage to the endothelium. We have proven the safety of standard CXL but lack data on the medium- to long-term safety of accelerated procedures in thin corneas," he said.

To tackle the root of the problem, Price said that it is necessary to reduce the need for treating thin corneas. In the majority of cases, corneas below the 400 μm threshold are the result of late diagnosis or deferred therapy. This accounts for the variable prevalence rate of thin corneas reported by surgeons in different socioeconomic environments, which ranges from approximately 30% in India to 5% to 10% in Europe and the U.S.

"We need better screening programs for kids at school to treat corneas before they become thin. We are hoping to eliminate the need for corneal transplant due to keratoconus, and the key is to do earlier diagnosis," Price said. "We spend a lot of time educating

doctors in our area of the country and treat kids down to 10 years of age with really good results. One of the encouraging things is that we are not grafting the people we have cross-linked, which is a huge improvement and says a lot about the efficacy of the procedure." – *by Michela Cimberle*

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Farhad Hafezi, MD, PhD, professor of ophthalmology at the University of Geneva and medical director of the ELZA Institute, can be reached at 2 Webereistrasse, 8953 Dietikon, Switzerland; email: farhad@hafezi.ch.

Soosan Jacob, MS, FRCS, DNB, head of cornea and refractive services and senior consultant ophthalmologist at Dr. Agarwal's Eye Hospital, can be reached at 19 Cathedral Road, Chennai-600 086, India; email: dr_soosanj@hotmail.com.

A. John Kanellopoulos, MD, director of the LaserVision Clinical and Research Institute in Athens, Greece, and Clinical Professor of Ophthalmology at NYU School of Medicine, can be reached at 115 E. 61st St., New York, NY 10065 U.S.A.; email: ajk@brilliantvision.com.

Cosimo Mazzotta MD, PhD, research consultant in the Department of Medical, Surgical and Neurosciences, Siena University Hospital, can be reached at cgmazzotta@libero.it.

Francis W. Price Jr., MD, can be reached at Price Vision Group, 9002 N. Meridian St., Suite 100, Indianapolis, IN 46260 U.S.A.; email: fprice@pricevisiongroup.net.

Miguel Rechichi, MD, PhD, can be reached at Eye Center Catanzaro, Via Sirleto 35, 88100 Catanzaro, Italy; email: miguel.rechichi@libero.it.

Disclosures: Hafezi is chief scientific officer of EMAGine SA and was named co-inventor of PCT/CH 2012/000090 and PCT/CH 2014/000075 applications. Kanellopoulos is a consultant to Avedro. The other sources have no relevant financial disclosures.