

Advances in epi-on techniques may establish new gold standard in corneal cross-linking

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In the lively debate over the protocols for corneal collagen cross-linking, epithelium-on techniques have a special place. A transepithelial treatment has advantages in terms of noninvasiveness and safety, but the barrier effect of the epithelium, attenuating riboflavin penetration, UV light absorption and oxygen diffusion, seemed difficult to overcome. Recent developments, however, have brought the epithelium-on option back to the forefront. If the promising results that have been recently documented are confirmed in the long term by larger-scale clinical trials, the transepithelial approach might become the new gold standard.

“CXL is intrinsically an adjustable, customizable procedure. By modifying the chemical and physical variables involved in the treatment, we have been able to overcome the problems that made epithelium-on protocols fail in the past. The new epithelium-on procedures are as effective as the traditional epi-off,” **Cosimo Mazzotta, MD, PhD**, said.

Mazzotta, a cross-linking pioneer of the Siena group, has devoted his efforts over the past few years to optimizing new cross-linking protocols.



According to Cosimo Mazzotta, MD, PhD, the transepithelial cross-linking approach will likely replace epi-off protocols in the future.

Source: Cosimo Mazzotta, MD, PhD

“I believe there will be just epi-on in the future, but the jury is still out. Let the studies provide the evidence we need,” he said.

According to **Peter S. Hersh, MD**, medical monitor of the studies leading to FDA approval of cross-linking in the United States, there is a lot of interest and great expectation in the U.S. for the new epi-on procedure.

“It holds the potential to decrease patient discomfort, healing time and the amount of time patients need to be out of their contact lenses afterward. It decreases the potential for infection and diminishes the amount of corneal haze. So far, the literature still supports the use of epi-off in patients with progressive keratoconus, but if we can get an epi-on procedure that works as effectively, in the U.S. and elsewhere, that is the way we want to go,” he said.

In the U.S., a study on the Avedro Boost Epi-On procedure is currently recruiting more than 200 patients.

“It is a well-controlled trial, which should give us the

answers we need,” Hersh said.

Previous failures

Previous attempts to perform CXL through the epithelium had disappointing results. Dextran-enriched riboflavin formulas were not able to adequately penetrate the tight junctions of the epithelium and diffuse well into the stroma.

“UVA irradiation was therefore not efficient enough to trigger the release of free radicals and collagen photoreticulation. There was hardly any visible effect, no haze, no demarcation line, no keratocyte loss, no nerve plexus lesions,” **David Touboul, MD, PhD**, said.

As a reference center for keratoconus, the University Hospital of Bordeaux, France, was involved in the studies with Ricrolin TE (Sooft).



David Touboul

“We treated approximately 60 patients with a long-term follow-up of 1 or 2 years, and we had a 30% failure rate, three times more than the progression rate after epi-off CXL,” Touboul said.

Iontophoresis, consisting of the application of a small electric current to the cornea to enhance riboflavin penetration, also performed below expectations.

“It had an effect, but UVA penetration remained irregular and unpredictable. The demarcation line was not deep enough, and there was little keratocyte apoptosis,” Touboul said.

Hersh and co-authors reached the same conclusions in a study published last year in the *Journal of Cataract and Refractive Surgery*.

“The issues involved with epi-on are: Is it effective? Is it long lasting? And how are the results compared to standard CXL? What we found in our own study in the U.S. is that it is effective, but the robustness of the effects that we were finding, with outcomes of change in keratometry and changes in vision, were less robust than we found in our studies of epi-off,” he said. “However, recent advances that introduced parameter changes in UVA total power, the way it is administered, as well as the addition of oxygen, are encouraging. We need to further evaluate efficacy in long-term controlled trials,” he said.

Four parameter changes

The new approach to transepithelial CXL has introduced four important parameter changes, which, combined, allow the treatment to cross the epithelial barrier.

First is the increased riboflavin concentration, from 0.1% to 0.25%, and second is the increased UVA fluence.

“A major cause of failure with previous attempts was that fluence was the same as in standard cross-linking. We have now increased fluence by 30%, from 5.4 J/cm² to 7.2 J/cm², which compensates for the 30% UVA energy absorption by the epithelium alone,” Mazzotta said.

The other two changes were based on the discovery that oxygen is the main driver of the cross-link reaction. The role of the epithelium in relation to oxygen consumption and diffusion into the stroma was reconsidered in light of this discovery.

“The epithelium consumes 40% of the oxygen, as much as the stroma, while the endothelium accounts for the remaining 20%. Since the epithelium is 10 times thinner than the stroma, the actual epithelial oxygen consumption is 10 times higher than the stromal oxygen consumption. This is a crucial factor we have learned to take into account,” Mazzotta said.

Two strategies were adopted to increase oxygen diffusion. The first was the use of pulsed light, which was demonstrated to increase intraoperative oxygen availability as compared with the continuous light treatment. The second was the intraoperative use of supplemental oxygen.



Peter S. Hersh

“The Boost goggles of the Boost Epi-On procedure, which the patient wears during UV light application, create a hyperoxic environment. Intraoperative oxygen diffusion is increased by a factor of five as compared to the 21% oxygenation in normoxic conditions. This compensates for the epithelial oxygen consumption and enhances oxygen diffusion in the stroma, leading to the formation of free radicals and cross-linking reaction,” Mazzotta said.

Iontophoresis and Boost goggles

The first three changes — higher riboflavin concentration, increased fluence and pulsed light delivery — were also introduced in his new iontophoresis protocol with encouraging results, Mazzotta said.

“With the new enhanced fluence pulsed light iontophoresis protocol, without the additional oxygen, the demarcation line was visible in 90% of the eyes as compared with 30% of the original iontophoresis protocol. Treatment penetration was up to 300 μm, quite similar to Dresden epi-off, while it was previously no more than 200 μm. Mean reduction of Kmax was 1.8 D, also similar to epi-off,” Mazzotta said.

Twenty-four eyes of 20 patients were treated, with a follow-up of 3 years.

With Boost goggles, customized topography-guided CXL, also known as CuRV (customized remodeled vision), was performed in 25 patients in Italy. Six-month data are encouraging, he said.

“What I have noticed in comparison with the new iontophoresis is that the addition of oxygen enhances penetration, resulting in an even deeper demarcation line. We need now further studies to develop standardized nomograms for energy delivery in relation to corneal thickness because this deeper effect could be a problem in thinner corneas,” Mazzotta said.

Avoiding complications and pain

At Aristotle University of Thessaloniki, Greece, **Miltos Balidis, MD, PhD**, treated more than 40 cases with the CuRV procedure.

“At the moment what seems to be really attractive is that we can go quite deep, and we can go quite deep in a customized way, which is even better. All the cases we have with 9 months of follow-up show a demarcation line at a depth of 270 μm or more, and 95% have a demarcation line at a depth of 300 μm or more, which accounts for 60% to 70% of corneal thickness,” he said.

Most of the CXL complications are related to the bandage contact lens used after the procedure, which is necessary to protect the cornea during the epithelial healing process.

“Epithelial healing is delayed even more than after PRK, probably because of the effect of UV irradiation on the stem cells. Delayed healing has been associated with central haze and central scar, and bandage contact lenses have been shown to increase the risk of infection,” Balidis said.

With epi-on CXL, these complications will become a thing of the past, he said.

Having no pain will be another advantage.

“We’ll feel more comfortable treating eyes with early-stage keratoconus, which is eight or nine out of 10 cases, to stop progression or even avoid progression and maintain good vision,” Balidis said.

Biological effect and eye rubbing

Boost Epi-On is currently being evaluated also in Toulouse, France, another reference center for keratoconus. Early results show a significant decrease in Kmax of 1.43 D and a well-defined demarcation line.

“As a reference center, we are connected with Toulouse, and I am looking forward to trying the treatment,” Touboul said.

In his opinion, CXL is effective mainly because it stops eye rubbing. All of his CXL patients are involved in a study in which corneal sensitivity is measured and eye rubbing habits are assessed in a questionnaire.

“Almost all of them say they no longer feel the need to rub their eyes. The more important effect is not corneal stiffening, but the biological effect, the interaction with the keratocytes and with the nerves,” he said. “There is a dialogue between endothelium and epithelium through the keratocytes meshwork, and with CXL you stop that interaction.”

He is hoping that transepithelial CXL will show comparable biological effects to epi-off.

Many papers start with the definition of keratoconus as “a non-inflammatory disease,” but Touboul strongly believes that this is a wrong assumption. Inflammatory processes are involved and connected with eye rubbing in a cycle that CXL has the power to interrupt.

Pediatric patients

Transepithelial CXL may be an opportunity for younger patients, in whom the epithelium-off procedure represents a problem, according to Balidis.

“Now that we have increased the efficacy, we can perform epi-on customized procedures without the worries, the contact lens-related problems, the suffering of the child and the uneasiness of parents because of postoperative pain,” he said.

Eye rubbing is difficult to control in children and causes even greater damage because the cornea is softer.

“I don’t perform CXL at the first visit. I wait 1 or 2 months to see if it is progressing, but if it is, we must act promptly and follow the child closely. Epi-on in these cases, if it works as well as epi-off, is a very good option, a painless way of helping the child stop eye rubbing,” Touboul said.

Hersh, on the other hand, would recommend epi-on only in children who are not amenable to an epi-off, such as very young children or children with disabilities.

“I have seen patients with epi-on in a progressive age range who continue to progress. Of course, it is anecdotal, but based on the long-term data of the current literature, I would still recommend an epi-off approach in a pediatric population with progressing keratoconus,” he said.

Mazzotta, despite being an advocate of epi-on, would also not recommend it in pediatric patients.

“At a young age, keratoconus progression is very aggressive, and epi-off has so far ensured good stabilization at more than 10 years. Epi-on will be the future also for these patients, but at the moment we should stick to the evidence,” he said.

Thin corneas

Opinions are divided on the treatment of thin corneas. Epi-on is a good option and the way to go according to Hersh and Balidis, while Mazzotta prefers epi-off with his “nomogram M,” which allows the accelerated procedure to be customized to corneas of a wide range of thickness values, including very thin corneas. According to Touboul, the debate on thin corneas is not interesting, because when the cornea is very thin, it is already too late for cross-linking and it is probably time for keratoplasty. In less extreme cases, he prefers corneal rings, which have an equally good impact on biomechanics.

Soosan Jacob, MS, FRCS, DNB, of Dr. Agarwal’s Eye Hospital in Chennai, India, has had good results with contact lens-assisted collagen cross-linking (CACXL) in thin corneas. This method has been shown to provide about 60% to 70% UV transmission through the riboflavin-soaked contact lens to the corneal stroma.



Soosan
Jacob

“Currently we are very satisfied with our results with CACXL and also very happy that these results have been shown to be repeatable in peer-reviewed published studies from different centers around the world. In fact, we have been able to avoid DALK in many patients by combining CACXL with corneal allogenic intrastromal ring segments (CAIRS), another technique I personally developed. CAIRS are a form of intracorneal rings made of allogenic donor corneal tissue. They provide good flattening of the cornea, regularization and improvement of topography, centralization of the cone, and improvements in UDVA, spectacle CDVA and refractive error. They also help in redistributing corneal stress forces. When combined with CACXL, the treatment becomes very effective in thin corneas as well,” she said.

Presently, she is treating up to about 280 μm epithelium off with CACXL, using a few drops of distilled water in those few cases in which the functional corneal thickness is still slightly short of 400 μm even after placing the contact lens.

However, Jacob looks at the new epi-on protocols with interest. If the efficacy of epi-on is unequivocally proven, she believes that it could be combined with CACXL in advanced cases.

“However, we need consistent data from multicenter studies on efficacy and stability. I think the jury will be out until then,” she said.

Secondary ectasia and other special cases

Post-LASIK ectasia requires case-by-case evaluation, according to Hersh. If progression is fast, he recommends an epi-off procedure, while epi-on would be good in cases that are relatively stable.

"You don't disturb the LASIK flap and it is easier for the patients, but a closer follow-up is recommended to make sure they don't progress," he said.

"Although it is a rare complication, we see a lot of these cases because they are referred to us," Touboul said. "Most of the time eye rubbing is also in the equation."

It is important to separate early postoperative ectasia, due to crossing the line with huge flaps and too much photoablation, from long-term ectasia related to inflammation dry eye and eye rubbing, he said.

"In these late cases, I do epi-off with intracorneal segments to stiffen the cornea because progression is fast. However, I would welcome the possibility of using epi-on in the future," he said.

Epi-on is also an opportunity for patients who are at a greater risk for poor corneal healing and for patients with corneal scars, as it is better to leave the epithelium in place, according to Hersh.

"When you remove the epithelium, eyes with corneal scars are at increased risk of scarring and haze," he said.

The standard in routine practice

For some specialists, transepithelial CXL has already become the standard in routine clinical practice. Mazzotta treats with epi-on in almost every patient older than age 21 years.

"It gives me the chance to perform the treatment in both eyes simultaneously because there is less pain, a lower risk of infection and functional recovery is faster. This is a significant advantage for patients with bilateral keratoconus," he said.

In some bilateral cases, he uses epi-off in the worst eye and epi-on in the better eye.

Of the two procedures, iontophoresis and Boost Epi-On, he trusts the first one more, at least for the time being and until further evidence is produced in favor of the second option.

"We have yet to prove whether the addition of oxygen is necessary overall or if it may not be redundant since pulsed light already increases intraoperative oxygen availability. My new iontophoresis protocol has shown excellent results at 3 years, without supplemental oxygen," he said.

Balidis uses epi-on in the early stages of keratoconus, 1 and 2, in thin corneas or in young patients. For stage 2 to 3, a combined topography-guided ablation is needed. Topography-guided transepithelial PRK followed by 9-minute accelerated CXL protocol is the procedure of choice, he said.

"This was my standard procedure a few years ago but now is only left for the most difficult cases in which I need to regularize the cornea," he said.

There is an extra cost with Boost Epi-On, but it is reasonable, in the range of 150 euros to 200 euros, he said.

"When we perform customized procedure with the Mosaic system, the cost per procedure is four times higher than the standard Dresden and three times than accelerated KXL. But the advantages of a customized, trouble-free, painless epi-on procedure are several. We are trying to raise public awareness on CuRV epi-on. As a result, we popularize the technique and increase the number of procedures. This is a way of decreasing the price for the patient and expanding our standard of care. Our center is considered a center of excellence in the region, specifically for a holistic keratoconus care," Balidis said. – *by Michela Cimberle*

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Disclosures: Balidis reports he is a consultant and researcher for Avedro, Avellino Labs, Thea and Bausch + Lomb. Hersh reports he serves on the medical advisory board of Avedro. Jacob reports she has a patent pending for special trephines, shaped corneal segments, and devices and processes used to manufacture CAIRS segments. Mazzotta reports he is a consultant for Avedro. Touboul reports no relevant financial disclosures.

